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**Last Review Status/Date:** December 2015

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## Hyperbaric Oxygen Therapy

### Description

Hyperbaric oxygen therapy (HBOT) involves breathing 100% oxygen at a pressure of more than 1.5 and 3.0 atmospheres (atm). Hyperbaric oxygen therapy is generally applied systemically with the patient inside a hyperbaric chamber. It can also be applied topically; that is, the body part to be treated is isolated e.g., in an inflatable bag and exposed to pure oxygen. HBOT has been investigated for various conditions that have potential to respond to increased oxygen delivery to the tissues

### Background

Hyperbaric oxygen therapy (HBOT) is a technique of delivering higher pressures of oxygen to the tissues. Two methods of administration are available. In systemic or large chamber hyperbaric oxygen, the patient is entirely enclosed in a pressure chamber and breathes oxygen at a pressure greater than 1 atmosphere (atm, the pressure of oxygen at sea level). Thus, this technique relies on systemic circulation to deliver highly oxygenated blood to the target site, typically a wound. In addition, systemic hyperbaric oxygen therapy can be used to treat systemic illness, such as air or gas embolism, carbon monoxide poisoning, clostridial gas gangrene, etc. Treatment may be carried out either in a monoplace chamber pressurized with pure oxygen or in a larger, multiplace chamber pressurized with compressed air, in which case the patient receives pure oxygen by mask, head tent or endotracheal tube.

Note that this evidence review does not address topical oxygen therapy in the absence of pressurization.

### Regulatory Status

In May 2005, the ATA Monoplace Hyperbaric System (ATA Hyperbaric Chamber Manufacturing, Inc.) was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing hyperbaric devices.

In 2013, FDA published a statement warning that non-FDA approved uses of HBOT may endanger the health of patients.(1) If patients mistakenly believe that HBOT devices have been proven safe for uses not cleared by FDA, they may delay or forgo other proven medical therapies.

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### Related Policies

None

### Policy

*\*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Systemic hyperbaric oxygen pressurization may be considered **medically necessary** in the treatment of the following conditions:

- non-healing diabetic wounds of the lower extremities in patients who meet the following 3 criteria:
  1. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes; and
  2. Patient has a wound classified as Wagner grade 3 or higher (see Policy Guidelines); and
  3. Patient has no measurable signs of healing after 30 days of an adequate course of standard wound therapy;
- acute traumatic ischemia e.g. crush injuries, reperfusion injury, compartment syndrome;
- decompression sickness;
- gas embolism, acute;
- cyanide poisoning, acute;
- acute carbon monoxide poisoning;
- soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) and osteoradionecrosis;
- pre- and post-treatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw;
- gas gangrene (i.e., clostridial myonecrosis);
- profound anemia with exceptional blood loss: only when blood transfusion is impossible or must be delayed; and
- chronic refractory osteomyelitis

Hyperbaric oxygen pressurization is considered **not medically necessary** in the treatment of the following conditions:

- compromised skin grafts or flaps;
- acute osteomyelitis
- bisphosphonate-related osteonecrosis of the jaw
- necrotizing soft-tissue infections;
- acute thermal burns;
- acute surgical and traumatic wounds;
- chronic wounds, other than those in patients with diabetes who meet the criteria specified in the medically necessary statement;
- spinal cord injury;
- traumatic brain injury;
- inflammatory bowel disease (Crohn disease or ulcerative colitis);

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- brown recluse spider bites;
- bone grafts;
- carbon tetrachloride poisoning, acute;
- cerebrovascular disease, acute (thrombotic or embolic) or chronic;
- fracture healing;
- hydrogen sulfide poisoning;
- intra-abdominal and intracranial abscesses;
- lepromatous leprosy;
- meningitis;
- Pseudomembranous colitis (antimicrobial agent-induced colitis);
- radiation myelitis;
- sickle cell crisis and/or hematuria;
- demyelinating diseases, e.g., multiple sclerosis, amyotrophic lateral sclerosis;
- retinal artery insufficiency, acute;
- retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment;
- pyoderma gangrenosum;
- acute arterial peripheral insufficiency;
- acute coronary syndromes and as an adjunct to coronary interventions, including but not limited to, percutaneous coronary interventions and cardiopulmonary bypass;
- idiopathic sudden sensorineural hearing loss (ISSNHL);
- refractory mycoses: mucormycosis, actinomycosis, candidobolus coronato;
- cerebral edema, acute;
- migraine;
- in vitro fertilization;
- cerebral palsy;
- tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy;
- delayed onset muscle soreness;
- idiopathic femoral neck necrosis;
- chronic arm lymphedema following radiotherapy for cancer;
- radiation-induced injury in the head and neck; except as noted above in the medically necessary statement;
- early treatment (beginning at completion of radiation therapy) to reduce adverse effects of radiation therapy;
- autism spectrum disorders.
- Bell's palsy
- acute ischemic stroke;
- motor dysfunction associated with stroke;
- herpes zoster; and
- vascular dementia
- fibromyalgia; and
- mental illness (ie, posttraumatic stress disorder, generalized anxiety disorder or depression).

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## Policy Guidelines

### Systemic Hyperbaric Oxygen

The Wagner classification system of wounds is defined as follows:

- grade 0, no open lesion;
- grade 1, superficial ulcer without penetration to deeper layers;
- grade 2, ulcer penetrates to tendon, bone, or joint;
- grade 3, lesion has penetrated deeper than grade 2 and there is abscess, osteomyelitis, pyarthrosis, plantar space abscess, or infection of the tendon and tendon sheaths;
- grade 4, wet or dry gangrene in the toes or forefoot;
- grade 5, gangrene involves the whole foot or such a percentage that no local procedures are possible and amputation (at least at or below the knee level) is indicated.

Below are suggestions from the Undersea and Hyperbaric Medical Society's (UHMS) 2008 Hyperbaric Oxygen Therapy Committee report on utilization of hyperbaric oxygen therapy (HBOT) (2):

- Enhancement of healing in problem wounds: Treatments are performed for 90 to 120 minutes. The initial treatment schedule depends on the severity of disease. More serious conditions may require twice daily treatments; when stabilized, this can decrease to once daily. Utilization review is required after the initial 30 days of treatment and at least once every additional 30 days.
- Crush injury, compartment syndrome and other acute traumatic ischemias:
  - Reperfusion injury: 1 treatment.
  - Crush injury: 8 treatments (three times per day for 2 days, then twice a day for 2 days and daily for 2 days)
  - Compartment syndrome: 3 treatments (twice a day for 1 day and one treatment on day 2)
- Decompression sickness: The majority of cases respond to a single treatment. Patients with residual defects after the initial session should receive additional treatments until they achieve clinical stability (generally no more than 5-10 treatments). Utilization review is recommended after 10 treatments.
- Gas embolism, acute: It is recommended that treatments continue until there is no additional improvement; this typically occurs after 1-2 treatments but occasionally up to 5-10. Utilization review is recommended after 10 treatments.
- Acute carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning: Some patients improve after a single treatment. Patients who fail to demonstrate a full recovery should receive additional treatments. In patients with persistent neurologic dysfunction after the initial treatment, further treatment can occur within 6-8 hours and can be continued once or twice daily until there is no additional improvement in cognitive function. Utilization review is mandatory after the fifth treatment.
- Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) and osteoradionecrosis: Most treatment courses for radiation injury will be 30-60 treatments (once daily for 90 to 120 minutes). Utilization review is recommended after 60 treatments.
- Mandibular osteoradionecrosis: The initial course of treatment for patients with stage 1 osteoradionecrosis is 30 sessions, followed by only minor bony debridement. If response is

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adequate, an additional 10 treatments are given. If patients are not responding they are considered stage II and they receive more extensive surgical debridement, followed by 10 additional treatments. Patients who present as stage III patients receive 30 treatments followed by mandibular segmental resection and then an additional 10 treatments.

