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## Medical Policy



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**\*Current Policy Effective Date: 1/1/25**  
(See policy history boxes for previous effective dates)

### **Title: Hyperbaric Oxygen Therapy, Systemic and Topical**

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#### **Description/Background**

Hyperbaric oxygen therapy (HBOT) is a technique for delivering higher pressures of oxygen to tissue. Two methods of administration are available: systemic and topical.

##### **Systemic HBOT**

In systemic or large hyperbaric oxygen chambers, the patient is entirely enclosed in a pressure chamber and breathes oxygen at a pressure greater than one atmosphere (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. Systemic HBOT can be used to treat systemic illness, such as air or gas embolism, carbon monoxide poisoning, or clostridial gas gangrene. Treatment may be carried out either in a monoplace chamber pressurized with pure oxygen or in a larger, multi-place chamber pressurized with compressed air, in which case the patient receives pure oxygen by mask, head tent, or endotracheal tube.

##### **Topical HBOT**

Topical hyperbaric therapy is a technique of delivering 100% oxygen directly to an open, moist wound at a pressure slightly higher than atmospheric pressure. It is hypothesized that the high concentrations of oxygen diffuse directly into the wound to increase the local cellular oxygen tension, which in turn promotes wound healing. Devices consist of an appliance to enclose the wound area (frequently an extremity) and a source of oxygen; conventional oxygen tanks may be used. The appliances may be disposable and may be used without supervision in the home by well-trained patients. Topical hyperbaric therapy has been investigated as a treatment of skin ulcerations resulting from diabetes, venous stasis, postsurgical infection, gangrenous lesion, decubitus ulcers, amputations, skin graft, burns, or frostbite.

## **Adverse Events**

HBOT is a generally safe therapy, with an estimated adverse side effect rate of 0.4%.<sup>(1)</sup> Adverse events may occur either from pressure effects or the oxygen. The pressure effect (barotrauma) may affect any closed air-filled cavity such as ears, sinus, teeth, and lungs. Pain and/or swelling may occur at these sites as pressure increases during the procedure and decreases as the procedure is ending. Oxygen toxicity may affect the pulmonary, neurologic, or ophthalmologic systems. Pulmonary symptoms include a mild cough, substernal burning, and dyspnea. Neurologic effects include tunnel vision, tinnitus, nausea, and dizziness. Ophthalmologic effects include retinopathy in neonates, cataract formation, and transient myopic vision changes.

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

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## **Regulatory Status**

Since 1979, the Food and Drug Administration (FDA) has cleared multiple topical and systemic hyperbaric oxygen administration devices through the 510(k) pathway. In 2013 (updated 2021), the FDA published a statement warning that non-FDA approved uses of hyperbaric oxygen therapy (HBOT) may endanger the health of patients.<sup>(2)</sup> If patients mistakenly believe that HBOT devices have been proven safe for uses not cleared by FDA, they may delay or forgo proven medical therapies.

As of July 2021, the FDA has cleared hyperbaric chambers for the following disorders:

- Air and gas bubbles in blood vessels
- Anemia (severe anemia when blood transfusions cannot be used)
- Burns (severe and large burns treated at a specialized burn center)
- Carbon monoxide poisoning
- Crush injury
- Decompression sickness (diving risk)
- Gas gangrene
- Hearing loss (complete hearing loss that occurs suddenly and without any known cause)
- Infection of the skin and bone (severe)
- Radiation injury
- Skin graft flap at risk of tissue death
- Vision loss (when sudden and painless in one eye due to blockage of blood flow)
- Wounds (non-healing, diabetic foot ulcers).

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## Medical Policy Statement

The safety and effectiveness of systemic hyperbaric oxygen therapy have been established for some conditions. It may be considered a useful therapeutic option when indicated for specified conditions.

Topical hyperbaric oxygen therapy is experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes.

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## Inclusionary and Exclusionary Guidelines

**Note:** In some contracts, hyperbaric oxygen therapy (HBOT) may be excluded when performed in the office setting. Check with carrier for location restrictions.

### Inclusions:

The following conditions are effectively treated by **systemic** hyperbaric oxygen therapy:

- Acute peripheral arterial insufficiency
- Acute traumatic peripheral ischemia: HBOT is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened
- Carbon monoxide poisoning/intoxication, acute
- Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management
- Crush injuries and suturing of severed limbs. HBOT is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.
- Cyanide poisoning, acute
- Decompression illness
- Diabetic wounds of the lower extremities in patients who meet **ALL** the following criteria:
  - A diagnosis of type 1 or type 2 diabetes with a lower extremity wound that is due to diabetes
  - The use of HBOT 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.
  - A wound classified as Wagner grade III or higher
    - 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 the below the knee level) is indicated.)

- Standard wound care in individuals with diabetic wounds includes **ALL** the following:
  - The assessment of an individual's vascular status and correction of any vascular problems in the affected limb if possible
  - The optimization of nutritional status
  - Optimization of glucose control
  - Debridement by any means to remove devitalized tissue
  - Maintenance of a clean, bed of granulation tissue with appropriate moist dressings
  - Appropriate off-loading
  - Necessary treatment to resolve any infection that might be present.
- Gas embolism, acute
- Gas gangrene (i.e., clostridial myonecrosis)
- Osteoradionecrosis as an adjunct to conventional treatment
- Pre and post treatment for individuals undergoing dental surgery (non-implant related) of an irradiated jaw
- Preparation and preservation of compromised skin grafts (not for primary management of wounds)
- Profound anemia with exceptional blood loss: only when blood transfusion is impossible or must be delayed
- Progressive necrotizing soft tissue infections
- Refractory mycoses: mucormycosis, actinomycosis, *Conidiobolus coronata* only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment\*
- Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis)
- Idiopathic sudden sensorineural hearing loss (ISSHL) when:
  - hyperbaric oxygen therapy (HBOT) is combined with steroid therapy within 2 weeks of onset of ISSHL
  - hyperbaric oxygen therapy (HBOT) is combined with steroid therapy as salvage within 1 month of onset of ISSHL
- Central retinal artery occlusion (including CaHA (calcium hydroxylapatite) cosmetic filler injection likely due to an embolism)
- Branch Retinal Artery Occlusion
- Susac's Syndrome

\* Generally, these patients present with clinically severe situations where therapeutic options are limited. Subject matter expert experience and limited available evidence support that hyperbaric oxygen treatment may offer therapeutic benefit in these cases.

### **Exclusions:**

- Topical hyperbaric oxygen therapy for all conditions
- Systemic hyperbaric oxygen pressurization is considered investigational in the treatment of the following conditions, (this list may not be all-inclusive):
  - Acute coronary syndromes and as an adjunct to coronary interventions, including but not limited to percutaneous coronary interventions and cardiopulmonary bypass
  - Acute peripheral artery insufficiency (outside of other listed medically necessary indications involving arterial insufficiency)
  - Acute or chronic cerebral vascular insufficiency
  - Acute ischemic stroke
  - Acute osteomyelitis

- Acute thermal and chemical pulmonary damage, i.e. smoke inhalation with pulmonary insufficiency
- Acute surgical and traumatic wounds, not meeting criteria specified under inclusions
- Arthritic diseases
- Autism spectrum disorders
- Bell palsy
- Bisphosphonate-related osteonecrosis of the jaw
- Bone grafts
- Brown recluse spider bites
- Carbon tetrachloride poisoning, acute
- Cardiogenic shock
- Cerebral edema; acute
- Cerebral palsy
- Cerebrovascular disease, acute (thrombotic or embolic) or chronic
- Chronic arm lymphedema following radiotherapy for cancer
- Chronic peripheral vascular insufficiency
- Chronic wounds other than those in patients with diabetes who meet the criteria specified in the inclusions.
- Cosmetic use
- Delayed onset muscle soreness
- Demyelinating diseases, e.g., multiple sclerosis, amyotrophic lateral sclerosis
- Fibromyalgia
- Fracture healing
- Hepatic necrosis
- Herpes zoster
- Hydrogen sulfide poisoning
- Idiopathic femoral neck necrosis
- Inflammatory bowel disease (Crohn disease or ulcerative colitis)
- Intra-abdominal and intracranial abscesses
- In vitro fertilization
- Lepromatous leprosy
- Meningitis
- Mental illness (e.g., posttraumatic stress disorder, generalized anxiety disorder or depression)
- Migraine
- Motor dysfunction associated with stroke
- Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease)
- Organ storage
- Organ transplantation
- Pseudomembranous colitis (antimicrobial agent-induced colitis)
- Pulmonary emphysema
- Pyoderma gangrenosum
- Radiation-induced injury in the head and neck
- Retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment
- Senility
- Septicemia, aerobic
- Septicemia (anaerobic) and infection other than clostridial
- Sickle cell crisis and/or hematuria

- Skin burns (thermal), acute
- Spinal cord injury
- Tetanus
- Traumatic brain injury
- Tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy
- Vascular dementia

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

**Established codes:**

99183      G0277

**Other codes (investigational, not medically necessary, etc.):**

A4575      E0446

*Note: Code(s) 99183 and G0277 may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.*

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**Rationale**

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Evidence for a majority of the indications consists of Cochrane systematic reviews, which focus on summarizing RCTs, and when possible, conducting pooled analyses of results.

**Clinical Context and Therapy Purpose**

The indications being reviewed in this policy are as follows:

- Topical hyperbaric oxygen therapy (HBOT) for:
  - Wounds, burns or infections - managed by neurologists and primary care providers in an outpatient clinical setting.
- Systemic HBOT for:
  - Acute coronary syndrome - managed by emergency physicians, cardiologists, and intensivists in an inpatient clinical setting
  - Acute ischemic stroke - managed by emergency physicians, cardiologists, and intensivists in an inpatient clinical setting
  - Acute surgical and traumatic wounds - managed by emergency care providers and surgeons in an inpatient clinical setting
  - Acute thermal burns - managed by burn specialists and surgeons in an inpatient clinical setting
  - Autism spectrum disorder - managed by behavioral therapists and psychologists in an outpatient clinical setting
  - Bell Palsy - managed by neurologists and primary care providers in an outpatient clinical setting
  - Bisphosphonate related osteonecrosis of the jaw - managed by surgeons, dentists, and oral maxillofacial surgeons in both inpatient and outpatient clinical settings
  - Carbon monoxide poisoning - managed in the emergency care setting by emergency medicine physicians
  - Cerebral palsy - managed by physical therapists, physiatrists and primary care providers in an outpatient clinical setting
  - Chronic diabetic ulcers - managed by surgeons, wound care specialists, podiatrists and primary care providers in a clinical setting
  - Chronic refractory osteomyelitis - managed by orthopedic surgeons, wound specialists, and primary care providers
  - Delayed-onset muscle soreness - managed by physical therapists, physiatrists, and primary care providers in an outpatient clinical setting
  - Fibromyalgia - managed by neurologists, physiatrists, physical therapists, and primary care providers in an outpatient clinical setting
  - Herpes zoster - managed by infectious disease specialists and primary care providers in an outpatient clinical setting
  - Idiopathic femoral neck necrosis - managed by orthopedic surgeons in an inpatient clinical setting
  - Idiopathic sudden sensorineural hearing loss - managed by otolaryngologists and primary care providers in an outpatient clinical setting
  - Individuals with cancer who are undergoing radiotherapy or chemotherapy - managed by oncologists in an outpatient clinical setting
  - Inflammatory bowel disease - managed by gastroenterologists and primary care providers in a clinical setting
  - Migraine headache - managed by neurologists and primary care providers in an outpatient clinical setting
  - Motor dysfunction associated with stroke - managed by physical therapists, physiatrists, and primary care providers in an outpatient clinical setting
  - Multiple sclerosis - managed by neurologists and primary care providers in an outpatient clinical setting
  - Necrotizing soft tissue infections - managed by surgeons, wound care specialists, and infectious disease specialists in an inpatient clinical setting

- Radionecrosis, osteoradionecrosis and treatment of irradiated jaw - managed by radiation oncologists, orthopedic surgeons and oral maxillofacial surgeons potentially in both inpatient and outpatient clinical settings
- Radiotherapy adverse events - managed by oncologists and primary care providers in an outpatient clinical setting
- Traumatic brain injury – managed by emergency physicians, neurologists, physiatrists, physical therapists and primary care providers in an outpatient clinical setting
- Vascular Dementia - managed by neurologists and primary care providers in an outpatient clinical setting

The purpose of topical/systemic HBOT is to provide a treatment option that is an alternative or an improvement on existing therapies in patients with the indication being reviewed.

The four components of a PICO question were used to select literature to inform these reviews.

- **Populations**

- The relevant population of interest is individuals with wounds, burns, or infections. Subpopulations with chronic diabetic ulcers, acute thermal burns, and necrotizing soft tissue infections who are treated with systemic HBOT are addressed separately later in this evidence review.

- **Interventions**

- The therapy being considered is topical and/or systemic HBOT.

- **Comparators**

- Comparators of interest include dressings, debridement, and medication. Medications prescribed may include topical antibiotics and antiseptics. Pain and anxiety management medication may also be used. Topical/Systemic HBOT may be used as an adjunct to care.

- **Outcomes**

- The general outcomes of interest include overall survival, symptoms, change in disease status and functional outcomes. The existing literature evaluating topical/systemic HBOT as a treatment for the indication being discussed reported follow-up at 12 weeks. However, longer follow-up is necessary to fully observe outcomes. Therefore, at least one year of follow-up is considered necessary to demonstrate efficacy.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- d. Studies with duplicative or overlapping populations were excluded.



## TOPICAL HYPERBARIC OXYGEN FOR WOUNDS, BURNS, OR INFECTIONS

de Smet et al (2017) conducted a systematic review of various oxygen therapies (oxygen dressing therapy, topical oxygen therapy, HBOT, inspired oxygen therapy).(3) Three RCTs evaluating topical oxygen therapy for chronic wound healing were identified (see Table 1). One RCT (N=100) administered treatment for 20 minutes 3 times per day for 12 days to the treatment group and standard care to the control group. The number of patients experiencing complete wound healing, defined as complete epithelialization of the wound without drainage, was 16 in the experimental group and 1 in the control group ( $p<.001$ ). Two of the RCTs, which had overlapping populations with refractory venous ulcers ( $n=83$  in one and  $n=132$  in the other) administered treatment for 180 minutes 2 times per day for 12 weeks to the treatment group and conventional compression dressing to the control group. In all trials, patients in the treatment group experienced significantly higher proportions of healed ulcers and significantly faster healing times.

**Table 1. Systematic Reviews of Trials Assessing Topical Hyperbaric Oxygen for Wounds**

| Study (Year)                      | Literature Search | Studies | Participants   | N (Range)                 | Design | Results  |
|-----------------------------------|-------------------|---------|--|---------------------------|--------|--|
| de Smet et al (2017) <sup>3</sup> | Feb 2016          | 3       | Stage II-IV sacral or ischial pressure ulcers (1 RCT)<br>Refractory venous ulcers (2 RCTs) | 315 <sup>a</sup> (83-132) | RCT    | <ul style="list-style-type: none"><li>• Results not pooled</li><li>• In all trials, patients in the treatment group experienced significantly higher wound healing rates</li></ul> |

RCT: randomized controlled trial.

<sup>a</sup> Two of the trials had overlapping populations, so there were not 315 unique patients.

### Section Summary: Topical Hyperbaric Oxygen for Wounds, Burns, or Infections

A systematic review identified three RCTs on the use of topical HBOT for chronic wound healing. The results showed topical oxygen therapy improved wound healing, but there was heterogeneity in the trial populations and treatment regimens. There is a small RCT on topical HBOT for diabetic foot ulcers; it showed no differences in outcomes between the treatment and control group. No controlled studies on topical HBOT for patients with burns or infections were identified. The data are insufficient to draw conclusions about the effect on the net health outcome.

## SYSTEMIC HYPERBARIC OXYGEN THERAPY

There is limited comparative evidence for HBOT. The policy is based on the best available evidence, and is largely informed by clinical input and guidelines.

HBOT refers to treatment at pressures greater than 1.4 atmospheres absolute, administered in a hard-sided hyperbaric chamber that meets applicable safety standards. Tissue oxygen tensions greater than 250mmHg are required to halt the alpha toxin production of clostridial infection. This level of tissue oxygen tension can only be achieved with HBOT treatment. (It

should be noted that Group A streptococcus produces a toxin similar to the alpha toxin of *Clostridium myonecrosis* infections.)

### **Progressive Necrotizing Soft Tissue Infections**

Necrotizing soft tissue infection (NSTI) is a set of disorders characterized by a rapidly progressive infection with necrosis or gangrene. No definition of "progressive" was identified. However, definition of NSTI includes progression of infection despite antibiotic therapy. UHMC clinical input speaks to progressive NSTI in terms of NSTI while receiving broad spectrum antibiotics with either performed or planned therapeutic and diagnostic surgical debridement. The UHMC input also notes that frozen section soft-tissue biopsy is the gold standard of diagnosis, but is not feasible in practice. There are no unique clinical considerations based on the wound characteristics, site and/or depth of infection or time to treatment. By their very nature, NSTI are life and limb threatening.

### **Central Retinal Artery Occlusion (CRAO) and Other Retinal Conditions**

CRAO is relatively rare yet devastating diagnosis with poor prognosis for spontaneous recovery. Factors which influence outcome include the length of time of occlusion, the anatomical site of the occlusion, and the presence of a patent cilioretinal artery. The diagnosis of CRAO is typically and reliably made with a fundoscopic exam. Advanced diagnostic studies can confirm CRAO but are not required for the diagnosis. Treatments for CRAO include ocular massage, anterior chamber paracentesis, fibrinolysis, and ocular pressure lowering agents. However, none of these demonstrate improved outcomes compared to control. The FDA has added CRAO to the list of cleared indications for HBOT.

CRAO is a rare complication associated with CaHA (calcium hydroxylapatite) cosmetic filler injection, likely due to embolism.

