

<b>2.01.04</b>		<b>Hyperbaric Oxygen Therapy</b>	
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<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 68

### Policy Statement

- I. Topical hyperbaric oxygen therapy is considered **investigational**.
  
- II. Systemic hyperbaric oxygen pressurization may be considered **medically necessary** in the treatment of **any** of the following conditions:
  - A. Acute carbon monoxide poisoning
  - B. Acute cyanide poisoning
  - C. Acute gas embolism
  - D. Acute traumatic ischemia (e.g., crush injuries, reperfusion injury, compartment syndrome)
  - E. Chronic refractory osteomyelitis
  - F. Compromised skin grafts or flaps
  - G. Decompression sickness
  - H. Gas gangrene (i.e., clostridial myonecrosis)
  - I. Nonhealing diabetic wounds of the lower extremities in patients who meet **all** of the following criteria:
    1. Individual has a wound classified as [Wagner](#) grade 3 or higher
    2. Individual has no measurable signs of healing after 30 days of an adequate course of standard wound therapy
    3. Individual has type 1 or type 2 diabetes and has a lower-extremity wound due to diabetes
  - J. Pre- and posttreatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw
  - K. Profound anemia with exceptional blood loss and **either** of the following:
    1. When blood transfusion is impossible
    2. When blood transfusion must be delayed
  - L. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis)
  - M. Osteoradionecrosis
  
- III. Systemic hyperbaric oxygen pressurization is considered **investigational** in all other situations, including but not limited to, the treatment of the following conditions:
  - A. Acute arterial peripheral insufficiency
  - B. Acute carbon tetrachloride poisoning
  - C. Acute cerebral edema
  - D. Acute coronary syndromes and as an adjunct to coronary interventions, including but not limited to, percutaneous coronary interventions and cardiopulmonary bypass
  - E. Acute ischemic stroke
  - F. Acute osteomyelitis
  - G. Acute retinal artery insufficiency
  - H. Acute surgical and traumatic wounds not meeting criteria specified in the medically necessary statement
  - I. Acute thermal burns
  - J. Autism spectrum disorder
  - K. Bell palsy
  - L. Bisphosphonate-related osteonecrosis of the jaw
  - M. Bone grafts
  - N. Brown recluse spider bites
  - O. Cerebral palsy
  - P. Cerebrovascular disease, acute (thrombotic or embolic) or chronic

- Q. Chronic arm lymphedema following radiotherapy for cancer
- R. Chronic wounds, other than those in patients with diabetes who meet the criteria specified in the medically necessary statement
- S. Delayed-onset muscle soreness
- T. Demyelinating diseases (e.g., multiple sclerosis, amyotrophic lateral sclerosis)
- U. Early treatment (beginning at completion of radiotherapy) to reduce adverse events of radiotherapy
- V. Fibromyalgia
- W. Fracture healing
- X. Herpes zoster
- Y. Hydrogen sulfide poisoning
- Z. Idiopathic femoral neck necrosis
- AA. Idiopathic sudden sensorineural hearing loss
- BB. In vitro fertilization
- CC. Inflammatory bowel disease (Crohn disease or ulcerative colitis)
- DD. Intra-abdominal and intracranial abscesses
- EE. Lepromatous leprosy
- FF. Meningitis
- GG. Mental illness (i.e., posttraumatic stress disorder, generalized anxiety disorder or depression)
- HH. Migraine
- II. Motor dysfunction associated with stroke
- JJ. Necrotizing soft tissue infections
- KK. Pseudomembranous colitis (antimicrobial agent-induced colitis)
- LL. Pyoderma gangrenosum
- MM. Radiation myelitis
- NN. Radiation-induced injury in the head and neck, except as noted earlier in the medically necessary statement
- OO. Refractory mycoses: mucormycosis, actinomycosis, conidiobolus coronato
- PP. Retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment
- QQ. Senility related disorders including dementia, vascular dementia, and cognitive impairment
- RR. Sickle cell crisis and/or hematuria
- SS. Spinal cord injury
- TT. Traumatic brain injury
- UU. Tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

### Topical Hyperbaric Oxygen

HCPCS code A4575 is used to describe a disposable topical hyperbaric oxygen appliance that creates a "chamber" around the wound area which is pressurized with "hyperbaric oxygen." Conventional oxygen tanks, typically gas, are used to supply the oxygen. An example of such a device is the AOTI Hyper-Box™.

This policy addresses topical hyperbaric oxygen therapy (HBOT) but not topical oxygen wound care.

Topical HBOT may be performed in the office, clinic, or may be self-administered by the patient in the home. Typically, the therapy is offered for 90 minutes per day for 4 consecutive days. After a 3-day break, the cycle is repeated. The regimen may last for 8 to 10 weeks.

### Systemic Hyperbaric Oxygen

The Wagner classification system categorizes wounds 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

Following are recommended indications from the Undersea and Hyperbaric Medical Society's (UHMS) 2019 Hyperbaric Oxygen Therapy Committee report on utilization of HBOT (14th edition):

- Air or gas embolism: Usual treatment involves 1-2 sessions using 2.82 ATA of oxygen but occasionally up to 5 to 10. Utilization review is recommended after 10 treatments.
- Carbon monoxide poisoning and carbon monoxide complicated by cyanide poisoning: Compressions should be between 2.4 and 3.0 ATA with a maximum duration of 60-100 minutes. Utilization review is mandatory after the fifth treatment.
- Clostridial myositis and myonecrosis (gas gangrene): Treatment should be administered for 90 minutes 3 times within the first 24 hours with 3.0 ATA of oxygen, then twice daily for the next 2-5 days. Utilization review is indicated after 10 treatments.
- Crush injury, compartment syndrome, and other acute traumatic ischemias
  - Crush Injuries: Treatments should be given 90 minutes three times a day for 10 days. Pressures should be 2.0 ATA of oxygen in monoplace chambers and 2.4 ATA of oxygen in multiplace chambers.
  - Reperfusion injury: 1 treatment
  - Compartment syndrome: 3 treatments (twice a day for 1 day and 1 treatment on day 2)
- Decompression sickness: Treatment may vary depending on the type of decompression sickness. 5 to 10 treatments per individual is recommended. Utilization review is recommended after 10 treatments.
- Central retinal artery occlusion
- Diabetic foot ulcer
- Healing of other problem wounds
- Severe anemia: The patient initially can be treated with 2.0-3.0 ATA of oxygen. Treatment can occur for periods of up to 3 or 4 hours 3 to 4 times a day if patients receive intratreatment air breaks.
- Intracranial abscess: Treatment should be administered at 2.0-2.5 ATA of oxygen for 60-90 minutes once or twice daily, depending upon the severity of the condition.
- Necrotizing soft tissue infections: HBOT treatments are given at a pressure of 2.0-2.5 ATA of oxygen and range from 90 minutes twice daily during the initial phase of therapy. Treatment at 2.8-3.0 ATA is recommended, using the gas-gangrene protocol of 3 treatments in the first 24 hours.
- Refractory osteomyelitis): Treatment should be given for 90-120 minutes at 2.3-2.5 ATA of oxygen once daily. Approximately 20-40 postoperative treatments should be delivered over a 4-6 week period.
- Delayed radiation injury (soft tissue and bony necrosis): Treatment should be administered for 90-120 minutes at 2.0 to 2.5 ATA of oxygen daily. No more than 40 treatments should be performed.
- Compromised grafts and flaps: Initial treatment is for 90-120 minutes at 2.0-2.5 ATA of oxygen. No more than 20 treatments per individual is recommended.

- Acute thermal burn injury: Treatments should be given for 90 minutes 3 times within the first 24 hours, and twice daily thereafter at 2.0-2.4 ATA (atmospheres absolute) of oxygen. Treatment beyond 20-30 sessions is usually utilized to optimize grafting success.
- Sudden sensorineural hearing loss: The recommended treatment profile consists of 100% O<sub>2</sub> at 2.0 to 2.5 atmospheres absolute for 90 minutes daily for 10 to 20 treatments. The 2.4 ATA treatment pressure is probably most practical, especially for facilities with multiplace chamber operations.

**Coding**

The following CPT code may be used for hyperbaric oxygen therapy:

- **99183:** Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session (This code is billed one per treatment)

The following HCPCS codes may be used for hyperbaric oxygen therapy:

- **A4575:** Topical hyperbaric oxygen chamber, disposable
- **E0446:** Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories
- **G0277:** Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval\*

**\*Note:** Treatment time (for billing purposes) starts at the beginning of chamber pressurization and ends when chamber depressurization is finished. There must be more than 15 minutes in order to bill an interval (see PG Table 1)

**PG Table 1. Unit Calculation for G0277**

	Number of Units for G0277
0-15 Minutes	0
16-45 Minutes	1
46-75 Minutes	2
76-105 Minutes	3
106-135 Minutes	4
136-165 Minutes	5

Continued treatment with HBO therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.

**Description**

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

**Related Policies**

- N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

Since 1979, the U.S. Food and Drug Administration (FDA) has cleared multiple topical and systemic hyperbaric oxygen administration devices through the 510(k) pathway. In 2013, the FDA published a statement warning that non-FDA approved uses of 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 the FDA, they may delay or forgo proven medical therapies.

## Rationale

### Background

#### Hyperbaric Oxygen Therapy

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

#### Topical Hyperbaric Oxygen Therapy

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.

#### Systemic Hyperbaric Oxygen Therapy

In systemic or large hyperbaric oxygen chambers, the patient is entirely enclosed in a pressure chamber and breathes oxygen at a pressure greater than 1 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, multiplace chamber pressurized with compressed air, in which case the patient receives pure oxygen by mask, head tent, or endotracheal tube.

### 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.

## Literature Review

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.

## Topical Hyperbaric Oxygen Therapy for Wounds, Burns, or Infections

### Clinical Context and Therapy Purpose

The purpose of topical hyperbaric oxygen therapy (HBOT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with wounds, burns, or infections.

The question addressed in this evidence review is: Does the use of topical hyperbaric oxygen as a treatment for wounds, burns, or infections improve net health outcomes?

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest is individuals with wounds, burns, or infections.

### *Interventions*

The therapy being considered is topical HBOT.

### *Comparators*

Comparators of interest include dressings, débridement, and medication. Medications prescribed may include topical antibiotics and antiseptics. Pain and anxiety management medication may also be used. Topical HBOT may be used as an adjunct to these comparators. Patients with wounds, burns, or infections are actively managed by emergency care providers, dermatologists, wound care specialists, and primary care providers in a clinical setting.

