PHP_2.01.04	Hyperbaric Oxygen Therapy		
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State Guidelines

As of the publication of this policy, there are no applicable Medi-Cal guidelines (Provider Manual or All Plan Letter). Please refer to the Policy Statement section below.

Policy Statement

In the absence of any State Guidelines, please refer to the criteria below.

I. Topical hyperbaric oxygen therapy is considered **investigational**.

II. Systemic hyperbaric oxygen pressurization may be considered **medically necessary** in the treatment of **any** of the following conditions:
   A. Acute carbon monoxide poisoning
   B. Acute cyanide poisoning
   C. Acute gas embolism
   D. Acute traumatic ischemia (e.g., crush injuries, reperfusion injury, compartment syndrome)
   E. Central retinal artery occlusion
   F. Chronic refractory osteomyelitis
   G. Compromised skin grafts or flaps
   H. Decompression sickness
   I. Gas gangrene (i.e., clostridial myonecrosis)
   J. Idiopathic sudden sensorineural hearing loss (SSNHL) and **either** of the following:
      1. When hyperbaric oxygen therapy (HBOT) is combined with steroid therapy within 2 weeks of onset of SSNHL
      2. When hyperbaric oxygen therapy (HBOT) is combined with steroid therapy as salvage within 1 month of onset of SSNHL
   K. Nonhealing diabetic wounds of the lower extremities in patients who meet **all** of the following criteria:
      1. Individual has a wound classified as Wagner grade 3 or higher
      2. Individual has no measurable signs of healing after 30 days of an adequate course of standard wound therapy
      3. Individual has type 1 or type 2 diabetes and has a lower-extremity wound due to diabetes
   L. Pre- and posttreatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw
   M. Profound anemia with exceptional blood loss and **either** of the following:
      1. When blood transfusion is impossible
      2. When blood transfusion must be delayed
   N. Progressive necrotizing soft tissue infections
   O. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis)
   P. Osteoradionecrosis

III. Systemic hyperbaric oxygen pressurization is considered **investigational** in all other situations, including but not limited to, the treatment of the following conditions:

A. Acute arterial peripheral insufficiency (outside of other listed medically necessary indications involving arterial insufficiency)
B. Acute carbon tetrachloride poisoning
C. Acute cerebral edema
D. Acute coronary syndromes and as an adjunct to coronary interventions, including but not limited to, percutaneous coronary interventions and cardiopulmonary bypass
E. Acute ischemic stroke
F. Acute osteomyelitis
G. Acute surgical and traumatic wounds not meeting criteria specified in the medically necessary statement
H. Acute thermal burns
I. Autism spectrum disorder
J. Bell palsy
K. Bisphosphonate-related osteonecrosis of the jaw
L. Bone grafts
M. Brown recluse spider bites
N. Cerebral palsy
O. Cerebrovascular disease, acute (thrombotic or embolic) or chronic
P. Chronic arm lymphedema following radiotherapy for cancer
Q. Chronic wounds, other than those in patients with diabetes who meet the criteria specified in the medically necessary statement
R. Delayed-onset muscle soreness
S. Demyelinating diseases (e.g., multiple sclerosis, amyotrophic lateral sclerosis)
T. Early treatment (beginning at completion of radiotherapy) to reduce adverse events of radiotherapy
U. Fibromyalgia
V. Fracture healing
W. Herpes zoster
X. Hydrogen sulfide poisoning
Y. Idiopathic femoral neck necrosis
Z. In vitro fertilization
AA. Inflammatory bowel disease (Crohn disease or ulcerative colitis)
BB. Intra-abdominal and intracranial abscesses
CC. Lepromatous leprosy
DD. Meningitis
EE. Mental illness (i.e., posttraumatic stress disorder, generalized anxiety disorder or depression)
FF. Migraine
GG. Motor dysfunction associated with stroke
HH. Pseudomembranous colitis (antimicrobial agent-induced colitis)
II. Pyoderma gangrenosum
JJ. Radiation myelitis
KK. Radiation-induced injury in the head and neck, except as noted earlier in the medically necessary statement
LL. Refractory mycoses: mucormycosis, actinomycosis, conidiobolus coronato
MM. Retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment
NN. Vascular dementia
OO. Sickle cell crisis and/or hematuria
PP. Spinal cord injury
QQ. Traumatic brain injury
RR. Tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy

Policy Guidelines

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

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

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

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

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

Following are recommended indications from the Undersea and Hyperbaric Medical Society's (UHMS) 20 23 Hyperbaric Oxygen Therapy Committee report on utilization of HBOT (15th edition):

- Air or gas embolism
- Arterial insufficiencies: Central retinal artery occlusion; Hyperbaric oxygen therapy for selected problem wounds
- Carbon monoxide poisoning and carbon monoxide complicated by cyanide poisoning
- Clostridial myonecrosis (gas gangrene)
- Acute traumatic ischemias
- Decompression sickness
- Severe anemia
- Intracranial abscess
- Necrotizing soft tissue infections
- Refractory osteomyelitis
- Delayed radiation injury (soft tissue and bony necrosis)
- Compromised grafts and flaps
- Acute thermal burn injury
- Sudden sensorineural hearing loss
- Avascular necrosis (aseptic osteonecrosis).[1]

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

Progressive Necrotizing Soft Tissue Infections

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

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL)

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

Central Retinal Artery Occlusion (CRAO) and Other Retinal Conditions

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

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

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

Acute Peripheral Artery Insufficiency

For this policy review, the indication of acute peripheral artery insufficiency is too broad to include as a stand-alone indication for HBOT.

Acute peripheral artery insufficiency is not included in the FDA list of approved conditions for HBOT. The Undersea and Hyperbaric Medical Society guidelines (15th edition) include peripheral artery insufficiency as an indication for HBOT related to diabetic foot ulcers and non-healing arterial insufficiency ulcers but does not have a stand-alone indication for acute peripheral artery insufficiency.

Acute arterial Insufficiencies (AAI) are interruptions, complete or partial, of perfusion that put the tissues distal to the interruption at risk for loss of function or dying. AAIs thereby span all arteries including a variety of conditions already included in this review (e.g., central retinal artery occlusion, ischemic stroke, compartment syndrome). Acute peripheral artery insufficiency (also called peripheral arterial insufficiency) would be a subtype of AAI. Peripheral artery insufficiency is also referred to as

peripheral artery disease (PAD). PAD is defined by the American Heart Association (AHA) as a narrowing of the peripheral arteries that carry blood away from the heart to other parts of the body, and is typically further defined to narrowed arteries reducing blood flow to the arms or legs. The AHA states the most common type of PAD is lower-extremity PAD. In 2024, the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines published a Guideline for the Management of Lower Extremity PAD.[2] The Guideline suggests that HBOT may have a limited role, and states HBOT: "*may be considered as an adjunctive therapy to revascularization for wound healing in the context of CLTI (chronic limb threatening ischemia) and diabetic foot ulcers*". No other mention of HBOT is made, including no mention of HBOT for acute limb ischemia.

Timing and Duration of HBOT Treatment
While broad indications are given above, the decision to treat with HBOT and timing of HBOT should be made on a case-by-case basis. For example, acute arterial ischemias have a spectrum of times that vary by tissue type: minutes for neurological tissues, hours for muscle, days for skin and bone, and even longer for relatively avascular connective tissues, cartilage, and adnexal structures. Even for indications with guideline-based time periods there are case studies showing improvement outside of such windows. For example, the Undersea and Hyperbaric Medical Society Committee recommends HBOT treatment for central retinal artery occlusion (CRAO) within 24 hours of onset, as studies demonstrate the outcome of HBOT is improved with early treatment. However, successful cases have been reported in which treatment began later, sometimes up to weeks later. Given the safety of HBOT, the lack of successful alternative medical treatments, the debilitating impact of vision loss, and the challenges faced in getting a patient to a hyperbaric facility, it is difficult to provide a specific time cutoff after which HBOT should not be tried for CRAO.

As such, no broad statements or specific statements as to timing of HBOT can be provided.