In addition to CRAO, there are related clinical syndromes for which HBOT could be considered. This includes individuals with branch retinal artery occlusion, particularly those with complete or near complete blindness in the contralateral eye. Also, Susac's Syndrome which is a rare disorder thought to be an autoimmune endotheliopathy causing vascular injury and deposition of thrombotic material in the lumen of small vessels. Treatments for this syndrome include steroids, anticoagulation, and IVIG; HBOT might improve visual acuity for these individuals.

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

Idiopathic sudden sensorineural hearing loss (ISSHL) is an abrupt loss of hearing, typically unilaterally, without a definitive or identifiable cause upon investigation, as is the case for 90% of sudden sensorineural hearing loss patients. The degree of hearing loss is typically defined as a loss of 30 decibels or more across 3 contiguous frequencies on audiogram. The hearing loss initially occurring on one side can occur subsequently on the contralateral side in the future. The exact etiology of ISSHL has not been elucidated but of the major proposed mechanisms may be mitigated by HBOT. ISSHL is included in the FDA approved uses of HBOT.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR DIABETIC ULCERS**

Sharma et al (2021) (4) conducted a systematic review and meta-analysis of 14 studies (N=768) comparing the effect of HBOT with standard care on diabetic foot ulcers (Table 2). Study authors noted that various modalities can be considered standard care including, but not

limited to, debridement, antibiotics and blood sugar control. However, the specific standard care modality in each included study was not reported. HBOT duration ranged from 45 to 120 minutes (median 90 minutes). All included studies had methodological limitations, including selection, performance, detection, attrition and reporting bias. The review found those treated with standard care were less likely to have complete ulcer healing versus HBOT, based on pooled analysis of 11 studies (odds ratio [OR], 0.29; 95% confidence interval [CI], 0.14 to 0.61; I<sup>2</sup>=62%). Results were consistent when stratified according to duration of follow-up of less than 1 year (7 studies; OR, 0.63; 95% CI, 0.39 to 1.02; I<sup>2</sup>=1%) and at 1 year (4 studies; OR, 0.16; 95% CI, 0.03 to 0.82; I<sup>2</sup>=83%), although the risk estimate wasn't statistically significant for studies with less than one year follow-up. A funnel plot analysis for this outcome was asymmetrical, suggesting publication bias. Risk of major amputation was also significantly lower with HBOT compared to standard care based on pooled analysis of 7 studies (OR, 0.60; 95% CI, 0.39 to 0.92; I<sup>2</sup>=24%). There were no clear differences between groups in minor amputation (9 studies; OR, 0.89; 95% CI, 0.71 to 1.12) or mortality (3 studies; OR, 0.55; 95% CI, 0.25 to 1.24). Standard care was associated with an increased risk of adverse events compared with HBOT (7 studies; OR, 1.68; 95% CI, 1.07 to 2.65).

A Cochrane review of RCTs on HBOT for chronic wounds was published by Kranke et al in 2015 (see Table 2). (8) Reviewers identified 12 RCTs (total N=577) comparing the effect of HBOT on chronic wound healing with an alternative treatment approach that did not use HBOT. Ten of the 12 trials evaluated HBOT in patients with diabetes (N=531). The trials were assessed as moderate quality using the GRADE system. HBOT regimens varied across studies, ranging from 3.0 atmospheres absolute (ATA) for 45 minutes to 2.2 ATA for 120 minutes. In a pooled analysis of 5 trials, a significantly higher proportion of ulcers had healed at the end of treatment (i.e., 6 weeks) in the group receiving HBOT than in the group not receiving HBOT, but there was no statistically significant difference in the risk of major amputations between groups.

A systematic review by Elraiayah et al (2016) evaluated adjunctive therapies (HBOT, arterial pumps, and pharmacologic agents) used to treat diabetic foot ulcers (see Table 2). (9) RCTs and nonrandomized cohort studies were included. The RCTs were rated as low-to-moderate quality using the GRADE system. A pooled analysis of six RCTs found a significantly higher healing rate and a significantly lower major amputation rate (odds ratio, 0.30; 95% confidence interval, 0.10 to 0.89) with HBOT than with control.

**Table 2. Systematic Reviews of Trials Assessing HBOT for Diabetic Foot Ulcers**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|--------------|-------------------|---------|--------------|---|--------|---------|
|--------------|-------------------|---------|--------------|---|--------|---------|

|                                       |          |    |   |      |              |   |
|---------------------------------------|----------|----|---|------|--------------|---|
| Kranke et al (2015) <sup>8</sup> .    | Feb 2015 | 12 | Patients with chronic wounds associated with venous or arterial disease, diabetes, or external pressure | 577  | RCTs         | 10 of 12 trials focused on patients with diabetic foot ulcers (n=531)<br>Pooled analysis of 5 of 10 trials (n=205) reported higher heal rates with HBOT (RR=2.3; 95% CI, 1.2 to 4.6) and no difference in amputation risk (RR=0.4; 95% CI, 0.1 to 2.2)  |
| Elraiyyah et al (2016) <sup>9</sup> . | Oct 2011 | 18 | Patients with diabetic foot ulcers  | 1526 | RCTs, cohort | 16 of 18 trials included HBOT as a treatment option and 6 of those were RCTs<br>Pooled analysis of the 6 RCTs (n=340) reported higher heal rate with HBOT (OR=14.3; 95% CI, 7.1 to 28.7) and lower amputation risk (OR=0.3; 95% CI, 0.1 to 0.9)   |
| Sharma et al (2021) <sup>4</sup> .    | Sep 2020 | 14 | Patients with diabetic foot ulcers  | 768  | RCTs, CCTs   | 12 RCTs and 2 CCTs compared HBOT with undefined standard care<br>Pooled analysis found HBOT significantly associated with complete ulcer healing (ST vs. HBOT: OR 0.29, 95% CI 0.14 to 0.61) and lower risk of major amputation (HBOT vs. ST: OR 0.60, 95% CI 0.39 to 0.92) when compared with standard care. |

CI: confidence interval; HBOT: hyperbaric oxygen therapy; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk.

### **Section Summary: Diabetic Ulcers**

Three systematic reviews have been published that included trials and cohort studies. Pooled analyses of RCTs found significantly higher wound healing rates with HBOT than with control conditions. One of the two meta-analyses, but not the other, found that HBOT was associated with a significantly lower rate of major amputation.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR CARBON MONOXIDE POISONING**

A Cochrane review by Buckley et al (2011) included six RCTs evaluating HBOT for carbon monoxide poisoning (see Table 3). (10) Four of the six trials were assessed as having a high risk of bias due to nonblinding of treatment allocation. The trials had substantial methodologic and statistical heterogeneity. The outcome of interest was dichotomous, presence or absence of signs or symptoms indicative of neurologic injury at four to six weeks after study inclusion. Two of the six RCTs found that HBOT reduced the likelihood of neurologic sequelae at one month and four others did not find a significant effect. A pooled analysis of the six trials did not find a significant effect of HBOT on neurologic injury. Reviewers concluded that there was

insufficient evidence to determine whether HBOT reduces the risk of adverse neurologic outcomes after carbon monoxide poisoning. Quality of the evidence was deemed very low, using the GRADE system.

**Table 3. Systematic Reviews of Trials Assessing HBOT for Carbon Monoxide Poisoning**

| Study (Year)                       | Literature Search | Studies | Participants  | N    | Design | Results   |
|------------------------------------|-------------------|---------|---|------|--------|---|
| Buckley et al (2011) <sup>10</sup> | Jun 2010          | 6       | Nonpregnant adults with acute carbon monoxide poisoning | 1361 | RCTs   | <ul style="list-style-type: none"> <li>• Studies extremely heterogeneous in: severity of CO poisoning, HBOT regimens, and comparators</li> <li>• Pooled analyses of 6 trials (N=1361) reported no statistical difference in neurologic deficits between treatment groups (OR=0.78; 95% CI, 0.54 to 1.12)</li> </ul> |

CI: confidence interval; CO: carbon monoxide; HBOT: hyperbaric oxygen therapy; OR: odds ratio; RCT: randomized controlled trial.

### Nonrandomized Comparative Studies

Nakajima et al (2020) conducted a retrospective cohort study comparing the effect of HBOT versus control (no HBOT) on mortality and morbidity in patients with carbon monoxide poisoning.<sup>(85)</sup> The median number of HBOT sessions was 3(range 2 to 5). After propensity score matching of study participants (N=4,068) the study found no significant difference between groups in in-hospital mortality (mean rate difference -0.4%, 95% confidence interval -1.0 to 0.2%). Results were consistent across subgroups according to severity of carbon monoxide poisoning, age and number of HBOT sessions. However, the study found HBOT associated with lower rates of depressed mental status (mean difference -3.2%, 5%confidence interval -4.9% to -1.5%) and reduced activities of daily living (mean difference -5.3%, 95% confidence interval-7.8% to -2.7%) relative to no HBOT.

### Section Summary: Systemic HBOT for Carbon Monoxide Poisoning

A Cochrane review identified six RCTs, the majority of which did not find a significant effect of HBOT on health outcomes. In addition, a pooled analysis of RCT data did not find a significant effect of HBOT on neurologic injuries and the quality of the evidence was considered very low. Practicing standards have evolved possibly beyond the available evidence. So, consideration of specialty society guidelines and subject matter expert input have led to acknowledgement that HBOT can be effective in this condition.

## SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR RADIONECROSIS, OSTEORADIONECROSIS, AND TREATMENT OF IRRADIATED JAW

Bennett et al (2016) published a Cochrane review on HBOT for late radiation tissue injury (see Table 4).<sup>(11)</sup> Reviewers identified 14 RCTs. In a pooled analysis of three studies, a significantly higher proportion of patients with osteoradionecrosis achieved complete mucosal cover after HBOT than with control treatments (RR=1.30; 95% CI, 1.09 to 1.55). In addition, a pooled analysis of two trials found a significantly lower risk of wound dehiscence after surgery to repair mandibular osteoradionecrosis with HBOT than with control treatments (RR=4.23; 95% CI, 1.06 to 16.83). A single trial found a significantly higher likelihood of successful healing with HBOT than with antibiotics for tooth extraction in irradiated jaws (absolute risk reduction, 25%; p=.02). There were insufficient data to conduct meta-analyses on other outcomes.

Borab et al (2017) published a systematic review focusing on the use of HBOT to treat the subgroup of patients with late radiation tissue injury who had skin necrosis (see Table 4). (12) Reviewers identified eight studies, including a large observational cohort and several case series. No RCTs were identified. The risk of bias was high due to the design of the included studies. The studies reported improved healing, though, without a comparator, interpretation of the results is limited.

Ravi et al (2017) published a systematic review on the use of HBOT to treat patients who had received radiotherapy for head and neck cancer. (13) Ten prospective case series and comparative studies were identified. Qualitative summaries of outcomes were provided, but pooled analyses were not performed. Outcomes of interest included osteonecrosis and dental implant survival (see Table 4). Other outcomes of interest included salivary gland function and quality of life, which are discussed in the Radiotherapy Adverse Events section.

**Table 4. Systematic Reviews of Studies Assessing HBOT for Radionecrosis, Osteoradionecrosis, and Treatment of Irradiated Jaw**

| Study (Year)                       | Literature Search | Studies | Participants  | N   | Design  | Results   |
|------------------------------------|-------------------|---------|---|-----|---|---|
| Bennett et al (2016) <sup>11</sup> | Dec 2015          | 14      | Patients with late radiation tissue injury (including necrosis) and patients treated with large-dose radiotherapy likely to induce early necrosis | 753 | RCTs  | <ul style="list-style-type: none"> <li>• Pooled analyses of 3 trials of patients with osteoradionecrosis (n=246) found a higher rate of complete mucosal cover after HBOT vs control (RR=1.3; 95% CI, 1.1 to 1.5)</li> <li>• Pooled analyses of 2 trials (n=264) found a lower risk of wound dehiscence following surgery to repair mandibular osteoradionecrosis in patients treated with HBOT vs control (RR=4.2; 95% CI, 1.1 to 16.8)</li> </ul> |
| Borab et al (2017) <sup>12</sup>   | May 2016          | 8       | Patients with radiation-induced skin necrosis   | 720 | Observational cohort and case series                        | <ul style="list-style-type: none"> <li>• Adding across the studies, 80% reported complete healing and 86% reported symptom improvement</li> <li>• Studies had no comparators</li> </ul>   |
| Ravi et al (2017) <sup>13</sup>    | Dec 2016          | 10      | Patients who received radiotherapy for head and neck cancer   | 375 | Prospective case series and prospective comparative studies | <ul style="list-style-type: none"> <li>• Osteonecrosis prevention: 1 case series and 1 comparative study (n=77) reported low osteonecrosis rates with HBOT</li> <li>• Dental implant survival: 1 case series and 2 comparative studies (n=122) report mixed results, with 2 studies finding implant survival improved with HBOT and another finding no difference in survival</li> </ul>  |

CI: confidence interval; HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial; RR: relative risk.

### **Section Summary: Systemic HBOT for Radionecrosis, Osteoradionecrosis, and Treatment of Irradiated Jaw**

A Cochrane review of RCTs found that HBOT improved some radionecrosis and osteoradionecrosis outcomes and resulted in better outcomes prior to tooth extraction in an irradiated jaw. Observational studies focused on skin necrosis and reported high rates of

healing with HBOT, though with no comparators, interpretation of results is limited. Prospective observational studies using HBOT for treatment on patients with head and neck cancer receiving HBOT, have reported low osteonecrosis rates and inconsistent results for dental implant survival. The number of RCTs evaluating HBOT for these indications, especially in irradiated jaws, is limited.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR CHRONIC REFRACTORY OSTEOMYELITIS**

No prospective clinical trials on chronic or refractory osteomyelitis were identified in literature searches. The evidence for the use of HBOT in chronic osteomyelitis has been primarily based on case series.

Savvidou et al (2018) conducted a qualitative systematic review of HBOT as an adjunctive treatment of chronic osteomyelitis. (34) Adjuvant HBOT was effective in 16 (80%) of 20 cohort studies and 19 (95%) of 20 case series. Overall, 308 (73.5%) of 419 patients with complete data achieved a successful outcome with no relapses reported.

Among the larger case series, Maynor et al (1998) reviewed the records of all patients with chronic osteomyelitis of the tibia seen at a single institution.(14) Follow-up data were available on 34 patients who had received a mean of 35 adjunctive HBO treatments (range, 6-99). Of the 26 patients with at least two 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.

Davis et al (1986) reviewed outcomes for 38 patients with chronic refractory osteomyelitis treated at another U.S. institution.(15) Patients received HBOT until the bone was fully recovered with healthy vascular tissue; this resulted in a mean of 48 daily treatments (range, 8-103 treatments). After a mean post-treatment follow-up of 34 months, 34 (89%) of 38 patients remained clinically free of infection (i.e., drainage-free and no tenderness, pain, or cellulitis). Success rates from several smaller case series (N range, 13-15 patients), all conducted in Taiwan (1998- 2000), ranged from 79% to 92% (16-18) A high percentage of refractory patients in these series had successful outcomes.

### ***Section Summary: Systemic HBOT for Chronic Refractory Osteomyelitis***

Only case series data are available; no RCTs or comparative nonrandomized trials were identified. Case series tended to find high rates of successful outcomes in patients with chronic refractory osteomyelitis treated with HBOT. However, controlled studies are needed to determine conclusively that HBOT improves health outcomes in patients with chronic refractory osteomyelitis compared to other interventions. Practicing standards have evolved possibly beyond the available evidence. So, consideration of specialty society guidelines and subject matter expert input have led to acknowledgement that HBOT can be effective in this condition.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR ACUTE THERMAL BURNS**

In 2004, a Cochrane review assessed HBOT for thermal burns (see Table 5).(19) Two RCTs were identified. Sample sizes were 16 and 125. Both trials were judged by reviewers to have poor methodologic quality. Reviewers concluded that the evidence was insufficient to permit conclusions on whether HBOT improves health outcomes in patients with acute thermal burns.



No additional trials were identified when an updated literature search was conducted in 2009 (the 2004 publication date continues to be used).

**Table 5. Systematic Reviews of Trials Assessing HBOT for Acute Thermal Burns**

| Study (Year)                            | Literature Search | Studies | Participants  | N   | Design | Results   |
|---|-------------------|---------|---|-----|--------|---|
| Villanueva et al (2009) <sup>19</sup> . | Jun 2009          | 5       | Patients with thermal injuries to the epidermis, subcutaneous tissues, vessels, nerve, tendons, or bone | 141 | RCTs   | <ul style="list-style-type: none"> <li>One trial (N=125) reported no difference in length of stay, mortality, or number of surgeries between HBOT and control groups</li> <li>One trial (N=16) reported shorter healing times (19.7 days vs 43.8 days; <math>p&lt;0.001</math>) with HBOT vs control, and an RR for failed graft without HBOT of 2.0 (95% CI 0.5 to 8.0)</li> </ul> |

CI: confidence interval; HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial; RR: relative risk.

### **Section Summary: Systemic HBOT for Acute Thermal Burns**

A Cochrane review identified two RCTs on HBOT for thermal burns. Both were judged to have poor methodologic quality. There is insufficient evidence from well-conducted controlled studies to permit conclusions on the impact of HBOT on health outcomes in patients with acute thermal burns.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR ACUTE SURGICAL AND TRAUMATIC WOUNDS**

A Cochrane review (2103) of RCTs on HBOT for acute surgical and traumatic wounds was published by Eskers et al (see Table 6). (20) HBOT was administered at pressures above one atmosphere (atm). To be included, studies had to compare HBOT with a different intervention or compare two HBOT regimens; also, studies had to measure wound healing objectively. Four RCTs met reviewers' inclusion criteria. Trials ranged in size from 10 to 135 participants. Due to differences among trials regarding patient population, comparison intervention, and outcome measurement, results could not be pooled. The primary outcome examined by Cochrane reviewers (wound healing) was not reported in either of the two trials comparing HBOT with usual care and was not reported in the trial comparing HBOT with dexamethasone or heparin. Complete wound healing was reported in the RCT comparing active HBOT with sham HBOT. In this study (N=36), there was a statistically higher rate of wound healing in the group, though the time point for outcome measurement in this trial was unclear. Also, there was no statistically significant difference between groups in the meantime to wound healing.