- Gas gangrene (i.e., clostridial myonecrosis): Recommended are three 90-minute treatments during the first 24 hours and then two treatments per day for the next 2-5 days, depending on the patient's initial response. Utilization review is indicated after 10 treatments.
- Severe anemia: HBOTHBOT can be considered for severe anemia when patients cannot receive blood products due to medical, religious, or strong personal preference reasons. Treatment can occur for periods of up to 3 or 4 hours three to four times a day if patients receive intra-treatment air breaks. HBOTHBOT treatment should be continued with taper of both time and frequency until red blood cells have been satisfactorily replaced by patient regeneration or the patient can undergo transfusion.
- Chronic refractory osteomyelitis: No recommendations were made for the total number of treatments required. For patients who respond to initial treatment with antibiotics, surgical debridement and HBOTHBOT, therapy should be continued for approximately 4-6 weeks. Utilization review is indicated after 30-40 sessions.

## Benefit Applications

The BCBS FEP contract stipulates that FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may only be assessed based on medical necessity.

The BCBS FEP contract affects coverage for hyperbaric oxygen therapy. Refer to the current FEP Service Benefit Plan brochure for additional information and guidance.

## Rationale

Assessment of efficacy for therapeutic interventions involves a determination of whether the intervention improves health outcomes. The optimal study design for a therapeutic intervention is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may be adequate if there is an established link between the intermediate outcome and true health outcomes. When the primary outcomes are subjective (eg, pain, depression), sham-controlled RCTs are needed to assess the effect of the intervention beyond that of a placebo effect.

### Systemic Hyperbaric Oxygen

The original policy on systemic HBOTHBOT was based on the 1996 guidelines published by the Undersea and Hyperbaric Medical Society (UHMS) and was subsequently revised in 1999 with 3 TEC Assessments. (3-5) The TEC Assessments had conclusions similar to UHMS, except, in contrast to the UHMS guidelines, they concluded that there was insufficient evidence to conclude that HBOT treatment improved the net health outcome for the following indications:

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- compromised skin grafts
- acute thermal burns
- chronic refractory osteomyelitis
- necrotizing soft tissue infections
- brown recluse spider bites

The TEC Assessments also concluded that there was insufficient evidence to permit conclusions on the use of HBOTHBOT for treatment of brain injury; spinal cord injury; and Crohn's disease, indications not addressed by the 1996 UHMS Guidelines. Literature updates have focused on identifying new RCTs and meta-analyses of RCTs, particularly on indications considered not medically necessary at the time of the update.

### *Chronic Wounds*

Several systematic reviews of RCTs have been published. A Cochrane review of RCTs on HBOT treatment for chronic wounds was published by Kranke and colleagues in 2012. (6) The authors identified 9 RCTs with a total of 471 participants that compared the effect of HBOT on chronic wound healing compared to an alternative treatment approach that did not use HBOT. Eight of the 9 trials included in the review evaluated HBOT therapy in patients with diabetes. The remaining trial addressed HBOT for patients with venous ulcers; that study had only 16 participants and the comparator treatment was not specified. In a pooled analysis of data from 3 trials, a significantly higher proportion of ulcers had healed at the end of the treatment period (6 weeks) in the group receiving HBOT compared to the group not receiving HBOT (RR: 5.20; 95% CI: 1.25 to 21.7). Pooled analyses, however, did not find significant differences between groups in the proportion of ulcers healed in the HBOT versus non-HBOT-treated groups at 6 months (2 trials) or 12 months (3 trials). There were insufficient data to conduct pooled analyses of studies evaluating HBOT for treating patients with chronic wounds who did not have diabetes. The most recently published trial conducted with diabetic patients was double-blind and included 75 diabetic patients with chronic wounds who had failed at least 2 months of treatment at a diabetic foot clinic. (6) After 12 months, the healing rate was 61% in the hyperbaric oxygen group and 27% in the sham hyperbaric group; this difference was statistically significant,  $p=0.009$ .

In 2013, O'Reilly et al published a systematic review of studies on HBOT for treatment of diabetic ulcers.(7)The authors identified 6 RCTs and 6 non-RCTs that compared HBOT with standard wound care or sham therapy in patients with diabetes who had nonhealing lower-limb ulcers. Pooled analyses of observational studies found statistically significant benefits of HBOT on rates of major amputation, minor amputation, and the proportion of wounds healed at the end of the study period. However, in pooled analyses of RCT data, the stronger study design, there were no statistically significant differences between groups on key outcomes. This included the rate of major amputation (RR=0.40; 95% CI, 0.07 to 2.23;  $p=0.29$ ), minor amputation (RR=0.79; 95% CI, 0.19 to 3.30,  $p=0.75$ ) and the proportion of unhealed wounds at the end of the study period (RR=0.54, 95% CI, 0.26 to 1.13,  $p=0.1$ ).

Systematic reviews have had mixed findings on the impact of HBOT on diabetic ulcers. A Cochrane review found short-term, but not long-term benefit on wound healing, and a 2013 meta-analysis did not find significant benefits of HBOT on outcomes in RCTs, but did find an effect in non-RCTs. There is insufficient evidence on HBOT for treatment of chronic wounds in patients without diabetes.

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### *Acute Surgical and Traumatic wounds*

In 2013, a updated Cochrane review of RCTs on HBOT for acute surgical and traumatic wounds was published by Eskes et al.(8) HBOT was defined as use of 100% oxygen at pressures above 1 atm. To be included, studies needed to compare HBOT with a different intervention or compare 2 HBOT regimens; in addition, studies needed to objectively measure wound healing. A total of 4 met the review's inclusion criteria. The studies ranged in size from 10 to 135 participants. Due to differences among studies in terms of patient population, comparison intervention, outcome measurement, etc., study results could not be pooled. The primary outcome examined by Cochrane reviewers, wound healing, was not reported in either of the 2 trials comparing HBOT with usual care and was not reported in the 1 trial comparing HBOT with dexamethasone or heparin. Complete wound healing was reported in the 1 RCT comparing active HBOT with sham HBOT. In this small study (n=36), there was a statistically higher rate of wound healing in the group; the time point for outcome measurement in this study was unclear. In the sham-controlled study, there was no statistically significant difference between groups in the meantime to wound healing.

Another 2014 systematic review of studies on HBOT for acute wounds, published by Dauwe et al, included randomized and nonrandomized controlled studies.(9) The review included 8 studies, with sample sizes ranging from 5 to 125 patients. Four studies were randomized, 3 were prospective nonrandomized controlled studies, and 1 was a retrospective nonrandomized controlled study. As in the Eskes systematic review, data were not pooled. The authors noted that 7 of the 8 studies reported achieving statistical significance in their primary endpoints, but the end points differed among studies (eg, graft survival, length of hospital stay, wound size). Moreover, the studies were heterogeneous in terms of treatment regimens, patient indications (eg, burns, face lifts), and study designs, making it difficult to draw conclusions about the effect of HBOT on acute wound treatment.

There is insufficient evidence supporting HBOT for treatment of acute wounds; additional evidence from high-quality RCTs is needed.

### *Carbon Monoxide Poisoning*

A 2011 Cochrane review of 7 RCTs concluded that the available evidence is insufficient to determine whether adverse neurologic outcomes in patients with carbon monoxide poisoning are reduced with HBOT. (10) In 2008, the American College of Emergency Physicians published a clinical policy on critical issues in carbon monoxide poisoning. (11) Their literature review indicated there was only Level C evidence (preliminary, inconclusive, or conflicting evidence) for treatment of acute carbon monoxide poisoning. The 2008 Undersea and Hyperbaric Medical Society (UHMS), however, lists carbon monoxide poisoning as an indication for HBOT therapy.