Recommended treatment dose and number of treatment sessions per the UHMS Hyperbaric Oxygen Therapy Committee (15th edition, 2023) include:

- **Acute traumatic ischemia** – there are 3 stages of wound healing. Treatment recommended varies based on stage, and ranges from 2-3 times per day for 2-3 days for acute inflammatory stage, 14 days for repair stage, and up to a month for remodeling.
- **Carbon monoxide poisoning** – Use up to 3 atmospheres absolute (ATA) for 1 to 3 sessions or to clinical plateau.
- **Central Retinal Artery Occlusion (CRAO)**– Recommend 2 to 2.8 ATA or U.S. Navy Table 6 or equivalent. Treat twice daily to clinical plateau, which typically occurs in less than a week, plus 3 days. Hyperbaric treatments 2-3 times daily may be necessary until the angiogram normalizes or the patient has no further improvement for 3 treatments.
- **Clostridial myositis, Clostridial myonecrosis (Gas gangrene)-** Recommend 3 ATA pressure for 90 minutes, 2-3 times in the first 24 hours, and then 2 times daily for the next 2-5 days. Review is indicated after 10 treatments.
- **Chronic refractory osteomyelitis –** Typically, once daily, 5-7 days per week for 90-120 minutes using 2-3 ATA, and continued for 4-6 weeks. 20-40 sessions typically needed, although might be situations where up to 60 sessions are needed. Patients with refractory stage 3 or 4 osteomyelitis are most likely to benefit from adjunctive hyperbaric oxygen therapy, especially when complicated by adverse local or systemic factors.
- **Compartment syndrome** – Use 2 to 2.4 ATA, usually twice a day for 2 days but sometimes might need 3 times a day. After fasciotomy, twice a day for 7-14 days.
- **Compromised skin grafts and flaps –** Use 2 to 2.5 ATA twice daily for up to 20 sessions.
- **Crush injury** – similar to acute traumatic ischemia above. The UHMS notes that HBOT should be started as close as possible to the time of injury; 3 or more treatments during the first 24 to 72 hours are recommended; 1-2 times per day for 14 days if in the repair phase; daily use for 3-6 weeks during remodeling.

- **Cyanide poisoning** – Patients with cyanide poisoning frequently present with simultaneous carbon monoxide poisoning. Treatment protocol recommended is the same as for carbon monoxide poisoning.
- **Decompression sickness** – Use U.S. Navy Treatment Table 6 or equivalent, typically up to 2.8 ATA, for 1 session up to a clinical plateau. Typically, no more than 1 to 2 treatment sessions are needed.
- **Diabetic lower extremity wounds, selected individuals and healing of other problem wounds** –Use 2 to 2.5 ATA daily, should see effects by 2-3 weeks; course of outpatient therapy is typically 30 sessions but might require up to 40 sessions. For HBOT to continue, reevaluation at 30-day intervals must show continued progress in healing.
- **Necrotizing soft-tissue infections** – Use 2 to 2.5 ATA twice daily until stabilization occurs, often occurs within 7-10 treatments. If differential diagnosis includes the possibility of Clostridial myositis and/or myonecrosis and/or remains unclear, 2.8-3 ATA pressures are warranted with 3 treatments in the first 24-48 hours. Avoidance of premature cessation of HBOT is advised, and once extension of necrosis has been halted then once daily treatments over an extended period until the infection is well controlled is recommended. This might require 30 treatments. Review after 30 treatments.
- **Radiation Necrosis** –Most treatments range from 2-2.5 ATA for 40-60 treatments, and review should occur after 60 treatments.
    1. **Mandibular osteoradionecrosis, laryngeal necrosis, other soft tissue head and neck, chest wall necrosis, radiation cystitis, radiation proctitis, miscellaneous abdominal pelvic injuries, cutaneous necrosis** – 2 to 2.4 ATA daily for 90 minutes.
    2. **Neoadjuvant hyperbaric oxygen therapy before dental extractions** – 2 to 2.4 ATA, typically 20 treatments before extraction and 10 treatments after.
- **Sudden sensorineural heating loss** – Recommend 2 to 2.5 ATA for 10 to 20 sessions.
- **Severe Anemia** –Use 2 to 3 ATA for 3 or 4 times a day until there is replacement of red blood cells by regeneration or transfusion.[1,3]

Coding
See the Codes table for details.