A systematic review of studies on HBOT for acute wounds, published by Dauwe et al (2014), included RCTs and controlled nonrandomized studies (see Table 6).(21) Reviewers included eight studies, with sample sizes ranging from 5 to 125 patients. Four studies were randomized, three were prospective observational studies, and one was a retrospective observational study. As in the Eskes systematic review, data were not pooled. Reviewers noted that seven of the eight studies reported statistically significant findings for their primary end points, but the end points differed among studies (e.g., graft survival, hospital length of stay, wound size). Moreover, the studies were heterogeneous regarding treatment regimens, patient indications (e.g., burns, facelifts), and study designs making it difficult to draw conclusions about the effect of HBOT on acute wound treatment.



Zhou et al (2014) published a systematic review of Chinese studies assessing the use of HBOT in the management of compromised skin flaps and grafts. (35) Among 16 controlled studies comparing routine therapy to HBOT, healing and survival rates ranged from 35.0% to 86.5% and 77.9% to 100%, respectively. Among a subset of studies assessing skin flaps post-mastectomy, the overall therapeutic efficacy rate was 62.5%. Several studies suggested higher success rates when HBOT is initiated as soon as possible following surgery. Limitations of this analysis include heterogeneity in treatment protocols, wound sites and etiologies, and underlying comorbidities. The authors acknowledge that the therapeutic efficacy of HBOT in compromised skin flaps needs to be validated in future randomized, controlled studies but encourage shared decision-making in the absence of Level I evidence.

**Table 6. Systematic Reviews of Trials Assessing HBOT for Acute Surgical and Traumatic Wounds**

| Study (Year)                     | Literature Search | Studies | Participants  | N                           | Design   | Results  |
|----------------------------------|-------------------|---------|---|-----------------------------|--|--|
| Eskes et al (2013) <sup>20</sup> | Aug 2013          | 4       | Patients with acute wounds (skin injuries occurring due to surgery or trauma) | 229                         | RCTs   | <ul style="list-style-type: none"> <li>• Three of four trials did not include wound healing as an outcome measure</li> <li>• A small trial (N=36) reported patients receiving HBOT had significantly higher wound healing rate vs sham; however, no difference in time to healing</li> </ul> |
| Dauwe et al (2014) <sup>21</sup> | Oct 2012          | 8       | Patients with acute wounds, grafts, and flaps                                 | 256                         | RCTs and nonrandomized studies   | <ul style="list-style-type: none"> <li>• HBOT may augment healing of acute wounds</li> <li>• Not indicated for routine wound management</li> </ul>   |
| Zhou et al (2014)                | 1994-2013         | 23      | Patients with compromised skin flaps and grafts                               | 626 (HBOT)<br>583 (control) | RCTs (12), nonrandomized comparative studies (4), and single-arm studies (7) | <ul style="list-style-type: none"> <li>• HBOT may improve the survival rate of compromised skin grafts and flaps</li> <li>• Initiation of HBOT within 72 hours is associated with improved outcomes</li> </ul>   |

HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial.

### **Section Summary: Systemic HBOT for Acute Surgical and Traumatic Wounds**

Two systematic reviews identified four RCTs; one of the reviews also included nonrandomized studies. One systematic review identified 16 small Chinese controlled studies on the use of HBOT for compromised skin grafts and flaps. Heterogeneity among studies (e.g., in patient population, comparison group, outcomes) prevented pooling of study findings and limits the ability to draw definitive conclusions about the impact of HBOT on health outcomes in patients with acute and traumatic wounds. Additional evidence from high-quality RCTs is needed.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW**

An unblinded RCT by Freiburger et al (2012) evaluated use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw (see Tables 7 and 8).(22) The investigators did a per-protocol analysis (actual treatment received) due to treatment of crossovers between the treatment groups. Participants were evaluated at 3, 6, 12, and 18 months. At three months, significantly more patients receiving HBOT as an adjunct to standard

care experienced improvements in lesion size and number compared with patients receiving only standard care. When the change from baseline to 6, 12, or 18 months was examined, there were no statistically significant differences between groups in the proportion of patients with improvement or in the proportion of those who healed completely at any time point. This trial had a number of methodologic limitations (e.g., unblinded, crossover, per-protocol analysis 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.

**Table 7. Characteristics of Trials Assessing HBOT for Bisphosphonate-Related Osteonecrosis of the Jaw**

| Study (Year)                          | Countries     | Sites           | Dates     | Participants  | Treatment  |  |
|---------------------------------------|---------------|-----------------|-----------|---|--|--|
|                                       |               |                 |           |   | Active (n=25)  | Comparator (n=21)  |
| Freiberger et al (2012) <sup>22</sup> | United States | NR <sup>a</sup> | 2006-2010 | Patients with bisphosphonate-related osteonecrosis of the jaw | <ul style="list-style-type: none"> <li>Hyperbaric oxygen plus standard oral care</li> <li>100% oxygen at 2 ATA</li> <li>40 treatments</li> </ul> | Standard oral care (antiseptic rinses, surgery, and antibiotics) |

ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; NR: not reported.

<sup>a</sup> Number of sites not reported, though all oncologists, dentists, and oral-maxillofacial surgeons in the referral area of central North Carolina, southern Virginia, and northern South Carolina were eligible to participate.

**Table 8. Results of Trials Assessing HBOT for Bisphosphonate-Related Osteonecrosis of the Jaw**

| Study (Year)                          | Improved, % (n) |                       |           |                       | Healed, % (n) |                       |                       |
|---------------------------------------|-----------------|-----------------------|-----------|-----------------------|---------------|-----------------------|-----------------------|
|                                       | 3 Months        | Between-Group P-Value | 18 Months | Between-Group P-Value | 3 Months      | Between-Group P-Value | Between-Group P-Value |
| Freiberger et al (2012) <sup>22</sup> | 46              |                       | 46        |                       | 46            |                       |                       |
| HBOT                                  | 68.0 (25)       | 0.03                  | 58.3 (12) | 0.31                  | 36.0 (25)     | 0.04                  | 1.0                   |
| Control                               | 35.0 (20)       |                       | 33.3 (6)  |                       | 10.0 (20)     |                       |                       |

HBOT: hyperbaric oxygen therapy.

### **Section Summary: Systemic HBOT for Bisphosphonate-Related Osteonecrosis of the Jaw**

One RCT has evaluated HBOT for patients with bisphosphonate-related osteonecrosis of the jaw. This unblinded study reported initial benefits at the three-month follow-up; however, there were no significant benefits of HBOT for most health outcomes compared with standard care in the long-term (six months to two years). Additional evidence from RCTs is needed to permit conclusions on the impact of HBOT on health outcomes in patients with bisphosphonate-related osteonecrosis of the jaw.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR PROGRESSIVE NECROTIZING SOFT TISSUE INFECTIONS**

A Cochrane review by Levett et al (2015) evaluated the literature on HBOT as adjunctive therapy for necrotizing fasciitis. (23) No RCTs were identified. A 2021 systematic review conducted by Hedetoft et al included 31 retrospective cohort studies assessing the effect of adjunctive HBOT for treating necrotizing soft-tissue infections (necrotizing fasciitis, Fournier's gangrene and gas gangrene). (24) Ten studies assessed to have critical (very high) risk of bias were excluded from meta-analyses. Pooled results from the remaining 21 studies found HBOT associated with a reduced risk of in-hospital mortality (OR, 0.44; 95% CI, 0.33 to 0.58;  $I^2=8\%$ ),

but the duration of follow-up for mortality was not reported. Results were consistent when studies were stratified according to moderate (5 studies; OR, 0.39; 95% CI, 0.28 to 0.55;  $I^2=0\%$ ) and serious (high) risk of bias (16 studies; OR, 0.51; 95% CI, 0.33 to 0.80;  $I^2=17\%$ ). Publication bias favoring HBOT was present for this outcome based on funnel plot analysis. For other outcomes, including major amputation and length of hospital stay, there were no statistically significant differences between HBOT use and non-use. Evidence on adjunctive HBOT and the need for surgical debridement was mixed. One study with low/moderate risk of bias reported a higher number of debridements with HBOT use versus non-use (mean difference, 1.8; 95% CI, 1.15 to 2.45), but the mean difference between HBOT use and non-use in a pooled analysis of 5 studies with methodological flaws was not statistically significant (mean difference, 0.63; 95% CI, -0.49 to 1.75).

### **Section Summary: Systemic HBOT for Necrotizing Soft Tissue Infections**

No RCTs have evaluated HBOT for necrotizing soft tissue infection. A systematic review of retrospective cohort studies with methodological limitations suggested that HBOT use may reduce the risk of in-hospital mortality, but these results were subject to publication bias.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR ACUTE CORONARY SYNDROME**

A Cochrane review by Bennett et al (2015) identified six trials (total N=665) evaluating HBOT for acute coronary syndrome (see Table 9). (26) Included studies were published between 1973 and 2007. All studies included patients with acute myocardial infarction; a study also included individuals with unstable angina. Additionally, all trials used HBOT, administered between two and three ATA, for 30 to 120-minute sessions, as an adjunct to standard care. Control interventions varied; only a trial described using a sham therapy to blind participants to treatment group allocation. In a pooled analysis of data from five trials, there was a significantly lower risk of mortality in patients who received HBOT compared with a control intervention. Due to the variability of outcome reporting across studies, few other pooled analyses could be conducted. Three trials reported outcomes related to left ventricular function. One did not find a statistically significant improvement in contraction with HBOT, while two trials showed left ventricular ejection fraction improved significantly with HBOT. Reviewers noted that, although some evidence from small trials correlated HBOT with a lower risk of death, larger trials with high-quality methods were needed to determine which patients, if any, could be expected to derive benefit from HBOT.

**Table 9. Systematic Reviews of Trials Assessing HBOT for Acute Coronary Syndrome**

| Study (Year)                       | Literature Search | Studies | Participants   | N   | Design | Results  |
|------------------------------------|-------------------|---------|--|-----|--------|--|
| Bennett et al (2015) <sup>26</sup> | Jun 2010          | 6       | Adults with acute coronary syndrome, with or without S-T segment elevation | 665 | RCTs   | <ul style="list-style-type: none"> <li>• Pooled analyses of 5 trials (n=614) reported a lower mortality rate for patients in the HBOT group vs the control (RR=0.58; 95% CI, 0.36 to 0.92)</li> <li>• Left ventricular outcomes, 3 trials total: 1 trial reported no difference in contraction (RR=0.09; 95% CI, 0.01 to 1.4) and pooled analyses of 2 trials</li> </ul> |

(n=190) found significant improvements in LVEF with HBOT (MD=5.5%; 95% CI, 2.2% to 8.8%)

CI: confidence interval; HBOT: hyperbaric oxygen therapy; LVEF: left ventricular ejection fraction; MD: mean difference; RCT: randomized controlled trial; RR: relative risk.

### **Section Summary: Systemic HBOT for Acute Coronary Syndrome**

A Cochrane review of six RCTs found insufficient evidence that HBOT is safe and effective for acute coronary syndrome. One pooled analysis of data from five RCTs found a significantly lower rate of death with HBOT than with a comparison intervention; however, larger, higher quality trials are needed. Three trials measuring left ventricular function report inconsistent results.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR ACUTE ISCHEMIC STROKE**

In a Cochrane systematic review of RCTs, Bennett et al (2014) evaluated HBOT for acute ischemic stroke (see Table 10). (27) Reviewers identified 11 RCTs (total N=705) that compared HBOT with sham HBOT or no treatment. Reviewers could only pool study findings for one outcome (mortality at 3-6 months), and no difference was detected between the treatment groups for that outcome. There was heterogeneity in the participants enrolled and in the clinical and functional outcomes measured across the studies.

**Table 10. Systematic Reviews of Trials Assessing HBOT for Acute Ischemic Stroke**

| Study (Year)                       | Literature Search | Studies | Participants  | N   | Design | Results   |
|------------------------------------|-------------------|---------|---|-----|--------|---|
| Bennett et al (2014) <sup>27</sup> | Apr 2014          | 11      | Patients with acute ischemic stroke, defined as sudden neurologic deficit of vascular origin for which hemorrhage was excluded by CT or MRI | 705 | RCTs   | Pooled analyses of 4 trials (n=144) found no difference in mortality at 3 to 6 mo (RR=0.97; 95% CI, 0.34 to 2.75) |

CI: confidence interval; CT: computed tomography; HBOT: hyperbaric oxygen therapy; MRI: magnetic resonance imaging; RCT: randomized controlled trial; RR: relative risk.

### **Section Summary: Systemic HBOT for Acute Ischemic Stroke**

A Cochrane review of RCTs conducted a pooled analysis (four RCTs), which found no significant difference in mortality rates at three to six months when patients with acute ischemic stroke were treated with HBOT or a sham intervention. Additional RCT data is needed to permit conclusions on the impact of HBOT on the health outcome in patients with acute ischemic stroke.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR MOTOR DYSFUNCTION ASSOCIATED WITH STROKE**

Efrati et al (2013) published an RCT evaluating HBOT for the treatment of neurologic deficiencies associated with a history of stroke (see Tables 11 and 12). (28) Patients in the treatment group were evaluated at baseline and two months. For patients in the delayed treatment control group, outcomes were evaluated at four months after crossing over and receiving HBOT. Outcome measures included the National Institutes of Health Stroke Scale (NIHSS), which was measured by physicians blinded to the treatment group, and several patient-reported (QOL) and functional status measures. At the two-month follow-up, there was statistically significantly greater improvement in function in the HBOT group than in the control group, as measured by the NIHSS, QOL scales, and the ability to perform activities of daily

living (ADLs). These differences in outcome measures were accompanied by improvements in single-photon emission computed tomography imaging in the regions affected by stroke. For the delayed treatment control group, there was a statistically significant improvement in function after HBOT than before HBOT. This RCT raises the possibility that HBOT may induce improvements in function and QOL for poststroke patients with motor deficits. However, the results are not definitive for a number of reasons. This RCT was small and enrolled a heterogeneous group of poststroke patients. It was not double-blind and most outcome measures, except for NIHSS, were patient-reported and thus prone to the placebo effect. Also, there was a high total dropout rate (20%) at the two-month follow-up. Therefore, larger, double-blind studies with longer follow-up are needed to corroborate these results.

**Table 11. Characteristics of Trials Assessing HBOT for Motor Dysfunction Associated With Stroke**

| Study (Year)                      | Countries | Sites | Dates     | Participants   | Treatment   | Comparator (n=29)                  |
|-----------------------------------|-----------|-------|-----------|--|---|------------------------------------|
|                                   |           |       |           |  | Active (n=30)   |                                    |
| Efrati et al (2013) <sup>28</sup> | Israel    | 1     | 2008-2010 | Patients ≥18 y with ischemic or hemorrhagic stroke 6 to 36 mo prior to inclusion with ≥1 motor dysfunction | <ul style="list-style-type: none"> <li>• Hyperbaric oxygen</li> <li>• 100% oxygen at 2 ATA</li> <li>• 40 times over 2 mo</li> </ul> | Same as active, delayed after 2 mo |

ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy.

**Table 12. Results of Trials Assessing HBOT for Motor Dysfunction Associated with Stroke**

| Study (Year)                      | National Institutes of Health Stroke Scale |           |                       | Activities of Daily Living <sup>a</sup> |            |                       |
|-----------------------------------|--|-----------|-----------------------|---|------------|-----------------------|
|                                   | Baseline                                   | 2 Months  | Between-Group P-Value | Baseline                                | 2 Months   | Between-Group P-Value |
| Efrati et al (2013) <sup>28</sup> | 50   | 50        |                       | 50                                      | 50         |                       |
| Mean HBOT (SD)                    | 8.5 (3.6)                                  | 5.5 (3.6) | 0.004                 | 16.1 (6.5)                              | 12.8 (7.3) | 0.02                  |
| Mean control (SD)                 | 8.7 (4.1)                                  | 8.3 (4.3) |                       | 17.4 (9.5)                              | 17.5 (9.5) |                       |

HBOT: hyperbaric oxygen; SD: standard deviation.

<sup>a</sup> Activities of Daily Living: 16 functions scored across a range whether patient was independent to did not perform at all. Range: 0 (best) to 51 (worst).

### **Section Summary: Systemic HBOT for Motor Dysfunction Associated with Stroke**

One crossover RCT identified evaluated HBOT in patients with a recent history of stroke. The RCT found better outcomes at two months with HBOT versus delayed treatment. However, the trial had a number of methodologic limitations, which make it difficult to draw conclusions about the efficacy of HBOT for this indication. Double-blind RCTs that address potential bias in subjective outcomes and studies with adequate follow-up are needed.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR BELL PALSY**

Holland et al (2012) published a Cochrane review evaluating HBOT in adults with moderate-to-severe Bell palsy.<sup>(29)</sup> The literature search, conducted through January 2012, identified one RCT with 79 participants, but this trial did not meet reviewers' prescribed preselection

standards because the outcome assessor was not blinded to treatment allocation. The trial was therefore excluded with no further analysis.

### **Section Summary: Systemic HBOT for Bell Palsy**

There is a lack of evidence on use of HBOT for Bell palsy. A Cochrane review did not identify any eligible RCTs; the single RCT identified lacked blinded outcome assessment. Well-conducted RCTs are needed.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR TRAUMATIC BRAIN INJURY**

Table 13 summarizes key measurement tools for assessing severity of brain injury.