Two blinded randomized trials were discussed in both the Cochrane and American College of Emergency Physicians reviews. One is a study by Scheinkestel and colleagues, a double-blind, RCT comparing HBOT to normobaric oxygen in patients with carbon monoxide poisoning. (12) The authors reported that HBOT therapy did not benefit patient outcomes of neuropsychological performance when HBOT therapy was completed and at 1-month follow-up. This study was limited, however, by a high rate (46%) of patients who were lost to follow-up. Moreover, the trial has been criticized for administering 100% normobaric oxygen for at least 72 hours between treatments, which has been called a toxic dose

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of oxygen. (13) The critiques also mention that there was an unusually high rate of neurologic sequelae after the treatment period, which could be due in part to the high dose of oxygen and/or the high rate of cognitive dysfunction in the study population (69% were poisoned by carbon monoxide through suicide attempts).

The other blinded trial by Weaver and colleagues also compared HBOT and normobaric oxygen. (14) Patients received either 3 sessions of HBOT or 1 session of normobaric oxygen plus 2 sessions of exposure to normobaric room air. The primary outcome was the rate of cognitive sequelae at 6 weeks. A battery of neuropsychological tests assessed cognitive function. At the 6-week follow-up, the intention to treat analysis found that 19 of 76 (25.0%) in the HBOT group and 35 of 76 (46.1%) in the control group had cognitive sequelae; the difference was statistically significant,  $p=0.007$ . There was a high rate of follow-up at 6 weeks, 147 of 152 (97%) of randomized patients. Enrollment in the study was stopped early because an interim analysis found HBOT to be effective. A follow-up study, that included 147 patients from the randomized trial and 75 who had been eligible for the trial but had not enrolled, was published in 2007. (15) Of the group treated with HBOT ( $n=75$ ), cognitive sequelae were identified in 10 of 58 (17%) at 6 months and 9 of 62 (14%) at 12 months. Of the group not treated with HBOT ( $n=163$ ), 44 of 146 (30%) at 6 months and 27 of 149 (18%) at 12 months had cognitive sequelae. (The follow-up rate was higher at 12 months because the investigators received additional funding for data collection.) Thus given the Weaver trial results the use of hyperbaric oxygen therapy for acute carbon monoxide poisoning is considered medically necessary.

#### *Radionecrosis and Osteoradionecrosis*

Several systematic reviews of RCTs have been published. A 2008 Cochrane review by Esposito et al. reviewed the use of HBOT therapy in patients requiring dental implants. (16) The authors identified 1 randomized trial involving 26 patients. The authors concluded that despite the limited amount of clinical research available, it appears that HBOT therapy in irradiated patients requiring dental implants may not offer any appreciable clinical benefits. They indicate that there is a need for more RCTs to ascertain the effectiveness of HBOT in irradiated patients requiring dental implants.

In 2012, Bennett and colleagues published a Cochrane review on hyperbaric oxygen therapy (HBOT) for late radiation tissue injury. (17) The authors identified 11 RCTs; there was variability among trials and study findings were not pooled for the primary outcomes of survival, complete resolution of necrosis or tissue damage, and improvement in a late effects symptom scale. In a pooled analysis of 3 studies, a significantly higher proportion of patients with osteoradionecrosis achieved complete mucosal cover after hyperbaric oxygen treatment compared to control (risk ratio [RR]: 1.30, 95% CI: 1.09 to 1.55). From their review of the literature, the authors concluded that data from small trials “suggest that for people with LRTI (*Late Radiation Tissue Injury*) affecting the head, neck, anus, and rectum, [HBOT] is associated with improved outcome. HBOT also appears to reduce the chance of ORN (*osteoradionecrosis*) following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues. The application of HBOT to selected patients and tissues may be justified.”

HBOT has long been used to treat soft tissue and bone radiation necrosis and for pre- and post-treatment of dental surgery (non-implant-related) in an irradiated jaw.

#### *Bisphosphonate-related Osteonecrosis of the Jaw*



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An unblinded RCT was published by Freiburger and colleagues in 2012 on use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw. (18) Forty-nine patients were randomly assigned to HBOT in addition to standard care (n=22) or standard care alone (n=27). Five patients in the standard care group received HBOT treatment and 1 patient assigned to the HBOT group declined HBOT. The investigators decided to do a *per* protocol analysis (actual treatment received) because of the relatively large degree of crossover. Participants were evaluated at 3, 6, 12 and 18 months. Data were available on 46 patients, 25 received HBOT in addition to standard care and 21 received standard care alone. The primary outcome measure was change in oral lesion size or number. When change from baseline to last available follow-up was examined 17 of 25 (68%) of HBOT-treated patients had improvement in oral lesion size or number compared to 8 of 21 (38%) in the standard care group, p=0.043. When change from baseline to 6, 12 or 18 months was examined, there was not a statistically significant difference between groups in the proportion of patients with improvement. In addition, the proportion of patients who healed completely did not differ significantly between groups at any time point. This single trial does not report consistent findings of benefit across outcome measures. It also has a number of methodological limitations, e.g., unblinded, cross-over, and analysis performed on a *per-protocol* basis rather than intention to treat. A disadvantage of the *per-protocol* analysis is that randomization is not preserved and the two groups may differ on characteristics that affect outcomes. As a result, this trial is insufficient to conclude that HBOT improves health outcomes for patients with bisphosphonate-related osteonecrosis of the jaw.

### *Osteomyelitis*

No prospective clinical trials on chronic refractory osteomyelitis or acute refractory osteomyelitis were identified in updated searches. The justification for the use of HBOT in chronic osteomyelitis has been primarily based on case series. Among the larger case series, Maynor and colleagues reviewed the records of all patients with chronic osteomyelitis of the tibia seen at one institution. (19) Follow-up data were available on 34 patients who had received a mean of 35 adjunctive HBOT treatments (range, 6 to 99). Of the 26 patients with at least 2 years of follow-up after treatment, 21 (81%) remained drainage free. Twelve of 15 (80%) with follow-up data at 60 months had remained drainage free. A study by Davis and colleagues reviewed outcomes for 38 patients with chronic refractory osteomyelitis treated at another U.S. institution. (20) Patients received HBOT treatment until the bone was fully recovered with healthy vascular tissue; this resulted in a mean of 48 daily HBOT treatments (range, 8 to 103). After a mean post-treatment follow-up of 34 months, 34 of 38 (89%) patients remained clinically free of infection (i.e., drainage free and no tenderness, pain, or cellulitis). Success rates from several smaller case series, all conducted in Taiwan, are 12 of 13 (92%) patients, 11 of 14 (79%) patients, and 13 of 15 (86%) patients. (21-23) Given the high percentage of refractory patients in these series who had successful outcomes, the use of HBOT for chronic refractory osteomyelitis is determined to be medically necessary. HBOT treatment for acute osteomyelitis refractory to medical treatment remains not medically necessary.

### *Fracture Healing*

In 2012, Bennett and colleagues published a Cochrane review on HBOT to promote fracture healing and treat non-union fractures. (24) The investigators did not identify any published RCTs on this topic that compared HBOT to no treatment, sham or another intervention and reported bony union as an outcome.

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### *Compromised Skin Grafts and Flaps*

In 2006, Friedman and colleagues published a systematic review of literature on use of HBOT for treating skin flaps and grafts. (25) No RCTs were found. The authors identified 2 retrospective case series on use of HBOT for clinically compromised skin grafts and flaps. The series had sample sizes of 65 and 26, respectively; both were published in the 1980s based on treatment provided in the 1970s and 1980s.

### *Necrotizing Soft Tissue Infections*

A 2015 Cochrane review by Levett et al evaluated the literature on HBOT as adjunctive therapy for necrotizing fasciitis.(26) No RCTs were identified. Previously, in 2005, a systematic review by Jallali et al identified only a few retrospective studies with small sample sizes.(27) Findings of these studies were inconsistent. A 2009 retrospective cohort study compared outcomes in 48 patients at 1 center who received adjunctive HBOT for necrotizing soft issue infections with those in 30 patients at a different center who did not receive HBOT.(28) There was no significant difference in the mortality rate between the 2 groups (4/48 [8%]) in the HBOT group, 4/30 [13%] in the non-HBOT group;  $p=0.48$ ). The median number of days in the intensive care unit and the median number of days in the hospital also did not differ significantly. There was a higher median number of débridement procedures per person in the HBOT group (3.0) than in the non-HBOT group (2.0) ( $p=0.03$ ).