Description

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

Summary of Evidence
For individuals with wounds, burns or infections who receive topical hyperbaric oxygen therapy (HBOT), the evidence includes a systematic review, case series, and a randomized controlled trial (RCT). Relevant outcomes are overall survival (OS), symptoms, change in disease status, and functional outcomes. The systematic review identified 3 RCTs including patients with sacral pressure ulcers, ischial pressure ulcers, and refractory venous ulcers. All trials reported that healing improved significantly after HBOT than after standard of care. Pooling of results was not possible due to heterogeneity in patient populations and treatment regimens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with chronic diabetic ulcers who receive systemic HBOT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms and change in disease status. Meta-analyses of RCTs found significantly higher diabetic ulcer healing rates with HBOT than with control conditions. Two of the 3 meta-analyses found that HBOT was associated with a significantly lower

rate of major amputation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with carbon monoxide poisoning who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are OS and symptoms. A meta-analysis in a Cochrane review of low-quality RCT data did not find HBOT to be associated with a significantly lower risk of neurologic deficits after carbon monoxide poisoning. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals with acute thermal burns who receive systemic HBOT, the evidence includes a systematic review of 2 RCTs. Relevant outcomes are OS, symptoms, and change in disease status. Both RCTs were judged to have poor methodologic quality. Evidence from well-conducted controlled trials is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with acute surgical and traumatic wounds who receive systemic HBOT, the evidence includes RCTs, controlled nonrandomized studies, and systematic reviews. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. There was considerable heterogeneity across the 4 RCTs identified (e.g., patient population, comparison group, treatment regimen, outcomes). This heterogeneity prevented pooling of trial findings and limits the ability to definitively conclude the impact of HBOT on health outcomes for patients with acute surgical and traumatic wounds. Additional evidence from high-quality RCTs is needed. A systematic review of controlled Chinese studies suggests HBOT may increase the survival rate of compromised skin grafts and flaps when initiated within 72 hours; however, risk of bias in the original Chinese publications cannot be evaluated. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with bisphosphonate-related osteonecrosis of the jaw who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and change in disease status. The RCT was unblinded and reported initial benefits at 3-month follow-up; however, there were no significant benefits of HBOT for most health outcomes compared with standard care in the long-term (6 months to 2 years). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with acute coronary syndrome who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. A Cochrane review identified 6 RCTs. There were 2 pooled analyses, 1 found significantly lower rates of death with HBOT and the other reported inconsistent results in left ventricular function. Additional RCT data are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with motor dysfunction associated with stroke who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and functional outcomes. The RCT, which used a crossover design, found better outcomes with HBOT at 2 months than with delayed treatment. However, the trial had a number of methodologic limitations (e.g., lack of patient blinding, heterogeneous population, high dropout rate) that make it difficult to evaluate the efficacy of HBOT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with traumatic brain injury who receive systemic HBOT, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. RCTs were heterogeneous regarding intervention protocols, patient populations, and outcomes reported. Systematic reviews conducted pooled analyses only on a minority of the published RCTs, and these findings were inconsistent. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with inflammatory bowel disease who receive systemic HBOT, the evidence includes 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.

For individuals with idiopathic sudden sensorineural hearing loss who receive systemic HBOT, the evidence includes systematic reviews. Relevant outcomes are symptoms, change in disease status, and functional outcomes. A Cochrane review of RCTs had mixed findings from studies that included individuals with tinnitus. Some outcomes (i.e., improvement in hearing of all frequencies, >25% return of hearing) were better with HBOT than with a control intervention, but more than 50% return of hearing did not differ significantly between groups. There was important variability in the patients enrolled in the studies. A subsequent systematic review had similarly limited conclusions due to the inclusion of non-randomized studies. A third review found a higher proportion of patients with hearing recovery with HBOT compared to medical treatment alone, but the analysis was limited to 2 RCTs with methodological limitations. One RCT published subsequent to the systematic reviews

found a positive effect of HBOT plus steroid combination therapy on measures of auditory function compared to either HBOT or steroids alone, but other outcomes were not reported and the study had numerous relevance, design, and conduct limitations. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with autism spectrum disorder who receive systemic HBOT, the evidence includes an RCT and a systematic review. Relevant outcomes are symptoms and functional outcomes. A Cochrane review identified a single RCT on HBOT for autism spectrum disorder and this trial did not find significantly better parental-assessed or clinician-assessed outcomes with HBOT compared with sham. A subsequent controlled trial reached the same conclusion. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cerebral palsy who receive systemic HBOT, the evidence includes 2 RCTs and an observational study. Relevant outcomes are symptoms and functional outcomes. One RCT was stopped early due to futility, and the other did not find significantly better outcomes with HBOT than with a sham intervention. The observational study focused on sleep disorders in children with cerebral palsy and reported improvements with the HBOT treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals with idiopathic femoral neck necrosis who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCT, which had a small sample, only reported short-term (i.e., 6-week) outcomes. Larger well-conducted RCTs reporting longer-term outcomes are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a migraine who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The Cochrane review conducted a pooled analysis including 3 of the 11 trials. Meta-analysis of these 3 RCTs found significantly greater relief of migraine symptoms with HBOT than with a comparator intervention within 45 minutes of treatment. Longer-term data are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with herpes zoster who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and change in disease status. The RCT was unblinded and only reported short-term (i.e., 6-week) outcomes. Additional well-conducted RCTs with longer follow-up are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with fibromyalgia who receive systemic HBOT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Only 2 RCTs were identified, and both reported positive effects of HBOT on tender points and pain. However, the trials had relatively small samples and methodologic limitations (e.g., quasi-randomization, no or uncertain sham control for a condition with subjective outcomes susceptible to a placebo effect). Moreover, the HBOT protocols varied. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Additional Information