**Table 13. Brain Injury Assessment Scales Outcome Measures**

| <b>Outcome</b>   | <b>Description</b>   | <b>Administration</b>               | <b>Scoring</b>  | <b>MCID</b>   |
|--|--|-------------------------------------|---|---|
| Glasgow Coma Scale (GCS)                               | Assesses impairment of conscious level in response to stimuli            | Physician-administered              | Likert-type scale; lower numbers, more severe TBI: <ul style="list-style-type: none"> <li>• eye opening (0 [not testable]–4)</li> <li>• verbal response (0–5)</li> <li>• motor response (0–6)</li> </ul> Total Score: <ul style="list-style-type: none"> <li>• Severe: ≤ 8</li> <li>• Moderate: 9–12</li> <li>• Mild: 13–15</li> </ul>  | NR  |
| Glasgow Outcome Scale (GOS)                            | Categorizes outcomes of patients after TBI                               | Physician-administered              | <ol style="list-style-type: none"> <li>1. Death</li> <li>2. Persistent vegetative state: minimal responsiveness</li> <li>3. Severe disability: conscious but disabled; dependent on others for daily support</li> <li>4. Moderate disability: disabled but independent; can work in sheltered setting</li> <li>5. Good recover: resumption of normal life despite minor deficits</li> </ol> | Unfavorable outcome: 1-3  |
| PTSD Checklist (PCL)                                   | A 17-item measure that reflects the DSM-IV symptoms of PTSD              | Self-administered                   | <ul style="list-style-type: none"> <li>• Likert-type scale (0: not at all–4: extremely)</li> <li>• Total score range: 17–85</li> <li>• PTSD cut point score for DoD screening: 31–33</li> </ul>   | <ul style="list-style-type: none"> <li>• Response to treatment: ≥ 5 points</li> <li>• Clinically meaningful: ≥ 10 points</li> </ul> |
| Rivermead Post-Concussion Symptoms Questionnaire (RPQ) | Assesses severity of somatic, cognitive, and emotional symptoms for mTBI | Self-administered or by interviewer | <ul style="list-style-type: none"> <li>• 16 Likert-type questions</li> <li>• Score range: 0–84</li> <li>• Higher values indicate more severe symptoms</li> </ul>  | 10% improvement   |

DoD: Department of Defense; MCID: minimum clinically important difference; mTBI: mild traumatic brain injury; NR: not reported; PTSD: posttraumatic stress disorder; RPQ: Rivermead Post-Concussion Symptoms Questionnaire; TBI: traumatic brain injury.

### **Study Selection Criteria**

Methodologically credible studies were selected using the principles described in the first indication.

### **Review of Evidence**



# Systematic Reviews

A meta-analysis by Wang et al (2016) addressed HBOT for treatment of traumatic brain injury (TBI see Table 15).(30) Eight studies (total N=519) met the eligibility criteria. HBOT protocols varied across studies in the levels of oxygen and the length and frequency of treatments. The primary outcome was change in the Glasgow Coma Scale score. A pooled analysis of two studies found a significantly greater improvement in the mean Glasgow Coma Scale score in the HBOT group compared with control groups. Mortality (a secondary outcome) was reported in three of the eight studies. Pooled analysis of these three studies found a significantly lower overall mortality rate in the HBOT group than in the control group.

Another systematic review, by Crawford et al (2017), did not conduct pooled analyses (see Table 14). (31) Reviewers identified 12 RCTs evaluating HBOT for patients with TBI. Four trials, all rated as having acceptable quality, addressed patients with mild TBI and compared HBOT with sham. None found statistically significant differences between groups on outcomes (i.e., post-concussive symptom severity, psychological outcomes). Seven trials evaluated HBOT for acute treatment of patients with moderate-to-severe TBI. Four were rated as acceptable quality and three as low quality. Study protocols and outcomes varied, and none used a sham control. Three acceptable quality studies with standard care controls reported the Glasgow Outcome Scale (GOS) score and mortality rate. In two of these, outcomes were better with HBOT than standard care; in the third study, outcomes did not differ significantly.

A Cochrane review by Bennet et al (2012) evaluated HBOT as adjunctive therapy for acute TBI (see Table 14) (32) Reviewers identified seven RCTs comparing a standard intensive treatment regimen with the same treatment regimen plus HBOT. Reviewers did not include studies with interventions in specialized acute care settings. The HBOT regimens varied among studies; e.g., the total number of individual sessions varied from 3 to 40. None of the trials used sham treatment or blinded staff treating patients, and only one had blinding of outcome assessment. Allocation concealment was inadequate in all studies. The primary outcomes of the review were mortality and functional outcomes. A pooled analysis of data from 4 trials showed that adding HBOT to standard care decreased mortality but did not improve functional outcome at final follow-up. The unfavorable functional outcome was commonly defined as a Glasgow Outcome Scale score of 1, 2, or 3, which are described as “dead,” “vegetative state,” or “severely disabled,” respectively. Studies were generally small and judged to have a substantial risk of bias.

The systematic review and pooled analysis by Hart et al (2019) evaluated HBOT for mild traumatic brain injury (mTBI)–associated post-concussive symptoms (PCS) and posttraumatic stress disorder (PTSD).(33) Data were aggregated from four Department of Defense (DoD) studies that included participant-level data on 254 patients assigned to either HBOT or sham intervention. An additional three studies with summary-level participant data were summarized (n=135). The authors assessed changes from baseline to postintervention on PCS, PTSD, and neuropsychological measures (Table 14). The DoD data analyses indicated improvements with HBOT for PCS, measured by the Rivermead Total Score. Statistically significant improvements were seen for PTSD based on the PTSD Checklist Total Score, as well as for verbal memory based on CVLT-II Trial 1-5 Free Recall.

**Table 14. Systematic Reviews of Trials Assessing HBOT for Traumatic Brain Injury**

| Study<br>(Year) | Literature<br>Search | Studies | Participants | N | Design | Results |
|-----------------|----------------------|---------|--------------|---|--------|---------|
|-----------------|----------------------|---------|--------------|---|--------|---------|

|                                     |          |                 |  |     |                                    |  |
|-------------------------------------|----------|-----------------|--|-----|------------------------------------|--|
| Hart et al (2019) <sup>33</sup>     |          | 7<br>(4 by DoD) | Patients (primarily US Service personnel) with mild traumatic brain injury | 389 |                                    | DoD Analysis: <ul style="list-style-type: none"> <li>Improvement in mean Rivermead Total Score (-2.3 points; 95% CI, -5.6 to 1.0; p=.18)</li> <li>Improvement in mean PTSD Checklist Total Score (-2.7 points; 95% CI, -5.8 to 0.4; p=.089)</li> <li>Improvement in mean verbal memory based on CVLT-II Trial 1-5 Free Recall (mean=3.8; 95% CI, 1.0 to 6.7; p=.01)</li> </ul> |
| Wang et al (2016) <sup>30</sup>     | Dec 2014 | 8               | Patients with mild or severe traumatic brain injury                        | 519 | RCTs and 2-arm prospective studies | <ul style="list-style-type: none"> <li>Pooled analyses of 2 trials (n=120) found significant improvements in GCS score change (3.1; 95% CI, 2.3 to 3.9) in HBOT vs control</li> <li>Pooled analyses of 3 trials (n=263) found lower risk of mortality among patients treated with HBOT vs controls (OR=0.3; 95% CI, 0.2 to 0.6)</li> </ul>                                     |
| Crawford et al (2017) <sup>31</sup> | Aug 2014 | 12              | Military and civilian patients with traumatic brain injury                 |     | RCTs                               | <ul style="list-style-type: none"> <li>Pooled analyses not performed</li> <li>Among 3 trials with GCS outcomes, 2 reported improvements with HBOT and 1 found no difference</li> <li>4 trials assessed as acceptable quality did not find significant differences in symptom severity or psychological outcomes</li> </ul>   |
| Bennett et al (2012) <sup>32</sup>  | Mar 2012 | 7               | Patients with acute traumatic brain injury following blunt trauma          | 571 | RCTs                               | <ul style="list-style-type: none"> <li>Pooled analyses of 4 trials (n=385) found that adding HBOT to standard care decreased mortality vs standard care alone (RR=0.7; 95% CI, 0.5 to 0.9)</li> <li>Pooled analyses of 4 trials (n=380) reported no difference in functional status at final follow-up between groups (RR=1.9; 95% CI, 0.9 to 4.1)</li> </ul>                  |

CI: confidence interval; DoD: Department of Defense; GCS: Glasgow Coma Scale; HBOT: hyperbaric oxygen therapy; OR: odds ratio; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; RR: relative risk.

## Clinical Trials

The DoD-sponsored RCT, “Brain Injury and Mechanisms of Action in Hyperbaric Oxygen for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (mTBI) (BIMA),” completed in 2016,<sup>(38)</sup> was the first to include post-intervention follow-up beyond three to six months. Hart et al (2019) describe BIMA, which assessed HBOT for U.S. service members with mTBI.<sup>(39)</sup> BIMA was initially planned for 12-month follow-up but was amended to include PCS and PTSD, quality of life, pain, depression, anxiety, and alcohol use assessments at 24 and 36 months. Investigators saw no significant differences at 24 or 36 months between the HBOT and sham groups, and group mean scores had returned to near pre-intervention values. In addition, Churchill et al (2019) reported on the chamber- and protocol-related adverse events (AEs) in the HOPPS and BIMA trials. <sup>(42)</sup> In addition to AEs, they assessed the success of maintaining the blind with a low-pressure sham control group. Of the total 4,245 total chamber sessions, AEs were rare, at 1.1% in the HOPPS study and 2.2% in BIMA. Most AEs were minor, non-limiting barotrauma, and a few were headaches. Results of a questionnaire that followed the intervention showed that the sham group blind was adequately maintained in both trials.



Weaver et al (2019) evaluated BIMA and a second RCT of U.S. service members for the efficacy of HBOT in treating persistent PCS after mTBI.(40) The second study, titled “A Pilot Phase II Study of Hyperbaric Oxygen for Persistent Post-concussive Symptoms After Mild Traumatic Brain Injury (HOPPS),” was completed in 2012.(41) The three outcomes assessed in the pooled analyses of the two studies were symptoms, cognitive impairment, and functional impairment; they were weighted and grouped into different domains to calculate the composite outcome score. A total of 143 service members were randomized to receive either HBOT (1.5 ATA, > 99% oxygen) or sham therapy (1.2 ATA, room air). In HOPPS, composite total scores improved from baseline for HBOT (mean,  $-2.9 \pm 9.0$ ) and sham treatment ( $-2.9 \pm 6.6$ ), but the groups did not differ significantly from each other ( $p = .33$ ). The BIMA trials results showed a greater improvement from baseline in the HBOT group ( $-3.6 \pm 6.4$ ) versus sham ( $-0.3 \pm 5.2$ ;  $p = .02$ ). The authors concluded that composite total scores in HOPPS and BIMA were consistent with primary study results.

### **Section Summary: Systemic HBOT for Traumatic Brain Injury**

A number of RCTs and systematic reviews have been published. Pooled analyses were only conducted on a minority of the published RCTs, and these analyses had mixed findings. Additionally, there was overlap in RCTs included in the reviews. There is a lack of consistent evidence from well-conducted trials that HBOT improves the health outcome for patients with TBI.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR INFLAMMATORY BOWEL DISEASE**

A systematic review by McCurdy et al (2022) examined the evidence on HBOT for a range of IBD phenotypes (Crohn disease, ulcerative colitis; see Table 15).(36) The review was not limited by study design, and included 3 small RCTs (N=40) (43,44,45) and 16 case series. All 3 of the RCTs were conducted in patients with ulcerative colitis. The included case series generally enrolled less than 30 patients each, with the exception of one study, conducted in Russia, that enrolled 519 patients. Overall, a total sample size for the systematic review across phenotypes was 844. Pooled response rates are reported in Table 15. Results from the individual RCTs were mixed. Two RCTs found a benefit for HBOT compared with standard medical care, but they were small studies ( $n=10$  and  $20$ ) and were likely underpowered to detect between-group differences. In addition, one of the trials only included prior HBOT responders (44) and one (43) was stopped early due to enrollment difficulties. The third RCT found no benefit of HBOT compared with standard care, and was also stopped early due to futility. (45) Quality assessment of the included studies judged 2 of the 3 included RCTs to be at high risk of bias. Study authors concluded that although HBOT was associated with high response rates across phenotypes, high-quality evidence was very limited, and well-designed RCTs are needed to confirm the effect of HBOT in patients with IBD.

**Table 15. Systematic Reviews of Studies Assessing HBOT for Inflammatory Bowel Disease**

| Study (Year)         | Literature Search | Studies | Participants                         | N  | Design                   | Results   |
|----------------------|-------------------|---------|--------------------------------------|--|--------------------------|---|
| McCurdy et al (2022) | Nov 2020          | 19      | Patients with various IBD phenotypes | <ul style="list-style-type: none"> <li>Ulcerative colitis (<math>n=383</math>);</li> <li>Crohn disease (<math>n=250</math>)</li> <li>Perianal fistula (<math>n=118</math>)</li> <li>Enterocutaneous fistula (<math>n=21</math>)</li> </ul> | 3 RCTs<br>16 case series | Ulcerative colitis (5 studies): 86% (66% to 95%)<br>Crohn disease (2 studies): 86% (81% to 90%)<br>Perianal fistula (10 studies): |

|   |   |
|---|---|
| <ul style="list-style-type: none"> <li>• Inflammatory pouch disorders (n=60)</li> <li>• Dermatologic manifestation of IBD (n=12)</li> </ul> | 75% (66% to 83%)<br>Pouch disorder (2 studies): 65% (52% to 76%)<br>Enterocutaneous fistula (3 studies): 85% (61% to 95%) |
|---|---|

CI: confidence interval; HBOT: hyperbaric oxygen therapy; IBD: inflammatory bowel disease; RCT: randomized controlled trial.

### **Section Summary: Systemic HBOT for Inflammatory Bowel Disease**

Three RCTs have reported mixed findings in patients with ulcerative colitis. A systematic review of RCTs and observational studies found high rates of bias in the literature (e.g., attrition, reporting bias).

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS**

### **Systematic Reviews**

A Cochrane review by Bennett et al (2012) on HBOT for idiopathic sudden sensorineural hearing loss (ISSNHL) and/or tinnitus identified seven RCTs (N=392; see Table 16).(46) Randomization procedures were only described in 1 study, and only 1 study stated they blinded participants to treatment group assignment using sham therapy. Six studies included time-based entry criteria for hearing loss and/or tinnitus (48 hours in 3 studies, 2 weeks in 2 studies, 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 ranged from 10 to 25). All trials reported the change in hearing following treatment, but specific outcomes varied. Two trials reported the proportion of participants with more than 50% and more than 25% 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 the control groups at the level of 50% or higher but did find a significantly higher rate of improvement at the level of 25% or higher (see Table 16). A pooled analysis of four trials found a significantly greater mean improvement in hearing over all frequencies with HBOT compared with control. Reviewers 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 the use of HBOT for treating ISSNHL.

Rhee et al (2018) performed a systematic review and meta-analysis through February 2018 for patients comparing HBO plus medical therapy (MT) with MT alone for SSNHL treatment.(47) Randomized clinical trials and nonrandomized studies were included. The main outcomes considered were complete hearing recovery, any hearing recovery, and absolute hearing gain. Nineteen studies (3 randomized and 16 nonrandomized) with a total of 2401 patients (mean age, 45.4 years; 55.3% female) were included. In the HBOT+MT group, rates of complete hearing recovery and any hearing recovery were 264/897 (29.4%) and 621/919 (67.6%), respectively, and in the MT alone group were 241/1167 (20.7%) and 585/1194 (49.0%), respectively. Pooled HBOT+MT also showed favorable pooled results from random-effects models for both complete hearing recovery (OR, 1.61; 95% CI, 1.05-2.44) and any hearing recovery (OR, 1.43; 95% CI, 1.20-1.67). The study was limited by the following: (1) differences in clinical and methodological characteristics of selected studies, (2) considerable

heterogeneity, (3) the possibility of measured or unmeasured confounder effects, and (4) difficulty in evaluating the benefit of treatment due to a substantial proportion of patients experiencing spontaneous recovery.

A third systematic review, conducted by Joshua et al (2021) (49) included 3 RCTs comparing HBOT with medical treatment, all published in 2018 and none of which were included in either the Bennett or Rhee systematic reviews. Inclusion criteria for studies in the Joshua review differed from the previous reviews in that: 1) only randomized studies were included and 2) diagnosis of ISSNHL was based on American Academy of Otolaryngology Head and Neck Surgery criteria. In addition, the literature search was limited to studies published beginning in January 2020. HBOT interventions were 60 or 90 minutes in duration, for time periods ranging from 10 to 20 days and medical treatment included a use of steroids (oral and/or intravenous) alone or in combination with antiviral medications and/or hemorheologic therapy. The patients included in the studies were clinically heterogenous, with baseline hearing loss ranging from moderate to profound in 2 studies and was unreported in the third study. The proportion of patients with hearing recovery, based on a  $\geq 10$  point audiometric gain, was significantly higher with HBOT compared with control based on pooled analysis of 2 studies (OR, 4.32; 95% CI, 1.60 to 11.68;  $I^2=0\%$ ). Limitations of these results include the fact that the included studies were judged to have moderate (2 studies) and high (1 study) risk of bias and the small number of participants in both HBOT (n=88) and medical treatment (n=62) groups.