### *Refractory Mycoses*

No clinical trials on refractory mycoses (mucormycosis, actinomycosis, canidiobolus coronato) and cerebral edema were found.

### *Acute Peripheral Arterial Insufficiency*

No clinical trial publications were identified that demonstrated benefit in HBOT for acute peripheral arterial insufficiency. (29)

### *Acute Coronary Syndromes*

A 2012 Cochrane review by Bennett and colleagues identified 6 trials with a total of 665 patients evaluating HBOT for acute coronary syndrome. (30) All of the studies included patients with acute myocardial infarction (MI); one study also included individuals presenting with unstable angina. Additionally, all trials used HBOT as an adjunct to standard care. Control interventions varied; only 1 trial described using a sham therapy to blind participants to treatment group allocation. In a pooled analysis of data from 5 trials, there was a significantly lower rate of death in patients who received HBOT compared to a control intervention (RR: 0.58: 0.36 to 0.92). Due to variability of outcome reporting in the studies, few other pooled analyses could be conducted. A pooled analysis of data from 3 trials on improvements in left ventricular function did not find a statistically significant benefit of HBOT treatment (RR: 0.09; 95% CI: 0.01 to 1.4). The authors noted that, although there is some evidence from small trials that HBOT treatment is associated with a lower risk of death, larger trials with high methodologic quality are needed in order to determine which patients, if any, can be expected to derive benefit from HBOT.

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One of the trials was by Sharifi and colleagues and randomly assigned 69 patients with unstable angina or MI to receive or not receive HBOT after a percutaneous coronary intervention (PCI). (31) The 24 patients randomly assigned to the HBOT group reported only 1 adverse event (death, MI, coronary artery bypass, or revascularization of target lesion), compared to 13 in the 37 control patients. However, this study lacked adequate detail, e.g., on the type of PCI performed, to permit scientific conclusions. In another RCT of 64 patients, Alex and colleagues concluded both neuropsychometric dysfunction and inflammatory response can be reduced postcardiopulmonary bypass when HBOT pretreatment is given. (32) Based on the above evidence, the treatment of acute coronary syndromes is considered not medically necessary.

#### *Acute Ischemic Stroke*

In a 2014 update of a Cochrane systematic review, Bennett et al evaluated HBOT for acute ischemic stroke.(33) The investigators identified 11 RCTs, with a total of 705 participants, that compared HBOT with sham HBOT or no treatment. The authors were only able to pool study findings for 1 outcome (mortality at 3-6 months). A pooled analysis of data from 4 trials with a total of 106 participants did not find a significant benefit of HBOT compared with a control condition for this outcome (RR=0.97; 95% CI, 0.34 to 2.75).

#### *Motor Dysfunction Associated with Stroke*

In 2013, Efrati and colleagues published an RCT evaluating HBOT therapy for treatment of neurologic deficiencies associated with a history of stroke. (34) The study included 74 patients with at least 1 motor dysfunction who had an ischemic or hemorrhagic stroke 6-36 months prior to study participation. Participants were randomly assigned to receive 2 months of HBOT treatment (40 daily sessions, 5 days per week, n=30) or delayed treatment (n=32). Patients were evaluated at baseline and 2 months. For patients in the delayed treatment control group, outcomes were evaluated at 4 months after crossing-over and receiving HBOT treatment. Twenty-nine of 32 patients (91%) in the delayed treatment group crossed over to the active intervention. Outcome measures included the National Institutes of Health Stroke Scale (NIHSS), which was measured by physicians blinded to treatment group, and several patient reported quality of life and functional status measures.

At 2 months' follow-up, there was statistically significantly greater improvement in function in the HBOT group compared to the control group as measured by the NIHSS, quality of life scales and the ability to perform activities of daily living (ADLs). These differences in outcome measures were accompanied by improvements in SPECT imaging in the regions affected by stroke. For the delayed treatment the control group, there was a statistically significant improvement in function after HBOT treatment compared to before treatment. This RCT raises the possibility that HBOT may induce improvements in function and quality of life for post-stroke patients with motor deficits. However, the results are not definitive for a number of reasons. This RCT is small and enrolled a heterogeneous group of post-stroke patients. The study was not double-blind and the majority of outcome measures, except for the NIHSS, were patient reported and thus prone to the placebo effect. Also, there was a high total dropout rate of 20% at the two-month follow-up point. Therefore, larger, double-blind studies with longer follow-up are needed to corroborate these results. Because of these limitations in the evidence, HBOT is considered not medically necessary for treating motor dysfunction associated with stroke.

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### *Bell's Palsy*

In 2012, Holland and colleagues published a Cochrane review evaluating HBOT treatment in adults with Bell's palsy. (35) The authors identified one RCT with 79 participants, and this study did not meet the Cochrane review methodologic standards because the outcome assessor was not blinded to treatment allocation. Due to the publication of the Cochrane review and the finding of insufficient evidence, Bell's palsy is considered not medically necessary.

### *Traumatic Brain Injury*

A 2012 Cochrane systematic review addressed HBOT as adjunctive treatment for traumatic brain injury. (36) The investigators identified 7 RCTs with a total of 571 participants comparing a standard intensive treatment regimen to the same treatment regimen with the addition of HBOT. The review did not include studies in which interventions occurred in a specialized acute care setting. The HBOT regimens varied among studies; for example, the total number of individual sessions varied from 3 to 30-40. No trial used sham treatment or blinded the staff members who were treating the patients, and only 1 had blinding of outcome assessment. Allocation concealment was inadequate in all of the studies. The primary outcomes of the review were mortality and functional outcomes. A pooled analysis of data from 4 trials that reported this outcome found a statistically significantly greater reduction in mortality when HBOT was added to a standard treatment regimen (RR: 0.69, 95% CI: 0.54 to 0.88). However, when data from the 4 trials were pooled, the difference in the proportion of patients with an unfavorable functional outcome at final follow-up did not quite reach statistical significance (RR: 0.71, 95% CI: 0.50 to 1.01). Unfavorable outcome was commonly defined as a Glasgow Outcome Score (GOS) of 1, 2 or 3 which are described as 'dead', 'vegetative state' or 'severely disabled'. Studies were generally small and were judged to have substantial risk of bias.

Several trials on mild traumatic brain injury in military populations have been published and they did not find significant benefits of HBOT compared with sham treatment.(37-39) The first trial, published by Wolf et al in 2012, included 50 military service members, 48 of whom were male, with combat-related mild traumatic brain injury. Participants were randomized to 30 sessions of HBOT over 8 weeks (n=25) or a sham intervention (room air at 1.3 atmosphere, absolute [ata]) (n=25). The primary outcome measures were scores on the Immediate Post-Concussive Assessment and Cognitive Testing (ImPACT) and Post-Traumatic Disorder Check List–Military Version (PCL-M) instruments. Patients were evaluated after every 5 treatment sessions and at 6 weeks postexposure. Forty-eight of 50 participants (96%) completed the study. There were no statistically significant differences on the ImPACT total mean score or the PCL-M composite score at any time point. For example, at the 6-week follow-up, mean composite PCL-M scores were 41.6 in the HBOT group and 40.6 in the sham-control group (p=0.28). While the sample size was relatively small, the study was powered to detect clinically significant differences among groups on the cognitive tests.