### *Outcomes*

The general outcomes of interest are overall survival (OS), symptoms, change in disease status, and functional outcomes. Based on the site and severity of the wound, burn, or infection, patients may require prolonged physical and occupational support to evaluate symptoms. Additionally, the existing evidence on the use of topical HBOT involves studies that treat patients for 12 weeks, but information on follow-up was limited. Therefore, follow-up should be determined based on the site and severity of the wound, burn, or infection and can range from months to a year after starting treatment.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

de Smet et al (2017) conducted a systematic review of various oxygen therapies (oxygen dressing therapy, topical oxygen therapy, HBOT, inspired oxygen therapy).<sup>3</sup> 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) 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 Therapy for Wounds, Burns, or Infections

A systematic review identified 3 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 for Chronic Diabetic Ulcers

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with chronic diabetic ulcers.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for chronic diabetic ulcers improve net health outcomes?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with chronic diabetic ulcers.

### ***Interventions***

The therapy being considered is systemic HBOT.

### ***Comparators***

Comparators of interest include standard wound care and advanced wound therapy. Standard wound care can include offloading of the wound with appropriate therapeutics, dressings, debridement antibiotic therapy, and blood glucose control. Advanced wound therapy can include the application of recombinant growth factors and wound coverage with heterogeneous dressings. Systemic HBOT may be used as an adjunct to these comparators.

### ***Outcomes***

The general outcomes of interest are symptoms and change in disease status. The existing literature evaluating systemic HBOT as a treatment for chronic diabetic ulcers has varying lengths of follow-up, ranging from none to 22 months. While studies included in the systematic reviews described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

#### **Systematic Reviews**

Sharma et al (2021)<sup>4</sup>, 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;  $I^2=62%$ ). Results were consistent when stratified according to duration of followup of less than 1 year (7 studies; OR, 0.63; 95% CI, 0.39 to 1.02;  $I^2=1%$ ) and at 1 year (4 studies; OR, 0.16; 95% CI, 0.03 to 0.82;  $I^2=83%$ ), although the risk estimate wasn't statistically significant for studies with less than one year followup. 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;  $I^2=24%$ ). 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 (2015) (see Table 2).<sup>5</sup> Reviewers identified 12 RCTs (N=577 participants) 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 Grading of Recommendations, Assessment, Development, and Evaluation (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 Elraiyah et al (2016) evaluated adjunctive therapies (HBOT, arterial pumps, and pharmacologic agents) used to treat diabetic foot ulcers (see Table 2).<sup>6</sup> RCTs and nonrandomized cohort studies were included. The RCTs were rated as low-to-moderate quality using the GRADE system. A pooled analysis of 6 RCTs found a significantly higher healing rate and a significantly lower major amputation rate (OR, 0.30; 95% CI, 0.10 to 0.89) with HBOT than with control.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Kranke et al (2015) <sup>5</sup>	Feb 2015	12	Patients with chronic wounds associated with venous or arterial disease, diabetes, or external pressure	577	RCTs	<ul style="list-style-type: none"> <li>10 of 12 trials focused on patients with diabetic foot ulcers (n=531)</li> <li>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)</li> </ul>
Elraiyah et al (2016) <sup>6</sup>	Oct 2011	18	Patients with diabetic foot ulcers	1526	RCTs, cohort	<ul style="list-style-type: none"> <li>16 of 18 trials included HBOT as a treatment option and 6 of those were RCTs</li> <li>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)</li> </ul>
Sharma et al (2021) <sup>4</sup>	Sep 2020	14	Patients with diabetic foot ulcers	768	RCTs, CCTs	<ul style="list-style-type: none"> <li>12 RCTs and 2 CCTs compared HBOT with undefined standard care</li> <li>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.</li> </ul>

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

### Section Summary: Systemic Hyperbaric Oxygen Therapy for Chronic 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 2 meta-analyses found that HBOT was associated with a significantly lower rate of major amputation.

### Systemic Hyperbaric Oxygen Therapy for Carbon Monoxide Poisoning

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with carbon monoxide poisoning.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for carbon monoxide poisoning improve net health outcomes?

The following PICO was used to select literature to inform this review.

### **Populations**

The relevant population of interest is individuals with carbon monoxide poisoning.

### **Interventions**

The therapy being considered is systemic HBOT.

### **Comparators**

Comparators of interest include breathing oxygen at standard pressure and other supportive measures such as a ventilator. Systemic HBOT may be used as an adjunct to these comparators.

### **Outcomes**

The general outcomes of interest are OS and symptoms. The existing literature evaluating systemic HBOT as a treatment for carbon monoxide poisoning has varying lengths of follow-up. In the systematic review described below all reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

#### **Systematic Reviews**

A Cochrane review by Buckley et al (2011) included 6 RCTs evaluating HBOT for carbon monoxide poisoning (see Table 3).<sup>7</sup> Four of the 6 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 4 to 6 weeks after study inclusion. Two of the 6 RCTs found that HBOT reduced the likelihood of neurologic sequelae at 1 month and 4 others did not find a significant effect. A pooled analysis of the 6 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>7</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. Pooled analyses of 6 trials (N=1361) reported no statistical difference in</li> </ul>

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
						neurologic deficits between treatment groups (OR=0.78; 95% CI, 0.54 to 1.12)

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>8</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% CI -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%, 95% CI -4.9% to -1.5%) and reduced activities of daily living (mean difference -5.3%, 95% CI -7.8% to -2.7%) relative to no HBOT.

### Section Summary: Systemic Hyperbaric Oxygen Therapy for Carbon Monoxide Poisoning

A Cochrane review identified 6 RCTs, the majority of which did not find a significant effect of HBOT on health outcomes. A pooled analysis of the RCT data did not find a significant effect of HBOT on neurologic injuries and the quality of the evidence was considered very low. Evidence from a large cohort study also found no clear benefit of HBOT on in-hospital mortality.

### Systemic Hyperbaric Oxygen Therapy For Radionecrosis, Osteoradionecrosis, and Treatment of Irradiated Jaw

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with radionecrosis, osteoradionecrosis, and treatment of irradiated jaw.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for radionecrosis, osteoradionecrosis and treatment of irradiated jaw improve net health outcomes.

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is individuals with radionecrosis, osteoradionecrosis, and treatment of irradiated jaw.

#### *Interventions*

The therapy being considered is systemic HBOT.

#### *Comparators*

Comparators of interest include débridement and medication. Medications prescribed for radionecrosis may include corticosteroids and anticoagulants. For osteoradionecrosis, medications include vasodilators. Medication for the treatment of irradiated jaw can include antibiotics. Systemic HBOT may be used as an adjunct to these comparators.

#### *Outcomes*

The general outcomes of interest are symptoms and change in disease status. The existing literature evaluating systemic HBOT as a treatment for radionecrosis, osteoradionecrosis, and treatment of

irradiated jaw has varying lengths of follow-up, ranging from 3 weeks to 18 months. In the systematic reviews described below, nearly all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

#### Systematic Reviews

Bennett et al (2016) published a Cochrane review on HBOT for late radiation tissue injury (see Table 4).<sup>9</sup> Reviewers identified 14 RCTs. There was a moderate level of evidence for 2 pooled analyses. In a pooled analysis of 3 studies, a significantly higher proportion of patients with osteoradionecrosis achieved complete mucosal cover after HBOT compared with control treatments, and in a pooled analysis of 2 trials, a significantly lower risk of wound dehiscence after surgery to repair mandibular osteoradionecrosis with HBOT than with control treatments was reported. 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.

Borabet al (2017) published a systematic review focusing on the use of HBOT to treat the subgroup of patients with late radiation tissue injury had skin necrosis (see Table 4).<sup>10</sup> Reviewers identified 8 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.<sup>11</sup> 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>9</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</li> </ul>

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
						surgery to repair mandibular osteoradionecrosis in patients treated with HBOT vs control (RR=4.2; 95% CI, 1.1 to 16.8)
Borab et al (2017) <sup>10</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>11</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 Hyperbaric Oxygen Therapy 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 before 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

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with chronic refractory osteomyelitis.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for chronic refractory osteomyelitis improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is individuals with chronic refractory osteomyelitis.

#### *Interventions*

The therapy being considered is systemic HBOT.

### ***Comparators***

Comparators of interest include medication and surgical therapy. Medications prescribed for chronic refractory osteomyelitis may include intravenous antibiotics. Surgery can include débridement. Systemic HBOT may be used as an adjunct to these comparators.

### ***Outcomes***

The general outcomes of interest are symptoms and change in disease status. The existing literature evaluating systemic HBOT as a treatment for chronic refractory osteomyelitis report follow-up times ranging from 34 to 60 months, suggesting that extensive follow-up up to or more than 5 years is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

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.

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.<sup>12</sup> Follow-up data were available on 34 patients who had received a mean of 35 adjunctive HBOT sessions (range, 6 to 99 sessions). Of the 26 patients with at least 24 months of follow-up after treatment, 81% (21/26) remained drainage-free. At 60 months of follow-up, 80% (12/15), and at 84 months, 63% (5/8) remained drainage-free.

Davis et al (1986) reviewed outcomes for 38 patients with chronic refractory osteomyelitis treated at another U.S. institution.<sup>13</sup> Patients received HBOT until the bone was fully recovered with healthy vascular tissue; this resulted in a mean of 48 daily treatments (range, 8 to 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 to 15 patients), all conducted in Taiwan (1998 through 2000), ranged from 79% to 92%.<sup>14,15,16</sup> A high percentage of refractory patients in these series had successful outcomes.

### **Section Summary: Systemic Hyperbaric Oxygen Therapy 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 with other interventions.

### **Systemic Hyperbaric Oxygen Therapy for Acute Thermal Burns**

#### **Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acute thermal burns.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for acute thermal burns improve net health outcomes?

The following PICO was used to select literature to inform this review.

### **Populations**

The relevant population of interest is individuals with acute thermal burns.

### **Interventions**

The therapy being considered is systemic HBOT.

### **Comparators**

Comparators of interest include cooling therapy and medication. Medications prescribed for acute thermal burns may include antibiotics. Pain and anxiety medication may also be used. Systemic HBOT may be used as an adjunct to these comparators.

### **Outcomes**

The general outcomes of interest are OS, symptoms, and change in disease status. The existing literature evaluating systemic HBOT as a treatment for acute thermal burns does not report follow-up time. However, given that patients may require prolonged occupational and physical therapy based on the site and severity of the acute thermal burn, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

In 2004, a Cochrane review assessed HBOT for thermal burns (see Table 5).<sup>17</sup> Two RCTs were identified, published in 1974 and 1997. 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 have been identified in updated literature searches.

