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# Hyperbaric Oxygen ($HBO_2$) Therapy

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| Related Policies (if applicable) |
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| None |
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## Disclaimer

**Carefully check state regulations and/or the member contract.**
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Legislative Mandates

**EXCEPTION: For Illinois only:** Illinois Public Act 103-0123 (IL HB 1384) Coverage for Reconstructive Services requires the following policies amended, delivered, issued, or renewed on or after January 1, 2025 (Individual and family PPO/HMO/POS; Student; Group [Small Group; Mid-Market; Large Group Fully Insured PPO/HMO/POS] or Medicaid), to provide coverage for medically necessary services that are intended to restore physical appearance on structures of the body damaged by trauma.

**EXCEPTION: For Illinois only:** Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

## Coverage

**ALERT:** Health Care Services Corporation (HCSC) has created a form to facilitate review of requests for coverage of $HBO_2$ therapy, located on the "Provider / Forms" page of each HCSC web site, i.e., BCBSIL.com, BCBSMT.com, BCBSNM.com, BCBSOK.com, or BCBSTX.com.

**Topical Hyperbaric Oxygen Pressurization**

Topical hyperbaric oxygen ($THBO_2$) pressurization for any indication or clinical condition **is considered experimental, investigational and/or unproven**.

**NOTE 1:** This medical policy does not address $THBO_2$ therapy in the absence of pressurization (i.e., topical hyperbaric oxygen wound care). This policy does not address the use of topical oxygen systems that may be submitted with code E0446.

**Systemic Hyperbaric Oxygen Pressurization**

Systemic hyperbaric oxygen pressurization **may be considered medically necessary** for the treatment of the medical conditions listed on Table 1 below:

Requests and claims for treatment related to systemic hyperbaric oxygen pressurization therapy must be accompanied by ALL of the following documentation requirements when services are in excess of 1-month duration, and/or when services are in excess of the number of treatments listed in the grid below or listed as individual consideration:

- Documentation must include **at least two** of the following:
    1. Photo record(s), or
    2. Consultation reports, or
    3. Operative or treatment reports and/or other applicable hospital records (e.g., pathology report, history and physical), or
    4. Office records; **AND**
- For wounds, documentation should include the following additional information:
    1. Primary diagnosis,
    2. Secondary diagnosis,
    3. Contributing factors to the primary diagnosis,
    4. Co-morbid factors,
    5. Prior therapy,
    6. Wound description (cause, location, measurements [size, depth, undermining, granulation]),
    7. Wagner classification system grade level (see **NOTE 2**) and
    8. Whether this is initial treatment or extension of treatment.

**NOTE 2:** The Wagner classification system of wounds is defined as follows:

- Grade-0 = no open lesion;
- Grade-1 = superficial ulcer without penetration to deeper layers;
- Grade-2 = ulcer penetrates to tendon, bone, or joint;
- Grade-3 = lesion has penetrated deeper than grade-2 and there is abscess, osteomyelitis, pyarthrosis, plantar space abscess, or infection of the tendon and tendon sheaths;

- Grade-4 = wet or dry gangrene in the toes or forefoot; and
- 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.

The medical conditions and circumstances that **may be considered medical necessary** are listed in the grid below. This includes the number of treatments initially allowed for each approved condition. Approval of treatment or services beyond the number initially authorized requires review of pertinent medical record documentation. Additional information about these requirements is contained within the policy document.

**Table 1. Systemic Hyperbaric Oxygen Therapy**

| **IF THE MEDICALLY NECESSARY DIAGNOSIS IS:** | **THEN REVIEW:** (78) |
|---|---|
| Non-healing diabetic wounds, including foot wounds or marginally perfused wounds, of the lower extremities in diabetic patients who meet **all** the following three criteria:<br>• Individual has type 1 or type 2 diabetes and has a lower extremity wound due to diabetes, **AND**<br>• Individual has a wound classified as Wagner grade-3 or higher (see **NOTE 2** above for Wagner scale**)**, **AND**<br>• Individual has no measurable signs of healing after 30 days of an adequate course of standard wound therapy (See **NOTE 12**).<br>Acute postoperative foot surgical treatment for patients with Wagner grade-3 or higher diabetic foot ulcers.<br>(See **NOTE 3** below). | After 30 treatments. |
| Chronic refractory osteomyelitis. | After 30 treatments. |
| Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) and osteoradionecrosis (ORN) (See **NOTE 4** and **NOTE 5**). | After 20 treatments. |
| Crush injury, reperfusion injury, compartment syndrome, and other acute traumatic ischemia's (See **NOTE 6**). | After 12 treatments. |
| Venous stasis ulcer, only if venous surgery, local wound care, leg elevation, counterpressure support, and skin grafting fails. | After 12 treatments. |
| Compromised skin graft or flap, or for enhancement of healing in a selected problem wound. | After 12 treatments. |
| Gas gangrene (i.e., clostridial myonecrosis) and includes Meleney's postoperative gangrene ulcer (See **NOTE 7**). | After 10 treatments. |
| Soft tissue infections due to mixed aerobic and anaerobic organisms with tissue necrosis and refractory bacteroides infections. | After 10 treatments. |
| Decompression sickness (See **NOTE 8**). | After 10 treatments. |
| Acute air or gas embolism. | After 10 treatments. |
| Brown recluse spider bite. | After 5 treatments. |

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| Acute carbon monoxide poisoning (intoxication) AND/OR acute smoke inhalation (not chronic) with or without acute cyanide poisoning (See **NOTE 9**). | After 5 treatments. |
| Thermal burns, second- or third-degree burns involving 15% to 90% of total body surface and initiated within 24 hours of the burn injury. | After 5 treatments. |
| Idiopathic sudden sensorineural hearing loss (ISSNHL). | After 5 treatments. |
| Acute cyanide poisoning and may be complicated by carbon monoxide poisoning (See **NOTE 9**). | For individual consideration of number of treatments. |
| Exceptional blood loss anemia (profound/severe), as the result of class IV hemorrhage, $HBO_2$ is indicated when the patient will not accept blood replacement for medical or religious reasons **and** the following symptoms are present:<br>• Shock, systolic blood pressure below 90 mm Hg, or pressure maintained by vasopressors; and<br>• Disorientation to coma; and<br>• Ischemic changes of the myocardium as demonstrated on the electrocardiogram (EKG); and<br>• Ischemic gut.<br>(See **NOTE 10)**. | For individual consideration of number of treatments. |
| Selected refractory mycoses (mucormycosis, actinomycosis, or canibolus coronato). | For individual consideration of number of treatments. |
| Intracranial abscess. | For individual consideration of number of treatments. |
| Acute cerebral edema. | For individual consideration of number of treatments. |
| Arterial insufficiency ulcer (not acute) which persists after reconstructive surgery has restored large vessel perfusion (includes peripheral vessels). | For individual consideration of number of treatments. |
| Decubitus ulcers. | For individual consideration of number of treatments. |
| Pre- and post-treatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw. | For individual consideration of number of treatments. |

**Special Comment:** A course of treatment may range from less than 1 week to several months' duration, depending on the severity of the patient's condition and response to therapy. The average length of treatment is 2 to 4 weeks.

Systemic hyperbaric oxygen pressurization therapy **is considered experimental, investigational and/or unproven** in all other situations, including but not limited to, the following indications or clinical conditions and any diagnosis not previously listed as covered:

- Actinic keratosis (AK) or actinic skin damage;
- Amyotrophic lateral sclerosis;
- Arterial peripheral insufficiency, acute;
- Asthma;
- Autistic spectrum disorders;
- Avascular necrosis;
- Bell's palsy;
- Bone grafts;
- Carbon tetrachloride poisoning, acute;
- Cardiogenic shock;
- Cerebral palsy;
- Cerebrovascular accident (CVA), acute thrombotic or embolic, or chronic;
- Coronary syndromes, acute, and as an adjunct to coronary interventions, including but not limited to percutaneous coronary interventions (PCI) and cardiopulmonary bypass;
- Depression;
- Fibromyalgia;
- Fracture healing;
- Spinal cord injury, traumatic;
- Hepatic necrosis;
- Hepatitis;
- Herpes zoster;
- Human immunodeficiency virus infection or acquired immune deficiency syndrome (HIV/AIDS);
- Hydrogen sulfide poisoning;
- Idiopathic femoral neck necrosis;
- Ileus, postoperative;
- Inflammatory bowel disease, including Crohn's disease (CD), severe or refractory, or ulcerative colitis;
- Intra-abdominal abscesses;
- In-vitro fertilization;
- Ischemic stroke, acute;
- Lepromatous leprosy;
- Lyme disease;
- Lymphedema of arm, chronic, following radiotherapy for cancer;
- Meningitis;
- Mental illness, generalized anxiety disorder or depression;
- Migraine or cluster headaches;
- Motor dysfunction associated with stroke;
- Multiple sclerosis;

- Muscle soreness, delayed onset or sport's injury;
- Myocardial infarction (MI), acute;
- Organ transplantation or storage;
- Osteoarthritis;
- Osteomyelitis, acute;
- Osteonecrosis of the jaw, bisphosphonate-related;
- Pancreatitis, acute;
- Parkinson's disease;
- Post-traumatic stress disorder (PTSD), traumatic brain (head) injury (TBI) or other stress disorders;
- Pseudomembranous colitis, antimicrobial agent-induced colitis;
- Pulmonary emphysema;
- Pyoderma gangrenosum;
- Radiation-induced injury to head, neck, anus, or rectum (except proctitis);
- Radiation-myelitis;
- Radiation therapy, adverse effects, at any point of therapy, including early onset effects and delayed effects (i.e., extremity lymphedema associated with cancer radiation);
- Retinal artery insufficiency, acute within the first 24 hours of diagnosis;
- Retinopathy, as an adjunct to scleral buckling procedure in patients with sickle cell peripheral retinopathy and retinal detachment;
- Rheumatoid arthritis;
- Sickle cell crisis and/or hematuria;
- Senility;
- Septicemia, anaerobic (unrelated to clostridial), or systemic aerobic infection;
- Surgical and traumatic wounds, acute;
- Sudden deafness (unrelated to ISSNHL);
- Tetanus;
- Tumor sensitization for cancer treatments including but not limited to, radiotherapy or chemotherapy; AND
- Vascular dementia or chronic brain syndromes, neovascular causes (such as Pick's disease, Alzheimer's disease, and Korsakoff's disease).

**NOTE 3:** Treatments are usually given daily for 90 to 120-minutes. The initial treatment depends on severity of disease. More serious diabetic wounds may require twice daily treatments; and once stabilized, treatments may be done once daily.

**NOTE 4:** For soft-tissue radiation necrosis, review is required after each 20 treatments. Treatments are usually given daily for 90 to 120 minutes. Beyond 60 treatments, individual consideration is applied.