**Table 16. Systematic Reviews and Meta-Analyses of Trials Assessing HBOT for Idiopathic Sudden Sensorineural Hearing Loss**

| Study (Year)                      | Literature Search | Studies | Participants                                   | N    | Design              | Results   |
|-----------------------------------|-------------------|---------|--|------|---------------------|---|
| Bennett (2012) <sup>46</sup>      | May 2012          | 7       | Patients with idiopathic SSNHL and/or tinnitus | 392  | RCTs                | <ul style="list-style-type: none"> <li>• Pooled analyses of 2 RCTs (n=114) showed HBOT did not result in &gt;50% improvement in pure tone average threshold (RR=1.5; 95% CI, 0.9 to 2.8), but was able to achieve &gt;25% improvement (RR=1.4; 95% CI, 1.1 to 1.8)</li> <li>• Pooled analyses of 4 trials (n=169) found a significantly greater mean improvement in hearing over all frequencies with HBOT vs control (mean difference, 15.6 dB; 95% CI, 1.5 to 29.8 dB)</li> </ul> |
| Rhee (2018) <sup>47</sup>         | Feb 2018          | 19      | Patients with SSNHL                            | 2401 | 3 RCTs, 16 non RCTs | <ul style="list-style-type: none"> <li>• Pooled results significantly favored the HBOT and MT group over MT alone group for complete hearing recovery (pooled OR: 1.61; CI: 1.05-2.44) and for hearing recovery (pooled OR: 1.43, CI: 1.20-1.67)</li> </ul>   |
| Joshua et al (2021) <sup>49</sup> | Apr 2020          | 3       | Patients with SSNHL                            | 150  | 3 RCTs              | <ul style="list-style-type: none"> <li>• Pooled results from 2 RCTs favored HBOT over MT for hearing recovery, defined as <math>\geq 10</math> point audiometric gain (OR 4.32, 95% CI 1.60 to 11.68)</li> </ul>  |

CI: confidence interval; HBOT: hyperbaric oxygen therapy; MT: medical therapy; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SSNHL: sudden sensorineural hearing loss.

In their qualitative systematic review, Eryigit et al (2018) assessed the effectiveness of HBOT to treat patients with ISSNHL.(48) Sixteen clinical trials were included, with a total of 1759

operative ears, 580 of which received HBOT. All patients also received steroid treatment—either systemic, intravenous, or intratympanic injection. Most studies found that patients with severe or profound hearing loss who received steroids (any route of administration) plus HBOT saw statistically significant improvements (specified *p*-value range across studies: 0.0014–0.012), whereas those with a lower level of hearing loss did not see these improvements. Several studies reported no significant difference between case and control groups, but the studies that broke down the results by levels of hearing loss all showed that profound (or severe and profound) loss benefited from the addition of HBOT to steroid treatment.

## Randomized Controlled Trials

A 2022 RCT conducted by Cavaliere et al published subsequent to the systematic reviews described above compared HBOT and oral steroids, alone and in combination, in 171 adults with ISSNHL. (58) Study characteristics are summarized in Table 17.

**Table 17. Characteristics of Trials Assessing HBOT for ISSNHL**

| Study (Year)           | Countries | Sites         | Dates             | Participants   | Interventions   |  |                             |
|------------------------|-----------|---------------|-------------------|--|---|--|-----------------------------|
|                        |           |               |                   |  | HBOT (n=60)   | Oral Steroids (n=55)   | HBOT + Oral Steroids (n=56) |
| Cavaliere et al (2022) | Italy     | Single-center | Feb 2016–Dec 2019 | Adults with unilateral and/or bilateral ISSNHL onset within the last 30 days, unknown cause of hearing loss, and normal Eustachian tube function | HBOT 2.5 ATA; 90 min per session for 10 sessions total over 15 days | Oral prednisone 1 mg/kg per day (maximum dose of 60 mg/day) for 12-14 consecutive days | HBOT + oral prednisone      |

Abbreviations: ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; ISSNHL: idiopathic sudden sensorineural hearing loss.

Pure tone audiometry (PTA) testing was conducted at baseline and 20 days after treatment. ISSNHL was characterized at baseline as upsloping (hearing loss affecting 250 to 500 herz [Hz] more), flat (<20 decibel [dB] difference between the highest and lowest pure tone average threshold), downsloping (hearing loss affecting 4000 and 8000 Hz more) or profound (thresholds of ≥90 dB in each test frequency) at baseline. In the study, total or partial hearing recovery was based on change in PTA test results at follow-up, but the magnitude of change that constituted either total or partial recovery was not clearly defined. The study reported that all patients, regardless of intervention group, had a statistically significant improvement in mean PTA scores from baseline, and that HBOT alone or combination therapy with HBOT plus steroids resulted in greater recovery relative to steroid use alone. Other outcomes, including harms of treatment, were not reported.

The purpose of the study limitations tables (see Tables 18 and 19) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

**Table 18. Study Relevance Limitations of Trials Assessing HBOT for ISSNHL**

| Study                     | Population <sup>a</sup> | Intervention <sup>b</sup> | Comparator <sup>c</sup>   | Outcomes <sup>d</sup>  | Duration of Follow-up <sup>e</sup>   |
|---------------------------|-------------------------|---------------------------|---|--|--|
| Cavaliere et al<br>(2022) |                         |                           | 5. Lack of untreated control group (up to 65% of individuals with ISSNHL spontaneously recover) | 1,3,5. Outcomes limited to measures of auditory function; only narrative description of no complications (no harms data); no prespecified description of clinically significant difference | 1, 2. Duration of follow-up (20 days) insufficient to assess benefit and harms |
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Abbreviations: HBOT: hyperbaric oxygen therapy; ISSNHL: idiopathic sudden sensorineural hearing loss.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 19. Study Design and Conduct Limitations of Trials Assessing HBOT for ISSNHL**

| Study                     | Allocation <sup>a</sup> | Blinding <sup>b</sup>  | Selective Reporting <sup>c</sup> | Data Completeness <sup>d</sup> | Power <sup>e</sup>                 | Statistical <sup>f</sup> |
|---------------------------|-------------------------|--|----------------------------------|--------------------------------|------------------------------------|--------------------------|
| Cavaliere et al<br>(2022) | 5.                      | 1, 2. No description of blinding of study participants, staff or outcome assessors | 4. Study registration is unclear |                                | 1. Power calculations not reported |                          |
|                           |                         |  |                                  |                                |                                    |                          |
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|  | differences     |  |  |  |  |  |
|  | between         |  |  |  |  |  |
|  | treatment       |  |  |  |  |  |
|  | groups for age  |  |  |  |  |  |
|  | and magnitude   |  |  |  |  |  |
|  | of hearing loss |  |  |  |  |  |
|  | (the HBOT +     |  |  |  |  |  |
|  | steroid group   |  |  |  |  |  |
|  | was younger     |  |  |  |  |  |
|  | and had less    |  |  |  |  |  |
|  | hearing loss)   |  |  |  |  |  |

### **Section Summary: Systemic HBOT for Idiopathic Sudden Sensorineural Hearing Loss**

A Cochrane review of RCTs had mixed findings from studies that included individuals with tinnitus. Some outcomes (i.e., improvement in hearing of all frequencies, >25% return of hearing) were better with HBOT than with a control intervention, but more than 50% return of hearing did not differ significantly between groups. There was important variability in the patients enrolled in the studies. A subsequent systematic review had similarly limited conclusions due to the inclusion of non-randomized studies. A third review that had stricter inclusion criteria found HBOT increased the rate of hearing recovery, but the analysis was limited to 2 trials with methodological limitations. One RCT published subsequent to the systematic reviews found a positive effect of HBOT plus steroid combination therapy on measures of auditory function compared to either HBOT or steroids alone, but other outcomes were not reported and the study had numerous relevance, design, and conduct limitations.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR DELAYED-ONSET MUSCLE SORENESS**

In a Cochrane review Bennett et al (2005, updated 2010), identified nine small RCTs on HBOT for delayed-onset muscle soreness and closed soft tissue injury (see Table 20). (50) Included trials were published between 1996 and 2003. Methodologic quality was assessed as fair to high. Pooled analysis showed significantly higher pain in the group receiving HBOT compared with control. There were no between-group differences in long-term pain outcomes or other measures (e.g., swelling, muscle strength).

**Table 20. Systematic Reviews of Trials Assessing HBOT for DOMS**

| Study (Year)                       | Literature Search | Studies | Participants  | N   | Design | Results  |
|------------------------------------|-------------------|---------|---|-----|--------|--|
| Bennett et al (2010) <sup>50</sup> | Feb 2010          | 9       | Patients with acute closed soft tissue injuries or DOMS | 219 | RCTs   | <ul style="list-style-type: none"> <li>• 2 trials on closed soft tissue injuries: no significant difference in time to recovery, functional outcomes, or pain</li> <li>• 7 DOMS trials, pooled: significantly higher pain at 48 and 72 h in HBOT group, 0.9 (95% CI, 0.09 to 1.7); no differences in long-term pain, swelling, or muscle strength</li> </ul> |

CI: confidence interval; DOMS: delayed-onset muscle soreness; HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial.

### **Section Summary: Systemic HBOT for Delayed-Onset Muscle Soreness**



A Cochrane review of RCTs with fair to high methodologic quality found worse short-term pain outcomes with HBOT than with a control condition and no difference in longer term pain or other outcomes (e.g., swelling).

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR AUTISM SPECTRUM DISORDER**

A Cochrane review by Xiong et al (2016) identified 1 RCT evaluating systemic HBOT for people with autism spectrum disorder that met eligibility criteria.(51) Criteria included a hyperbaric oxygen intervention using 100% oxygen at more than 1 atm. The trial, published by Sampanthaviat (2012), was considered low-quality evidence as assessed by the GRADE approach. The trial randomized children with autism to receive 20 one-hour sessions with HBOT or sham air (n=30 per group).(52) The primary outcome measures were change in Autism Treatment Evaluation Checklist and Clinical Global Impression scores, evaluated separately by clinicians and parents. There were no statistically significant differences between groups for either primary outcome. Posttreatment clinician-assessed mean scores on Autism Treatment Evaluation Checklist were 52.4 in the HBOT group and 52.9 in the sham air group.

In their controlled trial, Rizzato et al (2018) examined the effect of HBOT on children diagnosed with autism. (59) The children in the HBOT group (n=8; mean age=7 y  $\pm$  2.33 y) and control group (n=7; mean age=6.6 y  $\pm$  2.7 y) completed the Aberrant Behavior Checklist-Community (ABC) before intervention (T0), after 40 sessions (1), and 1 months after the end of treatment (T2). The HBOT was also assessed with the Childhood Autism Rating Scale at T0 and T2. Total ABC scores had improved between T0 and T2 in both the intervention and control groups. The HBOT group mean score at T0 was 57.5  $\pm$  19.01 and 50.38  $\pm$  18.55 at T2 (p<.001). The control group's mean score at T0 was 103.6  $\pm$  20.38 and 59  $\pm$  25.25 at T2 (p <.05). The investigators concluded that their results do not support the use of HBOT in children diagnosed with autism.

A systematic review by Ghanizadeh (2012) (84) found conflicting results when reviewing 2 randomized controlled trials with a total of 89 participants with autistic disorder. (85) (86) The first study from the United States (85) included children 2 to 14 years of age. Sixteen children received HBOT with 1.3 atmospheres absolute (ATA) and 24% to 28% oxygen while 18 children received control treatment consisting of free airflow through the chamber at ambient pressure for 80 sessions of 1 hour each. Following completion of treatment and placebo conditions, all children were rated on the Social Responsiveness Scale. Analysis of data comparing scores on the Social Responsiveness Scale for both conditions found no significant difference between groups in social awareness, social cognition, social communication, or social motivation (all P values of > .05). Consistently, no significant differences were found based on direct observations or ratings of communication, socialization, and total scores on the Autism Diagnostic Observation Schedule—Generic tool. Overall, the authors concluded that HBO therapy with 24% oxygen at 1.3 ATA did not treat the children with autism.

Lerman et al (2008) evaluated the efficacy of HBOT in the treatment of 3 children aged 6 to 7 diagnosed with autism who were also receiving intensive behavioral intervention. (87) Following 40 1-hour sessions of HBOT (1.3 ATA with 88% [ $\pm$  3 %] oxygen), only 1 child experienced improvement in task engagement and spontaneous communication, while 2 children experienced minimal change from baseline performance. Although all of the participants demonstrated a gradual decrease in problem behavior, there was no demonstrable improvement noted for HBOT as compared with behavior therapy. A similar lack of compelling evidence was also noted in an open-label study evaluating 16 children with ASD

aged 3 to 10 throughout 40 HBOT sessions at 24% oxygen and 1.3 ATA. Quantity of adaptive behavior, stereotypy, and aberrant behavior were charted graphically from baseline through completion of HBOT for each participant. Based on visual inspection of the level, trend, and variability of graphed data, the researchers concluded that no marked improvement was demonstrated in any of the types of behavior after treatment with HBOT.

**Section Summary: Systemic HBOT for Autism Spectrum Disorder**

A Cochrane review identified a single small low-quality RCT on HBOT for autism spectrum disorder and that trial did not find did not find significantly improved outcomes with HBOT vs sham. A subsequent controlled trial reached the same conclusion, stating results do not support the use of HBOT for autism spectrum disorder. Other literature has suggested that there is insufficient evidence to support use of HBOT to treat children with ASD, and its use as a form of treatment is not recommended.

**SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR CEREBRAL PALSY**

Two published RCTs were identified on use of HBOT for cerebral palsy (see Tables 21 and 22). Lacey et al (2012) published a double-blind RCT that included 49 children ages three to eight years with spastic cerebral palsy.(54) Participants were randomized to 40 treatments with HBOT or hyperbaric air to simulate 21% oxygen at room air. The primary efficacy outcome was change in the Gross Motor Function Measure (GMFM-88) global. The trial 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.

Collet et al (2011) randomized 111 children with cerebral palsy to 40 treatments over a two-month period of either HBOT or slightly pressurized room air.(58) Investigators found similar improvements in outcomes such as gross motor function and activities of daily living in both treatment groups.

An observational study by Long et al (2017) evaluated the effects of HBOT as a treatment for sleep disorders in children with cerebral palsy (N=71).(55) Children, aged two to six years, underwent 60-minute sessions of 100% oxygen, at 1.6 ATA, for 15 to 20 sessions total. Results showed improvements in average time to fall asleep, average hours of sleep duration, and an average number of night awakenings after ten HBOT sessions compared with pretreatment.

**Table 21. Characteristics of Trials Assessing HBOT for Cerebral Palsy**

| Study (Year)                        | Countries     | Sites | Dates     | Participants                        | Treatment  |  |
|-------------------------------------|---------------|-------|-----------|-------------------------------------|--|--|
|                                     |               |       |           |                                     | Active   | Comparator   |
| Lacey et al (2012) <sup>54</sup> .  | United States | 2     | 2005-2009 | Children aged 3-8 y with spastic CP | <ul style="list-style-type: none"> <li>• n=25</li> <li>• Hyperbaric oxygen</li> <li>• 100% oxygen at 1.5 ATA</li> <li>• 40 times over 2 mo</li> </ul>  | <ul style="list-style-type: none"> <li>• n=24</li> <li>• Hyperbaric air</li> <li>• 14% oxygen at 1.5 ATA</li> <li>• 40 times over 2 mo</li> </ul>            |
| Collet et al (2001) <sup>55</sup> . | Canada        | 17    | NR        | Children aged 3-2 y with CP         | <ul style="list-style-type: none"> <li>• n=57</li> <li>• Hyperbaric oxygen</li> <li>• 100% oxygen at 1.75 ATA</li> <li>• 40 times over 2 mo</li> </ul> | <ul style="list-style-type: none"> <li>• n=54</li> <li>• Slightly pressurized air</li> <li>• 100% oxygen at 1.3 ATA</li> <li>• 40 times over 2 mo</li> </ul> |

ATA: atmospheres absolute; CP: cerebral palsy; HBOT: hyperbaric oxygen therapy; NR: not reported.



**Table 22. Results of Trials Assessing HBOT for Cerebral Palsy**

| Study (Year)                      | Mean Change<br>GMFM <sup>a</sup> (95% CI) | Between-<br>Group Difference<br>(95% CI) | Mean Change,<br>Functional Skill | Between-Group<br>Difference<br>(95% CI) |
|-----------------------------------|---|--|----------------------------------|---|
| Lacey et al(2012) <sup>54</sup>   | 46  |  | 46                               |   |
| HBOT                              | 1.5 (-0.3 to 3.3)                         | 0.9 (-1.5 to 3.3)                        | 4.4 (2.3 to 6.5)                 | 1.1 (-1.5 to 3.7)                       |
| HBAT                              | 0.6 (-1.0 to 2.2)                         |  | 3.3 (1.6 to 5.0)                 |   |
| Collet et al (2001) <sup>55</sup> |   |  | Mean Change,<br>PEDI Self Care   |   |
| HBOT                              | 2.9 (1.9 to 3.9)                          | -0.4 (-1.7 to 0.9)                       | 2.8 (1.6 to 4.0)                 | 0.1 (-1.8 to 2.0)                       |
| Slight pressure                   | 3.0 (2.1 to 3.9)                          |  | 2.7 (1.3 to 4.0)                 |   |

CI: confidence interval; GMFM: Gross Motor Function Measure; HBAT: hyperbaric air therapy; HBOT: hyperbaric oxygen therapy; PEDI: Pediatric Evaluation of Disability Inventory.

<sup>a</sup> Positive score represents improvement in function from baseline.

### **Section Summary: Systemic HBOT Cerebral Palsy**

Two RCTs and an observational study were identified. One RCT was stopped early due to futility and the other did not find significantly better outcomes with HBOT than with a sham intervention. The observational study, which focused on improving sleep in patients with cerebral palsy, reported improvements following HBOT.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR VASCULAR DEMENTIA**

A Cochrane review (2012) identified a small RCT evaluating HBOT for vascular dementia (see Table 23).<sup>(57)</sup> This 2009 RCT, conducted in China compared HBOT (30-day cycles of one hour/day for 24 days and six days of rest) plus donepezil to donepezil-only in 64 patients. The HBOT plus donepezil group had significantly better cognitive function after 12 weeks of treatment, though the confidence intervals were wide due to the small sample size. Reviewers judged the trial to be of poor quality because it was not blinded, and the methods of randomization and allocation concealment were not discussed.