A 2014 double-blind sham-controlled trial 2014 RCT by Cifu et al included 61 male Marines who had a history of mild traumatic brain injury and postconcussive syndrome.(38) To maintain blinding, all patients were pressured inside a hyperbaric chamber to 2.0 ata. They were randomized to breathe 1 of 3 oxygen-nitrogen gas mixes equivalent to: (1) 75% oxygen at 1.5 ata (n=21); (2) 100% oxygen at 2.0 ata (n=19); and (3) sham treatment with surface room air (n=21). Patients underwent 40 once-daily 60-minute sessions. Outcomes were assessed 3 months after the last exposure. The primary outcome was

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a clinically meaningful improvement, defined as a 10% difference between groups in the score on the 16-item Rivermead Post-Concussion Questionnaire (RPQ; (scale range, 50-84; higher values indicate more severe symptoms). At follow-up, there was no statistically significant difference among groups on RPQ-16 score ( $p=0.41$ ). A variety of secondary outcomes were also assessed. None, including measures of attention, cognition, or depression, differed significantly among groups at follow-up.

In 2015, Miller et al evaluated HBOT in 72 military service members with continuing symptoms at least 4 months after mild traumatic brain injury.(39) Patients were randomized to receive 40 daily HBOT sessions at 1.5 ata, 40 sham sessions consisting of room air at 1.2 ata, or standard care with no hyperbaric chamber sessions. The primary outcome was change in RPQ score. A cutoff of 15% improvement was deemed clinically important, which translates to a change score of at least 2 points on the RPQ-3 subscale. The proportion of patients who met the prespecified change of at least 2 points on the RPQ-3 was 52% in the HBOT group, 33% in the sham group, and 25% in the standard care-only group. The difference between rates in the HBOT and sham groups was not statistically significant ( $p=0.24$ ). None of the secondary outcomes significantly favored the HBOT group. A criticism of this study, as well as the other military population studies, was that the response in the sham group was not due to a placebo effect but to an intervention effect of slightly increased atmospheric pressure (1.2 ata).(40) Other researchers have noted that room air delivered at 1.2 ata would not be considered an acceptable therapeutic dose for any indication, and especially for a condition with persistent symptoms like postconcussive syndrome.

### *Inflammatory Bowel Disease*

A 2014 systematic review by Dulai et al examined the evidence on HBOT for inflammatory bowel disease (Crohn disease and ulcerative colitis). (41) The review was not limited by study design. The authors included 17 studies: 1 RCT, 2 case-control studies, 3 case series, and 11 case reports. The studies reported on a total of 613 patients, 286 with Crohn disease and 327 with ulcerative colitis. The only RCT identified was published in 2013; it was open-label and included 18 patients with ulcerative colitis.(42) Patients were randomized to treatment with standard medical therapy only ( $n=8$ ) or medical therapy plus HBOT ( $n=10$ ). The hyperbaric oxygen intervention consisted of 90 minutes of treatment at 2.4 atm, 5 days a week for 6 weeks (total of 30 sessions). The primary outcome was the Mayo score, which has a potential range of 0 to 12. (43) Patients with a score of 6 or more are considered to have moderate to severe active disease. At follow-up there was no significant difference between groups in the Mayo score; the median score at 6 months was 0.5 in the HBOT group and 3 in the control group (exact  $p$  value not reported). In addition, there were no significant differences in any of the secondary outcomes, including laboratory tests and fecal weight. This is a small study that may have been underpowered. Overall, the authors found that the studies had a high risk of bias, particularly in the areas of attrition and reporting bias.

In summary, there is insufficient evidence that HBOT is an effective for treating inflammatory bowel disease. Only 1 small RCT has been published and this study did not find a significant improvement in health outcomes when HBOT was added to standard medical therapy.

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### *Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL)*

In 2011, the Undersea and Hyperbaric Medical Society added idiopathic sudden sensorineural hearing loss (ISSNHL) within the past 14 days as an approved indication for HBOT therapy. (44) A 2012 Cochrane review on HBOT for ISSNHL and tinnitus identified 7 trials with a total of 392 participants. (45) All trials included patients with ISSNHL with and/or without tinnitus; 2 trials also included patients with tinnitus in the absence of ISSNHL. Randomization procedures were only described in one study, and only one study stated they blinded participants to treatment group assignment using sham therapy. Six of the studies included time-based entry criteria for hearing loss and/or tinnitus; this was 48 hours in 3 studies, 2 weeks in 2 studies (for acute presentation) and 6 months in 1 study. The dose of oxygen per treatment session and the treatment protocols varied among studies e.g., the total number of treatment sessions varied from 10 to 25.

All trials reported on change in hearing following treatment; but specific outcomes varied. Two trials reported the proportion of participants with greater than 50% return of hearing at the end of therapy. A pooled analysis of these studies did not find a statistically significant difference in outcomes between the HBOT and control groups (RR: 1.53, 95% CI: 0.86 to 2.78). In contrast, a pooled analysis of 2 trials reporting the proportion of participants with greater than 25% return of hearing at the end of therapy found a significantly higher rate of improvement after HBOT compared to a control intervention (RR: 1.39; 95% CI: 1.05 to 1.84). Moreover, a pooled analysis of 4 trials found a significantly greater mean improvement in hearing over all frequencies with HBOT compared to control (mean difference: 15.6 decibels (dB); 95% CI: 1.5 to 29.8). The authors stated that, due to methodologic shortcomings of the trials and the modest number of patients, results of the meta-analysis should be interpreted cautiously; they did not recommend use of HBOT for treating ISSNHL.

In 2013, Cvorovic et al published an RCT that included 50 patients with ISSNHL who had failed primary therapy with intravenous steroids. (46) Patients were randomized to receive HBOT (20 sessions, 5 daily sessions per week) or intratympanic steroid injection (4 injections in 13 days). The HBOT sessions consisted of 10 minutes of compression on air, 60 minutes of 100% oxygen at 2 ata, and 10 minutes of decompression on air. Outcomes were change in the mean hearing thresholds at each of 5 frequencies (0.25, 0.5, 1, 2, and 4 kHz). After treatment, there were no statistically significant differences in mean hearing thresholds at 4 of the 5 frequencies. The exception was 2 kHz, and at this frequency, the improvement was significantly greater in the HBOT group.

Due to methodologic limitations and variability among published studies, the evidence is insufficient to draw conclusions about the effect of HBOT on health outcomes in patients with ISSNHL. Thus, HBOT is considered not medically necessary for treating ISSNHL.

### *Cancer Treatment*

In an RCT of 32 patients, Heys and colleagues found no increase in 5-year survival in patients treated with HBOT prior to chemotherapy for locally advanced breast carcinoma to increase tumor vascularity. (47) This approach is being studied since studies in animal models have suggested that HBOT increases tumor vascularity and thus may make chemotherapy more effective. In a Cochrane review, Bennett and colleagues concluded that HBOT given with radiotherapy may be useful in tumor control;

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however, the authors expressed caution since significant adverse effects were common with HBOT and indicated further study would be useful. (48)

#### *In Vitro Fertilization*

Van Voorhis and colleagues reported that HBOT was well-tolerated in women undergoing ovarian follicular stimulation for in vitro fertilization; however, no outcomes were reported, and further study is needed. (49)

#### *Delayed-onset Muscle Soreness*

In a Cochrane review, Bennett and colleagues concluded that available evidence is insufficient to demonstrate beneficial outcomes with HBOT for delayed-onset muscle soreness and closed soft tissue injury. (50) It was noted that HBOT possibly even increases pain initially and further studies are needed..

#### *Autism Spectrum Disorders*

A 2012 systematic review of evidence on hyperbaric oxygen therapy for treatment of children with autism identified 2 RCTs with a total of 89 participants. (51) One of the 2 RCTs found better outcomes after hyperbaric oxygen compared to placebo treatment, and the other did not find significant differences in outcomes. The author concluded that additional sham-controlled trials with rigorous methodology are needed in order to draw conclusions about the efficacy of HBOT for treating autism. A 2012 review article also concluded that, although studies to date suggest that HBOT is safe and potentially effective, additional studies are warranted. (52) In particular, it was recommended that future studies use standardized behavioral measurement tools and also assess physiological biomarkers.