There is limited comparative evidence for HBOT. The review is thereby based on the best available evidence, relying largely on clinical input and guidelines.

2024 Input

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

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

Further details from clinical input are included in the Appendix.

2023 Input

Clinical input was sought to help determine whether the use of systemic HBOT in individuals with acute surgical or traumatic wounds and compromised skin grafts or flaps would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 2 specialty society-level responses.

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

Further details from clinical input are included in the Appendix.

2010 Input
Clinical input obtained in 2010 and guidelines from the Undersea and Hyperbaric Medical Society and the 10th European Consensus Conference on Hyperbaric Medicine support HBOT for the treatment of acute carbon monoxide poisoning. Thus, based on clinical input and guideline support, this indication may be considered medically necessary.

Clinical input obtained in 2010 and Undersea and Hyperbaric Medical Society guidelines support HBOT for the treatment of chronic refractory osteomyelitis. Thus, based on clinical input and guideline support, this indication may be considered medically necessary.

Related Policies

- N/A

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

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.[5] 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.

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

- Air and gas bubbles in blood vessels
- Anemia (severe anemia when blood transfusions cannot be used)
- Burns (severe and large burns treated at a specialized burn center)
- Carbon monoxide poisoning
- Crush injury
- Decompression sickness (diving risk)
- Gas gangrene
- Hearing loss (complete hearing loss that occurs suddenly and without any known cause)

- Infection of the skin and bone (severe)
- Radiation injury
- Skin graft flap at risk of tissue death
- Vision loss (when sudden and painless in one eye due to blockage of blood flow)
- Wounds (non-healing, diabetic foot ulcers).

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

Hyperbaric Oxygen Therapy

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

Topical Hyperbaric Oxygen Therapy

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

Systemic Hyperbaric Oxygen Therapy

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

Adverse Events

HBOT is a generally safe therapy, with an estimated adverse side effect rate of 0.4%.[4] Adverse events may occur either from pressure effects or the oxygen. The pressure effect (barotrauma) may affect any closed air-filled cavity such as ears, sinus, teeth, and lungs. Pain and/or swelling may occur at these sites as pressure increases during the procedure and decreases as the procedure is ending.

Oxygen toxicity may affect the pulmonary, neurologic, or ophthalmologic systems. Pulmonary symptoms include a mild cough, substernal burning, and dyspnea. Neurologic effects include tunnel vision, tinnitus, nausea, and dizziness. Ophthalmologic effects include retinopathy in neonates, cataract formation, and transient myopic vision changes.

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

Literature Review

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

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

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

Topical Hyperbaric Oxygen Therapy for Wounds, Burns, or Infections

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is topical 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:

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

Review of Evidence

de Smet et al (2017) conducted a systematic review of various oxygen therapies (oxygen dressing therapy, topical oxygen therapy, HBOT, inspired oxygen therapy).[6] Three RCTs evaluating topical oxygen therapy for chronic wound healing were identified (see Table 1). One RCT (n=100) administered treatment for 20 minutes 3 times per day for 12 days to the treatment group and standard care to the control group. The number of patients experiencing complete wound healing, defined as complete epithelialization of the wound without drainage, was 16 in the experimental group and 1 in the control group (p<.001). Two of the RCTs, which had overlapping populations with refractory venous ulcers (n=83 in one and n=132 in the other) administered treatment for 180 minutes 2 times per day for 12 weeks to the treatment group and conventional compression dressing to the control group. In all trials, patients in the treatment group experienced significantly higher proportions of healed ulcers and significantly faster healing times.