**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>17</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>• 1 trial (N=125) reported no difference in length of stay, mortality, or number of surgeries between HBOT and control groups</li> <li>• 1 trial (N=16) reported shorter healing times (19.7 days vs 43.8 days; p&lt;.001) 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 Hyperbaric Oxygen Therapy for Acute Thermal Burns**

A Cochrane review identified 2 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****Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acute surgical and traumatic wounds.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for acute surgical and traumatic wounds improve net health outcomes?

The following PICO was used to select literature to inform this review.

***Populations***

The relevant population of interest is individuals with acute surgical and traumatic wounds.

***Interventions***

The therapy being considered is systemic HBOT.

***Comparators***

Comparators of interest include dressings, débridement, and medication. Medications prescribed for acute surgical and traumatic wounds may include antibiotics and pain management. Systemic HBOT may be used as an adjunct to these comparators.

***Outcomes***

The general outcomes of interest are OS, symptoms, and change in disease status. The existing literature evaluating systemic HBOT as a treatment for acute surgical and traumatic wounds has varying lengths of follow-up, though many had short follow-up period of 6 to 7 days. Depending on the severity of the wounds, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

**Review of Evidence**

A Cochrane review of RCTs on HBOT for acute surgical and traumatic wounds was published by Eskes et al (2013) (see Table 6).<sup>18</sup> HBOT was administered at pressures above 1 atmosphere (atm). To be included, studies had to compare HBOT with a different intervention or compare 2 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 2 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 mean time 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).<sup>19</sup> Reviewers included 8 studies, with sample sizes ranging from 5 to 125 patients. Four studies were randomized, 3 were prospective observational studies, and 1 was a retrospective observational study. As in the Eskes et al (2013) systematic review, data were not pooled. Reviewers noted that 7 of the 8 studies reported statistically significant findings for their primary endpoints, but the endpoints 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.

**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>18</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>3 of 4 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>19</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>

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

### Section Summary: Systemic Hyperbaric Oxygen Therapy for Acute Surgical and Traumatic Wounds

Two systematic reviews identified 4 RCTs; 1 of the reviews also included nonrandomized studies. Heterogeneity among studies (e.g., in patient population, treatment regimen, comparison group, outcomes) prevented pooling of study findings and limited the ability to draw 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 Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with bisphosphonate-related osteonecrosis of the jaw.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for bisphosphonate-related osteonecrosis of the jaw improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### **Populations**

The relevant population of interest is individuals with bisphosphonate-related osteonecrosis of the jaw.

**Interventions**

The therapy being considered is systemic HBOT.

**Comparators**

Comparators of interest include medication and surgical therapy. Medications prescribed may consist of systemic antibiotics and systemic or topical antifungals. Systemic HBOT may be used as an adjunct to these comparators.

**Outcomes**

The general outcomes of interest are symptoms and change in disease status. The existing literature evaluating systemic HBOT as a treatment for bisphosphonate-related osteonecrosis of the jaw analyzed follow-up to 18 months. Though follow-up to 3-month showed initial benefits, the RCT reported below recommended longer term follow-up to analyze outcomes compared with standard of care. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy and superiority to comparators.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

**Review of Evidence**

An unblinded RCT by Freiburger et al (2012) evaluated the use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw (see Tables 7 and 8).<sup>20</sup> The investigators did a per-protocol analysis (actual treatment received) due to crossovers between the treatment groups. Participants were evaluated at 3, 6, 12, and 18 months. At 3 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 2 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)
Freiburger et al (2012) <sup>20</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>20</sup>	46		46		46		
HBOT	68.0 (25)	.03	58.3 (12)	.31	36.0 (25)	.04	1.0
Control	35.0 (20)		33.3 (6)		10.0 (20)		

HBOT: hyperbaric oxygen therapy.

### Section Summary: Systemic Hyperbaric Oxygen Therapy for Bisphosphonate-Related Osteonecrosis of the Jaw

One RCT evaluated HBOT for patients with bisphosphonate-related osteonecrosis of the jaw. This unblinded study reported initial benefits at the 3-month follow-up; however, there were no significant benefits of HBOT for most health outcomes compared with standard care in the long-term (6 months to 2 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 Necrotizing Soft Tissue Infections Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with necrotizing soft tissue infections.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for necrotizing soft tissue infections improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is individuals with necrotizing soft tissue infections.

#### *Interventions*

The therapy being considered is systemic HBOT.

#### *Comparators*

Comparators of interest include medication and surgical therapy. Medications prescribed for necrotizing soft tissue infection may include antibiotics. Surgical therapy can include debridement. Systemic HBOT may be used as an adjunct to these comparators.

#### *Outcomes*

The general outcomes of interest are OS, symptoms, and change in disease status. The existing literature evaluating systemic HBOT as a treatment for necrotizing soft tissue infections has varying lengths of follow-up. However, given the severity of the infection, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

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

**Review of Evidence**

A Cochrane review by Levett et al (2015) evaluated the literature on HBOT as adjunctive therapy for necrotizing fasciitis.<sup>21</sup> 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).<sup>22</sup> 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 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 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 Hyperbaric Oxygen Therapy 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 risk of in-hospital mortality, but these results were subject to publication bias.

**Systemic Hyperbaric Oxygen Therapy for Acute Coronary Syndrome****Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acute coronary syndrome.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for acute coronary syndrome improve net health outcomes?

The following PICO was used to select literature to inform this review.

***Populations***

The relevant population of interest is individuals with acute coronary syndrome.

***Interventions***

The therapy being considered is systemic HBOT.

***Comparators***

Comparators of interest include medication and surgical therapy. Medication prescribed for the treatment of acute coronary syndrome may include thrombolytics, nitroglycerin, antiplatelet drugs, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blocks and statins. Surgical therapy can include angioplasty and stenting and coronary bypass surgery. Systemic HBOT may be used as an adjunct to these comparators.

### Outcomes

The general outcomes of interest are OS, symptoms, change in disease status, and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for acute coronary syndrome has varying lengths of follow-up. However, longer term follow-up does provide better opportunity for analyses of outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

A Cochrane review by Bennett et al (2015) identified 6 trials ( N=665 patients) evaluating HBOT for acute coronary syndrome (see Table 9).<sup>23</sup> 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 2 and 3 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 5 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 2 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>23</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 (n=190) found significant improvements in LVEF with HBOT (MD=5.5%; 95% CI, 2.2% to 8.8%)</li> </ul>

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

### Section Summary: Systemic Hyperbaric Oxygen Therapy for Acute Coronary Syndrome

A Cochrane review of 6 RCTs found insufficient evidence that HBOT is safe and effective for acute coronary syndrome. One pooled analysis of data from 5 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**

### **Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acute ischemic stroke.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for acute ischemic stroke improve net health outcomes?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with acute ischemic stroke.

### ***Interventions***

The therapy being considered is systemic HBOT.

### ***Comparators***

Comparators of interest include administration of tissue plasminogen activator and endovascular procedures. Systemic HBOT may be used as an adjunct to these comparators.

### ***Outcomes***

The general outcomes of interest are OS, symptoms, change in disease status, and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for acute ischemic stroke has varying lengths of follow-up, ranging from none to 6 months. In the systematic review described below, all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, 6 months to 1 year or more of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

In a Cochrane systematic review of RCTs, Bennett et al (2014) evaluated HBOT for acute ischemic stroke (see Table 10).<sup>24</sup> Reviewers identified 11 RCTs ( N=705 participants) that compared HBOT with sham HBOT or no treatment. Reviewers could pool study findings for only 1 outcome (mortality at 3 to 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>24</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 Hyperbaric Oxygen Therapy for Acute Ischemic Stroke

A Cochrane review of RCTs conducted a pooled analysis of 4 RCTs and found no significant difference in mortality rates at 3 to 6 months when patients with acute ischemic stroke were treated with HBOT or a sham intervention. Additional RCT data are 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

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with motor dysfunction associated with stroke.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for motor dysfunction associated with stroke improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is individuals with motor dysfunction associated with stroke.

#### *Interventions*

The therapy being considered is systemic HBOT.

#### *Comparators*

Comparators of interest include physical therapy. Systemic HBOT may be used as an adjunct to these comparators.

#### *Outcomes*

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for motor dysfunction associated with stroke had a treatment-group follow-up time of 2 months. In the RCT described below, longer follow-up was recommended to fully observe outcomes. Therefore, 3 months to 1 year or more of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

Efrati et al (2013) published an RCT evaluating HBOT for treatment of neurologic deficiencies associated with a history of stroke (see Tables 11 and 12).<sup>25</sup> Patients in the treatment group were evaluated at baseline and 2 months. For patients in the delayed treatment control group, outcomes were evaluated at 4 months after crossing over and receiving HBOT. Outcome measures included the National Institutes of Health Stroke Scale, which was measured by physicians blinded to treatment group, and several patient-reported quality of life (QOL) and functional status measures. At the 2-month follow-up, there was a statistically significant improvement in function in the HBOT group compared with the control group, as measured by the National Institutes of Health Stroke Scale, QOL scales, and the ability to perform activities of daily living. 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 compared with before HBOT. This RCT raises the possibility that HBOT may induce improvements in function and QOL for post-stroke patients with motor deficits. However, the results are not definitive, as the RCT was small and enrolled a heterogeneous group of post-stroke patients. The trial was not double-blind and most outcome measures, except for National Institutes of Health Stroke Scale, were patient-reported and prone to the placebo effect. Also, there was a high total dropout rate (20%) at the 2-month follow-up. 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	
					Active (n=30)	Comparator (n=29)
Efrati et al (2013) <sup>25</sup>	Israel	1	2008-2010	Patients $\geq$ 18 y with ischemic or hemorrhagic stroke 6 to 36 mo prior to inclusion with $\geq$ 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>25</sup>	50	50		50	50	
Mean HBOT (SD)	8.5 (3.6)	5.5 (3.6)	.004	16.1 (6.5)	12.8 (7.3)	.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 Hyperbaric Oxygen Therapy for Motor Dysfunction Associated With Stroke

One crossover RCT evaluated HBOT in patients with a recent history of stroke. The RCT reported better outcomes at 2 months with HBOT than with delayed treatment. However, the trial had a number of methodologic limitations, making 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**

### **Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with Bell palsy.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for Bell palsy improve net health outcomes?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with Bell palsy.

### ***Interventions***

The therapy being considered is systemic HBOT.

### ***Comparators***

Comparators of interest include self-care (e.g., artificial tears, eyepatch) and medication. Medications prescribed for Bell palsy may include steroids and antiviral drugs. Systemic HBOT may be used as an adjunct to these comparators.

### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and functional outcomes. There is a lack of published information analyzing the efficacy of systemic HBOT in individuals with Bell palsy. However, in order to analyze long term outcomes of function, symptoms, and change in disease status, follow-up ranging from 3 months or 1 year or more is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

Holland et al (2012) published a Cochrane review evaluating HBOT in adults with moderate-to-severe Bell palsy.<sup>26</sup> The literature search, conducted through January 2012, identified 1 RCT with 79 participants, but this trial did not meet reviewers' prespecified selection standards because the outcome assessor was not blinded to treatment allocation. The trial was therefore excluded with no further analysis.

### **Section Summary: Systemic Hyperbaric Oxygen Therapy 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**

### **Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with traumatic brain injury (TBI).

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for TBI improve net health outcomes?

The following PICO was used to select literature to inform this review.

### **Populations**

The relevant population of interest is individuals with TBI.

### **Interventions**

The therapy being considered is systemic HBOT.

### **Comparators**

Comparators of interest include medication, surgical therapy, and rehabilitation protocols. Medications prescribed for TBI may include diuretics, anti-seizure drugs, and coma-inducing drugs. Emergency surgery is used to minimize damage to brain tissues and can follow on the removal of hematomas, repairing skull fractures, stopping bleeding in the brain, and opening a window in the skull. Systemic HBOT may be used as an adjunct to these comparators.

### **Outcomes**

The general outcomes of interest are OS, symptoms, change in disease status, and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for TBI has varying lengths of follow-up. In the systematic reviews described below, all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

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

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

Outcome	Description	Administration	Scoring	MCID
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: <math>\leq 8</math></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</li> </ol>	Unfavorable outcome: 1-3

Outcome	Description	Administration	Scoring	MCID
PTSD Checklist (PCL)	A 17-item measure that reflects the DSM-IV symptoms of PTSD	Self-administered	<p>life despite minor deficits</p> <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: <math>\geq 5</math> points</li> <li>Clinically meaningful: <math>\geq 10</math> 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; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; 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 following principles:

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

### Review of Evidence

#### Systematic Reviews

A meta-analysis by Wang et al (2016) assessed HBOT for TBI (see Table 14 ).<sup>27</sup> Eight studies ( N=519 participants) 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 2 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 3 of the 8 studies. Pooled analysis of these 3 studies found a significantly lower overall mortality rate in the HBOT group than in the control group.

Another systematic review, by Crawford et al (2016), did not conduct pooled analyses (see Table 14).<sup>28</sup> Reviewers identified 12 RCTs evaluating HBOT for patients with TBI. Using the Scottish Intercollegiate Guidelines Network (SIGN) 50 criteria, 8 trials were rated acceptable and 4 rated low. 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., postconcussive symptom severity, psychological outcomes). Seven trials evaluated HBOT for the acute treatment of patients with moderate-to-severe TBI. Four were rated as acceptable quality and 3 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 score and mortality rate. In 2 of them, outcomes were better with HBOT than with standard care; in the third study, outcomes did not differ significantly.

A Cochrane review by Bennett et al (2012) evaluated HBOT as adjunctive therapy for acute TBI (see Table 14).<sup>29</sup> Reviewers identified 7 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 1 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).<sup>30</sup> Data were aggregated from 4 Department of Defense (DoD) studies that included participant-level data on 254 patients assigned to either HBOT or sham intervention. An additional 3 studies with summary-level participant data were summarized (n=135). The authors assessed changes from baseline to post-intervention 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 the California Verbal Learning Test (CVLT) -II Trial 1-5 Free Recall.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Hart et al (2019) <sup>30</sup> .		7 (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>27</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 (2016) <sup>28</sup> .	Aug 2014	12	Military and civilian patients with		RCTs	<ul style="list-style-type: none"> <li>Pooled analyses not performed</li> <li>Among 3 trials with GCS outcomes, 2 reported</li> </ul>

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
			traumatic brain injury			<p>improvements with HBOT and 1 found no difference</p> <ul style="list-style-type: none"> <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>29</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; CVLT: California Verbal Learning Test; 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

Several trials on mild TBI in military populations have been published; they did not find significant benefits of HBOT compared with sham treatment.<sup>31,32,33</sup> Miller et al (2015) evaluated HBOT in 72 military service members with symptoms continuing at least 4 months after mild TBI in the "Hyperbaric Oxygen Therapy (HBO2) for Persistent Post-concussive Symptoms After Mild Traumatic Brain Injury (mTBI) (HOPPS)" trial.<sup>33</sup> Patients were randomized to 40 daily HBOT sessions at 1.5 atm, 40 sham sessions consisting of room air at 1.2 atm or standard care with no hyperbaric chamber sessions. The primary outcome was change in Rivermead Post-Concussion Symptoms Questionnaire score. A cutoff of 15% improvement was deemed clinically important, which translates to a change score of at least 2 points on the Rivermead Post-Concussion Symptoms Questionnaire-3 subscale. The proportion of patients who met this prespecified change on the Rivermead questionnaire was 52% in the HBOT group, 33% in the sham group, and 25% in the standard care-only group. The difference between rates in the HBOT and sham groups was not statistically significant ( $p=.24$ ). None of the secondary outcomes significantly favored the HBOT group. A criticism of this trial, as well as the other military population studies, was that patient response in the sham group was not due to a placebo effect but to an intervention effect of slightly increased atmospheric pressure (1.2 atm).<sup>34</sup> Other researchers have noted that room air delivered at 1.2 atm would not be considered an acceptable therapeutic dose for any indication, and especially for a condition with persistent symptoms like PCS.

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>35</sup> was the first to include post-intervention follow-up beyond 3 to 6 months. Hart et al (2019) described BIMA, which assessed HBOT for U.S. service members with mTBI.<sup>36</sup> BIMA 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. Churchill et al (2019) reported on the chamber- and protocol-related adverse events (AEs) in the HOPPS and BIMA trials.<sup>37</sup> In addition to AEs, they assessed the success of maintaining the blind with a low-pressure sham control group. Of the total 4245 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 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.<sup>38</sup> 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.<sup>39</sup> The 3 outcomes assessed in the pooled analyses of the 2 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 trial 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 Hyperbaric Oxygen Therapy for Traumatic Brain Injury**

A number of RCTs and systematic reviews have been published. Several RCTs focused on U. S. service members with mild TBI and found that the HBOT and sham group results did not differ significantly. In addition, pooled analyses were only conducted on a minority of the published RCTs, and these analyses had inconsistent findings. Additionally, there was some 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**

#### **Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with inflammatory bowel disease (IBD).

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for IBD improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest is individuals with IBD.

#### ***Interventions***

The therapy being considered is systemic HBOT.

#### ***Comparators***

Comparators of interest include medication and surgical therapy. Medications prescribed for IBD may include anti-inflammatory drugs, immune systems suppressors, antibiotics, anti-diarrheal medications, pain relievers, iron supplements, and calcium and vitamin D supplements. Surgical therapy can include ileal pouch anal anastomosis. Systemic HBOT may be used as an adjunct to these comparators.

#### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for IBD has varying lengths, though many of the studies in the systematic review reported below only followed patients during treatment or for a short time after. Nearly all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

A systematic review by Dulai et al (2014) examined the evidence on HBOT for IBD (Crohn disease, ulcerative colitis; see Table 15).<sup>40</sup> The review was not limited by study design. One RCT identified was published in 2013; it was open-label and included 18 patients with ulcerative colitis.<sup>41</sup> Patients were randomized to standard medical therapy only (n=8) or medical therapy plus HBOT (n=10). The hyperbaric oxygen intervention consisted of 90 minutes of treatment at 2.4 atm, 5 days a week for 6 weeks (total of 30 sessions). The primary outcome was the Mayo score, which has a potential range of 0 to 12, consisting of 4 components (bleeding, stool frequency, physician assessment, and endoscopic appearance) rated from 0 to 3, and added for a final score.<sup>42</sup> Patients with a score of 6 or more are considered to have moderate-to-severe active disease. At follow-up, there was no significant difference between groups in the Mayo score; the median score at 6 months was 0.5 in the HBOT group and 3 in the control group (p-value not reported). Also, there were no significant differences in any secondary outcomes, including laboratory tests and fecal weight. This small trial might have been underpowered. Overall, reviewers found that the selected studies had a high risk of bias, due to attrition and reporting bias.

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

Study (Year)	Literature Search	Participants	N	Design	Results
Dulai et al (2014) <sup>40</sup>	Dec 2013	17 Patients with ulcerative colitis or Crohn disease	<ul style="list-style-type: none"> <li>• Ulcerative colitis (n=327);</li> <li>• Crohn disease (n=286)</li> </ul>	<ul style="list-style-type: none"> <li>• 11 case reports</li> <li>• 3 case series</li> <li>• 2 case-control</li> <li>• 1 RCT</li> </ul>	<ul style="list-style-type: none"> <li>• Overall HBOT response rate across studies: 86%</li> <li>• 1 RCT (N=18) reported no difference in outcomes among patients with ulcerative colitis treated with HBOT vs HBOT plus medical therapy</li> </ul>

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

### Section Summary: Systemic Hyperbaric Oxygen Therapy for Inflammatory Bowel Disease

Only 1 small RCT has been published, and it did not find a significant improvement in health outcomes when HBOT was added to standard medical therapy. A systematic review of RCTs and observational studies found heterogeneity in HBOT protocols and high rates of bias in the literature (e.g., attrition, reporting bias).

### Systemic Hyperbaric Oxygen Therapy for Idiopathic Sudden Sensorineural Hearing Loss Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with idiopathic sudden sensorineural hearing loss (ISSNHL).

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for ISSNHL improve net health outcomes?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with ISSNHL.

### ***Interventions***

The therapy being considered is systemic HBOT alone or as an adjunct to medical therapy.

### ***Comparators***

Comparators of interest include medical therapy. Medications prescribed for ISSNHL may include systemic and intratympanic steroids, antiviral and hemodilution agents and, mineral, vitamin, and herbal supplements.

### ***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and functional outcomes. Follow-up for the evaluation of systemic HBOT as a treatment for ISSNHL would be weeks to months after early intervention. Longer follow-up of at least 1 year is necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

#### **Systematic Reviews**

A Cochrane review by Bennett et al (2012) on HBOT for ISSNHL and/or tinnitus identified 7 RCTs (N=392; see Table 16).<sup>43</sup> Treatment of tinnitus is covered in evidence review 8.01.39. Studies were small and generally of poor quality. 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 across studies (e.g., the total number of treatment sessions ranged from 10 to 25). All trials reported on 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 4 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 HBOT plus medical therapy (MT) with medical therapy alone for ISSNHL treatment.<sup>44</sup> 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 to 2.44) and any hearing recovery (OR, 1.43; 95% CI, 1.20 to 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 measure 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)<sup>45</sup>, 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 audometric 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 et al (2012) <sup>43</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 et al (2018) <sup>44</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>45</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 audometric 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.<sup>46</sup> 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: .0014 to .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.