One of the RCTs was by Rossignol and colleagues. (53) This double-blind trial included 62 children, ages 2-7 years, who met Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for autistic disorder. The active treatment was hyperbaric treatment at 1.3 atmospheres (atm) and 24% oxygen in a hyperbaric chamber. (This regimen differs from standard HBOT treatment which uses 100% oxygen and a pressure of at least 1.4 atm.) The other group received a sham treatment consisting of 1.03 atm and ambient air (21% oxygen). Both groups received 40 sessions of active or sham treatment lasting 60 minutes each over a period of 4 weeks. The equipment, procedures, etc. in the 2 groups were as similar as possible to maintain blinding. The investigators, participants, parents, and clinic staff were blinded to treatment group. Only the hyperbaric technician, who had no role in outcome assessment, was aware of group assignment. After completion of the 4-week study, families with children in the control group were offered the active intervention. When asked at the end of the study, there was no significant difference in the ability of parents to correctly guess the group assignment of their child.

The outcomes were change compared to baseline after 4 weeks on the following scales: Aberrant Behavior Checklist (ABC) total score and 5 subscales; Autism Treatment Evaluation Checklist (ATEC) total score and 4 subscales; and Clinical Global Impression-Improvement (CGI) overall functioning score and 18 subscales. P values of <0.05 were considered statistically significant; there was no adjustment for multiple comparisons. The analysis included all children who completed at least one complete session. Of the 33 children assigned to active treatment, 30 were included in the analysis, and 29

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completed all 40 treatments. Of the 29 children assigned to the control treatment, 26 completed all 40 sessions and were included in the analysis.

There was no significant between-group improvement on the ABC total score, any of the ABC subscales, or on the ATEC total score. Compared to the control group, the treatment group had a significant improvement in 1 of 4 subscales of the ATEC, the sensory/cognitive awareness subscale. The change from baseline on this subscale was a mean of 16.5 in the treatment group and a mean of 5.4 in the control group, a difference of 11.1 ( $p=0.037$ ). (Note: due to an administrative error, baseline ATEC was not collected at one site, and thus data were not available for 23 children in the treatment group and 21 children in the control group). On the physician-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 (very much improved) or 2 (much improved) compared to 2/26 (8%) in the control group ( $p=0.047$ ). On the parental-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 or 2 compared to 4/26 (15%) in the control group ( $p=0.22$ , not statistically significant). (The exact numbers receiving scores of 1 vs. 2 were not reported). Change in mean CGI scores were also reported, but this may be a less appropriate way to analyze these data. Among the parental-rated CGI subscales, significantly more children were rated as improved in the treatment group compared to control on 2 out of 18 subscales, receptive language ( $p=0.017$ ) and eye contact ( $p=0.032$ ).

A key limitation of this study was that the authors reported only outcomes at 4 weeks, directly after completion of the intervention. It is not known whether there are any long-term effects. Additional follow-up data cannot be obtained because members of the control group crossed over to the intervention after 4 weeks. Other limitations include lack of adjustment for multiple comparisons and unclear clinical significance of the statistically significant outcomes. The Undersea and Hyperbaric Medical Society (UHMS) issued a position paper after publication of the Rossignol et al. study stating that they still did not recommend routine treatment of autism with HBOT. (53)

An additional 2012 RCT, published after the 2012 systematic review had been completed, was conducted in Thailand and randomly assigned 60 children with autism to receive 20 one-hour sessions with HBOT or sham air treatment ( $n=30$  per group). (54) The primary outcome measures were change in the ATEC and CGI, evaluated separately by clinicians and parents. There were no statistically significant differences between groups on any of the primary outcomes. For example, post-treatment clinician-assessed mean scores on the ATEC were 52.4 in the HBOT group and 52.9 in the sham air group. In summary, there is insufficient evidence from rigorous RCTs that HBOT improves health outcomes for patients with autism spectrum disorder.

### *Amyotrophic Lateral Sclerosis*

In updated searches, no randomized trials were found evaluating HBOT for treatment of amyotrophic lateral sclerosis. In a small case series, Steele et al. treated 5 patients with HBOT and reported some improvements in fatigue but noted that further study is needed, and attention to placebo effects must be given. (55)



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### *Cerebral Palsy*

Two published RCTs were identified. In 2012, Lacey and colleagues published a double-blind RCT that included 49 children age 3-8 with spastic cerebral palsy. (56) Participants were randomized to receive 40 treatments with either HBOT (n=25) or hyperbaric air to simulate 21% oxygen at room air (n=24). The primary efficacy outcome was change in the Gross Motor Function Measure (GMFM-88) global score after the 8 week treatment period. The study was stopped early due to futility, when an interim analysis indicated that there was less than a 2% likelihood that a statistically significant difference between groups would be found. At the time of the interim analysis, the post-treatment GMFM-88 global score was a mean of 40.8 (SD: 33.4) in the HBOT group and 41.2 (SD: 29.6) in the hyperbaric air group. The between-group difference was 0.9 (95% CI: -1.5 to 3.3), p-value=0.54.

Previously, in 2001, Collet et al. randomly assigned 111 children with cerebral palsy to 40 treatments over a 2-month period of either HBOT (n=57) or slightly pressurized room air (n=54). (57) The authors found HBOT produced similar improvements in outcomes such as gross motor function and activities of daily living in both groups as slightly pressurized air. Thus, cerebral palsy is not a medically necessary indication of HBOT therapy.

### *Vascular Dementia*

A 2012 Cochrane review identified 1 RCT evaluating HBOT for the treatment of vascular dementia. (58) The 2009 study, conducted in China compared HBOT plus donepezil to donepezil-only in 64 patients. The HBOT and donepezil group had significantly better cognitive function after 12 weeks of treatment, as assessed by the Mini-Mental State Examination. The Cochrane investigators judged the trial to be of poor methodological quality because it was not blinded and the methods of randomization and allocation concealment were not discussed. This single trial with limitations provides insufficient evidence on the efficacy of HBOT treatment on vascular dementia; thus, HBOT is considered not medically necessary for this indication.

### *Radiotherapy Adverse Effects*

In 2010, Spiegelberg and colleagues conducted a systematic review of studies on HBOT therapy to prevent or treat radiotherapy-induced head and neck injuries associated with treatment of malignant tumors. (59) The authors identified 20 studies. Eight of the studies included control groups, their sample sizes ranged from 19 to 78 individuals. Four (50%) of the studies with a control group concluded that HBOT was effective, and the other 4 did not conclude that the HBOT was effective. The authors noted a paucity of RCTs but did not state the number of RCTs that they identified in their review.

A study by Teguh and colleagues published in 2009 included 17 patients with oropharyngeal or nasopharyngeal cancer who were treated with radiation therapy; the study was conducted in The Netherlands. (60) HBOT was used to prevent adverse events following radiotherapy. Eight patients were randomly assigned to receive 30 sessions of HBOT, beginning within 2 days of completing radiation therapy, and 9 patients received no additional treatment. All patients were included in the analysis. Quality-of-life outcomes were assessed, and the primary outcome was specified as xerostomia at 1 year. Quality-of-life measures did not differ significantly between groups in the acute phase (first 3 months). For example, 1 month after treatment, the mean visual analog scale (VAS) score for

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xerostomia (0-to-10 scale) was 5 in the HBOT group and 6 in the control group. However, at 1 year, there was a statistically significant difference between groups; the mean VAS score for xerostomia was 4 in the HBOT group and 7 in the control group ( $p=0.002$ ). Also at 1 year, the mean quality-of-life score for swallowing (0-to-100 scale) was 7 in the HBOT group and 40 in the control group ( $p=0.0001$ ). The study is limited by the small sample size and the wide fluctuation over the follow-up period in quality of life ratings.