**NOTE 5:** The initial course of treatment for patients with Grade I osteoradionecrosis include $HBO_2$ followed by debridement. For patients presenting at Grade II or if the wound is not responsive to treatment, consider extensive debridement, followed by additional $HBO_2$. For

patients presenting at Grade III, $HBO_2$ is started followed by mandibular segmental resection with additional HBOT. Beyond the initial therapy course, individual consideration is applied.

**NOTE 6:** Three treatments per day for 48-hours followed by two treatments per day over the second 48-hours and one treatment per day over the third period of 48-hours. Beyond this time period, individual consideration is applied.

**NOTE 7:** Treatments may be as often as three during the first 24-hours for 90-minutes, then 2-sessions per day for the next 2- to 5-days, depending on the patient's initial response.

**NOTE 8:** Treatment times vary; depending on length of time elapsed between symptoms and initiation of treatment and between residual symptoms after initial treatment. The majority of cases respond to a single treatment. Usual time between treatments ranges from 90-minutes to 14-hours. Repetitive treatments may be necessary, depending on the patient's response.

**NOTE 9:** Treatments will vary based on persistent neurologic dysfunction after the initial treatment and may be as frequent as once or twice daily, until there is no additional improvement in cognitive function.

**NOTE 10:** HBOT is continued as needed and discontinued when the red blood cells have been replaced in numbers to alleviate the precipitating signs and symptoms.

**NOTE 11**: Breathing 100% $O_2$ at one atmosphere **without** the use of a pressurized chamber is **not** considered to be $HBO_2$ pressurization.

**NOTE 12**: Standard wound care in patients with diabetic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present.

## Policy Guidelines

None.

## Description

**Hyperbaric Oxygen Therapy**
Hyperbaric oxygen therapy (HBOT) is a technique for delivering higher pressures of oxygen ($O_2$) to tissue. Two methods of delivery are available: topical and systemic.

<u>Topical HBOT (THBOT)</u>

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

Systemic HBOT

In systemic or large hyperbaric oxygen chambers, the patient is entirely enclosed in a pressure chamber and breathes oxygen at a pressure greater than 1 atmosphere (atm; the pressure of oxygen at sea level). Thus, this technique relies on systemic circulation to deliver highly oxygenated blood to the target site, typically a wound. 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. Typically, the therapy is offered for 90 minutes per day for 4 consecutive days. After a 3-day break, the cycle is repeated. This regimen may last for 8- to 10-weeks.

Adverse Events

HBOT is a generally safe therapy, with an estimated adverse side effect rate of 0.5%. (1) 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 uncontrolled coughing, mild burning on inhalation, and dyspnea. Neurologic effects include hiccups, irritability and anxiety, tinnitus and hearing disturbances, nausea, and dizziness. Ophthalmologic effects include retinopathy of prematurity in neonates, cataract formation (long term exposure), and retinal edema.

**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. (2) 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

The medical policy was created in May 1990 and was based on a search of the PubMed database and subsequently on the Undersea and Hyperbaric Medical Society (UHMS) Guidelines and the Centers for Medicare and Medicaid Services (CMS) National Coverage Determination policy. The most recent literature search was performed through April 28, 2023.

Medical policies assess the clinical evidence to determine whether the use of a 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 to 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 a technology, 2 domains are examined: the relevance and the 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 (HBOT) for Wounds, Burns, or Infections**

Clinical Context and Therapy Purpose

The purpose of topical HBOT is to provide a treatment option that is an alternative or an improvement on existing therapies in individuals with wounds, burns, or infections.

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

*Populations*

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

*Interventions*

The therapy being considered is topical HBOT.

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

*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.

de Smet et al. (2017) conducted a systematic review of various oxygen therapies (oxygen dressing therapy, topical oxygen therapy, HBOT, inspired oxygen therapy). (3) Three RCTs evaluating topical $O_2$ therapy for chronic wound healing were identified (see Table 2). 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 ($p<0.001$). 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 2. 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) (3) | Feb 2016 | 3 | • Stage II-IV sacral or ischial pressure ulcers (1 RCT)<br>• Refractory venous ulcers (2 RCTs) | 315[a] (83-132) | RCT | • Results not pooled<br>• In all trials, patients in the treatment group experienced significantly higher wound healing rates |

RCT: randomized controlled trial; N/n: number;
[a] Two of the trials had overlapping populations, so there were not 315 unique patients.

Section Summary: Topical HBOT 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 (HBOT) for Chronic Diabetic Ulcers**
Clinical Context and Therapy Purpose
The purpose of systemic HBOT is to provide a treatment option that is an alternative or an improvement on existing therapies in individuals with chronic diabetic ulcers.

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

*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 various 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 one 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.

Systematic Reviews

Sharma et al. (2021) (4) conducted a systematic review and meta-analysis of 14 studies (N=768) comparing the effect of HBOT with standard care on diabetic foot ulcers (Table 3). 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 follow up 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 follow up. A funnel plot analysis for this outcome was asymmetrical, suggesting publication bias. Risk of major amputation was also significantly lower with HBOT compared to standard care based on pooled analysis of 7 studies (OR, 0.60; 95% CI, 0.39 to 0.92; $I^2$=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 3). (5) Reviewers identified 12 RCTs (total 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 3). (6) 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 3. Systematic Reviews of Trials Assessing HBOT for Chronic Diabetic Foot Ulcers**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Kranke et al. (2015) (5) | Feb 2015 | 12 | Patients with chronic wounds associated with venous or arterial disease, diabetes, or external pressure | 577 | RCTs | • 10 of 12 trials focused on patients with diabetic foot ulcers (n=531)<br>• Pooled analysis of 5 of 10 trials (n=205) reported higher heal rates with HBOT (RR=2.3; 95% CI, 1.2 to 4.6) and no difference in amputation risk (RR=0.4; 95% CI, 0.1 to 2.2) |
| Elraiyah et al. (2016) (6) | Oct 2011 | 18 | Patients with diabetic foot ulcers | 1526 | RCTs Cohorts | • 16 of 18 trials included HBOT as a treatment option and 6 of those were RCTs<br>• Pooled analysis of the 6 RCTs (n=340) reported higher heal rate with HBOT (OR=14.3; 95% CI, 7.1 to 28.7) and lower amputation risk (OR=0.3; 95% CI, 0.1 to 0.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sharma et al. (2021) (4) | Sep 2020 | 14 | Patients with diabetic foot ulcers | 768 | RCTs, CCTs | • 12 RCTs and 2 CCTs compared HBOT with undefined standard care<br>• Pooled analysis found HBOT significantly associated with complete ulcer healing (ST vs. HBOT: OR 0.29, 95% CI 0.14 to 0.61) and lower risk of major amputation (HBOT vs. ST: OR 0.60; 95% CI, 0.39 to 0.92) when compared with standard care. |

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

Section Summary: Systemic HBOT for Chronic Wounds 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 or an improvement on existing therapies in individuals with carbon monoxide poisoning.

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

*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 one 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.

Systematic Reviews

A Cochrane review by Buckley et al. (2011) included 6 RCTs evaluating HBOT for carbon monoxide poisoning (see Table 4). (7) Four of the 6 trials were assessed as having a high risk of bias due to non-blinding 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 4. Systematic Reviews of Trials Assessing HBOT Therapy for Carbon Monoxide Poisoning**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Buckley et al. (2011) (7) | Jun 2010 | 6 | Non-pregnant adults with acute carbon monoxide poisoning | 1361 | RCTs | • Studies extremely heterogeneous in: severity of CO poisoning, HBOT regimens, and comparators |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | • Pooled analyses of 6 trials (n=1361) reported no statistical difference in neurologic deficits between treatment groups (OR=0.78; 95% CI, 0.54 to 1.12) |

CI: confidence interval; CO: carbon monoxide; HBOT therapy: hyperbaric oxygenation therapy; N/n: number; 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. (8) 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% Cl; -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% Cl; -4.9% to -1.5%) and reduced activities of daily living (mean difference, -5.3%; 95% Cl; -7.8% to -2.7%) relative to no HBOT.

Section Summary: Systemic HBOT 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 or an improvement on existing therapies in individuals with radionecrosis, osteoradionecrosis, and treatment of irradiated jaw.

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

*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 debridement 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.

Systematic Reviews
Bennett et al. (2016) published a Cochrane review on HBOT for late radiation tissue injury (see Table 5). (9) 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=0.02). There were insufficient data to conduct meta-analyses on other outcomes.

Borab et al. (2017) published a systematic review focusing on the use of HBOT to treat the subgroup of patients with late radiation tissue injury had skin necrosis (see Table 5). (10) 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. (11) 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 5). Other outcomes of interest included salivary gland function and quality of life, which are discussed in the Radiotherapy Adverse Events section.

**Table 5. 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) (9) | 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 | • Pooled analyses of 3 trials of patients with osteoradionecrosis (n=246) found a higher rate of complete mucosal cover after HBOT versus control (RR=1.3; 95% CI, 1.1 to 1.5)<br>• Pooled analyses of 2 trials (n=264) found a lower risk of wound dehiscence following surgery to repair mandibular osteoradionecrosis in patients treated with HBOT versus control (RR=4.2; 95% CI, 1.1 to 16.8) |
| Borab et al. (2017) (10) | May 2016 | 8 | Patients with radiation-induced skin necrosis | 720 | OBS cohort and case series | • Adding across the studies, 80% reported complete healing and 86% reported symptom improvement<br>• Studies had no comparators |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ravi et al. (2017) (11) | Dec 2016 | 10 | Patients who received radiotherapy for head and neck cancer | 375 | PRO case series and PCS | • Osteonecrosis prevention: 1 case series and 1 comparative study (n=77) reported low osteonecrosis rates with HBOT<br>• 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 |

CI: confidence interval; CO: carbon monoxide; $HBO_2$ therapy: hyperbaric oxygenation therapy; N/n: number; OBS: observational; PRO: prospective; PCS: prospective comparative studies; RCT: randomized controlled trial; RR: relative risk.

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

A Cochrane review of RCTs found that HBOT improved some radionecrosis and osteoradionecrosis outcomes and resulted in better outcomes 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 or an improvement on existing therapies in individuals with chronic refractory osteomyelitis.

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

*Populations*

The relevant population of interest is individuals with chronic refractory osteomyelitis. Osteomyelitis is considered refractory with failed response to definitive surgical debridement and a 4 to 6 week course of appropriate antibiotic therapy.

*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 debridement. 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.

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

Savvidou et al. (2018) conducted a qualitative systematic review of HBOT as an adjunctive treatment of chronic osteomyelitis. (12) Adjuvant HBOT was effective in 16 (80%) of 20 cohort studies and 19 (95%) of 20 case series. Overall, 308 (73.5%) of 419 patients with complete data achieved a successful outcome with no relapses reported.