### **Section Summary: Systemic Hyperbaric Oxygen Therapy 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 rate of hearing recovery, but the analysis was limited to 2 trials with methodological limitations.

### **Systemic Hyperbaric Oxygen Therapy for Delayed-Onset Muscle Soreness Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with delayed-onset muscle soreness.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for delayed-onset muscle soreness improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### ***Populations***

The relevant population of interest is individuals with delayed-onset muscle soreness.

#### ***Interventions***

The therapy being considered is systemic HBOT.

#### ***Comparators***

Comparators of interest include conservative care (e.g., massage) and medication (e.g., pain relief). Systemic HBOT may be used as an adjunct to these comparators.

#### ***Outcomes***

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for delayed-onset muscle soreness has varying lengths of follow-up. In the systematic review described below, all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 month of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

In a Cochrane review, Bennett et al (2005; updated 2010) identified 9 small RCTs on HBOT for delayed-onset muscle soreness and closed soft tissue injury (see Table 17).<sup>47</sup> 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 17. Systematic Reviews of Trials Assessing HBOT for DOMS**

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2010) <sup>47</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 Hyperbaric Oxygen Therapy 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

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with autism spectrum disorder.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for autism spectrum disorder improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is individuals with autism spectrum disorder.

#### *Interventions*

The therapy being considered is systemic HBOT.

#### *Comparators*

Comparators of interest include behavioral therapy and medication. Behavioral therapy may include anger management, family therapy, applied behavior analysis, etc. Medications prescribed may include antipsychotics. Systemic HBOT may be used as an adjunct to these comparators.

#### *Outcomes*

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for autism spectrum disorder had a follow-up of 10 weeks. However, longer term follow-up may show difference between the intervention and comparators. Therefore, at least 6 months of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

A Cochrane review by Xiong et al (2016) identified 1 RCT evaluating systemic HBOT for people with autism spectrum disorder that met eligibility criteria (see Table 18).<sup>48</sup> Criteria included a hyperbaric oxygen intervention using 100% oxygen at more than 1 atm. The trial, published by Sampanthaviat et al (2012), was considered low-quality evidence as assessed by the GRADE approach. The trial randomized children with autism to receive 20 1-hour sessions with HBOT or sham air (n=30 per group).<sup>49</sup> 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. Post-treatment clinician-assessed mean scores on Autism Treatment Evaluation Checklist were 52.4 in the HBOT group and 52.9 in the sham air group.

**Table 18. Systematic Reviews of Trials Assessing HBOT for Autism Spectrum Disorder**

Study (Year)	Literature Search	Studies	Participants	N	Design	Results Mean Difference
Xiong et al (2016) <sup>48</sup>	Dec 2015	1	Children aged 3-9 y with autism spectrum disorder	60	RCT	<ul style="list-style-type: none"> <li>• Parental assessed ATEC: 1.2 (95% CI, -2.2 to 4.6)</li> <li>• Clinician assessed ATEC: 1.5 (95% CI, -1.3 to 4.5)</li> </ul>

ATEC: Autism Treatment Evaluation Checklist; CI: confidence interval; HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial.

In their controlled trial, Rizzato et al (2018) examined the effect of HBOT on children diagnosed with autism.<sup>50</sup> The children in the HBOT group (n=8; mean age=7 y ± 2.33 y) and control group (n=7; mean age=6.6 y ± 2.7 y) completed the Aberrant Behavior Checklist-Community (ABC) before intervention (T0), after 40 sessions (T1), 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 ± 19.01 and 50.38 ± 18.55 at T2 ( $p < .001$ ). The control group's mean score at T0 was 103.6 ± 20.38 and 59 ± 25.25 at T2 ( $p < .05$ ). The investigators concluded that their results do not support the use of HBOT in children diagnosed with autism.

### Section Summary: Systemic Hyperbaric Oxygen Therapy 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 significantly improved outcomes with HBOT versus sham. A subsequent controlled trial reached the same conclusion, stating results do not support the use of HBOT for autism spectrum disorder.

### Systemic Hyperbaric Oxygen Therapy for Cerebral Palsy

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with cerebral palsy (CP).

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for CP improve net health outcomes?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with CP.

### ***Interventions***

The therapy being considered is systemic HBOT.

### ***Comparators***

Comparators of interest include physical therapy and medication. Medications directed at isolated (e.g., onabotulinumtoxinA) and generalized spasticity (e.g., diazepam, dantrolene, and baclofen) may be prescribed for CP. Systemic HBOT may be used as an adjunct to these comparators.

### ***Outcomes***

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for CP has varying lengths of follow-up. In the trials described below, all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

Two published RCTs were identified on use of HBOT for CP (see Tables 19 and 20). Lacey et al (2012) published a double-blind RCT that included 49 children ages 3 to 8 years with spastic CP.<sup>51</sup> 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 global score. 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 (2001) randomized 111 children with CP to 40 treatments over a 2-month period of HBOT or slightly pressurized room air.<sup>52</sup> 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 CP (N=71).<sup>53</sup> Children, aged 2 to 6 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 10 HBOT sessions compared with pretreatment.

**Table 19. Characteristics of Trials Assessing HBOT for Cerebral Palsy**

Study (Year)	Countries	Sites	Dates	Participants	Active	Treatment
						Comparator
Lacey et al (2012) <sup>51</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>52</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 20. Results of Trials Assessing HBOT for Cerebral Palsy**

Study (Year)	Mean Change GMFM <sup>a</sup> (95% CI)	Between-Group Difference (95% CI)	Mean Change, Functional Skill	Between-Group Difference (95% CI)
Lacey et al (2012) <sup>51</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>52</sup>			Mean Change, 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 Hyperbaric Oxygen Therapy for 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 CP, reported improvements following HBOT.

### Systemic Hyperbaric Oxygen Therapy for Vascular Dementia

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with vascular dementia.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for vascular dementia improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### Populations

The relevant population of interest is individuals with vascular dementia.

#### Interventions

The therapy being considered is systemic HBOT.

**Comparators**

Comparators of interest are rehabilitation and medication (e.g., cognition-enhancing medication). Systemic HBOT may be used as an adjunct to these comparators.

**Outcomes**

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for vascular dementia reported follow-up at 12 weeks. However, longer follow-up is necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

**Review of Evidence**

A Cochrane review (2012) identified a small RCT evaluating HBOT for vascular dementia (see Table 21).<sup>54</sup> This 2009 RCT, conducted in China, compared HBOT (30-day cycles of 1 hour/day for 24 days and 6 days of rest) plus donepezil to donepezil-only in 64 patients. The HBOT plus donepezil group had significantly improved 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 21. Systematic Reviews of Trials Assessing HBOT for Vascular Dementia**

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Xiao et al (2012) <sup>54</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 Hyperbaric Oxygen Therapy 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****Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with radiotherapy adverse events.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for radiotherapy adverse effects improve net health outcomes?

The following PICO was used to select literature to inform this review.

### ***Populations***

The relevant population of interest is individuals with radiotherapy adverse events.

### ***Interventions***

The therapy being considered is systemic HBOT.

### ***Comparators***

Comparators of interest include medication. Medications to treat cardiovascular and pulmonary adverse events (e.g., pentoxifylline), gastrointestinal toxicity (e.g., amifostine, antidiarrheals), radiation-induced emesis (5-HT<sub>3</sub>), radiation cystitis (e.g., phenazopyridine, oxybutynin, and flavoxate), and sexual dysfunction (e.g., sildenafil and tadalafil) may be prescribed. Systemic HBOT may be used as an adjunct to these comparators.

### ***Outcomes***

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for radiotherapy adverse events has varying lengths of follow-up. In the systematic reviews and RCTs described below, nearly all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

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

### **Review of Evidence**

#### **Systematic Reviews**

Spiegelberg et al (2010) conducted a systematic review of studies on HBOT to prevent or treat radiotherapy-induced head and neck injuries associated with the treatment of malignant tumors (see Table 22).<sup>55</sup> Reviewers identified 20 studies. Protocols and conclusions varied across the studies. Eight studies included control groups; their sample sizes ranged from 19 to 78 subjects. Four studies with a control group concluded that HBOT was effective; the other 4 did not. Reviewers noted a paucity of RCTs, though they did not state how many RCTs were included in the review, because studies were only identified only as prospective or retrospective.

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 22).<sup>11</sup> 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 previously (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.<sup>56</sup> 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 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 22. Systematic Reviews of Studies Assessing HBOT for Radiotherapy Adverse Events**

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Spiegelberg et al (2010) <sup>55</sup> ,	Jun 2009	20	Patients who have received RT for malignant tumors in the head and neck	695	Prospective and retrospective studies	<ul style="list-style-type: none"> <li>• Due to the heterogeneity among studies, pooled analysis was not possible</li> <li>• 8 studies had control groups and 4 concluded that HBOT was effective and 4 concluded that HBOT was not</li> </ul>
Ravi et al (2017) <sup>11</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: 2 case series (n=96) reported that patients receiving HBOT experienced improvements in salivary flow rates</li> <li>• Quality of life: 3 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>56</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; RCT: randomized controlled trial; RT: radiotherapy; SF-36: 36-Item Short-Form Health Survey.

### Randomized Controlled Trials

Several RCTs were identified in literature searches. A trial by Teguh et al (2009), included in the reviews, evaluated 17 patients with oropharyngeal or nasopharyngeal cancer who were treated with radiotherapy; the trial was conducted in the Netherlands.<sup>57</sup> HBOT was used to prevent adverse events following radiotherapy. Eight patients were randomized to 30 sessions of HBOT, administered within 2 days of completing radiotherapy, and 9 patients to no additional treatment. QOL

outcomes were assessed, and the primary outcome was xerostomia at 1 year. QOL measures did not differ significantly between groups in the acute phase (first 3 months). One month after treatment, the mean visual analog scale score (0-to-10 scale) for xerostomia was 5 in the HBOT group and 6 in the control group. However, at 1 year, there was a statistically significant difference between groups in mean QOL score (0-to-100 scale) for swallowing, (7 in the HBOT group and 40 in the control group,  $p < .001$ ). The trial is limited by its small sample size and wide fluctuations over the follow-up in QOL ratings.