In 2010, Gothard and colleagues in the U.K. published findings of a RCT using HBOT therapy to treat arm lymphedema occurring after radiotherapy for cancer. (61) Fifty-eight patients with arm lymphedema (at least 15% increase in arm volume) following cancer treatment were randomized in a 2:1 ratio to receive HBOT ( $n=38$ ) or usual care without HBOT ( $n=20$ ). Fifty-three patients had baseline assessments and 46/58 (79%) had 12-month assessments. At the 12-month follow-up, there was not a statistically significant difference in the change from baseline in arm volume. The median change from baseline was -2.9% in the treatment group and -0.3% in the control group. The study protocol defined response as at least an 8% reduction in arm volume relative to the contralateral arm. According to this definition, 9 of 30 (30%) of patients in the HBOT group were considered responders compared with 3 of 16 (19%) in the control group; the difference between groups was not statistically significant. Other outcomes, e.g., quality-of-life scores on the Short-Form (SF)-36, were similar between groups.

There are limited data on the use of HBOT in patients with arm lymphedema or radiation-induced injury in the head and neck after radiotherapy and on early use of HBOT after radiotherapy to reduce adverse effects.

#### *Idiopathic Femoral Neck Necrosis*

A double-blind RCT that evaluated HBOT therapy to treat femoral head necrosis was published in 2010 by Camporesi and colleagues. (62) The study included 20 adult patients with idiopathic unilateral femoral head necrosis. Patients received 30 treatments over 6 weeks with either HBOT at 2.5 ATA ( $n=10$ ) or a sham treatment consisting of hyperbaric air ( $n=10$ ). The mean severity of pain on a 0-to-10 scale was significantly lower in the HBOT group than the control group after 30 sessions ( $p<0.001$ ) but not after 10 or 20 sessions. (The article did not report exact pain scores). Several range-of-motion outcomes were also reported; degrees were the unit of measurement. At the end of the initial treatment period, extension, abduction and adduction, but not flexion, were significantly greater in the HBOT group compared to the control group. Longer-term comparative data were not available because the control group was offered HBOT at the end of the initial 6-week treatment period. This single, small short-term RCT represents insufficient data on which to draw conclusions about the efficacy of HBOT for treating femoral head necrosis.

#### *Migraine*

A Cochrane review by Bennett and colleagues identified RCTs that evaluated the effectiveness of systemic HBOT therapy for preventing or treating migraine headache compared to another treatment or a sham control. (63) In a search of the literature through May 2008, 5 trials with a total of 103 patients were identified that addressed treatment of acute migraine with HBOT. A pooled analysis of 3 trials (total of 43 patients) found a statistically significant increase in the proportion of patients with substantial relief of migraine within 45 minutes of HBOT treatment (relative risk [RR]: 5.97, 95% confidence interval [CI]:

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1.46-24.38,  $p=0.001$ ). No other pooled analyses were conducted due to variability in the outcomes reported in the trials. The meta-analysis does not report data on treatment effectiveness beyond the immediate post-treatment period, and the methodological quality of trials was moderate to low, e.g., randomization was not well-described in any trial.

### *Herpes Zoster*

In 2012, Peng and colleagues in China published an RCT evaluating HBOT as a treatment of herpes zoster. (64) Sixty-eight patients with herpes zoster diagnosed within the previous 2 weeks were randomized to 30 sessions of HBOT therapy ( $n=36$ ) or medication treatment ( $n=32$ ). Pharmacotherapy included antiviral, pain, nerve nutritive and antidepressive medication. Therapeutic efficacy was calculated at the end of the 3-week treatment period and included the proportion of patients who were healed (i.e., complete subsidence of pain and rash) or improved (i.e., significant pain relief and rash subsistence). Rates of therapeutic efficacy were 97.2% in the HBOT group and 81.3% in the medication group. The difference between groups was statistically significant,  $p<0.05$ . In the HBOT group, 22 of 36 patients (61%) were considered to be healed and 13 (36%) were improved. In the medication group, 17 of 32 (53%) patients were healed and 9 (28%) were improved. Limitations of the study include a lack of blinding and lack of long-term follow-up. The evidence from this single RCT is insufficient to draw conclusions about the effect of HBOT on health outcomes for patients with herpes zoster.

### *Fibromyalgia*

One quasi-randomized trial and 1 delayed-treatment RCT on HBOT for fibromyalgia were identified. In 2004, a study by Yildiz et al included 50 patients with fibromyalgia who had ongoing symptoms despite medical and physical therapy. (65) On an alternating basis, patients were assigned to HBOT or a control group. HBOT consisted of fifteen 90-minute sessions at 2.4 ata (1 session per day, 5 d/wk). The control group breathed room air at 1 ata on the same schedule. Baseline values on the 3 outcomes were similar in the 2 groups. After the course of HBOT treatment, the mean (SD) number of tender points were 6.04 (1.18) in the HBOT group and 12.54 (1.10) in the control group. The mean (SD) pain threshold was 1.33 kg (0.12) and 0.84 kg (0.12), respectively, and the mean VAS was 31.54 (8.34) and 55.42 (6.58), respectively. In the study abstract, the authors stated that there were statistically significant differences between the HBOT and the control groups after 15 therapy sessions, but the table presenting outcomes lacked the notation used to indicate between-group statistical significance. It is not clear whether the control group actually received a sham intervention that would minimize any placebo effect (ie, whether the control intervention was delivered in a hyperbaric chamber). The authors stated that the study was double-blind but did not specify any details of patient blinding.

In 2015, Efrati et al published an RCT that included 60 female patients who had fibromyalgia for at least 2 years and were symptomatic. (66) Patients were randomized to an immediate 2-month course of HBOT or delayed HBOT after 2 months. The HBOT protocol was forty 90-minute sessions of 100% oxygen at 2 ata (1 session per day, 5 d/wk). Forty-eight of 60 patients (80%) completed the study and were included in the analysis. After the initial 2 months, outcomes including number of tender points, pain threshold, and QOL (SF-36) were significantly better in the immediate treatment group than the delayed treatment group (which received no specific intervention during this time). After the delayed treatment group had undergone HBOT, outcomes were significantly improved compared with scores prior to HBOT treatment. These findings are consistent with a clinical benefit of HBOT, but also with a

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placebo effect. A sham-control is needed to confirm the efficacy of HBOT in the treatment of fibromyalgia and other conditions where primary end points are pain and other subjective outcomes.

The above studies were few in number with relatively small sample sizes and they have methodological limitations (eg, quasi-randomization and no or uncertain sham control for a condition with subjective outcomes susceptible to a placebo effect). Moreover, the HBOT protocol varied (eg, 15 HBOT sessions vs 40 HBOT sessions). Thus, the evidence is insufficient to draw conclusions about the impact of HBOT on health outcomes for patients with fibromyalgia.

### *Mental Illness*

A Rapid Response Report from the Canadian Agency for Drugs and Technologies in Health searched the literature through July 2014 on the clinical effectiveness of HBOT for treatment of adults with posttraumatic stress disorder, generalized anxiety disorder, and/or depression. (67) The review's inclusion criteria were health technology assessments, systematic reviews, meta-analyses, RCTs, or nonrandomized studies comparing HBOT with any active treatment and reporting clinical outcomes. No eligible studies were identified.

### *Multiple Sclerosis*

A Cochrane review of RCTs on HBOT for multiple sclerosis was published by Bennett et al in 2004. (68) The authors identified 9 RCTs, with a total of 504 participants, that compared the effects of HBOT with placebo or no treatment. The primary outcome of the review was score on the Expanded Disability Status Scale (EDSS). A pooled analysis of data from 5 trials (n=271) did not find a significant difference in change in the mean EDSS after 20 HBOT treatments versus control (mean difference [MD], -0.07; 95% CI, -0.23 to 0.09). Moreover, a pooled analysis of data from 3 trials (n=163) comparing HBOT and placebo did not find a significant difference in mean EDSS after 6 months of follow-up (MD = -0.22; 95% CI, -0.54 to 0.09).