Among the larger case series, Maynor et al. (1998) reviewed the records of all patients with chronic osteomyelitis of the tibia seen at a single institution. (13) Follow-up data were available on 34 patients who had received a mean of 35 adjunctive HBOT sessions (range, 6-99 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. (14) Patients received HBOT until the bone was fully recovered with healthy vascular tissue; this resulted in a mean of 48 daily treatments (range, 8-103 treatments). After a mean post-treatment follow-up of 34 months, 34 (89%) of 38 patients remained clinically free of infection (i.e., drainage-free and no tenderness, pain, or cellulitis). Success rates from several smaller case series (number range, 13-15 patients), all conducted in Taiwan (1998-2000), ranged from 79% to 92%. (15-17) A high percentage of refractory patients in these series had successful outcomes.

Section Summary: 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 or an improvement on existing therapies in individuals with acute thermal burns.

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

*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.

In 2004, a Cochrane review assessed HBOT for thermal burns (see Table 6). (18) 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 identified in updated literature searches.

**Table 6. Systematic Reviews of Trials Assessing HBOT Therapy for Acute Thermal Burns**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Villanueva et al. (2009) (18) | Jun 2009 | 5 | Patients with thermal injuries to the epidermis, subcutaneous tissues, vessels, nerve, tendons, or bone | 141 | RCTs | • 1 trial (n=125) reported no difference in length of stay, mortality, or number of surgeries between HBOT and control groups<br>• 1 trial (n=16) reported shorter healing times (19.7 days versus 43.8 days; p<0.001) with HBOT versus control, and an RR for failed graft without HBOT of 2.0 (95% CI, 0.5 to 8.0) |

CI: confidence interval; $HBO_2$ therapy: hyperbaric oxygenation therapy; N/n: number; RCT: randomized controlled trial; RR: relative risk.

Section Summary: Systemic HBOT 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 or an improvement on existing therapies in individuals with acute surgical and traumatic wounds.

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

*Populations*

The relevant population of interest is individuals with acute surgical and traumatic wounds. A subset of individuals with acute surgical or traumatic wounds may be treated with HBOT to salvage compromised skin grafts or flaps.

*Interventions*

The therapy being considered is systemic HBOT.

*Comparators*

Comparators of interest include dressings, debridement, 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.

A Cochrane review of RCTs on HBOT for acute surgical and traumatic wounds was published by Eskes et al. (2013) (see Table 7). (19) 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 HBO 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 7). (20) Reviewers included 8 studies, with sample sizes ranging from 5 to 125 patients. Four studies were randomized, 3 were prospective observational studies, and one 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 end points, but the end points differed among studies (e.g., graft survival, hospital length of stay, wound size). Moreover, the studies were heterogeneous regarding treatment regimens, patient indications (e.g., burns, facelifts), and study designs making it difficult to draw conclusions about the effect of HBOT on acute wound treatment.

Zhou et al. (2014) published a systematic review of Chinese studies assessing the use of HBOT in the management of compromised skin flaps and grafts. (21) Among 16 controlled studies comparing routine therapy to HBOT, healing and survival rates ranged from 35.0% to 86.5% and 77.9% to 100%, respectively. Among a subset of studies assessing skin flaps post-mastectomy, the overall therapeutic efficacy rate was 62.5%. Several studies suggested higher success rates when HBOT is initiated as soon as possible following surgery. Limitations of this analysis include heterogeneity in treatment protocols, wound sites and etiologies, and underlying comorbidities. The authors acknowledge that the therapeutic efficacy of HBOT in compromised skin flaps needs to be validated in future randomized, controlled studies but encourage shared decision-making in the absence of Level I evidence.

**Table 7. Systematic Reviews of Trials Assessing $HBO_2$ Therapy for Acute Surgical and Traumatic Wounds**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Eskes et al. (2013) (19) | Aug 2013 | 4 | Patients with acute wounds (skin injuries occurring due to surgery or trauma) | 229 | RCTs | • 3 of 4 trials did not include wound healing as an outcome measure<br>• A small trial (n=36) reported patients receiving HBOT had significantly |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | higher wound healing rate versus sham; however, no difference in time to healing |
| Dauwe et al. (2014) (20) | Oct 2012 | 8 | Patients with acute wounds, grafts, and flaps | 256 | RCTs and non-RCTs studies | • HBOT may augment healing of acute wounds<br>• Not indicated for routine wound management |
| Zhou et al. (2013) (21) | 1994-2013 | 23 | Patients with compromised skin flaps and grafts | 626 (HBOT) 583 (control) | RCTs (12), nonrandomized comparative studies (4), and single-arm studies (7) | • HBOT may improve the survival rate of compromised skin grafts and flaps<br>• Initiation of HBOT within72 hours is associated with improved outcomes |

HBOT therapy: hyperbaric oxygenation therapy; N/n: number; RCT: randomized controlled trial.

Section Summary: Systemic HBOT for Acute Surgical and Traumatic Wounds

Two systematic reviews identified 4 RCTs; 1 of the reviews also included nonrandomized studies. One systematic review identified 16 small Chinese controlled studies on the use of HBOT for compromised skin grafts and flaps. Heterogeneity among studies (e.g., in patient population, 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 or an improvement on existing therapies in individuals with bisphosphonate-related osteonecrosis of the jaw.

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

*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.

An unblinded RCT by Freiberger et al. (2012) evaluated the use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw (see Tables 8 and 9). (22) The investigators did a per-protocol analysis (actual treatment received) because of the relatively large amount of crossover. 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 8. Characteristics of Trials Assessing HBOT for Bisphosphonate-Related Osteonecrosis of the Jaw**

| | | | | | Treatment | |
|---|---|---|---|---|---|---|
| **Study (Year)** | **Countries** | **Sites** | **Dates** | **Participants** | **Active (n=25)** | **Comparator (n=21)** |
| Freiberger et al. (2012) (22) | United States | NR[a] | 2006-2010 | Patients with bisphosphonate-related osteonecrosis of the jaw | • $HBO_2$ plus standard oral care<br>• 100% $O_2$ at 2 ATA<br>• 40 treatments | Standard oral care (antiseptic rinses, surgery, and antibiotics) |

ATA: atmospheres absolute; HBOT Therapy: hyperbaric oxygen therapy; NR: not reported; $O_2$: oxygen; RCT: randomized controlled trial;

[a] 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 9. Results of Trials Assessing HBOT for Bisphosphonate-Related Osteonecrosis of the Jaw**

| | **Improved, % (n)** | | | | **Healed, % (n)** | | |
|---|---|---|---|---|---|---|---|
| **Study (Year)** | **3 mos** | **Between-Group p-Value** | **18 mos** | **Between-Group p-Value** | **3 mos** | **Between-Group p-Value** | **Between-Group p-Value** |
| Freiberger et al. (2012) (22) | 46 | | 46 | | 46 | | |
| *HBOT* | 68.0 (25) | 0.03 | 58.3 (12) | 0.31 | 36.0 (25) | 0.04 | 1.0 |
| *Control* | 35.0 (20) | | 33.3 (6) | | 10.0 (20) | | |

HBOT Therapy: hyperbaric oxygen therapy; mos: months; N/n: number.

Section Summary: Systemic HBOT 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 or an improvement on existing therapies in individuals with necrotizing soft tissue infections.

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

*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.

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

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

**Systemic Hyperbaric Oxygen Therapy for Acute Coronary Syndromes**

Clinical Context and Therapy Purpose

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

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

*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.

A Cochrane review by Bennett et al. (2015) identified 6 trials (total n=665 patients) evaluating HBOT for acute coronary syndrome (see Table 10). (25) Included studies were published between 1973 and 2007. All studies included patients with acute myocardial infarction (MI); 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 rate of death 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 10. Systematic Reviews of Trials Assessing HBOT for Acute Coronary Syndrome**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Bennett et al. (2015) (25) | Jun 2010 | 6 | Adults with acute coronary syndrome, with or without S-T segment elevation | 665 | RCTs | • Pooled analyses of 5 trials (n=614) reported a lower mortality rate for patients in the HBOT group versus the control (RR=0.58; 95% CI, 0.36 to 0.92)<br>• 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%) |

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

Section Summary: 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 or an improvement on existing therapies in individuals with acute ischemic stroke.

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

*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 one 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.

In a Cochrane systematic review of RCTs, Bennett et al. (2014) evaluated HBOT for acute ischemic stroke (see Table 11). (26) Reviewers identified 11 RCTs (total n=705 participants) that compared HBOT with sham HBOT or no treatment. Reviewers could pool study findings for only 1 outcome (mortality at 3-6 months), and no difference was detected between the treatment groups for that outcome. There was heterogeneity in the participants enrolled and in the clinical and functional outcomes measured across the studies.

**Table 11. Systematic Reviews of Trials Assessing HBOT for Acute Ischemic Stroke**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Bennett et al. (2014) (26) | 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 months (RR=0.97; 95% CI, 0.34 to 2.75) |

CI: confidence interval; CT: computed tomography; HBOT therapy: hyperbaric oxygenation therapy; LVEF: left ventricular ejection fracture; MRI: magnetic resonance imaging; MD: mean difference; N/n: number; RCT: randomized controlled trial; RR: relative risk.

Section Summary: Systemic HBOT 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 or an improvement on existing therapies in individuals with motor dysfunction associated with stroke.

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

*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.

Efrati et al. (2013) published an RCT evaluating HBOT for treatment of neurologic deficiencies associated with a history of stroke (see Tables 12 and 13). (27) 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 (NIHSS), 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 (ADLs). These differences in outcome measures were accompanied by improvements in single-photon emission computed tomography (SPECT) 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 poststroke 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 NIHSS, 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 12. Characteristics of Trials Assessing HBOT for Motor Dysfunction Associated With Stroke**

| | | | | | Treatment | |
|---|---|---|---|---|---|---|
| **Study (Year)** | **Countries** | **Sites** | **Dates** | **Participants** | **Active (n=30)** | **Comparator (n=29)** |
| Efrati et al. (2013) (27) | Israel | 1 | 2008-2010 | Patients ≥18 years with ischemic or hemorrhagic stroke 6 to 36 months prior to inclusion with ≥1 motor dysfunction | • $HBO_2$<br>• 100% $O_2$ at 2 ATA<br>• 40 times over 2 months | Same as active, delayed after 2 months |

ATA: atmospheres absolute; HBOT Therapy: hyperbaric oxygen therapy; $O_2$: oxygen; RCT: randomized controlled trial.