In a trial not included in the reviews, Gothard et al (2010) in the U.K. published findings of an RCT using HBOT for arm lymphedema occurring after radiotherapy for cancer.<sup>58</sup> Fifty-eight patients with arm lymphedema (at least 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 of patients in the HBOT group were considered responders compared with 3 (19%) of 16 in the control group ( $p = \text{not significant}$ ). 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.<sup>59</sup> 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 on a 0 to 100 score. A post hoc analysis determined the minimal clinically important difference to be 9 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 to 40 treatments within 60 to 80 days. No study-specific treatment was administered to the standard care group. The trial included 4 visits, and at the fourth visit, the mean Expanded Prostate Index Composite urinary total score in the HBOT group had increased 17.8 points (standard deviation [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 ( $p = .0012$ ).

### Prospective Clinical Trials

A prospective cohort study by Sherlock et al (2018) evaluated HBOT for managing radiation-induced xerostomia (dry mouth).<sup>60</sup> They compared saliva volume (objective), QOL scoring, and visual analog scale of discomfort (subjective) measurements taken before HBOT treatment, and after 30 90-minute sessions completed over 6 weeks, and a review at 12 weeks from the start of HBOT. Fifty-three treatment courses in 51 patients were eligible for inclusion in the statistical analysis, 78.4% of whom had been treated for oral cancer (2 patients repeated the treatment due to symptom relapse). All domains had improved significantly at the end of treatment: saliva volume,  $p = .016$ ; visual analog scale score,  $p < .001$ ; QOL score,  $p < .001$ . The only adverse reactions were minor middle ear barotrauma, occurring in 21% of patients (1.4% of all compression cycles). The authors concluded that HBOT may be a safe and effective option for treating symptoms of xerostomia after radiation therapy.

**Section Summary: Systemic Hyperbaric Oxygen Therapy for Radiotherapy Adverse Events**

Three systematic reviews included 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. The available RCTs had mixed findings. One found no short-term benefit and some benefits of HBOT 12 months after radiotherapy, while the other did not find a significant benefit of HBOT 12 months after radiotherapy. 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. An observational study for dry mouth (xerostomia) caused by radiotherapy found some benefit to HBOT.

**Systemic Hyperbaric Oxygen Therapy for Idiopathic Femoral Neck Necrosis****Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with idiopathic femoral neck necrosis.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for femoral neck necrosis improve net health outcomes?

The following PICO was used to select literature to inform this review.

***Populations***

The relevant population of interest is individuals with idiopathic femoral neck necrosis.

***Interventions***

The therapy being considered is systemic HBOT.

***Comparators***

Comparators of interest include physical therapy, medication, and surgical therapy. Medications prescribed to treat idiopathic femoral neck necrosis may include non-steroidal anti-inflammatory drugs, osteoporosis drugs, cholesterol-lowering drugs, and blood thinners. Systemic HBOT may be used as an adjunct to these comparators.

***Outcomes***

The general outcomes of interest are symptoms, change in disease status, and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for idiopathic femoral neck necrosis analyzed HBOT therapy at 6 weeks of follow-up. Longer follow-up is necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

**Review of Evidence**

A double-blind RCT evaluating HBOT for treatment of femoral head necrosis was published by Camporesi et al (2010) (see Tables 23 and 24).<sup>61</sup> The trial included 20 adults with idiopathic unilateral femoral head necrosis. Patients received HBOT or a sham treatment of hyperbaric air. 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 ( $p<.001$ ) 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 6-week treatment period.

**Table 23. 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>61</sup>	United States	1	NR	Patients with unilateral femoral neck necrosis	<ul style="list-style-type: none"> <li>Hyperbaric oxygen</li> <li>100% oxygen at 2.5 ATA</li> <li>30 sessions over 6 wk</li> </ul>	<ul style="list-style-type: none"> <li>Hyperbaric air</li> <li>30 sessions over 6 wk</li> </ul>

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

**Table 24. 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>61</sup>				
HBOT	7.5 (4.0-20.0)	NS	20.0 (15.0-20.0)	<.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 Hyperbaric Oxygen Therapy 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

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with migraine headache.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for migraine headache improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### Populations

The relevant population of interest is individuals with migraine headache.

#### Interventions

The therapy being considered is systemic HBOT.

#### Comparators

Comparators of interest include medication. Medications prescribed to treat migraines may include antipsychotics, analgesics, non-steroidal anti-inflammatory drugs, stimulants, nerve pain relievers, Triptan, and neurotoxins. Systemic HBOT may be used as an adjunct to these comparators.

**Outcomes**

The general outcomes of interest are symptoms, change in disease status, and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for migraine has varying lengths of follow-up. In the systematic reviews described below, nearly all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 month of follow-up is considered necessary to demonstrate efficacy.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

**Review of Evidence**

A Cochrane review by Bennett et al (2015) identified 11 RCTs ( N=209 patients) comparing the effectiveness of systemic HBOT for preventing or treating migraine headache or cluster headaches with another treatment or a sham control (see Table 25).<sup>62</sup> A pooled analysis of 3 trials focusing on migraine headaches (n=58 patients) found a statistically significant increase in the proportion of patients with substantial relief of a 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 25. 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>62</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 need for rescue medication</li> </ul>

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

**Section Summary: Systemic Hyperbaric Oxygen Therapy for Migraine**

A Cochrane review identified 11 RCTs on HBOT for a 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 the availability of outcomes specific to the immediate post-treatment period, the variability of outcomes across trials, and generally low methodologic quality of trials.

**Systemic Hyperbaric Oxygen Therapy for Herpes Zoster****Clinical Context and Therapy Purpose**

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with herpes zoster.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for herpes zoster infection improve net health outcomes?

The following PICO was used to select literature to inform this review.

### **Populations**

The relevant population of interest is individuals with herpes zoster.

### **Interventions**

The therapy being considered is systemic HBOT.

### **Comparators**

Comparators of interest include medication. Medications prescribed to treat herpes zoster may include anti-viral drugs, anesthetics, non-steroidal anti-inflammatory drugs, analgesics, and nerve pain relievers. Systemic HBOT may be used as an adjunct to these comparators.

### **Outcomes**

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for herpes zoster described below, reported outcomes of interest, but longer follow-up are necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

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

### **Review of Evidence**

Peng et al (2012) in China published an RCT evaluating HBOT for herpes zoster (see Tables 26 and 27).<sup>63</sup> Sixty-eight patients with herpes zoster were randomized to HBOT with medication or medication treatment alone. The following outcomes were measured after 3 weeks of treatment: therapeutic efficacy, days to blister resolution, days to scar formation, and pain. Patient 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 26. 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>63</sup>	China	NR	2008-2010	Patients diagnosed with herpes zoster within 2 wk	<ul style="list-style-type: none"> <li>• Hyperbaric oxygen</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 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 27. 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>63</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  $p < .05$ .

### Section Summary: Systemic Hyperbaric Oxygen Therapy for 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

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with fibromyalgia.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for fibromyalgia improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is individuals with fibromyalgia.

#### *Interventions*

The therapy being considered is systemic HBOT.

#### *Comparators*

Comparators of interest include medication. Medications prescribed for fibromyalgia may include selective serotonin reuptake inhibitors, analgesics, non-steroidal anti-inflammatory drugs, nerve pain relievers, and muscle relaxants. Systemic HBOT may be used as an adjunct to these comparators.

#### *Outcomes*

The general outcomes of interest are symptoms, change in disease status, and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for fibromyalgia has varying lengths of follow-up. In the systematic reviews described below, all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

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 2 years (see Tables 28 and 29).<sup>64</sup> Patients were randomized to an immediate 2-month course of HBOT or delayed HBOT after 2 months. Forty-eight (80%) of 60 patients completed the trial. After the initial 2 months, outcomes including a 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 2 months before HBOT treatment. These findings are not only consistent with a 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 28 and 29).<sup>65</sup> 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 28. Characteristics of Trials Assessing HBOT for Fibromyalgia**

Study (Year)	Countries	Sites	Dates	Participants	Active	Treatment
						Comparator
Efrati et al (2015) <sup>64</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>Hyperbaric oxygen</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>65</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>Hyperbaric oxygen</li> <li>100% oxygen at 2.4 ATA</li> <li>1 session/day for 5 d</li> <li>Fifteen 90-min sessions</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> <li>Fifteen 90-minute sessions</li> </ul>

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

**Table 29. 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
Efrati et al(2015) <sup>64</sup> .	50			50		
Mean HBOT (SD)	17.3 (1.4)	8.9 (6.0)	<.001	0.5 (1.2)	1.7 (0.8)	<.001
Mean control (SD)	17.7 (0.7)	17.2 (1.1)		0.7 (0.5)	0.6 (0.5)	
Yildiz et al (2004) <sup>65</sup> .	50			50		

	Tender Points			Pain Threshold		
Mean HBOT (SD)	15.0 (1.5)	6.0 (1.2)	<.001	0.7 (0.1)	1.3 (0.1)	<.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 Hyperbaric Oxygen Therapy 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 protocols 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

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with multiple sclerosis (MS).

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for MS improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### Populations

The relevant population of interest is individuals with MS.

#### Interventions

The therapy being considered is systemic HBOT.

#### Comparators

Comparators of interest include medication. Medications prescribed to treat MS include chemotherapy, anti-inflammatory drugs, immunosuppressive drugs, and steroids. Systemic HBOT may be used as an adjunct to these comparators.

#### Outcomes

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for MS has varying lengths of follow-up, ranging from 4 weeks to 6 months. In the systematic review described below, nearly all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

#### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

#### Review of Evidence

Bennett et al (2010) published a systematic review on the use of HBOT for treatment of MS (see Table 30).<sup>66</sup> Nine RCTs (N=504 participants) were identified that compared the effects of HBOT with placebo or no treatment. All trials used an initial course of 20 sessions over 4 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 Expanded Disability Status Scale score. A pooled analysis of data from 5 trials (n=271 patients) did not find a significant difference in mean Expanded Disability Status Scale score change after 20 HBOT treatments versus control or after 6 months of follow-up.

**Table 30. Systematic Reviews of Trials Assessing HBOT for Multiple Sclerosis**

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2010) <sup>66</sup>	Jul 2009	9	Patients with multiple sclerosis, at any state or course of the condition	504	RCT	EDSS score difference between groups: <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 Hyperbaric Oxygen Therapy for Multiple Sclerosis

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

### Systematic Hyperbaric Oxygen Therapy for Individuals with Cancer who are Undergoing Radiotherapy or Chemotherapy

#### Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with cancer who are undergoing radiotherapy or chemotherapy.

The question addressed in this evidence review is: Does the use of systemic hyperbaric oxygen as a treatment for individuals with cancer who are undergoing radiotherapy or chemotherapy improve net health outcomes?

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is individuals with cancer who are undergoing radiotherapy or chemotherapy.

#### *Interventions*

The therapy being considered is systemic HBOT.