### *Other indications*

For the indications listed below, insufficient evidence to support the use of HBOT was identified. Since 2000, there have been no published controlled trials or large case series (ie,  $\geq 25$  patients):

- bone grafts;
- carbon tetrachloride poisoning, acute;
- cerebrovascular disease, acute (thrombotic or embolic) or chronic;
- fracture healing;
- hydrogen sulfide poisoning;
- intra-abdominal and intracranial abscesses;
- lepromatous leprosy;
- meningitis;
- pseudomembranous colitis (antimicrobial agent-induced colitis);
- radiation myelitis;
- sickle cell crisis and/or hematuria;
- amyotrophic lateral sclerosis;

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- retinal artery insufficiency, acute;
- retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment;
- pyoderma gangrenosum;
- tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy;

### Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in June 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

### Practice Guidelines and Position Statements

In 2015, the Undersea and Hyperbaric Medical Society (UHMS) published a guideline on use of HBOT for treating diabetic foot ulcers. (69) Recommendations are:

- Suggest against using HBOT in patients with “Wagner Grade 2 or lower diabetic foot ulcers...”
- Suggest adding HBOT in patients with “Wagner Grade 3 or higher diabetic foot ulcers that have now shown significant improvement after 30 days of [standard of care] therapy...”
- Suggest “adding acute post-operative hyperbaric oxygen therapy to the standard of care” in patients with “Wagner Grade 3 or higher diabetic foot ulcers” who have just had foot surgery related to their diabetic ulcers.

In 2011, the Undersea and Hyperbaric Medical Society (UHMS) updated their list of indications considered appropriate for hyperbaric oxygen therapy. (70) These indications are as follows:

- Air or gas embolism
- Carbon monoxide poisoning and carbon monoxide complicated By cyanide poisoning
- Clostridial myositis and myonecrosis (gas gangrene)
- Crush injury, compartment syndrome and other acute traumatic ischemias
- Decompression sickness
- Arterial insufficiencies:
  - Central retinal artery occlusion;
  - Enhancement of healing in selected problem wounds
- Severe anemia
- Intracranial abscess
- Necrotizing soft tissue infections
- Osteomyelitis (refractory)
- Delayed radiation injury (soft tissue and bony necrosis)
- Skin grafts and flaps (compromised)
- Acute thermal burn injury
- Idiopathic sudden sensorineural hearing loss (ISSNHL) (patients with moderate to profound ISSNHL who present within 14 days of symptom onset)

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In 2012, the American Academy of Otolaryngology-Head and Neck Surgery published a clinical guideline on treatment of sudden hearing loss. (71) The guideline includes a statement that HBOT may be considered a treatment option for patients who present within 3 months of a diagnosis of idiopathic sudden sensorineural hearing loss. The document states, “Although HBOT is not widely available in the United States and is not recognized by many U.S. clinicians as an intervention for ISSNHL, the panel felt that the level of evidence for hearing improvement, albeit modest and imprecise, was sufficient to promote greater awareness of HBOT as an intervention for [this condition]”

### **U.S. Preventive Services Task Force Recommendations**

Not applicable

### **Summary of Evidence**

The evidence for the use of topical hyperbaric oxygen therapy (HBOT) in individuals who might respond to increased oxygen delivery to tissues includes primarily of case series and case reports. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. Only 1 randomized controlled trial (RCT) was published on any indication. This study, in patients with diabetic foot ulcers, had a small sample size and did not find a significant benefit of topical hyperbaric oxygen therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of systemic HBOT in individuals with nonhealing diabetic wounds of the lower extremities, acute traumatic ischemia, soft-tissue radiation necrosis (eg, radiation enteritis, cystitis, proctitis), osteoradionecrosis (ie, pre- and posttreatment), planned dental surgery (non-implant-related) of an irradiated jaw, gas gangrene, and profound anemia with exceptional blood loss when blood transfusion is impossible or must be delayed includes systematic reviews and/or recommendations from the Undersea and Hyperbaric Medical Society’s (UHMS). Relevant outcomes include overall survival, symptoms, change in disease status, and functional outcomes. For all of the above indications, evidence and/or USMS guidelines support use of HBOT. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in health outcomes.

The evidence for the use of systemic HBOT in individuals with any condition other than those specified in the previous paragraph includes systematic reviews, 1 or a few small RCTs or small uncontrolled studies. Relevant outcomes include overall survival, symptoms, change in disease status, and functional outcomes. The available studies do not demonstrate that HBOT improves relevant outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Medicare National Coverage**

As of April 1, 2003, the Centers for Medicare and Medicaid (CMS) added Medicare coverage of hyperbaric oxygen therapy for diabetic wounds of the lower extremities meeting certain criteria. Medicare coverage is provided for HBOT administered in a chamber for the following conditions:

1. Acute carbon monoxide intoxication,
2. Decompression illness,
3. Gas embolism,

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4. Gas gangrene,
5. Acute traumatic peripheral ischemia. HBOT therapy is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.
6. Crush injuries and suturing of severed limbs. As in the previous conditions, HBOT therapy would be an adjunctive treatment when loss of function, limb, or life is threatened.
7. Progressive necrotizing infections (necrotizing fasciitis),
8. Acute peripheral arterial insufficiency,
9. Preparation and preservation of compromised skin grafts (not for primary management of wounds),
10. Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management,
11. Osteoradionecrosis as an adjunct to conventional treatment,
12. Soft tissue radionecrosis as an adjunct to conventional treatment,
13. Cyanide poisoning,
14. Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment,
15. Diabetic wounds of the lower extremities in patients who meet the following three criteria:
  - a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
  - b. Patient has a wound classified as Wagner grade III or higher; and
  - c. Patient has failed an adequate course of standard wound therapy.

The use of HBOT therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30 –days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes: assessment of a patient’s vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present. Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of HBOT therapy. Continued treatment with HBOT therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.

Note: Medicare differs from BCBS policy in that it provides coverage for systemic HBOT therapy for acute carbon monoxide intoxication, actinomycosis, acute peripheral arterial insufficiency, compromised skin grafts or flaps, chronic refractory osteomyelitis, and necrotizing soft tissue infections. However, as noted here, literature searches did not reveal sufficient evidence to consider these appropriate indications for HBOT therapy.

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### Policy History

Date	Action	Reason
September 2012	New Policy	
March 2014	Update Policy	Policy updated with literature review. Bisphosphonate-related osteonecrosis of the jaw, motor dysfunction associated with stroke, herpes zoster and vascular dementia added as not medically necessary. References added; other references renumbered or removed. Additional conditions added as medically necessary.
December 2014	Update Policy	Policy updated with literature review through July 17, 2014. In investigational statement, severe or refractory Crohn's disease changed to inflammatory bowel disease (Crohn disease or ulcerative colitis). Clarification added to bullet point in not medically necessary statement on radiation-induced injury in the head and neck. Title changed from "Hyperbaric Oxygen Pressurization (HBO)" to "Hyperbaric Oxygen Therapy". References 2, 10, 12-13, 43-46, and 49 added.
December 2015	Update Policy	Policy updated with literature review through June 17, 2015; references 27, 34, 40, 41 and 66-70 added. Bullet points on (1) fibromyalgia and (2) mental illness (ie, posttraumatic stress disorder, generalized anxiety disorder or depression) added to the not medically necessary statement.

### Keywords

Hyperbaric Oxygen Therapy (HBOT)  
Oxygen, Hyperbaric Pressurization  
Topical Hyperbaric Oxygenation

**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 4, 2015 and is effective January 15, 2016.**

*Signature on File*

**Deborah M. Smith, MD, MPH**