**Table 13. Results of Trials Assessing HBOT for Motor Dysfunction Associated with Stroke**

| | **NIHSS** | | | **ADLs[a]** | | |
|---|---|---|---|---|---|---|
| **Study (Year)** | **Baseline** | **2 months** | **Between-Group p-Value** | **Baseline** | **2 months** | **Between-Group p-Value** |
| Efrati et al. (2013) (27) | 50 | 50 | | 50 | 50 | |
| *Mean HBOT (SD)* | 8.5 (3.6) | 5.5 (3.6) | 0.004 | 16.1 (6.5) | 12.8 (7.3) | 0.02 |
| *Mean control (SD)* | 8.7 (4.1) | 8.3 (4.3) | | 17.4 (9.5) | 17.5 (9.5) | |

ADLs: activities of daily living; HBOT: hyperbaric oxygen therapy; NIHSS: National Institutes of Health Stroke Scale; N/n: number; SD: standard deviation;

[a] ADLs are 16 functions scored across a range whether patient was independent to did not perform at all. Range: 0 (best) to 51 (worst).

Section Summary: Systemic HBOT for Motor Dysfunction Associated With Stroke

One crossover RCT 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 or an improvement on existing therapies in individuals with Bell palsy.

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

*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.

Holland et al. (2012) published a Cochrane review evaluating HBOT in adults with moderate-to-severe Bell palsy. (28) 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 HBOT for Bell Palsy

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

**Systemic Hyperbaric Oxygen Therapy for Traumatic Brain Injury (TBI)**

Clinical Context and Therapy Purpose

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

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

*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 14 summarizes key measurement tools for assessing severity of brain injury.

**Table 14. 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:<br>• eye opening (0 [not testable]–4)<br>• verbal response (0–5) | NR |

| | | | | |
|---|---|---|---|---|
| | | | • motor response (0–6)<br><br>Total Score:<br>• Severe: ≤ 8<br>• Moderate: 9–12<br>• Mild: 13–15 | |
| Glasgow Outcome Scale (GOS) | Categorized outcomes of patients after TBI | Physician-administered | 1. Death<br>2. Persistent vegetative state: minimal responsiveness<br>3. Severe disability: conscious but disabled; dependent on others for daily support<br>4. Moderate disability: disabled but independent; can work in sheltered setting<br>5. Good recover: resumption of normal life despite minor deficits | Unfavorable outcome: 1-3 |
| PTSD Checklist (PCL) | A 17-item measure that reflects the DSM-IV symptoms of PTSD | Self-administered | • Likert-type scale (0: not at all–4: extremely)<br>• Total score range: 17–85<br>• PTSD cut point score for DoD screening: 31–33 | • Response to treatment: ≥ 5 points<br>• Clinically meaningful: ≥ 10 points |
| Rivermead Post-Concussion Symptoms Questionnaire (RPQ) | Assesses severity of somatic, cognitive, and emotional symptoms for mTBI | Self-administered or by interviewer | • 16 Likert-type questions<br>• Score range: 0–84<br>• Higher values indicate more several symptoms | 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.

Systematic Reviews

A meta-analysis by Wang et al. (2016) assessed HBOT for treatment of TBI (see Table 15). (29) Eight studies (total 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. (2017), did not conduct pooled analyses (see Table 15). (30) Reviewers identified 12 RCTs evaluating HBOT for patients with TBI. Using the SIGN (Scottish Intercollegiate Guidelines Network) 50 criteria, 8 trials were rated acceptable and 4 rated low. Four trials, all rated as having acceptable quality, addressed patients with mild TBI (mTBI) and compared HBOT with sham. None found statistically significant differences between groups on outcomes (i.e., post-concussive symptom severity, psychological outcomes). Seven trials evaluated HBOT for the acute treatment of patients with moderate-to-severe TBI. Four were rated as acceptable quality and three as low quality. Study protocols and outcomes varied, and none used a sham control. Three acceptable quality studies with standard care controls reported the Glasgow Outcome Scale (GOS) score and mortality rate. In two of 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 15). (31) 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 one had blinding of outcome assessment.

Allocation concealment was inadequate in all studies. The primary outcomes of the review were mortality and functional outcomes. A pooled analysis of data from 4 trials showed that adding HBOT to standard care decreased mortality but did not improve functional outcome at final follow-up. The unfavorable functional outcome was commonly defined as a GOS 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 mTBI–associated post-concussive symptoms (PCS) and posttraumatic stress disorder (PTSD). (32) 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 15). 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 15. Systematic Reviews of Trials Assessing HBOT for Traumatic Brain Injury**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Hart et al. (2019) (32) | | 7 (4 by DoD) | Patients (primarily US Service personnel) with mild traumatic brain injury | 389 | | DoD Analysis:<br>• Improvement in mean Rivermead Total Score (-2.3 points; 95% CI, -5.6 to 1.0; p=.18)<br>• Improvement in mean PTSD Checklist Total Score (-2.7 points; 95% CI, -5.8 to 0.4; p=.089)<br>• 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) |
| Wang et al. (2016) (29) | Dec 2014 | 8 | Patients with mild or severe TBI | 519 | RCTs and 2-arm | • Pooled analyses of 2 trials (n=120) found significant |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | prospective studies | improvements in GCS score change (3.1; 95% CI, 2.3 to 3.9) in HBOT therapy versus control<br>• Pooled analyses of 3 trials (n=263) found lower risk of mortality among patients treated with HBOT therapy versus controls (OR=0.3; 95% CI, 0.2 to 0.6) |
| Crawford et al. (2017) (30) | Aug 2014 | 12 | Military and civilian patients with TBI | -- | RCTs | • Pooled analyses not performed<br>• Among 3 trials with GCS outcomes, 2 reported improvements with HBOT therapy and 1 found no difference<br>• 4 trials assessed as acceptable quality did not find significant differences in symptom severity or psychological outcomes |
| Bennett et al. (2012) (31) | Mar 2012 | 7 | Patients with acute TBI following blunt trauma | 571 | RCTs | • Pooled analyses of 4 trials (n=385) found that adding HBOT therapy to standard care decreased mortality versus standard care alone (RR=0.7; 95% CI, 0.5 to 0.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | • 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) |

CI: confidence interval; CT: computed tomography; GCS: Glasgow Coma Scale; $HBO_2$ therapy: hyperbaric oxygenation therapy; N/n: number; OR: odds ratio; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; RR: relative risk; TBI: traumatic brain injury.

Clinical Trials

The DoD-sponsored RCT, "Brain Injury and Mechanisms of Action in Hyperbaric Oxygen for Persistent Post-Concussive Symptoms after Mild Traumatic Brain Injury (mTBI) (BIMA)," completed in 2016, (33) was the first to include post-intervention follow-up beyond 3 to 6 months. Hart et al. (2019) describe BIMA, which assessed HBOT for U.S. service members with mTBI. (34) 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. In addition, Churchill et al. (2019) reported on the chamber- and protocol-related adverse events (AEs) in the HOPPS and BIMA trials. (35) 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. (36) 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. (37) 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 ± 9.0) and sham treatment (-2.9 ± 6.6), but the groups did not differ significantly from each other ($p$ =.33). The BIMA trials results showed a greater improvement from baseline in the HBOT group (-3.6 ± 6.4) versus sham (-0.3 ± 5.2; $p$=.02). The authors concluded that composite total scores in HOPPS and BIMA were consistent with primary study results.

Section Summary: Systemic HBOT for Traumatic Brain Injury

A number of RCTs and systematic reviews have been published. Pooled analyses were only conducted on a minority of the published RCTs, and these analyses had 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 (IBD)**

Clinical Context and Therapy Purpose

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

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

*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 one 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.

A systematic review by McCurdy et al. (2022) examined the evidence on HBOT for a range of IBD phenotypes (Crohn disease, ulcerative colitis; see Table 16). (38) The review was not limited by study design and included 3 small RCTs (N=40) (39, 40, 41) and 16 case series. All 3 of the RCTs were conducted in patients with ulcerative colitis. The included case series generally enrolled less than 30 patients each, with the exception of one study, conducted in Russia, that enrolled 519 patients. Overall, a total sample size for the systematic review across phenotypes was 844. Pooled response rates are reported in Table 15. Results from the individual RCTs were mixed. Two RCTs found a benefit for HBOT compared with standard medical care, but they were small studies (n=10 and 20) and were likely underpowered to detect between-group differences. In addition, one of the trials only included prior HBOT responders (40) and one (39) was stopped early due to enrollment difficulties. The third RCT found no benefit of HBOT compared with standard care and was also stopped early due to futility. (41) Quality assessment of the included studies judged 2 of the 3 included RCTs to be at high risk of bias. Study authors concluded that although HBOT was associated with high response rates across phenotypes, high-quality evidence was very limited, and well-designed RCTs are needed to confirm the effect of HBOT in patients with IBD.

**Table 16. Systematic Reviews of Studies Assessing HBOT for Inflammatory Bowel Disease**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| McCurdy et al. (2022) (38) | Nov 2020 | 19 | Patients with various IBD phenotypes | UC (n=383)<br><br>CD (n=250)<br><br>Perianal fistula (n=118)<br><br>Endocutaneous fistula (n=21)<br><br>Inflammatory pouch disorders (n=60)<br><br>Dermatologic manifestation of IBD (n=12) | 3 RTCs<br><br>16 case series | Ulcerative colitis (5 studies): 86% (66% to 95%)<br><br>CD (2 studies): 86% (81% to 90%)<br><br>Perianal fistula (10 studies): 75% (66% to 83%)<br><br>Pouch disorder (2 studies): 65% (52% to 76%)<br><br>Enterocutaneous fistula (3 studies): 85% (61% to 95%) |

CD: Crohn's disease; HBOT therapy: hyperbaric oxygenation therapy; IBD: inflammatory bowel disease; N/n: number; RCT: randomized controlled trial; UC: ulcerative colitis.

Section Summary: Systemic HBOT for Inflammatory Bowel Disease

Three RCTs have reported mixed findings in patients with ulcerative colitis. A systematic review of RCTs and observational studies found 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 (ISSNHL)**

Clinical Context and Therapy Purpose

The purpose of systemic HBOT is to provide a treatment option that is an alternative or an improvement on existing therapies for individuals with ISSNHL.

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

*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, and antiviral and hemodilution agents.

*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.