**Table 23. Systematic Reviews of Trials Assessing HBOT for Vascular Dementia**

| Study (Year)                    | Literature Search | Studies | Participants   | N  | Design | Results   |
|---------------------------------|-------------------|---------|--|----|--------|---|
| Xiao et al (2012) <sup>57</sup> | Dec 2011          | 1       | Patients with vascular dementia, according to DSM- IV criteria | 64 | RCT    | <ul style="list-style-type: none"> <li>• WMD of MMSE score: 3.5 (95% CI, 0.9 to 6.1)</li> <li>• WMD of HDS score: 3.1 (95% CI, 1.2 to 5.0)</li> </ul> |

CI: confidence interval; DSM-IV: Diagnostic and Statistical Manual for Mental Disorders Fourth Edition; HBOT: hyperbaric oxygen therapy; HDS: Hasegawa's Dementia Rating Scale; MMSE: Mini-Mental State Examination; RCT: randomized controlled trial; WMD: weighted mean difference.

### **Section Summary: Systemic HBOT for Vascular Dementia**

A Cochrane review identified an RCT judged to be of poor quality. This trial provided insufficient evidence to permit conclusions on the impact of HBOT on health outcomes in patients with vascular dementia.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR RADIOTHERAPY ADVERSE EVENTS**

This indication covers adverse events of radiotherapy other than osteoradionecrosis and treatment of irradiated jaw, which was covered in an earlier indication.

## Systemic Reviews

Ravi et al (2017) conducted a systematic review assessing the effect of HBOT on patients with head and neck cancer who had received radiotherapy (see Table 24). (13) Pooled analyses were not performed; however, summary results were discussed for the following outcomes: salivary gland function, osteonecrosis prevention, dental implant survival, and QOL.

Osteonecrosis prevention and dental implant survival outcomes were discussed in the earlier (see the Radionecrosis, Osteoradionecrosis, and Treatment of Irradiated Jaw section).

Villeirs et al (2020) conducted a systematic review on the effect of HBOT on cystitis following pelvic radiotherapy.(83) The review included 20 studies, only one of which was an RCT; the remaining studies were cohort studies. The number of HBOT sessions ranged widely from 1 to 179 (mean or median number of sessions was not reported). The review broadly assessed cystitis response across studies, generally based on the absence of hematuria. Complete response was achieved in a weighted mean of 63.6% of patients receiving HBOT (range 20% to 100%) while 35.2% of patients showed no response. In 11 studies reporting follow-up greater than 1 year, recurrence ranged from 0% to 40.7%. Other pooled outcomes were not reported.

**Table 24. Systematic Reviews of Studies Assessing HBOT for Radiotherapy Adverse Events**

| Study (Year)                         | Literature Search | Studies | Participants   | N   | Design  | Results  |
|--------------------------------------|-------------------|---------|--|-----|---|--|
| Ravi et al (2017) <sup>13</sup> .    | Dec 2016          | 10      | Patients who have received RT for head and neck cancer | 375 | Prospective case series and prospective comparative studies | <ul style="list-style-type: none"> <li>Salivary gland function: two case series (n=96) reported that patients receiving HBOT experienced improvements in salivary flow rates</li> <li>Quality of life: three case series (n=106) administered various QOL instruments (e.g., SF-36, EORTC, HADS), reporting that many subsets of the questionnaires (e.g., swallowing, pain, salivary quantity) showed significant improvements with HBOT</li> </ul> |
| Villeirs et al(2020) <sup>83</sup> , | May 2018          | 20      | Patients with RT-induced cystitis                      | 815 | RCTs, cohort studies and case series                        | <ul style="list-style-type: none"> <li>Based on evidence from 18 studies, HBOT was associated with 63.6% (range 20% to 100%) of patients achieving complete cystitis response; 35.2% of patients had no response to HBOT.</li> </ul>   |

EORTC: European Organization for Research and Treatment of Cancer; HADS: Hospital Anxiety and Depression Scale; HBOT: hyperbaric oxygen therapy; QOL: quality of life; RT: radiotherapy; SF-36: 36-Item Short-Form Health Survey.

## Randomized Controlled Trials

Trials not included in one of the systematic reviews are described below.

Gothard et al (2010) in the U.K. published findings of an RCT using HBOT for arm lymphedema occurring after radiotherapy for cancer.(61) Fifty-eight patients with arm lymphedema (at least a 15% increase in arm volume) following cancer treatment were randomized in a 2:1 ratio to HBOT (n=38) or usual care without HBOT (n=20). Fifty-three patients had baseline assessments, and 46 (79%) of 58 had 12-month assessments. At the 12-month follow-up, there was no statistically significant difference in the change from baseline in arm volume. 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. By this definition, 9 (30%) of 30 patients in the HBOT group were considered responders compared with 3 (19%) of 16 in the control group (p=NS). Other outcomes (e.g., QOL scores on the 36-Item Short-Form Health Survey [SF-36]) also did not differ significantly between groups.

A phase 2/3 RCT by Oscarsson et al (2019) not included in the Villiers systematic review assessed HBOT for late radiation-induced cystitis in adult cancer patients who had received pelvic radiotherapy.(62) Eighty-seven patients were randomized to either HBOT (n=42) or standard care (n=45). Eight patients withdrew consent directly after randomization, so 79 were included in the intention-to-treat analysis. The primary outcome was change in the urinary domain of the Expanded Prostate Index Composite Score, which is a patient-reported outcome measurement tool with 12 questions covering a range of urinary tract symptoms; each answer is given on a Likert scale, and the totals are calculated to a 0–100 score. A post hoc analysis determined the minimal clinically important difference to be nine points. Patients were required to have a baseline score of less than 80 to participate in the study. Patients in the HBOT group received 30–40 treatments within 60–80 days. No study-specific treatment was administered to the standard care group. The trial included four visits, and at the fourth visit, the mean Expanded Prostate Index Composite urinary total score in the HBOT group had increased by 17.8 points (SD=18.4), whereas the standard care group increased by 7.7 points (SD=15.5). The difference between the group means in the analysis was 10.1 points (95% CI: 2.2 to 18.1; p=.013). Possible confounding factors that could have influenced the total score were invasive surgery, body mass index, sex, age, and time from radiotherapy to inclusion. A secondary outcome was change in SF-36 total and domain scores. No significant differences in SF-36 scores were seen either from baseline or between groups, with the exception of the domain of “General Health,” which showed a significant improvement for the HBOT group (p=.0012).

### ***Section Summary: Systemic HBOT for Radiotherapy Adverse Effects***

Two systematic reviews few RCTs and provide limited evidence evaluating HBOT for radiotherapy adverse events. One review focused on salivary gland function, osteonecrosis prevention, dental implant survival, and QOL. An RCT not included in the reviews focused on arm lymphedema; it found no significant differences between study groups. Another RCT assessed HBOT for radiation-induced cystitis and found significant benefit by some measures but not others.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR IDIOPATHIC FEMORAL NECK NECROSIS**

A double-blind RCT evaluating HBOT for the treatment of femoral head necrosis was published in 2010 by Camporesi et al (see Tables 25 and 26).(63) The trial included 20 adults with idiopathic unilateral femoral head necrosis. Patients received HBOT or a sham treatment of hyperbaric air. The mean severity of pain on a 0-to-10 scale was significantly lower in the HBOT group than in the control group after 30 sessions (p<0.001) but not after 10 or 20

sessions. The trial did not report exact pain scores. Several range-of-motion outcomes were reported. At the end of the initial treatment period, extension, abduction, and adduction, but not flexion, was significantly greater in the HBOT group than in the control group. Longer-term comparative data were not available because the control group was offered HBOT after the initial six-week treatment period.

**Table 25. Characteristics of Trials Assessing HBOT for Femoral Neck Necrosis**

| Study (Year)                          | Countries     | Sites | Dates | Participants                                   | Treatment  |  |
|---------------------------------------|---------------|-------|-------|--|--|--|
|                                       |               |       |       |  | Active (n=10)  | Comparator (n=10)  |
| Camporesi et al(2010) <sup>63</sup> . | United States | 1     | NR    | Patients with unilateral femoral neck necrosis | <ul style="list-style-type: none"> <li>• HBOT</li> <li>• 100% oxygen at 2.5 ATA</li> <li>• 30 sessions over 6 wks</li> </ul> | <ul style="list-style-type: none"> <li>• Hyperbaric air</li> <li>• 30 sessions over 6 wks</li> </ul> |

ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; NR: not reported.

**Table 26. Results of Trials Assessing HBOT for Femoral Neck Necrosis**

| Study (Year)                           | Median (Range) Extension, After 10 Sessions | Between-Group Difference P Value | Median (Range) Extension, After 30 Sessions | Between-Group Difference P Value |
|--|---|----------------------------------|---|----------------------------------|
| Camporesi et al (2010) <sup>63</sup> . |   |                                  |   |                                  |
| HBOT                                   | 7.5 (4.0-20.0)                              | NS                               | 20.0 (15.0-20.0)                            | <0.001                           |
| HBAT                                   | 4.0 (3.0-6.0)                               |                                  | 3.0 (0.0-5.0)                               |                                  |

HBAT: hyperbaric air therapy; HBOT: hyperbaric oxygen therapy; NS: not significant.

### **Section Summary: Systemic HBOT for Idiopathic Femoral Neck Necrosis**

One small RCT (n=20) was identified. Six-week outcomes and results were mixed, with improvements reported in extension, abduction, and adduction, but not flexion. Significant improvements in pain were reported after 30 sessions, though no differences were detected after 10 or 20 sessions. This RCT does not provide sufficient data to permit conclusions about the efficacy of HBOT for femoral head necrosis.

## **SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR MIGRAINE HEADACHE**

A Cochrane review by Bennett et al (2015) 11 RCTs (total n=209) comparing the effectiveness of systemic HBOT for preventing or treating migraine headache or cluster headaches with another treatment or a sham control (see Table 27).<sup>(64)</sup> A pooled analysis of three trials focusing on migraine headaches (n=58) found a statistically significant increase in the proportion of patients with substantial relief of migraine within 45 minutes of HBOT. No other pooled analyses were conducted due to variability in outcomes reported across trials. The meta-analysis did not report data on treatment effectiveness beyond the immediate post-treatment period, and the methodologic quality of selected trials was moderate to low (e.g., randomization was not well-described in any trial).

**Table 27. Systematic Reviews of Trials Assessing HBOT for Migraine or Cluster Headaches**

| Study (Year)                       | Literature Search | Studies | Participants                                | N   | Design | Results   |
|------------------------------------|-------------------|---------|---|-----|--------|---|
| Bennett et al (2015) <sup>64</sup> | Jun 2015          | 11      | Patients with migraine or cluster headaches | 209 | RCT    | <ul style="list-style-type: none"> <li>For 3 trials focusing on migraine headaches (n=58) of low quality, HBOT was effective in relieving migraine (RR=6.21; 95% CI, 2.4 to 16.0)</li> <li>No evidence that HBOT can prevent migraine, reduce nausea or vomiting, or reduce the need for rescue medication</li> </ul> |

CI: confidence interval; HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial; RR: relative risk.

### Section Summary: Systemic HBOT for Migraine

A Cochrane review identified 11 RCTs on HBOT for migraine headache. However, only a single pooled analysis was conducted including 3 of the 11 trials. The pooled analysis found significantly greater relief of migraine symptoms with HBOT than with a comparator intervention within 45 minutes of treatment. Limitations included availability of outcomes specific to the immediate posttreatment period, the variability of outcomes across trials, and generally low methodologic quality of trials.

## SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR HERPES ZOSTER

Peng et al (2012) in China published an RCT evaluating HBOT for herpes zoster (see Table 28 and 29).<sup>(65)</sup> Sixty-eight patients with herpes were randomized to HBOT with medication or medication treatment alone. The following outcomes were measured after three weeks of treatment: therapeutic efficacy, days to blister resolution, days to scar formation, and pain. Patients receiving HBOT experienced significantly improved outcomes compared with patients receiving medication alone. Limitations of the trial included a lack of blinding and long-term follow-up.

**Table 28. Characteristics of Trials Assessing HBOT for Herpes Zoster**

| Study (Year)                    | Countries | Sites | Dates     | Participants                                      | Treatment   |   |
|---------------------------------|-----------|-------|-----------|---|---|---|
|                                 |           |       |           |   | Active (n=36)   | Comparator (n=32)   |
| Peng et al (2012) <sup>65</sup> | China     | NR    | 2008-2010 | Patients diagnosed with herpes zoster within 2 wk | <ul style="list-style-type: none"> <li>HBOT</li> <li>100% oxygen at 2.2 ATA</li> <li>2 sessions/day for 5 d</li> <li>Thirty 120-min sessions; plus medications that the control group received</li> </ul> | Medication alone, including: antiviral, nerve nutritive, pain relief, and antidepressives |

ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; NR: not reported.

**Table 29. Results of Trials Assessing HBOT for Herpes Zoster**

| Study (Year)                    | Efficacy <sup>a,b</sup> | Mean Days to Blister Resolution <sup>b</sup> | Mean Days to Scar Formation <sup>b</sup> | NPRS Score <sup>b</sup> |               |
|---------------------------------|-------------------------|--|--|-------------------------|---------------|
|                                 |                         |  |  | Pretreatment            | Posttreatment |
| Peng et al (2012) <sup>65</sup> | 68                      | 68   | 68                                       | 68                      | 68            |
| Mean HBOT and medication (SD)   | 97.2%                   | 2.8 (1.5)                                    | 11.1 (4.0)                               | 8.0 (1.8)               | 1.8 (2.7)     |

|                            |       |           |            |           |           |
|----------------------------|-------|-----------|------------|-----------|-----------|
| Mean medication alone (SD) | 81.3% | 3.3 (1.4) | 13.9 (4.3) | 8.1 (1.7) | 3.5 (4.1) |
|----------------------------|-------|-----------|------------|-----------|-----------|

HBOT: hyperbaric oxygen therapy; NPRS: Numeric Pain Rating Scale; SD: standard deviation.

<sup>a</sup> Calculation: (number cases with healing + number cases with improvement)/(total number cases × 100).

<sup>b</sup> Between-group difference  $p < 0.05$ .

### Section Summary: Herpes Zoster

One RCT was identified. Only short-term outcomes were reported. Outcomes at the end of treatment were significantly better in the HBOT group than in the medication group. Trial limitations included lack of blinding and long-term outcomes.

## SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR FIBROMYALGIA

One delayed treatment RCT and a quasi-randomized trial on HBOT for fibromyalgia were identified.

Efrati et al (2015) published an RCT that included 60 symptomatic women who had fibromyalgia for at least two years (see Table 30 and 31). (66) Patients were randomized to an immediate two-month course of HBOT or to delayed HBOT after two months. Forty-eight (80%) of 60 patients completed the trial. After the initial 2 months, outcomes including number of tender points, pain threshold, and QOL (SF-36) were significantly improved in the immediate treatment group than in the delayed treatment group. After the delayed treatment group had undergone HBOT, outcomes were significantly improved compared with scores in the two months before HBOT treatment. These findings are not only consistent with the clinical benefit of HBOT, but also with a placebo effect. A sham-control trial 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.

Yildiz et al (2004) assessed 50 patients with fibromyalgia (see Tables 30 and 31). (67) On an alternating basis, patients were assigned to HBOT or a control group. After HBOT treatment, the mean standard deviation, number of tender points, and mean visual analog scale scores were improved in patients receiving HBOT compared with controls. It is unclear whether the control group received a sham intervention that would minimize any placebo effect (i.e., whether the control intervention was delivered in a hyperbaric chamber). The authors stated that the trial was double-blind but did not provide details of patient blinding.

**Table 30. Characteristics of Trials Assessing HBOT for Fibromyalgia**

| Study (Year)                      | Countries | Sites | Dates     | Participants  | Treatment  |  |
|-----------------------------------|-----------|-------|-----------|---|--|--|
|                                   |           |       |           |   | Active   | Comparator   |
| Efrati et al (2015) <sup>66</sup> | Israel    | 1     | 2010-2012 | Patients with fibromyalgia based on: (1) widespread pain and (2) at least 11 of 18 tender points        | <ul style="list-style-type: none"> <li>• n=24</li> <li>• HBOT</li> <li>• 100% oxygen at 2 ATA</li> <li>• 1 session/day for 5 d</li> <li>• Forty 90-min sessions</li> </ul> | <ul style="list-style-type: none"> <li>• n=26</li> <li>• No treatment for 2 mo, then same treatment as active group</li> </ul> |
| Yildiz et al (2004) <sup>67</sup> | Turkey    | NR    | NR        | Patients meeting ACR criteria for fibromyalgia, with persistent symptoms despite medical therapy and PT | <ul style="list-style-type: none"> <li>• n=26</li> <li>• HBOT</li> <li>• 100% oxygen at 2.4 ATA</li> <li>• 1 session/day for 5 d</li> </ul>                                | <ul style="list-style-type: none"> <li>• n=24</li> <li>• Air</li> <li>• 1 ATA</li> <li>• 1 session/day for 5 d</li> </ul>      |

- Fifteen 90-min sessions
- Fifteen 90-minute sessions

ACR: American College of Rheumatology; ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; NR: not reported; PT: physical therapy.