#### *Comparators*

Comparators of interest include radiotherapy or chemotherapy without HBOT. Systemic HBOT may be used as an adjunct to these comparators.

#### *Outcomes*

The general outcomes of interest are OS and change in disease status. The existing literature evaluating systemic HBOT as a treatment for cancer who are undergoing radiotherapy or chemotherapy has varying lengths of follow-up, 6 months to 5 years. In the systematic review and RCT described below, nearly all studies reported at least 1 outcome of interest, but longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

### Review of Evidence

In a Cochrane review (2005),<sup>67</sup> which was updated in 2012,<sup>68</sup> Bennett et al (2018) identified 19 randomized and quasi-randomized trials ( N=2286 patients) comparing outcomes following radiotherapy with and without HBOT in patients with solid tumors (see Table 31). 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 31. 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 (2018) <sup>68</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=.03</math>)</li> <li>• 5-year mortality: RR=0.8 (<math>p=.03</math>)</li> <li>• 5-y recurrence: RR=0.8 (<math>p=.01</math>)</li> </ul> Uterine: <ul style="list-style-type: none"> <li>• 2-y recurrence: RR=0.6 (<math>p=.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>69</sup>

### Section Summary: Systemic Hyperbaric Oxygen Therapy 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 did 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:

- bone grafts;

- carbon tetrachloride poisoning, acute;
- cerebrovascular disease, acute (thrombotic or embolic) or chronic;
- fracture healing;
- hydrogen sulfide poisoning;
- intra-abdominal and intracranial abscesses;
- lepromatous leprosy;
- meningitis;
- pseudomembranous colitis (antimicrobial agent-induced colitis);
- radiation myelitis;
- sickle cell crisis and/or hematuria;
- amyotrophic lateral sclerosis;
- retinal artery insufficiency, acute;
- retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment;
- pyoderma gangrenosum;
- compromised skin grafts and flaps;
- brown recluse spider bites;
- spinal cord injury;
- refractory mycoses;
- acute peripheral arterial insufficiency;
- in vitro fertilization; or
- mental illness.

### Summary of Evidence

For individuals with wounds, burns or infections who receive topical HBOT, the evidence includes a systematic review, case series, and an RCT. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. The systematic review identified 3 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 chronic 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 3 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 OS 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.

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.

For individuals with acute thermal burns who receive systemic HBOT, the evidence includes a systematic review of 2 RCTs. Relevant outcomes are OS, 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 that the technology results in an improvement in the net health outcome.

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 OS, symptoms, change in disease status, and functional outcomes. There was considerable heterogeneity across the 4 RCTs identified (e.g., patient population, comparison group, treatment regimen, outcomes). This heterogeneity prevented pooling of trial findings and limits the ability to conclude the impact of HBOT on health outcomes for patients with acute surgical and traumatic wounds. Additional evidence from high-quality RCTs is needed. 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 outcomes are symptoms and change in disease status. The RCT was unblinded and reported initial benefits at 3-month follow-up; however, there were no significant benefits of HBOT for most health outcomes compared with standard care in the long-term (6 months to 2 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 OS, symptoms, change in disease status, and functional outcomes. A Cochrane review identified 6 RCTs. There were 2 pooled analyses, 1 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 that the technology results in an improvement in the net health outcome.

For individuals with acute ischemic stroke who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. Cochrane reviewers could only pool data for a single outcome (mortality at 3 to 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 2 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 OS, symptoms, change in disease status, and functional outcomes. RCTs were heterogeneous regarding intervention protocols, patient populations, and outcomes reported. Multiple RCTs of US military service members showed no statistical difference in outcomes between HBOT groups and those that received sham treatment. 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 an RCT, observational studies, and a systematic review. Relevant outcomes are symptoms, change in disease status and functional outcomes. One small RCT has been published, and this trial did not find a significant improvement in health outcomes when HBOT was added to standard medical therapy. 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. 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 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. A subsequent controlled trial reached the same conclusion. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cerebral palsy who receive systemic HBOT, the evidence includes 2 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. Three systematic reviews included few RCTs and provide limited evidence on the effect of HBOT. Two RCTs identified 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. An observational study for dry mouth (xerostomia) caused by radiotherapy found some benefit with HBOT. 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., 6-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 3 of the 11 trials. Meta-analysis of these 3 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., 6-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 2 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 versus 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 OS 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.

### **Supplemental Information**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **Clinical Input 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.

### **2010 Input**

In response to requests from Blue Cross Blue Shield Association, input was received from 6 physician specialty societies and 5 academic medical centers in 2010. Clinical input varied by condition. There was consensus that topical hyperbaric oxygen therapy (HBOT) and systemic HBOT for autism spectrum disorder and headache/migraine are investigational. There was also wide support for adding 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.

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

In 2016, the Society of Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine published guidelines on the management of the diabetic foot.<sup>70</sup> According to the guidelines, for diabetic foot ulcers that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 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 4 to 6 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.<sup>71</sup> 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 2019 UHMS Hyperbaric Oxygen Therapy Indications (14th edition) included the following indications as recommended:<sup>72</sup>

1. Air or Gas Embolism
2. Carbon Monoxide Poisoning and carbon monoxide complicated by cyanide poisoning
3. Clostridial Myositis and Myonecrosis (Gas Gangrene)
4. Crush Injury, Compartment Syndrome and Other Acute Traumatic Ischemias
5. Decompression Sickness
6. Central retinal artery occlusion
7. Diabetic foot ulcer
8. Healing of other problem wounds
9. Severe anemia
10. Intracranial abscess
11. Necrotizing soft tissue infections
12. Refractory osteomyelitis
13. Delayed radiation injury (soft tissue and bony necrosis)
14. Compromised grafts and flaps
15. Acute thermal burn injury
16. Sudden Sensorineural hearing loss.

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

In 2018, the American Academy of Otolaryngology-Head and Neck Surgery updated clinical guidelines on treatment of sudden hearing loss.<sup>73</sup> 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 2 weeks of onset of SSNH."

"Clinicians may offer, or refer to a physician who can offer, hyperbaric oxygen therapy (HBOT) combined with steroid therapy as salvage within 1 months of onset of SSNHL."

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

Not applicable.

### **Medicare National Coverage**

In 2003, the Centers for Medicare & Medicaid added Medicare coverage of HBOT for diabetic wounds of the lower extremities meeting certain criteria. As of the current coverage statement, Medicare coverage is provided for HBOT administered in a chamber for the following conditions<sup>74</sup>:

1. "Acute carbon monoxide intoxication,
2. Decompression illness,
3. Gas embolism,
4. Gas gangrene,
5. Acute traumatic peripheral ischemia. HBO 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 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 3 criteria:
  - a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
  - b. Patient has a wound classified as Wagner grade III or higher; and
  - c. Patient has failed an adequate course of standard wound therapy."

The use of 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: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, débridement 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 therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment."

Systemic HBOT for other indications is not covered, nor is topical HBOT for any indication.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 32.

**Table 32. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04472780	Effect of Hyperbaric Oxygen Therapy (HBOT) in Children With Autism Spectrum Disorder (ASD)	80	Oct 2021
NCT02407028	Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial	200	Jun 2023
NCT04316702	Hyperbaric Oxygen Therapy vs. Pharmaceutical Therapy in Patients Suffering From Fibromyalgia That Was Induced by Emotional Trauma: Prospective, Randomized, Two Active Arms Clinical Trial	60	Mar 2023
NCT04193722	The Effect of Hyperbaric Oxygen Therapy on Breast Cancer Patients With Late Radiation Toxicity	120	Sep 2023
NCT04049721	Use of Hyperbaric Oxygen Therapy for the Treatment of Crush Injuries	30	Sep 2023
NCT01986205	A Double-blind Randomized Trial of Hyperbaric Oxygen Versus Sham for Persistent Symptoms After Brain Injury	150	Dec 2023
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
<i>Unpublished</i>			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02085330	Hyperbaric Oxygen Therapy for Mild Cognitive Impairment	60	Feb 2017 (unknown; last updated 10/02/14)
NCT03147352	Pro-Treat - Prognosis and Treatment of Necrotizing Soft Tissue Infections: a Prospective Cohort Study	310	Jan 2018 (completed; last updated 06/24/19)
NCT02089594	Hyperbaric Oxygen Therapy Treatment of Chronic Mild Traumatic Brain Injury (mTBI)/Persistent Post-Concussion Syndrome (PCCS)	59	Mar 2019 (status unknown; last updated 4/18/17)
NCT03325959	Hyperbaric Oxygen versus Standard Pharmaceutical Therapies for Fibromyalgia Syndrome - Prospective, Randomized, Crossover Clinical Trial	70	Nov 2019 (status unknown; last updated 10/30/17)

NCT: national clinical trial.

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## Documentation for Clinical Review

### Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Diagnosis related to hyperbaric oxygen therapy
  - Previous treatment and response
- Proposed initial or continued treatment plan (including number of treatment sessions)
- Progress notes of ongoing treatment as applicable
- Operative/Procedure report(s)
- Current wound description (if applicable) including:
  - Wound location, size, and description of wound bed
  - Wagner wound classification
  - Wound therapy treatments over the last 30 days
  - Wound progress

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	99183	Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session
HCPCS	A4575	Topical hyperbaric oxygen chamber, disposable
	E0446	Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories
	G0277	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
05/16/1984	New Policy Adoption
10/11/1995	Policy Revision
06/07/2000	BCBSA Medical Policy adoption
08/01/2002	Administrative Review
12/01/2006	BCBSA Medical Policy adoption
12/10/2008	Policy Revision
07/02/2010	Policy revision with position change
01/21/2011	Coding Update

Effective Date	Action
09/27/2013	Policy revision with position change
05/02/2014	Policy title change from Hyperbaric Oxygen Therapy (HBOT) Policy revision with position change effective July 11, 2014
07/11/2014	Policy revision with position change
01/30/2015	Policy revision without position change Coding update
08/01/2016	Policy title change from Hyperbaric Oxygen Pressurization (HBO) Policy revision without position change
03/01/2017	Policy revision without position change
05/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
03/01/2020	Annual review. No change to policy statement. Literature review updated.
05/01/2020	Administrative update. Policy statement updated.
03/01/2021	Annual review. Policy guidelines and literature updated.
03/01/2022	Annual review. Policy statement and literature updated.
03/01/2023	Annual review. No change to policy statement.
08/01/2023	Policy statement, and literature review updated.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: [MedPolicy@blueshieldca.com](mailto:MedPolicy@blueshieldca.com)