Systematic Reviews

A Cochrane review by Bennett et al. (2012) on HBOT for ISSNHL and/or tinnitus identified 7 RCTs (n=392; see Table 17). (42) 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,

and 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 10-25). 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 17). 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 MT alone for ISSNHL treatment. (43) RCTs and nonrandomized studies were included. The main outcomes considered were complete hearing recovery, any hearing recovery, and absolute hearing gain. Nineteen studies (3 randomized and 16 nonrandomized) with a total of 2401 patients (mean age, 45.4 years; 55.3% female) were included. In the HBOT+MT group, rates of complete hearing recovery and any hearing recovery were 264/897 (29.4%) and 621/919 (67.6%), respectively, and in the MT alone group were 241/1167 (20.7%) and 585/1194 (49.0%), respectively. Pooled HBOT+MT also showed favorable pooled results from random-effects models for both complete hearing recovery (OR, 1.61; 95% CI, 1.05-2.44) and any hearing recovery (OR, 1.43; 95% CI, 1.20-1.67). The study was limited by the following: 1) differences in clinical and methodological characteristics of selected studies, 2) considerable heterogeneity, 3) the possibility of 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) (44), 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 ≥10-point audiometric gain, was significantly higher with HBOT compared with control based on pooled analysis of 2 studies (OR, 4.32; 95% CI, 1.60 to 11.68; $I^2$=0%). Limitations of these results include the fact that the included studies were judged to have moderate (2 studies) and high (1 study) risk of bias and the small number of participants in both HBOT (n=88) and medical treatment (n=62) groups.

**Table 17. 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) (42) | May 2012 | 7 | Patients with SSNHL and/or tinnitus | 392 | RCTs | • Pooled analyses of 2 studies (n=114) showed HBOT did not result in >50% improvement in pure tone average threshold (RR=1.5; 95% CI, 0.9 to 2.8), but was able to achieve >25% improvement (RR=1.4; 95% CI, 1.1 to 1.8)<br>• Pooled analyses of 4 trials (n=169) found a significantly greater mean improvement in hearing over all frequencies with HBOT versus control (mean difference, 15.6 dB; 95% CI, 1.5 to 29.8 dB) |
| Rhee et al. (2018) (43) | Feb 2018 | 19 | Patients with SSNHL | 2401 | 3 RCTs, 16 non-RCTs | • 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) |
| Joshua et al. (2021) (44) | Apr 2020 | 3 | Patients with SSNHL | 150 | 3 RCTs | • Pooled results from 2 RCTs favored HBOT over MT for hearing recovery, defined as |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | ≥10-point audiometric gain (OR 4.32; 95% CI, 1.60 to 11.68) |

CI: confidence interval; dB: decibels; HBOT therapy: hyperbaric oxygenation therapy; ISSNHL: idiopathic sudden sensorineural hearing loss; N/n: number; RCT: randomized controlled trial; RR: relative risk; MT: medical therapy.

In their qualitative systematic review, Eryigit et al. (2018) assessed the effectiveness of HBOT to treat patients with ISSNHL. (45) Sixteen clinical trials were included, with a total of 1759 operative ears, 580 of which received HBOT. All patients also received steroid treatment-either systemic, intravenous, or intratympanic injection. Most studies found that patients with severe or profound hearing loss who received steroids (any route of administration) plus HBOT saw statistically significant improvements (specified *p*-value range across studies: 0.0014–0.012), whereas those with a lower level of hearing loss did not see these improvements. Several studies reported no significant difference between case and control groups, but the studies that broke down the results by levels of hearing loss all showed that profound (or severe and profound) loss benefited from the addition of HBOT to steroid treatment.

Randomized Controlled Trials

A 2022 RCT conducted by Cavaliere et al. published subsequent to the systematic reviews described above compared HBOT and oral steroids, alone and in combination, in 171 adults with ISSNHL. (46) Study characteristics are summarized in Table 18.

**Table 18. Characteristics of Trials Assessing HBOT for ISSNHL**

| | | | | | **Interventions** | | |
|---|---|---|---|---|---|---|---|
| **Study (Year)** | **Countries** | **Sites** | **Dates** | **Participants** | **HBOT (n=60)** | **Oral Steroids (n=55)** | **HBOT+Oral Seroids (n=56)** |
| Cavaliere et al. (2022) (46) | Italy | Singe-center | Feb 2016-Dec 2019 | Adults with unilateral and/or bilateral ISSNHL onset within the last 30 days, unknown cause of hearing loss, and normal Eustachian | HBOT 2.5 ATA; 90 min per session for 10 sessions total over 15 days | Oral prednisone 1 mg/kg per day (maximum dose of 60 mg/day) for 12-14 consecutive days | HBOT + oral prednisone |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | tube function | | | |

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

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

The purpose of the study limitations tables (see Tables 19 and 20) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement.

**Table 19. Study Relevance Limitations of Trials Assessing HBOT for ISSNHL**

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Duration of Follow-up[e] |
|---|---|---|---|---|---|
| Cavaliere et al. (2022) (46) | | | 5. Lack of untreated control group (up to 65% of individuals with ISSNHL spontaneously recover) | 1,3,5. Outcomes limited to measures of auditory function; only narrative description of no complications (no harms data); no prespecified description of clinically significant difference | 1, 2. Duration of follow-up (20 days) insufficient to assess benefit and harms |

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 20. Study Design and Conduct Limitations of Trials Assessing HBOT for ISSNHL**

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Cavaliere et al. (2022) (46) | 5. Randomization was described as accomplished with the use of randomization software, but despite this, there were statistically significant baseline differences between treatment groups for age and magnitude of hearing loss (the HBOT + steroid group was younger and had less hearing loss) | 1, 2. No description of blinding of study participants, staff or outcome assessors | 4. Study registration is unclear | | 1. Power calculations not reported | |

Abbreviations: HBOT: hyperbaric oxygen therapy; ISSNHL: idiopathic sudden sensorineural hearing loss.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Systemic HBOT for Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL)
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 third review that had stricter inclusion criteria found HBOT increased the rate of hearing recovery, but the analysis was limited to 2 trials with methodological limitations. One RCT published subsequent to the systematic reviews found a positive effect of HBOT plus steroid combination therapy on measures of auditory function compared to either HBOT or steroids alone, but other outcomes were not reported, and the study had numerous relevance, design, and conduct limitations.

**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 or an improvement on existing therapies in individuals with delayed-onset muscle soreness.

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

*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.

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 21). (47) 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 21. Systematic Reviews of Trials Assessing HBOT for Delayed-Onset Muscle Soreness (DOMS)**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Bennett et al. (2005) (47) | Feb 2010 | 9 | Patients with acute closed soft tissue injuries or DOMS | 219 | RCTs | • 2 trials on closed soft tissue injuries: no significant difference in time to recovery, functional outcomes, or pain<br>• 7 DOMS trials, pooled: significantly higher pain at 48 and 72 hours in HBOT therapy group, 0.9 (95% CI, 0.09 to 1.7); no differences in long-term pain, swelling, or muscle strength |

CI: confidence interval; DOMS: delayed-onset muscle soreness; HBOT therapy: hyperbaric oxygenation therapy; N/n: number; RCT: randomized controlled trial.

Section Summary: Systematic HOBT 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 or an improvement on existing therapies in individuals with autism spectrum disorder.

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

*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.

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 22). (48) 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). (49) The primary outcome measures were change in Autism Treatment Evaluation Checklist (ATEC) 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 22. Systematic Reviews of Trials Assessing HBOT for Autism Spectrum Disorder**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Xiong et al. (2016) (48) | Dec 2015 | 1 | Children aged 3-9 years with autism spectrum disorder | 60 | RCT | • Parental assessed ATEC: 1.2 (95% CI, -2.2 to 4.6)<br>• Clinician assessed ATEC: 1.5 (95% CI, -1.3 to 4.5) |

ATEC: autism treatment evaluation checklist; CI: confidence interval; HBOT therapy: hyperbaric oxygenation therapy; N/n: number; RCT: randomized controlled trial.

In their controlled trial, Rizzato et al. (2018) examined the effect of HBOT on children diagnosed with autism. (50) 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 (1), and 1 months after the end of treatment (T2). The HBOT was also assessed with the Childhood Autism Rating Scale at T0 and T2. Total ABC scores had improved between T0 and T2 in both the intervention and control groups. The HBOT group mean score at T0 was 57.5 ± 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 HBOT for Autism Spectrum Disorder

A Cochrane review identified a single small low-quality RCT on HBOT for autism spectrum disorder and that trial did not find 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 (CP)**

Clinical Context and Therapy Purpose

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

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

*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.

Two published RCTs were identified on use of HBOT for cerebral palsy (see Tables 23 and 24). Lacey et al. (2012) published a double-blind RCT that included 49 children ages 3 to 8 years with spastic cerebral palsy. (51) Participants were randomized to 40 treatments with HBOT or hyperbaric air to simulate 21% $O_2$ 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 cerebral palsy to 40 treatments over a 2-month period of HBOT or slightly pressurized room air. (52) Investigators found similar improvements in outcomes such as gross motor function and activities of daily living in both treatment groups.

An observational study by Long et al. (2017) evaluated the effects of HBOT as a treatment for sleep disorders in children with cerebral palsy (n=71). (53) 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 23. Characteristics of Randomized Trials Assessing HBOT for Cerebral Palsy**

| | | | | | Treatment | |
|---|---|---|---|---|---|---|
| **Study (Year)** | **Countries** | **Sites** | **Dates** | **Participants** | **Active** | **Comparator** |
| Lacey et al. (2012) (51) | United States | 2 | 2005-2009 | Children aged 3-8 years with spastic CP | • n=25<br>• $HBO_2$<br>• 100% $O_2$ at 1.5 ATA<br>• 40 times over 2 months | • n=24<br>• $HBO_2$<br>• 14% $O_2$ at 1.5 ATA<br>• 40 times over 2 months |
| Collet et al. (2001) (52) | Canada | 17 | NR | Children aged 3-2 years with CP | • n=57<br>• $HBO_2$<br>• 100% $O_2$ at 1.75 ATA<br>• 40 times over 2 months | • n=54<br>• Slightly pressurized air<br>• 100% $O_2$ at 1.3 ATA<br>• 40 times over 2 months |

ATA: atmospheres absolute; CP: cerebral palsy; HBOT therapy: hyperbaric oxygenation therapy; N/n: number; NR: not reported; $O_2$: oxygen.

**Table 24. Results of Trials Assessing HBOT for Cerebral Palsy**

| **Study (Year)** | **Mean Change GMFM[a] (95% CI)** | **Between-Group Difference (95% CI)** | **Mean Change Functional Skill** | **Between-Group Difference (95% CI)** |
|---|---|---|---|---|
| **Lacey et al. (2012) (51)** | 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) (52)** | | | **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; N/n: number; PEDI: Pediatric Evaluation of Disability Inventory;
[a] Positive score represents improvement in function from baseline.

Section Summary: Systemic HBOT 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 cerebral palsy, 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 or an improvement on existing therapies in individuals with vascular dementia.

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

*Populations*

The relevant population of interest is individuals with vascular dementia.

*Interventions*

The therapy being considered is systemic HBOT.