**Table 31. Results of Trials Assessing HBOT for Fibromyalgia**

| Study (Year)                            | Tender Points |            |                       | Pain Threshold |            |                       |
|---|---------------|------------|-----------------------|----------------|------------|-----------------------|
|   | Baseline      | After HBOT | Between-Group P-Value | Baseline       | After HBOT | Between-Group P-Value |
| <b>Efrati et al (2015)<sup>66</sup></b> | 50            |            |                       | 50             |            |                       |
| Mean HBOT (SD)                          | 17.3 (1.4)    | 8.9 (6.0)  | <0.001                | 0.5 (1.2)      | 1.7 (0.8)  | <0.001                |
| Mean control (SD)                       | 17.7 (0.7)    | 17.2 (1.1) |                       | 0.7 (0.5)      | 0.6 (0.5)  |                       |
| <b>Yildiz et al (2004)<sup>67</sup></b> | 50            |            |                       | 50             |            |                       |
| Mean HBOT (SD)                          | 15.0 (1.5)    | 6.0 (1.2)  | <0.001                | 0.7 (0.1)      | 1.3 (0.1)  | <0.001                |
| Mean air (SD)                           | 15.3 (1.2)    | 12.5 (1.1) |                       | 0.7 (0.1)      | 0.8 (0.1)  |                       |

HBOT: hyperbaric oxygen therapy; SD: standard deviation.

### Section Summary: Systemic HBOT for Fibromyalgia

Two RCTs assessing HBOT for fibromyalgia were identified. Both had relatively small sample sizes and methodologic limitations (e.g., quasi-randomization, no or uncertain sham control for a condition with subjective outcomes susceptible to a placebo effect). Moreover, the HBOT protocol varied. Thus, the evidence is insufficient to permit conclusions on the impact of HBOT on health outcomes for patients with fibromyalgia.

## SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR MULTIPLE SCLEROSIS

Bennett et al (2010) published a systematic review on the use of HBOT for treatment of multiple sclerosis (see Table 32). (69) Nine RCTs (total n=504) were identified that compared the effects of HBOT with placebo or no treatment. All trials used an initial course of 20 sessions over four weeks, although dosages among studies varied from 1.75 ATA for 90 minutes to 2.5 ATA for 90 minutes. The primary outcome of the review was the Expanded Disability Status Scale score. A pooled analysis of data from five trials (n=271) did not find a significant difference in mean Expanded Disability Status Scale score change after 20 HBOT treatments vs control or after six months of follow-up.

**Table 32. Systematic Reviews of Trials Assessing HBOT for Multiple Sclerosis**

| Study (Year)                       | Literature Search | Studies | Participants  | N   | Design | Results   |
|------------------------------------|-------------------|---------|---|-----|--------|---|
| Bennett et al (2010) <sup>69</sup> | Jul 2009          | 9       | Patients with multiple sclerosis, at any state or course of the condition | 504 | RCT    | EDSS score difference between groups:<br><ul style="list-style-type: none"> <li>• At 4-wk follow-up: 0.07 (95% CI, -0.09 to 0.23)</li> <li>• At 6-mo follow-up: 0.22 (95% CI, -0.09 to 0.54)</li> </ul> |

CI: confidence interval; EDSS: Expanded Disability Status Scale; HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial.

### Section Summary: Systemic HBOT for Multiple Sclerosis



A Cochrane review of RCTs did not find a significant difference in outcomes when patients with multiple sclerosis were treated with HBOT vs a comparison intervention.

## SYSTEMIC HYPERBARIC OXYGEN THERAPY FOR INDIVIDUALS WITH CANCER WHO ARE UNDERGOING RADIOTHERAPY OR CHEMOTHERAPY

In a Cochrane review (2005) (50) which was updated in 2012,(46) and Bennett et al (2012) identified 19 randomized and quasi-randomized trials (N=2286) comparing outcomes following radiotherapy with and without HBOT in patients with solid tumors (see Table 33). The latest trial identified in the Cochrane search was published in 1999. Reviewers did not find any ongoing RCTs in this area. Results from the review reported that HBOT given with radiotherapy might be useful in tumor control in head and neck cancer. However, reviewers expressed caution because significant adverse events, such as severe radiation tissue injury (relative risk, 2.3;  $p<.001$ ) and seizures (relative risk, 6.8;  $p=.03$ ) occurred more frequently in patients treated with HBOT.

**Table 33. Systematic Reviews of Trials Assessing HBOT for Tumor Sensitization during Cancer Treatment With Radiotherapy**

| Study (Year)                       | Literature Search | Studies                                  | Participants   | N    | Design            | Results  |
|------------------------------------|-------------------|--|--|------|-------------------|--|
| Bennett et al (2012) <sup>70</sup> | Sep 2017          | 19, some including multiple cancer sites | <ul style="list-style-type: none"> <li>• Head and neck: 10 trials</li> <li>• Uterine: 7 trials</li> <li>• Urinary bladder: 5 trials</li> <li>• Bronchus: 1 trial</li> <li>• Rectum: 1 trial</li> <li>• Brain: 1 trial</li> <li>• Esophagus: 1 trial</li> </ul> | 2286 | RCT and quasi-RCT | Head and neck: <ul style="list-style-type: none"> <li>• 1-y mortality: RR=0.8 (<math>p=0.03</math>)</li> <li>• 5-year mortality: RR=0.8 (<math>p=0.03</math>)</li> <li>• 5-y recurrence: RR=0.8 (<math>p=0.01</math>)</li> </ul> Uterine: <ul style="list-style-type: none"> <li>• 2-y recurrence: RR=0.6 (<math>p=0.04</math>)</li> </ul> |

HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial; RR: relative risk.

In an RCT of 32 patients, Heys et al (2006) found no increase in 5-year survival for patients treated with HBOT to increase tumor vascularity before chemotherapy for locally advanced breast carcinoma.<sup>74</sup>

In an RCT of 32 patients, Heys et al (2006) found no increase in five-year survival for patients treated with HBOT to increase tumor vascularity before chemotherapy for locally advanced breast carcinoma.(71)

### **Section Summary: Systemic HBOT for Tumor Sensitization During Cancer Treatment: Radiotherapy or Chemotherapy**

A Cochrane review on the use of HBOT with radiotherapy and an RCT on the use of HBOT with chemotherapy were identified. While the Cochrane review found improvements in tumor control in patients with head and neck cancer, the adverse events accompanying HBOT treatment (e.g., radiation tissue injury, seizures) were significant. The RCT did not find a significant difference in survival in cancer patients who received HBOT before chemotherapy.

### **Other indications**

For the indications listed below, literature searches could not identify sufficient evidence to support the use of HBOT, such as systematic reviews and/or multiple well-conducted randomized controlled trials directly relevant to US-settings, assessing:



- amyotrophic lateral sclerosis;
- bone grafts;
- brown recluse spider bites;
- carbon tetrachloride poisoning, acute;
- cerebrovascular disease, acute (thrombotic or embolic) or chronic;
- fracture healing;
- hydrogen sulfide poisoning;
- in vitro fertilization;
- intra-abdominal and intracranial abscesses;
- lepromatous leprosy;
- meningitis;
- mental illness;
- pseudomembranous colitis (antimicrobial agent-induced colitis);
- pyoderma gangrenosum;
- radiation myelitis;
- retinal artery insufficiency, acute;
- retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment;
- sickle cell crisis and/or hematuria;
- spinal cord injury;
- tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy.

## **SUMMARY OF EVIDENCE**

There is limited comparative evidence for HBOT. The policy is based on the best available evidence and is largely informed by clinical input and guidelines. For individuals with necrotizing soft tissue infections, idiopathic sudden sensorineural hearing loss, or central retinal artery occlusion, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice.

For individuals with wounds, burns or infections who receive topical hyperbaric oxygen therapy (HBOT), the evidence includes a systematic review, case series, and a randomized controlled trial (RCT). Relevant outcomes are overall survival (OS), symptoms, change in disease status, and functional outcomes. The systematic review identified three RCTs including patients with sacral pressure ulcers, ischial pressure ulcers, and refractory venous ulcers. All trials reported that healing improved significantly after HBOT than after standard of care. Pooling of results was not possible due to heterogeneity in patient populations and treatment regimens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diabetic ulcers who receive systemic HBOT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms and change in disease status. Meta-analyses of RCTs found significantly higher diabetic ulcer healing rates with HBOT than with control conditions. Two of the three meta-analyses found that HBOT was associated with a significantly lower rate of major amputation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with carbon monoxide poisoning who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are overall survival and symptoms. A meta-analysis in a Cochrane review of low-quality RCT data did not find HBOT to be associated with a significantly lower risk of neurologic deficits after carbon monoxide poisoning. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. However, clinical input obtained in 2010 and guidelines from the Undersea and Hyperbaric Medical Society and the 10<sup>th</sup> European Consensus Conference on Hyperbaric Medicine support HBOT for the treatment of acute carbon monoxide poisoning. Thus, based on clinical input and guideline support, this indication may be considered medically necessary.

For individuals with radionecrosis, osteoradionecrosis, or treatment of irradiated jaw who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms and change in disease status. A meta-analysis in a Cochrane review of RCTs found evidence that HBOT improved radionecrosis and osteoradionecrosis outcomes and resulted in better outcomes before tooth extraction in an irradiated jaw. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with chronic refractory osteomyelitis who receive systemic HBOT, the evidence includes case series. Relevant outcomes are symptoms and change in disease status. The case series reported high rates of successful outcomes (no drainage, pain, tenderness, or cellulitis) in patients with chronic refractory osteomyelitis treated with HBOT. However, controlled studies are needed to determine conclusively the impact of HBOT on health outcomes compared with other interventions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. However, clinical input obtained in 2010 and Undersea and Hyperbaric Medical Society guidelines support HBOT for the treatment of chronic refractory osteomyelitis. Thus, based on clinical input and guideline support, this indication may be considered medically necessary.

For individuals with acute thermal burns who receive systemic HBOT, the evidence includes a systematic review of two RCTs. Relevant outcomes are overall survival, symptoms, and change in disease status. Both RCTs were judged to have poor methodologic quality. Evidence from well-conducted controlled trials is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with acute surgical and traumatic wounds who receive systemic HBOT, the evidence includes RCTs, controlled nonrandomized studies, and systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. There was considerable heterogeneity across the four RCTs identified (e.g., patient population, comparison group, treatment regimen, outcomes). This heterogeneity prevented pooling of trial findings and limits the ability to definitively conclude the impact of HBOT on health outcomes for patients with acute surgical and traumatic wounds. Additional evidence from high-quality RCTs is needed. A systematic review of controlled Chinese studies suggests HBOT may increase the survival rate of compromised skin grafts and flaps when initiated within 72 hours; however, risk of bias in the original Chinese publications cannot be evaluated. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with bisphosphonate-related osteonecrosis of the jaw who receive systemic HBOT, the evidence includes an RCT. Relevant outcome are symptoms and change in disease status. The RCT was unblinded and reported initial benefits at three-month follow-up; however, there were no significant benefits of HBOT for most health outcomes compared with standard care in the long-term (six months to two years). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with necrotizing soft tissue infections who receive systemic HBOT, the evidence includes systematic reviews. Relevant outcomes are OS, symptoms, and change in disease status. A Cochrane review did not identify any RCTs. Another systematic review of retrospective cohort studies with methodological limitations did not find consistent benefit of adjunctive HBOT use. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with acute coronary syndrome who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. A Cochrane review identified six RCTs. There were two pooled analyses, one found significantly lower rates of death with HBOT and the other reported inconsistent results in left ventricular function. Additional RCT data are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with acute ischemic stroke who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. Cochrane reviewers could only pool data for a single outcome (mortality at 3-6 months), and for that outcome, there was no significant difference between active and sham HBOT treatments. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with motor dysfunction associated with stroke who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and functional outcomes. The RCT, which used a crossover design, found better outcomes with HBOT at two months than with delayed treatment. However, the trial had a number of methodologic limitations (e.g., lack of patient blinding, heterogeneous population, high dropout rate) that make it difficult to evaluate the efficacy of HBOT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with Bell palsy who receive systemic HBOT, the evidence includes a systematic review. Relevant outcomes are symptoms, change in disease status, and functional outcomes. A Cochrane review did not identify any RCTs meeting selection criteria; the single RCT found did not have a blinded outcome assessment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with traumatic brain injury who receive systemic HBOT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. RCTs were heterogeneous regarding intervention

protocols, patient populations, and outcomes reported. Systematic reviews conducted pooled analyses only on a minority of the published RCTs, and these findings were inconsistent. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with inflammatory bowel disease who receive systemic HBOT, the evidence includes RCTs, observational studies, and a systematic review. Relevant outcomes are symptoms, change in disease status and functional outcomes. Three RCTs have reported mixed findings in patients with ulcerative colitis, with one study terminated early due to futility. A systematic review including the RCT and observational studies found a high rate of bias in the literature due to attrition and reporting bias. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with idiopathic sudden sensorineural hearing loss who receive systemic HBOT, the evidence includes systematic reviews. Relevant outcomes are symptoms, change in disease status, and functional outcomes. A Cochrane review of RCTs had mixed findings from studies that included individuals with tinnitus. Some outcomes (i.e., improvement in hearing of all frequencies, >25% return of hearing) were better with HBOT than with a control intervention, but more than 50% return of hearing did not differ significantly between groups. There was important variability in the patients enrolled in the studies. A subsequent systematic review had similarly limited conclusions due to the inclusion of non-randomized studies. A third review found a higher proportion of patients with hearing recovery with HBOT compared to medical treatment alone, but the analysis was limited to 2 RCTs with methodological limitations. One RCT published subsequent to the systematic reviews found a positive effect of HBOT plus steroid combination therapy on measures of auditory function compared to either HBOT or steroids alone, but other outcomes were not reported and the study had numerous relevance, design, and conduct limitations. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with delayed-onset muscle soreness who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms and functional outcomes. A Cochrane review of RCTs found worse short-term pain outcomes with HBOT than with control and no difference in longer term pain or other outcomes (e.g., swelling). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with autism spectrum disorder (ASD) who receive systemic HBOT, the evidence includes an RCT and a systematic review. Relevant outcomes are symptoms and functional outcomes. A Cochrane review identified a single RCT on HBOT for autism spectrum disorder and this trial did not find significantly better parental-assessed or clinician-assessed outcomes with HBOT compared with sham. Other literature has suggested that there is insufficient evidence to support use of HBOT to treat children with ASD, and its use as a form of treatment is not recommended. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

In 2013 (updated 2021), the FDA posted a warning to consumers regarding HBOT.<sup>(88)</sup> The Agency stated that HBOT has not been clinically proven to cure or be effective in the treatment of autism. The information warns against the use of HBOT for indications that are not FDA approved.

For individuals with cerebral palsy who receive systemic HBOT, the evidence includes two RCTs and an observational study. Relevant outcomes are symptoms and functional outcomes. One RCT was stopped early due to futility, and the other did not find significantly better outcomes with HBOT than with a sham intervention. The observational study focused on sleep disorders in children with cerebral palsy and reported improvements with the HBOT treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with vascular dementia who receive systemic HBOT, the evidence includes an RCT and a systematic review. Relevant outcomes are symptoms and functional outcomes. The Cochrane review identified only a single RCT with methodologic limitations. Well-conducted controlled trials are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with radiotherapy adverse events who receive systemic HBOT, the evidence includes RCTs, nonrandomized comparator trials, case series, and systematic reviews. Relevant outcomes are symptoms and functional outcomes. Two systematic reviews included few RCTs and provide limited evidence on the effect of HBOT. Two RCTs had inconsistent findings. One reported no short-term benefit with HBOT, but some benefits 12 months after radiotherapy; the other did not find a significant benefit of HBOT at 12-month follow-up. Another RCT assessed HBOT for radiation-induced cystitis and found significant benefit by some measures but not others. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with idiopathic femoral neck necrosis who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCT, which had a small sample, only reported short-term (i.e., six-week) outcomes. Larger well-conducted RCTs reporting longer term outcomes are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a migraine who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The Cochrane review conducted a pooled analysis including three of the 11 trials. Meta-analysis of these three RCTs found significantly greater relief of migraine symptoms with HBOT than with a comparator intervention within 45 minutes of treatment. Longer term data are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with herpes zoster who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and change in disease status. The RCT was unblinded and only reported short-term (i.e., six-week) outcomes. Additional well-conducted RCTs with longer follow-up are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with fibromyalgia who receive systemic HBOT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Only two RCTs were identified, and both reported positive effects of HBOT on tender points and pain. However, the trials had relatively small samples and methodologic limitations (e.g., quasi-randomization, no or uncertain sham control for a condition with subjective outcomes).

susceptible to a placebo effect). Moreover, the HBOT protocols varied. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with multiple sclerosis who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms and functional outcomes. A Cochrane review of RCTs did not find a significant difference in Expanded Disability Status Scale scores when patients with multiple sclerosis were treated with HBOT vs a comparator intervention. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cancer and are undergoing chemotherapy who receive systemic HBOT, the evidence includes an RCT and a systematic review. Relevant outcomes are overall survival and change in disease status. While the systematic review reported improvements in tumor control in patients with head and neck cancer who received HBOT, the adverse events accompanying the treatment (e.g., radiation tissue injury, seizures) were significant. The single RCT did not find a significant difference in survival for cancer patients who received HBOT before chemotherapy compared with usual care. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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## Supplemental Information

### CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

#### 2024 Input

Clinical input was sought to help determine whether the use of systemic HBOT in individuals with necrotizing soft tissue infections, idiopathic sudden sensorineural hearing loss, central retinal artery occlusion, or acute peripheral artery insufficiency would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 2 specialty society-level responses.

For individuals with necrotizing soft tissue infections, idiopathic sudden sensorineural hearing loss, central retinal artery occlusion, or acute peripheral artery insufficiency who receive HBOT, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice.

#### 2023 Input

Clinical input was sought to help determine whether the use of systemic hyperbaric oxygen therapy (HBOT) in individuals with acute surgical or traumatic wounds and compromised skin grafts or flaps would provide a clinically meaningful improvement in net health outcome and

whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 2 specialty society-level responses.

For individuals with acute surgical or traumatic wounds and compromised skin grafts or flaps who receive systemic HBOT, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice.