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT	
BEFORE <span style="color: red;">Red font: Verbiage to be removed</span>	AFTER <span style="color: blue;">Blue font: Verbiage Changes/Additions by BCBSA</span>
<p><b>Hyperbaric Oxygen Therapy 2.01.04</b></p> <p><b>Policy Statement:</b> Topical hyperbaric oxygen therapy is considered <b>investigational</b>.</p> <p>Systemic hyperbaric oxygen pressurization may be considered <b>medically necessary</b> in the treatment of <b>any</b> of the following conditions:</p> <ol style="list-style-type: none"> <li>I. Acute carbon monoxide poisoning</li> <li>II. Acute cyanide poisoning</li> <li>III. Acute gas embolism</li> <li>IV. Acute traumatic ischemia (e.g., crush injuries, reperfusion injury, compartment syndrome)</li> <li>V. Chronic refractory osteomyelitis</li> <li>VI. Compromised skin grafts or flaps</li> <li>VII. Decompression sickness</li> <li>VIII. Gas gangrene (i.e., clostridial myonecrosis)</li> <li>IX. Nonhealing diabetic wounds of the lower extremities in patients who meet <b>all</b> of the following criteria:               <ol style="list-style-type: none"> <li>a. <b>Patient</b> has a wound classified as <span style="color: blue;">Wagner</span> grade 3 or higher</li> <li>b. <b>Patient</b> has no measurable signs of healing after 30 days of an adequate course of standard wound therapy</li> <li>c. <b>Patient</b> has type 1 or type 2 diabetes and has a lower-extremity wound due to diabetes</li> </ol> </li> <li>X. Pre- and posttreatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw</li> <li>XI. Profound anemia with exceptional blood loss and <b>either</b> of the following:               <ol style="list-style-type: none"> <li>a. When blood transfusion is impossible</li> <li>b. When blood transfusion must be delayed</li> </ol> </li> <li>XII. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis)</li> <li>XIII. Osteoradionecrosis</li> </ol>	<p><b>Hyperbaric Oxygen Therapy 2.01.04</b></p> <p><b>Policy Statement:</b></p> <ol style="list-style-type: none"> <li>I. Topical hyperbaric oxygen therapy is considered <b>investigational</b>.</li> <li>II. Systemic hyperbaric oxygen pressurization may be considered <b>medically necessary</b> in the treatment of <b>any</b> of the following conditions:               <ol style="list-style-type: none"> <li>A. Acute carbon monoxide poisoning</li> <li>B. Acute cyanide poisoning</li> <li>C. Acute gas embolism</li> <li>D. Acute traumatic ischemia (e.g., crush injuries, reperfusion injury, compartment syndrome)</li> <li>E. Chronic refractory osteomyelitis</li> <li>F. Compromised skin grafts or flaps</li> <li>G. Decompression sickness</li> <li>H. Gas gangrene (i.e., clostridial myonecrosis)                   <ol style="list-style-type: none"> <li>I. Nonhealing diabetic wounds of the lower extremities in patients who meet <b>all</b> of the following criteria:                       <ol style="list-style-type: none"> <li>1. <span style="color: blue;">Individual</span> has a wound classified as <span style="color: blue;">Wagner</span> grade 3 or higher</li> <li>2. <span style="color: blue;">Individual</span> has no measurable signs of healing after 30 days of an adequate course of standard wound therapy</li> <li>3. <span style="color: blue;">Individual</span> has type 1 or type 2 diabetes and has a lower-extremity wound due to diabetes</li> </ol> </li> <li>J. Pre- and posttreatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw</li> <li>K. Profound anemia with exceptional blood loss and <b>either</b> of the following:                           <ol style="list-style-type: none"> <li>1. When blood transfusion is impossible</li> <li>2. When blood transfusion must be delayed</li> </ol> </li> <li>L. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis)</li> </ol> </li> </ol> </li> </ol>

## POLICY STATEMENT

BEFORE <b>Red font: Verbiage to be removed</b>	AFTER <b>Blue font: Verbiage Changes/Additions by BCBSA</b>
<p>Hyperbaric oxygen pressurization is considered <b>investigational</b> in all other situations, including but not limited to, the treatment of the following conditions:</p> <ol style="list-style-type: none"> <li>I. Acute arterial peripheral insufficiency</li> <li>II. Acute carbon tetrachloride poisoning</li> <li>III. Acute cerebral edema</li> <li>IV. Acute coronary syndromes and as an adjunct to coronary interventions, including but not limited to, percutaneous coronary interventions and cardiopulmonary bypass</li> <li>V. Acute ischemic stroke</li> <li>VI. Acute osteomyelitis</li> <li>VII. Acute retinal artery insufficiency</li> <li>VIII. Acute surgical and traumatic wounds</li> <li>IX. Acute thermal burns</li> <li>X. Autism spectrum disorder</li> <li>XI. Bell palsy</li> <li>XII. Bisphosphonate-related osteonecrosis of the jaw</li> <li>XIII. Bone grafts</li> <li>XIV. Brown recluse spider bites</li> <li>XV. Cerebral palsy</li> <li>XVI. Cerebrovascular disease, acute (thrombotic or embolic) or chronic</li> <li>XVII. Chronic arm lymphedema following radiotherapy for cancer</li> <li>XVIII. Chronic wounds, other than those in patients with diabetes who meet the criteria specified in the medically necessary statement</li> <li>XIX. Delayed-onset muscle soreness</li> <li>XX. Demyelinating diseases (e.g., multiple sclerosis, amyotrophic lateral sclerosis)</li> <li>XXI. Early treatment (beginning at completion of radiotherapy) to reduce adverse events of radiotherapy</li> <li>XXII. Fibromyalgia</li> <li>XXIII. Fracture healing</li> <li>XXIV. Herpes zoster</li> <li>XXV. Hydrogen sulfide poisoning</li> <li>XXVI. Idiopathic femoral neck necrosis</li> <li>XXVII. Idiopathic sudden sensorineural hearing loss</li> <li>XXVIII. In vitro fertilization</li> </ol>	<p>M. Osteoradionecrosis</p> <p>III. Systemic hyperbaric oxygen pressurization is considered <b>investigational</b> in all other situations, including but not limited to, the treatment of the following conditions:</p> <ol style="list-style-type: none"> <li>A. Acute arterial peripheral insufficiency</li> <li>B. Acute carbon tetrachloride poisoning</li> <li>C. Acute cerebral edema</li> <li>D. Acute coronary syndromes and as an adjunct to coronary interventions, including but not limited to, percutaneous coronary interventions and cardiopulmonary bypass</li> <li>E. Acute ischemic stroke</li> <li>F. Acute osteomyelitis</li> <li>G. Acute retinal artery insufficiency</li> <li>H. Acute surgical and traumatic wounds <b>not meeting criteria specified in the medically necessary statement</b></li> <li>I. Acute thermal burns</li> <li>J. Autism spectrum disorder</li> <li>K. Bell palsy</li> <li>L. Bisphosphonate-related osteonecrosis of the jaw</li> <li>M. Bone grafts</li> <li>N. Brown recluse spider bites</li> <li>O. Cerebral palsy</li> <li>P. Cerebrovascular disease, acute (thrombotic or embolic) or chronic</li> <li>Q. Chronic arm lymphedema following radiotherapy for cancer</li> <li>R. Chronic wounds, other than those in patients with diabetes who meet the criteria specified in the medically necessary statement</li> <li>S. Delayed-onset muscle soreness</li> <li>T. Demyelinating diseases (e.g., multiple sclerosis, amyotrophic lateral sclerosis)</li> <li>U. Early treatment (beginning at completion of radiotherapy) to reduce adverse events of radiotherapy</li> <li>V. Fibromyalgia</li> <li>W. Fracture healing</li> <li>X. Herpes zoster</li> </ol>

**POLICY STATEMENT**

<p style="text-align: center;"><b>BEFORE</b></p> <p style="text-align: center;"><b>Red font: Verbiage to be removed</b></p>	<p style="text-align: center;"><b>AFTER</b></p> <p style="text-align: center;"><b>Blue font: Verbiage Changes/Additions by BCBSA</b></p>
<p>XXIX. Inflammatory bowel disease (Crohn disease or ulcerative colitis)</p> <p>XXX. Intra-abdominal and intracranial abscesses</p> <p>XXXI. Lepromatous leprosy</p> <p>XXXII. Meningitis</p> <p>XXXIII. Mental illness (i.e., posttraumatic stress disorder, generalized anxiety disorder or depression)</p> <p>XXXIV. Migraine</p> <p>XXXV. Motor dysfunction associated with stroke</p> <p>XXXVI. Necrotizing soft tissue infections</p> <p>XXXVII. Pseudomembranous colitis (antimicrobial agent-induced colitis)</p> <p>XXXVIII. Pyoderma gangrenosum</p> <p>XXXIX. Radiation myelitis</p> <p>XL. Radiation-induced injury in the head and neck, except as noted earlier in the medically necessary statement</p> <p>XLI. Refractory mycoses: mucormycosis, actinomycosis, conidiobolus coronato</p> <p>XLII. Retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment</p> <p>XLIII. Senility related disorders including dementia, vascular dementia, and cognitive impairment</p> <p>XLIV. Sickle cell crisis and/or hematuria</p> <p>XLV. Spinal cord injury</p> <p>XLVI. Traumatic brain injury</p> <p>XLVII. Tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy</p>	<p>Y. Hydrogen sulfide poisoning</p> <p>Z. Idiopathic femoral neck necrosis</p> <p>AA. Idiopathic sudden sensorineural hearing loss</p> <p>BB. In vitro fertilization</p> <p>CC. Inflammatory bowel disease (Crohn disease or ulcerative colitis)</p> <p>DD. Intra-abdominal and intracranial abscesses</p> <p>EE. Lepromatous leprosy</p> <p>FF. Meningitis</p> <p>GG. Mental illness (i.e., posttraumatic stress disorder, generalized anxiety disorder or depression)</p> <p>HH. Migraine</p> <p>II. Motor dysfunction associated with stroke</p> <p>JJ. Necrotizing soft tissue infections</p> <p>KK. Pseudomembranous colitis (antimicrobial agent-induced colitis)</p> <p>LL. Pyoderma gangrenosum</p> <p>MM. Radiation myelitis</p> <p>NN. Radiation-induced injury in the head and neck, except as noted earlier in the medically necessary statement</p> <p>OO. Refractory mycoses: mucormycosis, actinomycosis, conidiobolus coronato</p> <p>PP. Retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment</p> <p>QQ. Senility related disorders including dementia, vascular dementia, and cognitive impairment</p> <p>RR. Sickle cell crisis and/or hematuria</p> <p>SS. Spinal cord injury</p> <p>TT. Traumatic brain injury</p> <p>UU. Tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy</p>