*Comparators*

Comparators of interest 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.

A Cochrane review (2012) identified a small RCT evaluating HBOT for vascular dementia (see Table 25). (54) 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 25. Systematic Reviews of Trials Assessing HBOT for Vascular Dementia**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Xiao et al. (2012) (54) | Dec 2011 | 1 | Patients with vascular dementia, according to DSM-IV criteria | 64 | RCT | • WMD of MMSE score: 3.5 (95% CI, 0.9 to 6.1)<br>• WMD of HDS score: 3.1 (95% CI, 1.2 to 5.0) |

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

Section Summary: 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 or an improvement on existing therapies in individuals with radiotherapy adverse events.

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

*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-HT3), 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.

Systemic Reviews

Ravi et al. (2017) conducted a systematic review assessing the effect of HBOT on patients with head and neck cancer who had received radiotherapy (see Table 26). (11) 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. (55) 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 26. Systematic Reviews of Studies Assessing HBOT for Radiotherapy Adverse Events**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Ravi et al. (2017) (11) | Dec 2016 | 10 | Patients who have received RT for head | 375 | Prospective case series and prospective | • Salivary gland function: 2 case series (n=96) reported that patients receiving |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | and neck cancer | | comparative studies | HBOT experienced improvements in salivary flow rates<br>• QOL: 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 |
| Villeirs et al. (2020) (55) | May 2018 | 20 | Patients with RT-induced cystitis | 815 | RCTs, cohort studies and case series | • 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. |

EORTC: European Organization for Research and Treatment of Cancer; HADS: Hospital Anxiety and Depression Scale; $HBO_2$ Therapy: hyperbaric oxygen therapy; N/n: number; QOL: quality of life; RT: radiotherapy; SF-36: 36-Item Short-Form Health Survey.

Randomized Controlled Trials

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

Gothard et al. (2010) in the U.K. published findings of an RCT using HBOT for arm lymphedema occurring after radiotherapy for cancer. (56) Fifty-eight patients with arm lymphedema (at least a 15% increase in arm volume) following cancer treatment were randomized in a 2:1 ratio to HBOT (n=38) or usual care without HBOT (n=20). Fifty-three patients had baseline assessments, and 46 (79%) of 58 had 12-month assessments. At the 12-month follow-up, there was no statistically significant difference in the change from baseline in arm volume. Median change from baseline was -2.9% in the treatment group and -0.3% in the control group. The study protocol defined response as at least an 8% reduction in arm volume relative to the

contralateral arm. By this definition, 9 (30%) of 30 of patients in the HBOT group were considered responders compared with 3 (19%) of 16 in the control group (p=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) assessed HBOT for late radiation-induced cystitis in adult cancer patients who had received pelvic radiotherapy. (57) Eighty-seven patients were randomized to either HBOT (n=42) or standard care (n=45). Eight patients withdrew consent directly after randomization, so 79 were included in the intention-to-treat analysis. The primary outcome was change in the urinary domain of the Expanded Prostate Index Composite Score, which is a patient-reported outcome measurement tool with 12 questions covering a range of urinary tract symptoms; each answer is given on a Likert scale, and the totals are calculated to a 0–100 score. A post hoc analysis determined the minimal clinically important difference to be 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 30–40 treatments within 60–80 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).

Section Summary: Systematic HBOT for Radiotherapy Adverse Events

Two 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. An RCT not included in the reviews focused on arm lymphedema; it found no significant differences between study groups. Another RCT assessed HBOT for radiation-induced cystitis and found significant benefit by some measures but not others.

**Systemic Hyperbaric Oxygen Therapy for Idiopathic Femoral Neck Necrosis**

Clinical Context and Therapy Purpose

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

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

*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.

A double-blind RCT evaluating HBOT for treatment of femoral head necrosis was published by Camporesi et al. (2010) (see Tables 27 and 28). (58) The trial included 20 adults with idiopathic unilateral femoral head necrosis. Patients received HBOT or a sham treatment of hyperbaric air. The mean severity of pain on a 0-to-10 scale was significantly lower in the HBOT group than in the control group after 30 sessions ($p<0.001$) but not after 10 or 20 sessions. The trial did not report exact pain scores. Several range-of-motion outcomes were reported. At the end of the initial treatment period, extension, abduction, and adduction, but not flexion, was significantly greater in the HBOT group than in the control group. Longer term comparative data were not available because the control group was offered HBOT after the initial 6-week treatment period.

**Table 27. Characteristics of Trials Assessing HBOT for Femoral Neck Necrosis**

| | | | | | Treatment | |
|---|---|---|---|---|---|---|
| **Study (Year)** | **Countries** | **Sites** | **Dates** | **Participants** | **Active (n=10)** | **Comparator (n=10)** |

| | | | | | | |
|---|---|---|---|---|---|---|
| Camporesi et al. (2010) (58) | United States | 1 | NR | Patients with unilateral femoral neck necrosis | • $HBO_2$<br>• 100% $O_2$ at 2.5 ATA<br>• 30 sessions over 6 weeks | • Hyperbaric air<br>• 30 sessions over 6 weeks |

ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; N/n: number; NR: not reported; $O_2$: oxygen.

**Table 28. 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) (58) | | | | |
| *HBOT* | 7.5 (4.0-20.0) | NS | 20.0 (15.0-20.0) | <0.001 |
| *HBAT* | 4.0 (3.0-6.0) | | 3.0 (0.0-5.0) | |

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

Section Summary: Systemic HBOT for Idiopathic Femoral Neck Necrosis

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

**Systemic Hyperbaric Oxygen Therapy for Migraine Headache**

Clinical Context and Therapy Purpose

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

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

*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.

A Cochrane review by Bennett et al. (2015) identified 11 RCTs (total 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 29). (59) 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 29. Systematic Reviews of Trials Assessing HBOT for Migraine or Cluster Headaches**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Bennett et al. (2015) (59) | Jun 2015 | 11 | Patients with migraine or cluster headaches | 209 | RCT | • 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)<br>• No evidence that HBOT can prevent migraine, |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | reduce nausea or vomiting, or reduce need for rescue medication |

CI: confidence interval; HBOT: hyperbaric oxygen therapy; N/n: number; RR: relative risk.

Section Summary: Systemic HBOT 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 or an improvement on existing therapies in individuals with herpes zoster.

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

*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 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.

Peng et al. (2012) in China published an RCT evaluating HBOT for herpes zoster (see Tables 30 and 31). (60) 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 30. Characteristics of Trials Assessing HBOT for Herpes Zoster**

| | | | | | Treatment | |
|---|---|---|---|---|---|---|
| **Study (Year)** | **Countries** | **Sites** | **Dates** | **Participants** | **Active (n=36)** | **Comparator (n=32)** |
| Peng et al. (2012) (60) | China | NR | 2008-2010 | Patients diagnosed with herpes zoster within 2 weeks | • $HBO_2$<br>• 100% $O_2$ at 2.2 ATA<br>• 2 sessions per day for 5 days<br>• Thirty 120-min sessions; plus medications that control group received | Medication alone, including: antiviral, nerve nutritive, pain relief, and antidepressives |

ATA: atmospheres absolute; HBOT Therapy: hyperbaric oxygen therapy; NR: not reported; $O_2$: oxygen.

**Table 31. Results of Trials Assessing HBOT for Herpes Zoster**

| **Study (Year)** | **Efficacy[a,b]** | **Mean Days to Blister Resolution[b]** | **Mean Days to Scar Formation[b]** | **NPRS Score[b]** | |
|---|---|---|---|---|---|
| | | | | **Pretreatment** | **Post-treatment** |
| **Peng et al. (2012) (60)** | 68 | 68 | 68 | 68 | 68 |
| Mean HBOT Therapy 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 Therapy: hyperbaric oxygen therapy; NPRS: Numeric Pain Rating Scale; SD: standard deviation;

[a] Calculation: (number cases with healing + number cases with improvement)/(total number cases × 100);
[b] Between-group difference p<0.05.

Section Summary: Systemic HBOT for Herpes Zoster
One RCT was identified. Only short-term outcomes were reported. Outcomes at the end of treatment were significantly better in the HBAOT group than in the medication group. Trail 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 or an improvement on existing therapies in individuals with fibromyalgia.

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

*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.

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 32 and 33). (61) 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 therapy, 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 32 and 33). (62) 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 VAS 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 32. Characteristics of Trials Assessing HBOT for Fibromyalgia**

| | | | | | **Treatment** | |
|---|---|---|---|---|---|---|
| **Study (Year)** | **Countries** | **Sites** | **Dates** | **Participants** | **Active** | **Comparator** |
| Efrati et al. (2015) (61) | Israel | 1 | 2010-2012 | Patients with fibromyalgia based on: 1) widespread pain and 2) at least 11 of 18 tender points | • n=24<br>• HBOT<br>• 100% $O_2$ at 2 ATA<br>• 1 session per day for 5 days<br>• Forty 90-minute sessions | • n=26<br>• No treatment for 2 months, then same treatment as active group |
| Yildiz et al. (2004) (62) | Turkey | NR | NR | Patients meeting ACR criteria for fibromyalgia, with persistent symptoms | • n=26<br>• HBOT<br>• 100% $O_2$ at 2.4 ATA | • n=24<br>• Air<br>• 1 ATA |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | despite medical therapy and PT | • 1 session per day for 5 days<br>• Fifteen 90-minute sessions | • 1 session per day for 5 days<br>• Fifteen 90-minute sessions |

ACR: American College of Rheumatology; ATA: atmospheres absolute; HBOT Therapy: hyperbaric oxygen therapy; N/n: number; NR: not reported; $O_2$: oxygen; PT: physical therapy.

**Table 33. 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) (61)** | 50 | | | 50 | | |
| Mean HBOT (SD) | 17.3 (1.4) | 8.9 (6.0) | <0.001 | 0.5 (1.2) | 1.7 (0.8) | <0.001 |
| Mean control (SD) | 17.7 (0.7) | 17.2 (1.1) | | 0.7 (0.5) | 0.6 (0.5) | |
| **Yildiz et al. (2004) (62)** | 50 | | | 50 | | |
| Mean HBOT (SD) | 15.0 (1.5) | 6.0 (1.2) | <0.001 | 0.7 (0.1) | 1.3 (0.1) | <0.001 |
| Mean air (SD) | 15.3 (1.2) | 12.5 (1.1) | | 0.7 (0.1) | 0.8 (0.1) | |

HBOT: hyperbaric oxygen therapy; SD: standard deviation.

Section Summary: Systemic HBOT for Fibromyalgia

Two RCTs assessing HBOT for fibromyalgia were identified. Both had relatively small sample sizes and methodologic limitations (e.g., quasi-randomization, no or uncertain sham control for a condition with subjective outcomes susceptible to a placebo effect). Moreover, the HBOT 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 (MS)**

Clinical Context and Therapy Purpose

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

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

*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.