### **2010 Input**

In response to requests, input was received through six physician specialty societies and 5 academic medical centers while this policy was under review in 2010. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. The clinical input varied depending on the condition. There was universal agreement that topical hyperbaric therapy and systemic HBOT for autism spectrum disorders and headache/migraine are investigational. There was also wide support for changing acute carbon monoxide poisoning, compromised skin grafts or flaps, chronic refractory osteomyelitis, and necrotizing soft tissue infections to the list of medically necessary indications for HBOT. Several reviewers acknowledged that there is a paucity of clinical trials on HBOT for compromised skin grafts/flaps, necrotizing soft tissue infections, and chronic refractory osteomyelitis. These reviewers commented on the support from basic science, animal studies, and retrospective case series, as well as lack of effective alternative treatments for these conditions. Based on the available evidence and clinical input, acute carbon monoxide poisoning and chronic refractory osteomyelitis were changed in 2010 to medically necessary indications for HBOT. However, despite the clinical input and given the limited published evidence, compromised skin grafts and flaps and necrotizing soft tissue infections are still considered investigational.

## **PRACTICE GUIDELINES AND POSITION STATEMENTS**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### **American College of Cardiology/American Heart Association**

In 2024, the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines published a Guideline for the Management of Lower Extremity PAD.(60) The Guideline was developed in collaboration with and endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Podiatric Medical Association, Association of Black Cardiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, Society of Interventional Radiology, and Vascular & Endovascular Surgery Society. The Guideline included the following statements relevant to this evidence review:



"Beyond wound care, hyperbaric oxygen therapy has been studied in the context of wound healing for CLTI as an adjunctive therapy to revascularization and may have a limited role in this population."

"Hyperbaric oxygen therapy may be considered as an adjunctive therapy to revascularization for wound healing in the context of CLTI (chronic limb threatening ischemia) and diabetic foot ulcers."

### **American College of Cardiology/American Stroke Association**

In 2019 the American Heart Association and American Stroke Association updated the guidelines for early management of acute ischemic stroke.(90) The guidelines were endorsed by the Society for Academic Emergency Medicine, the Neurocritical Care Society, the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons. The Guideline included the following statements relevant to this evidence review:

"The limited data available on the utility of HBO therapy for acute ischemic stroke (not related to cerebral air embolism) show no benefit. HBO therapy is associated with claustrophobia and middle ear barotrauma, as well as an increased risk of seizures. Given the confines of HBO chambers, the ability to closely/adequately monitor patients may also be compromised. HBO thus should be offered only in the context of a clinical trial or to individuals with cerebral air embolism."

### ***Society of Vascular Surgery et al***

The Society of Vascular Surgery (2016) in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine published guidelines on the management of the diabetic foot.(74) According to the guidelines, for diabetic foot ulcers that fail to demonstrate improvement (>50% wound area reduction) after a minimum of four weeks of standard wound therapy, adjunctive therapy such as HBOT is recommended (grade 1B). Also, for diabetic foot ulcers with adequate perfusion that fail to respond to four to six weeks of conservative management, HBOT is suggested (grade 2B).

### ***Undersea and Hyperbaric Medical Society***

In 2015, the Undersea and Hyperbaric Medical Society (UHMS) published guidelines on the use of HBOT for treating diabetic foot ulcers. (89) Recommendations in the current version include:

- 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 not 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.

The 2023 UHMS Hyperbaric Oxygen Therapy Indications (15<sup>th</sup> edition) included the following indications as recommended:(75)

1. Air or Gas Embolism
2. Arterial insufficiencies: Central Retinal Artery Occlusion; Hyperbaric oxygen Therapy for Selected Problem Wounds
3. Carbon Monoxide Poisoning and carbon monoxide complicated by cyanide poisoning
3. Clostridial Myonecrosis (Gas Gangrene)
- 4 . Acute Traumatic Ischemias
- 5 . Decompression Sickness
6. Severe Anemia
7. Intracranial Abscess
8. Necrotizing Soft Tissue Infections
9. Refractory osteomyelitis
10. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
11. Compromised Grafts and Flaps
12. Acute Thermal Burn Injury
13. Idiopathic Sudden Sensorineural Hearing Loss.
14. Avascular Necrosis (Aseptic Osteonecrosis).

### **American Academy of Otolaryngology-Head and Neck Surgery**

The American Academy of Otolaryngology-Head and Neck Surgery (2019) updated clinical guidelines on the treatment of sudden sensorineural hearing loss (SSNHL). (79) They give the following options regarding HBOT:

- "Clinicians may offer, or refer to a physician who can offer, hyperbaric oxygen therapy (HBOT) combined with steroid therapy within two weeks of onset of SSNHL."
- "Clinicians may offer, or refer to a physician who can offer, hyperbaric oxygen therapy (HBOT) combined with steroid therapy as salvage within one month of onset of SSNHL."

### **U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.

### **ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 34.

**Table 34. Summary of Key Trials**

| <b>NCT No.</b>     | <b>Trial Name</b>  | <b>Planned Enrollment</b> | <b>Completion Date</b> |
|--------------------|--|---------------------------|------------------------|
| <b>Ongoing</b>     |  |                           |                        |
| NCT02407028        | Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial   | 200                       | Jun 2027               |
| NCT04975867        | Targeted Temperature Management Combined With Hyperbaric Oxygen Therapy in Acute Severe Carbon Monoxide Poisoning: Multicenter Randomized Controlled Clinical Trial (TTM-COHB Trial)               | 46                        | Jul 2025               |
| NCT05289700        | Multicentric, Double-blind, Randomised Controlled Trial of Hyperbaric-oxygen Therapy (HBOT) Versus Placebo for Treating Vaso-Occlusive Crisis (VOC) in Sickle Cell Disease (SCD) After 8 Years Old | 100                       | Mar 2025               |
| <b>Unpublished</b> |  |                           |                        |

|             |  |     |          |
|-------------|--|-----|----------|
| NCT04193722 | The Effect of Hyperbaric Oxygen Therapy on Breast Cancer Patients With Late Radiation Toxicity | 189 | May 2023 |
|-------------|--|-----|----------|

NCT: national clinical trial.

## Government Regulations

### National:

#### National Coverage Determination – Manual 100-3; Chapter 1; Section 20.29 – Hyperbaric Oxygen Therapy; Effective Date: 4/3/17; Implementation Dates: 12/18/17

For purposes of coverage under Medicare, hyperbaric oxygen (HBO<sub>2</sub>) therapy is a modality in which the entire body is exposed to oxygen under increased atmospheric pressure.

#### A. **Covered Conditions**

Program reimbursement for HBO therapy will be limited to that which is administered in a chamber (including the one-man unit) and is limited to the following conditions:

1. Acute carbon monoxide intoxication
2. Decompression illness
3. Gas embolism
4. Gas gangrene
5. Acute traumatic peripheral ischemia. HBO<sub>2</sub> 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, HBO<sub>2</sub> 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:
  - You have type 1 or type 2 diabetes and has a lower extremity wound that is due to diabetes
  - You have a wound classified as Wagner grade III or higher and
  - You have failed an adequate course of standard wound therapy

The use of HBO 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:

- The assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible
- The 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 HBO therapy. Continued treatment with HBO<sub>2</sub> therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.

#### **B. *Noncovered Conditions***

All other indications not specified under §270.4(A) are not covered under the Medicare program. No program payment may be made for any conditions other than those listed in § 270.4(A).

No program payment may be made for HBO in the treatment of the following conditions:

1. Cutaneous, decubitus and stasis ulcers
2. Chronic peripheral vascular insufficiency
3. Anaerobic septicemia and infection other than clostridial
4. Skin burns (thermal)
5. Senility
6. Myocardial infarction
7. Cardiogenic shock
8. Sick cell anemia
9. Acute thermal and chemical pulmonary damage, i.e., smoke inhalation with pulmonary insufficiency
10. Acute or chronic cerebral vascular insufficiency
11. Hepatic necrosis
12. Aerobic septicemia
13. Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease)
14. Tetanus
15. Systemic aerobic infection
16. Organ transplantation
17. Organ storage
18. Pulmonary emphysema
19. Exceptional blood loss anemia
20. Multiple sclerosis

- 21. Arthritic diseases
- 22. Acute cerebral edema

### C. **Topical Application of Oxygen**

Section C-Topical Application of Oxygen has been removed from NCD 20.29. Effective for dates of service on and after (04/03/17), Medicare Administrative Contractors (MACs) acting within their respective jurisdictions may determine coverage of topical application of oxygen for chronic non-healing wounds.

#### **National Coverage Determination for Hyperbaric Oxygen (HBO) Therapy, April 3, 2017.**

“After examining the evidence, CMS has decided that no National Coverage Determination is appropriate at this time concerning the use of topical oxygen for the treatment of chronic wounds. We will amend NCD 20.29 by removing Section C, Topical Application of Oxygen and Medicare coverage of topical oxygen for the treatment of chronic wounds will be determined by the local contractors.”

MLN Matters - Topical Oxygen Therapy; Effective April 3, 2017

Per CR 10220, hyperbaric oxygen (HBO) Therapy (Section C, Topical Application of Oxygen) there shall be no coverage for any separate or additional payment for any physician's professional services related to this procedure.

#### **Local:**

There is no local coverage determination regarding hyperbaric oxygen therapy.

**Wound Care, L37228**; Effective date 4/16/18; Revision date: 4/27/23

“This policy does not address...hyperbaric oxygen therapy.”

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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### **Related Policies**

- Wound therapy (BCN only)

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September, 2024, the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

| <b>Policy Effective Date</b> | <b>BCBSM Signature Date</b> | <b>BCN Signature Date</b> | <b>Comments</b>   |
|------------------------------|-----------------------------|---------------------------|---|
| 3/24/06                      | 3/24/06                     | 4/7/06                    | Joint policy established  |
| 3/1/08                       | 12/11/07                    | 11/19/07                  | Routine maintenance   |
| 3/1/09                       | 12/9/08                     | 12/21/08                  | Routine maintenance   |
| 9/1/09                       | 6/16/09                     | 6/16/09                   | Routine maintenance<br>Decision to follow Medicare/NCD inclusions/exclusions  |
| 11/1/09                      | 8/18/09                     | 8/18/09                   | Routine maintenance   |
| 1/1/11                       | 10/12/10                    | 10/27/10                  | Routine maintenance<br>Updated exclusionary criteria  |
| 3/1/12                       | 12/13/11                    | 1/31/12                   | Routine maintenance   |
| 9/1/13                       | 6/18/13                     | 6/26/13                   | Routine maintenance, update to nomenclature for CPT code 99183  |
| 11/1/15                      | 8/18/15                     | 9/14/15                   | Combined systemic and topical HBOT into this policy; added "Systemic and Topical" to title; added the following as exclusions: Bell palsy, Bisphosphonate-related osteonecrosis of the jaw, Herpes Zoster, Vascular dementia, Motor Dysfunction Associated with Stroke; code C1300 deleted.   |
| 11/1/16                      | 9/23/16                     | 9/1/16                    | Routine maintenance <ul style="list-style-type: none"> <li>• In-line with BCBSA but incorporates NCD inclusion/exclusion bullets</li> </ul> Added Inclusions <ul style="list-style-type: none"> <li>• Actinomycosis, only as adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment</li> <li>• Acute carbon monoxide intoxication</li> </ul> Added exclusions <ul style="list-style-type: none"> <li>• ACS and as an adjunct to coronary interventions, including percutaneous coronary interventions</li> <li>• Acute ischemic stroke</li> </ul> |

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|  |  |  | <ul style="list-style-type: none"> <li>• Cardiogenic shock</li> <li>• Cerebral edema, acute</li> <li>• Chronic wounds, other than those situations under the inclusions</li> <li>• Early tx (beginning a completion of radiation therapy) to reduce side effects of radiation therapy</li> <li>• Exceptional blood loss anemia</li> <li>• Fibromyalgia</li> <li>• Idiopathic sudden sensorineural hearing loss</li> <li>• Inflammatory bowel disease (Crohn disease or ulcerative colitis)</li> <li>• Meningitis</li> <li>• Mental illness (i.e., posttraumatic stress disorder, generalized anxiety disorder or depression)</li> <li>• Multiple Sclerosis</li> <li>• Radiation-induced injury in the head and neck, except as noted under the inclusions</li> <li>• Skin burns (thermal)</li> </ul> <p>Inclusions and references updated</p> <p>Disclaimer added to inclusions for diagnoses which are inclusions for NCD but exclusions for BCBSA</p> <p>For several of the indications included, there is little published evidence to support the effectiveness of HBO therapy. However, there is little likelihood of RCTs being done for such relatively rare indications. Generally, these patients present with clinically severe situations where therapeutic options are limited. Subject matter expert experience and limited available evidence support that hyperbaric oxygen treatment may offer therapeutic benefit in these cases.</p> |
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| 11/1/17 | 8/15/17 | 8/15/17 | Routine maintenance with updates to rationale, references and Medicare information.   |
| 11/1/18 | 8/21/18 | 8/21/18 | Routine maintenance; references and rationale updated   |
| 11/1/19 | 9/5/19  |         | Routine maintenance   |
| 9/1/20  | 8/18/20 |         | Routine maintenance   |
| 9/1/21  | 6/15/21 |         | Routine maintenance. No change in policy status. Added references 85 and 86.  |
| 9/1/22  | 6/21/22 |         | Routine maintenance. No change in policy status. References updated.  |
| 9/1/23  | 6/13/23 |         | <ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• No change in policy status</li> <li>• References added to policy to support the E/I position of HBOT for treatment of autism spectra disorders (ASD).</li> <li>• Vendor: N/A (ky)</li> </ul>  |
| 9/1/24  | 6/18/24 |         | <ul style="list-style-type: none"> <li>• Routine maintenance</li> <li>• For clarification purposes – removed bullet with non-diabetic wounds from under the Inclusions section and Exclusions section. Updates made to Inclusions and Exclusion section.</li> <li>• Vendor: N/A</li> </ul> <p>Post JUMP:</p> <ul style="list-style-type: none"> <li>• For clarification purpose: we will only cover diabetic wounds meeting criteria under the Inclusions section.</li> <li>• Clarification: after chronic wounds under the Exclusions section – added other than those in patients with diabetes who meet the criteria specified in the inclusions.</li> <li>• After further evaluation/discussion – will maintain idiopathic sensorineural hearing loss as an exclusion, no new references to support this indication were found. (ky)</li> </ul> |



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| 1/1/25 | 10/15/24 |  | <ul style="list-style-type: none"> <li>○ Routine maintenance</li> <li>○ BCBSA updated policy 2.01.04 - Hyperbaric Oxygen Therapy September, 2024-based on the structured request for clinical input, guidelines, and FDA-labeled indications, progressive necrotizing soft tissue infections, idiopathic sudden sensorineural hearing loss, and central retinal artery occlusion were added to the medically necessary statements.</li> <li>○ Added idiopathic sudden sensorineural hearing loss and central retinal artery occlusion under the Inclusion section.</li> <li>○ Removed under Exclusions after soft-tissue radionecrosis:</li> <li>○ As an adjunct to conventional treatment</li> <li>○ Added under Exclusions:</li> <li>○ Acute peripheral artery insufficiency (outside of other listed medically necessary indications involving arterial insufficiency)</li> <li>○ Removed under Exclusions</li> <li>○ Idiopathic sudden sensorineural hearing loss</li> <li>○ Retinal artery insufficiency, acute</li> <li>○ Severe or refractory Crohn's disease (duplicative).</li> </ul> <p>Going forward this policy will now come to October JUMP.</p> <ul style="list-style-type: none"> <li>○ References added</li> <li>○ Vendor: N/A (ky)</li> </ul> <p>Post JUMP</p> <p>Added <b>soft tissues</b> to the below statement under Inclusions.</p> <ul style="list-style-type: none"> <li>○ Progressive necrotizing soft tissue infections</li> </ul> |

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|  |  |  | <ul style="list-style-type: none"> <li>○ Updated the Inclusions section with the below bullets for clarification:</li> <li>○ Central retinal artery occlusion (including CaHA (calcium hydroxylapatite) cosmetic filler injection likely due to an embolism)</li> <li>○ Branch Retinal Artery Occlusion</li> <li>○ Susac's Syndrome</li> </ul> <p>Added the below under Systemic Hyperbaric Oxygen Therapy section.</p> <ul style="list-style-type: none"> <li>○ There is limited comparative evidence for HBOT. The policy is based on the best available evidence, and is largely informed by clinical input and guidelines.</li> <li>○ Progressive Necrotizing Soft Tissue Infections</li> <li>○ Idiopathic Sudden Sensorineural Hearing Loss (ISSHL)</li> <li>○ Central Retinal Artery Occlusion (CRAO) and Other Retinal Conditions</li> </ul> <p>Added the below under Summary of Evidence:</p> <ul style="list-style-type: none"> <li>○ There is limited comparative evidence for HBOT. The policy is based on the best available evidence and is largely informed by clinical input and guidelines. For individuals with necrotizing soft tissue infections, idiopathic sudden sensorineural hearing loss, or central retinal artery occlusion, clinical input supports this use provides a clinically meaningful improvement in net health outcomes and indicates this use is consistent with generally accepted medical practice. (ky)</li> </ul> |
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Next Review Date:

4<sup>th</sup> Qtr, 2025



**BLUE CARE NETWORK BENEFIT COVERAGE**  
**POLICY: HYPERBARIC OXYGEN THERAPY, SYSTEMIC AND TOPICAL**

**I. Coverage Determination:**

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| <b>Commercial HMO<br/>(includes Self-Funded<br/>groups unless otherwise<br/>specified)</b> | Covered; Policy criteria apply.  |
| <b>BCNA (Medicare<br/>Advantage)</b>   | Refer to the Medicare information under the Government Regulations section of this policy. |
| <b>BCN65 (Medicare<br/>Complementary)</b>  | Coinsurance covered if primary Medicare covers the service.                                |

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- *Duplicate (back-up) equipment is not a covered benefit.*