Bennett et al. (2010) published a systematic review on the use of HBOT for treatment of MS (see Table 34). (63) Nine RCTs (N=504) were identified that compared the effects of HBOT with placebo or no treatment. All trials used an initial course of 20 sessions over 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 the Expanded Disability Status Scale score. A pooled analysis of data from 5 trials (n=271) 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 34. Systematic Reviews of Trials Assessing HBOT for Multiple Sclerosis**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Bennett et al. (2010) (63) | Jul 2009 | 9 | Patients with multiple sclerosis, at any state or | 504 | RCT | EDSS score difference between groups: |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | course of the condition | | | • At 4-week follow-up: 0.07 (95% CI, -0.09 to 0.23)<br>• At 6-month follow-up: 0.22 (95% CI, -0.09 to 0.54) |

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

Section Summary: Systemic HBOT for Multiple Sclerosis

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

**Systemic 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 or an improvement on existing therapies in individuals with cancer who are undergoing radiotherapy or chemotherapy.

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

*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.

In a Cochrane review (2005), (64) which was updated in 2012, (65) Bennett et al. (2012) identified 19 randomized and quasi-randomized trials (total n=2286 patients) comparing outcomes following radiotherapy with and without HBOT in patients with solid tumors (see Table 35). 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<0.001) and seizures (relative risk, 6.8; p=0.03) occurred more frequently in patients treated with HBOT.

**Table 35. Systematic Reviews of Trials Assessing HBOT for Tumor Sensitization during Cancer Treatment with Radiotherapy**

| Study (Year) | Literature Search | Studies | Participants | N | Design | Results |
|---|---|---|---|---|---|---|
| Bennett et al. (2012) (65) | Sep 2017 | 19, some including multiple cancer sites | • Head and neck: 10 trials<br>• Uterine: 7 trials<br>• Urinary ladder: 5 trials<br>• Bronchus: 1 rial<br>• Rectum: 1 trial<br>• Brain: 1 trial<br>• Esophagus: 1 trial | 2286 | RCT and quasi-RCT | Head and neck:<br>• 1-year mortality: RR=0.8 (p=0.03)<br>• 5-year mortality: RR=0.8 (p=0.03)<br>• 5-year recurrence: RR=0.8 (p=0.01)<br>Uterine:<br>• 2-year recurrence: RR=0.6 (p=04) |

HBOT: hyperbaric oxygen therapy; N/n: number; RCT: randomized control 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. (66)

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

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

**Fracture Healing**

In 2012, Bennett et al. published a Cochrane review on HBOT to promote fracture healing and treat nonunion fractures. (67) The reviewers indicated since HBOT was being utilized for various conditions and had been described as a possible modality for fracture healing. The investigators did not identify any published RCTs on this topic that compared HBOT with no treatment, sham or another intervention and reported bony union as an outcome.

Section Summary: Fracture Healing

Due to the lack of RCTs, it is not possible to conclude whether the use HBOT to promote fracture healing improves outcomes. As of this update, only 1 study was identified and it was suspended in 2012, with no further activity. A review of literature (July 2024) did not identify any new or ongoing studies in fracture healing.

**Additional Indications or Clinical Conditions**

There is a lack of scientific evidence from which conclusions can be made concerning the safety and efficacy of utilizing HBOT for various other indications mentioned as clinical conditions which are not a labeled indication by the FDA nor listed on the guidelines from the UHMS, or any other authoritative source, (68) such as:

- Actinic skin damage;
- Acute peripheral arterial insufficiency;
- Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's Disease;
- Arthritic diseases;
- Asthma;
- Avascular necrosis;
- Bone grafts;
- Carbon tetrachloride poisoning;
- Cardiogenic shock;
- Compromised skin grafts and flaps;
- Depression;
- Spinal cord injury;
- Hepatic necrosis;

- Hepatitis;
- Human immunodeficiency virus infection or acquired immune deficiency syndrome (HIV/AIDS);
- Hydrogen sulfide poisoning;
- Intra-abdominal and intracranial abscesses;
- In vitro fertilization (IVF);
- Lepromatous leprosy;
- Lyme disease;
- Lymphedema of arm;
- Meningitis;
- Mental illness;
- Motor dysfunction associated with stroke;
- Multiple sclerosis;
- Organ transplantation or storage;
- Parkinson's disease;
- Postoperative ileus or acute pancreatitis;
- Post-traumatic stress disorder (PTSD) or other stress disorders;
- Pseudomembranous colitis, antimicrobial agent-induced colitis;
- Pulmonary emphysema;
- Pyoderma gangrenosum;
- Radiation-induced injury to head, neck, anus, or rectum (except proctitis);
- Radiation-myelitis;
- Radiation tissue injury;
- Refractory mycoses;
- Retinal artery insufficiency;
- Retinopathy, as an adjunct to scleral buckling procedure in patients with sickle cell peripheral retinopathy and retinal detachment;
- Sickle cell crisis and/or hematuria;
- Senility;
- Septicemia, anaerobic (unrelated to clostridial), or systemic aerobic infection;
- Sport's injury;
- Stroke and cerebrovascular disease (acute [thrombotic or embolic] or chronic);
- Sudden deafness (unrelated to ISSNHL);
- Tetanus; and/or
- Vascular dementia or chronic brain syndromes, neovascular causes (such as Pick's disease, Alzheimer's disease, and Korsakoff's disease).

**Practice Guidelines and Position Statements**

Society of Vascular Surgery (SVS) et al.

In 2016, the SVS in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine published guidelines on the management of the diabetic foot. (69) 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 (UHMS)

In 2015, the UHMS published guidelines on the use of HBOT therapy for treating diabetic foot ulcers. (70) The 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 now shown significant improvement after 30 days of [standard of care] therapy…."
- Suggest "adding acute postoperative 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: (68)

- Air or gas embolism;
- Carbon monoxide poisoning and carbon monoxide complicated by cyanide poisoning;
- Clostridial myositis and myonecrosis (gas gangrene);
- Crush injury, compartment syndrome, and other acute traumatic ischemias;
- Decompression sickness;
- Central retinal artery occlusion;
- Diabetic foot ulcer;
- Healing of other problem wounds;
- Severe anemia;
- Intracranial abscess;
- Necrotizing soft tissue infections;
- Refractory osteomyelitis;
- Delayed radiation injury (soft tissue and bony necrosis);
- Compromised skin grafts and flaps;
- Acute thermal burn injury;
- Idiopathic sudden sensorineural hearing loss (ISSNHL) (patients with moderate to profound ISSNHL who present within 14 days of symptom onset).

UHMS has also published position statements that concluded there was insufficient evidence to recommend topical HBOT for chronic wounds (2005), (71) multiple sclerosis, (72) and autism spectrum disorder (2009). (73)

American Academy of Otolaryngology-Head and Neck Surgery (AAOHNS)

In 2019, the AAOHNS updated clinical guidelines on the treatment of sudden sensorineural hearing loss (SSNHL). (74) 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 month of onset of SSNHL."

The guideline provided a comprehensive list of evidence gaps and future research needs on the use of HBOT for SSNHL. These included, among others, the need for a standardized, evidence-based definition of SSNHL, the assessment of the prevalence of SSNHL, and the need for the development of standardized HBOT treatment protocols and standardized outcome assessments.

Tenth European Consensus Conference on Hyperbaric Medicine

The 10th European Consensus Conference on Hyperbaric Medicine (ECHM) convened in April 2016 to update HBOT therapy indication recommendations. (75) Evidence was assessed using a modified GRADE system with the DELPHI system for consensus evaluation. Table 36 presents the updated recommendations:

**Table 36. Recommendations on Hyperbaric Medicine** (Adapted from Mathieu et al. [2017]). (75)

| **Condition** | **SOR** | **LOE** |
|---|---|---|
| Carbon monoxide poisoning | Strong | Moderate |
| Open fractures with crush injury | Strong | Moderate |
| Prevention of osteoradionecrosis | Strong | Moderate |
| Osteoradionecrosis (mandible) | Strong | Moderate |
| Soft tissue radionecrosis (cystitis, proctitis) | Strong | Moderate |
| Decompression illness | Strong | Low |
| Gas embolism | Strong | Low |
| Anaerobic or mixed bacterial infection | Strong | Low |
| Sudden deafness | Strong | Moderate |
| Diabetic foot lesions | Weak | Moderate |
| Femoral head necrosis | Weak | Moderate |
| Compromised skin grafts and musculocutaneous flaps | Weak | Low |
| Central retinal artery occlusion | Weak | Low |
| Crush injury without fracture | Weak | Low |
| Osteoradionecrosis (other than mandible) | Weak | Low |
| Radio-induced lesions of soft tissues | Weak | Low |
| Radio-induced lesions of soft tissues (preventive) | Weak | Low |
| Ischemic ulcers | Weak | Low |
| Refractory chronic osteomyelitis | Weak | Low |
| Burns, second degree, >20% body surface area | Weak | Low |

| | | |
|---|---|---|
| Pneumatosis cystoides intestinalis | Weak | Low |
| Neuroblastoma, stage IV | Weak | Low |
| Brain injury in highly selected patients | Neutral | Low |
| Radio-induced lesions of larynx | Neutral | Low |
| Radio-induced lesions of central nervous system | Neutral | Low |
| Post-vascular procedure reperfusion syndrome | Neutral | Low |
| Limb replantation | Neutral | Low |
| Selected non-healing wounds, secondary to systemic process | Neutral | Low |
| Sickle cell disease | Neutral | Low |
| Interstitial cystitis | Neutral | Low |

LOE: level of evidence; SOR: strength of recommendation.

Following the publication of the European Consensus Conference on Hyperbaric Medicine update, a letter to the editor requested details on the modified GRADE system and commented on the lack of a reference list in the updated publication.

Dana Farber/Brigham and Women's Cancer Center

In 2017, the Dana Farber/Brigham and Women's Cancer Center conducted a systematic review of the evidence for HBOT therapy for the prevention and management of osteoradionecrosis (ORN) of the jaw. (76) The literature search, conducted in January 2016, identified 3 studies on the prevention of ORN (1 RCT, 2 retrospective cohorts) and 4 studies on the management of ORN (1 RCT, 3 retrospective cohorts). Based on results from these studies, the Center "does not recommend the routine use of HBO for the prevention or management of ORN. Adjunctive HBOT may be considered for use on a case-by-case basis in patients considered to be at exceptionally high risk who have failed conservative therapy and subsequent surgical resection."

**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 therapy administered in a chamber for the following conditions (see Table 37) (77):

**Table 37. CMS Medicare Coverage Approved Indications**

| No. | Indication |
|---|---|
| 1. | Acute carbon monoxide intoxication. |
| 2. | Decompression illness. |
| 3. | Gas embolism. |
| 4. | Gas gangrene. |
| 5. | Acute traumatic peripheral ischemia. HBOT is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened. |

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

HBOT: hyperbaric oxygen therapy; No: number; CMS: Centers for Medicare and Medicaid Services.

According to Medicare, "The use of $HBO_2$ therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30-days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present. Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of $HBO_2$ therapy. Continued treatment with $HBO_2$ therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment."

**Summary of Evidence**

Topical Hyperbaric Oxygen ($THBO_2$) Therapy

For individuals with wounds, burns or infections who receive $THBO_2$ therapy, the evidence includes a systematic review, case series, and a randomized controlled trial (RCT). Relevant outcomes are overall survival (OS), symptoms, change in disease status, and functional outcomes. The systematic review identified 3 RCTs including patients with sacral pressure ulcers, ischial pressure ulcers, and refractory venous ulcers. All trials reported that healing improved significantly after $THBO_2$ therapy 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.

Systemic Hyperbaric Oxygen (HBOT) Therapy

*Chronic Wounds*

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.

*Carbon Monoxide Poisoning*

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.

*Radionecrosis, Osteoradionecrosis, and Treatment of Irradiated Jaw*

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.

*Chronic Refractory Osteomyelitis*

For individuals with chronic refractory osteomyelitis who receive systemic HBOT, the evidence includes case series. Relevant outcomes are symptoms and change in disease status. The case series reported high rates of successful outcomes (no drainage, pain, tenderness, or cellulitis) in patients with chronic refractory osteomyelitis treated with HBOT. However, controlled studies are needed to determine conclusively the impact of HBOT on health outcomes compared with other interventions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

However, clinical input and Undersea and Hyperbaric Medical Society guidelines support HBOT for the treatment of chronic refractory osteomyelitis. Thus, based on clinical input and guideline support, this indication may be considered medically necessary.

*Acute Thermal Burns*

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.

*Acute Surgical and Traumatic Wounds*
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. A systematic review of controlled Chinese studies suggests HBOT may increase the survival rate of compromised skin grafts and flaps when initiated within 72 hours; however, risk of bias in the original Chinese publications cannot be evaluated. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

*Bisphosphonate-Related Osteonecrosis of the Jaw*
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.

*Necrotizing Soft Tissue Infections*
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.

*Acute Coronary Syndromes*
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, one found significantly lower rates of death with HBOT and the other reported inconsistent results in left ventricular function. Additional RCT data are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

*Acute Ischemic Stroke*

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 3-6 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.

*Motor Dysfunction Associated with Stroke*

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, and 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.

*Bell Palsy*

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.

*Traumatic Brain Injury*

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

*Inflammatory Bowel Disease*

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. Three RCTs have reported mixed findings in patients with ulcerative colitis, with one study terminated early due to futility. A systematic review including the RCT and observational studies found a high rate of bias in the literature due to attrition and reporting bias. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

*Idiopathic Sudden Sensorineural Hearing Loss*

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

*Delayed-Onset Muscle Soreness*

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.

*Autism Spectrum Disorders*

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.

*Cerebral Palsy*

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.

*Vascular Dementia*

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.

*Radiotherapy Adverse Effects*
For individuals with radiotherapy adverse events who receive systemic HBOT, the evidence includes RCTs, nonrandomized comparator trials, case series, and systematic reviews. Relevant outcomes are symptoms and functional outcomes. Two systematic reviews included few RCTs and provide limited evidence on the effect of HBOT. Two RCTs 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

*Idiopathic Femoral Neck Necrosis*
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.

*Migraine*
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.

*Herpes Zoster*
For individuals with herpes zoster who receive systemic HBOT, the evidence includes an RCT. Relevant outcome 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.

*Fibromyalgia*
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.

*Multiple Sclerosis*
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.

*Tumor Sensitization during Cancer Treatment: Radiotherapy or Chemotherapy*
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 $HBO_2$ therapy, 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 therapy before chemotherapy compared with usual care. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

*Fracture Healing*
For individuals with fractures that are not healing and nonunion fractures who receive systemic HBOT therapy, the evidence is lacking as there are no RCTs or published literature found during a systematic review. Relevant outcomes are symptoms and functional outcomes. Since the Cochrane review did not find any RCTs when patients were treated for nonunion or failing to heal fractures with HBOT therapy versus sham or another comparator intervention, assessment of relevant outcomes is difficult. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

*Other Conditions (Not Discussed Earlier)*
The evidence for the use of systemic HBOT in individuals with other conditions (not discussed earlier), i.e., crush injury, reperfusion injury, compartment syndrome, and other acute traumatic ischemias; venous stasis ulcers; compromised skin graft or flap, or for enhancement of healing in a selected problem wound; gas gangrene; soft tissue infections due to mixed aerobic and anaerobic organisms with tissue necrosis and refractory bacteroides infections; decompression sickness; acute air or gas embolism; brown recluse spider bite; acute cyanide poisoning; profound anemia with exceptional blood loss when blood transfusion is impossible or must be delayed; selected refractory mycoses; intracranial abscess; acute cerebral edema; non-acute arterial insufficiency ulcer; decubitus ulcers; planned dental surgery (non-implant-

related) of an irradiated jaw, and includes systematic reviews and/or recommendations from the UHMS's guidelines. Relevant outcomes include OS, symptoms, change in disease status, and functional outcomes. For all of these indications, evidence and/or UHMS guidelines support use of systemic HBOT. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in health outcomes.

The evidence for the use of systemic HBOT in individuals with any condition other than those specified in the prior paragraphs may include systematic reviews, small RCTs, case series, small uncontrolled studies, and/or anecdotal case review/summaries. Relevant outcomes include OS, symptoms, change in disease status, and functional outcomes. The available studies do not demonstrate that HBOT improves relevant outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 38.

**Table 38. Summary of Key Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ***Ongoing*** | | | |
| 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 2024 |
| 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 Later Radiation Toxicity | 120 | 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 | 46 | Jul 2025 |

| | | | |
|---|---|---|---|
| | Randomized Controlled Clinical Trial (TTM-COHB Trial) | | |
| ***Unpublished*** | | | |
| 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 10/30/2017) |

NCT: national clinical trial.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

| | |
|---|---|
| **CPT Codes** | 99183 |
| **HCPCS Codes** | A4575, G0277 |

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

| Policy History/Revision | |
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| **Date** | **Description of Change** |
| 10/15/2024 | Document updated with literature review. Coverage unchanged. References 1, 12, 21, 38-40, 46 and 78 added, some updated and others removed. |
| 11/15/2023 | Reviewed. No changes. |
| 08/01/2022 | Document updated with literature review. The following change was made to Coverage: Removed Wagner grade criteria from medical necessity statement on venous stasis ulcers. References 4, 22, 45, and 73 added; others removed. |
| 10/15/2021 | Document updated with literature review. The following changes were made in Coverage: Removed "radiation necrosis of non-neurologic tissue" from the existing experimental, investigational and/or unproven list. Note 12 language "Standard wound care in patients with diabetic wounds includes: assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible, optimization of nutritional status, optimization of glucose control, debridement by any means to remove devitalized tissue, maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings, appropriate off-loading, and necessary treatment to resolve any infection that might be present." moved from the end of the policy to the coverage section. References 11, 64 and 79 added. |
| 12/15/2020 | Document updated with literature review. Coverage unchanged. References 34, 39-43, 48-49, 51-53, 56, 64, 66, 72, 74, 76, and 84 added; several references removed. |
| 10/15/2019 | Reviewed. No changes. |
| 10/01/2018 | Document updated with literature review. Coverage unchanged. NOTEs renumbered, following addition of NOTE 1: "This medical policy does not address $THBO_2$ therapy in the absence of pressurization". References 1, 3, 9, 11-13, 19, 27-28, 31-32, 40, 44, 48, 64-66, 68-73 added; numerous references removed. |
| 07/15/2017 | Reviewed. No changes. |
| 10/01/2016 | Document updated with literature review. The following indication was added as medically necessary: acute postoperative foot surgical treatment for patients with Wagner grade-3 or higher diabetic foot ulcers. The |

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| | following indications were added as experimental, investigational and/or unproven: fibromyalgia and mental illness. |
| 05/01/2015 | Document updated with literature review. The following indications were added as experimental, investigational and/or unproven: Arthritic diseases, osteoarthritis or rheumatoid; Asthma; Cardiogenic shock; Depression; Inflammatory bowel disease; Hepatic necrosis; Hepatitis; Herpes zoster; Human immunodeficiency virus infection or acquired immune deficiency syndrome; Motor dysfunction associated with stroke; Organ transplantation or storage; Osteonecrosis of the jaw, bisphosphonate-related; Post-traumatic stress disorder or other stress disorders; Pulmonary emphysema; Senility; Sport's injury; Septicemia, anaerobic (unrelated to clostridial), or systemic aerobic infection; Tetanus; Ulcerative Colitis; Vascular dementia or chronic brain syndromes, neovascular causes (such as Pick's disease, Alzheimer's disease, and Korsakoff's disease). Title changed from Hyperbaric Oxygen ($HBO_2$) Pressurization. |
| 12/01/2013 | Document updated with literature review. The following was added: 1) New medically necessary indications for uses of $HBO_2$ therapy when criteria is met: Idiopathic sudden sensorineural hearing loss (ISSNHL); 2) New experimental, investigational and unproven indications for uses of $HBO_2$ therapy: Bell's palsy; idiopathic femoral neck necrosis; lymphedema of the arm; acute osteomyelitis; radiation-induced injury to head, neck, anus, or rectum; radiation necrosis of non-neurologic tissue; reduction of adverse effects at any point of therapy, including early onset effects and delayed effects; and acute surgical and traumatic wounds. Otherwise, coverage for all other indications remains unchanged. |
| 07/15/2011 | Coverage revised only. The following changes were made: 1) Systemic $HBO_2$ may be considered medically necessary to treat soft-tissue radiation necrosis, including radiation enteritis, cystitis, or proctitis; 2) Review of diabetic wounds may occur after 30 systemic $HBO_2$ treatments. |
| 03/01/2010 | Revised/updated entire document, $HBO_2$ may be considered medically necessary when clinical criteria are met. |
| 09/15/2008 | Coverage revised, Rationale revised, References revised. |
| 08/15/2007 | Revised/updated entire document. |
| 11/01/2000 | Revised/updated entire document. |
| 03/01/2000 | Revised/updated entire document. |
| 01/01/1996 | Revised/updated entire document. |
| 05/01/1996 | Medical policy number changed. |