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

Study (Year)	Literature Search	Studies	Participants	N (Range)	Design	Results
de Smet et al (2017)[6]	Feb 2016	3	Stage II-IV sacral or ischial pressure ulcers (1 RCT) Refractory venous ulcers (2 RCTs)	315[a] (83-132)	RCT	• Results not pooled • In all trials, patients in the treatment group experienced significantly higher wound healing rates

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

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

A systematic review identified 3 RCTs on the use of topical HBOT for chronic wound healing. The results showed topical oxygen therapy improved wound healing, but there was heterogeneity in the trial populations and treatment regimens. There is a small RCT on topical HBOT for diabetic foot ulcers; it showed no differences in outcomes between the treatment and control group. No controlled studies on topical HBOT for patients with burns or infections were identified. The data are insufficient to draw conclusions about the effect on the net health outcome.

Systemic Hyperbaric Oxygen Therapy for Chronic Diabetic Ulcers

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

Comparators of interest include standard wound care and advanced wound therapy. Standard wound care can include offloading of the wound with appropriate therapeutics, dressings, debridement antibiotic therapy, and blood glucose control. Advanced wound therapy can include the application of recombinant growth factors and wound coverage with 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 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Sharma et al (2021)[7] conducted a systematic review and meta-analysis of 14 studies (N=768) comparing the effect of HBOT with standard care on diabetic foot ulcers (Table 2). Study authors noted that various modalities can be considered standard care including, but not limited to, debridement, antibiotics and blood sugar control. However, the specific standard care modality in each included study was not reported. HBOT duration ranged from 45 to 120 minutes (median, 90 minutes). All included studies had methodological limitations, including selection, performance, detection, attrition and reporting bias. The review found those treated with standard care were less likely to have complete ulcer healing versus HBOT, based on pooled analysis of 11 studies (odds ratio [OR], 0.29; 95% confidence interval [CI], 0.14 to 0.61; I^2=62%). Results were consistent when stratified according to duration of 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 2).[8] Reviewers identified 12 RCTs (N=577) comparing the effect of HBOT on chronic wound healing with an alternative treatment approach that did not use HBOT. Ten of the 12 trials evaluated HBOT in patients with diabetes (n=531). The trials were assessed as moderate quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. HBOT regimens varied across studies, ranging from 3.0 atmospheres absolute (ATA) for 45 minutes to 2.2 ATA for 120 minutes. In a pooled analysis of 5 trials, a significantly higher proportion of ulcers had healed at the end of treatment (i.e., 6 weeks) in the group receiving HBOT than in the group not receiving HBOT, but there was no statistically significant difference in the risk of major amputations between groups.

A systematic review by Elraiyah et al (2016) evaluated adjunctive therapies (HBOT, arterial pumps, and pharmacologic agents) used to treat diabetic foot ulcers (see Table 2).[9] RCTs and nonrandomized cohort studies were included. The RCTs were rated as low-to-moderate quality using the GRADE system. A pooled analysis of 6 RCTs found a significantly higher healing rate and a significantly lower major amputation rate (OR, 0.30; 95% CI, 0.10 to 0.89) with HBOT than with control.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Kranke et al (2015)[8]	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) • 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)[9]	Oct 2011	18	Patients with diabetic foot ulcers	1526	RCTs, cohort	• 16 of 18 trials included HBOT as a treatment option and 6 of those were RCTs • 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)[7]	Sep 2020	14	Patients with diabetic foot ulcers	768	RCTs, CCTs	• 12 RCTs and 2 CCTs compared HBOT with undefined standard care • 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: hyperbaric oxygen therapy; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; ST: standard care.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Chronic Diabetic Ulcers

Three systematic reviews have been published that included trials and cohort studies. Pooled analyses of RCTs found significantly higher wound healing rates with HBOT than with control conditions. One of the 2 meta-analyses found that HBOT was associated with a significantly lower rate of major amputation.

Systemic Hyperbaric Oxygen Therapy for Carbon Monoxide Poisoning

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

A Cochrane review by Buckley et al (2011) included 6 RCTs evaluating HBOT for carbon monoxide poisoning (see Table 3).[10] Four of the 6 trials were assessed as having a high risk of bias due to nonblinding of treatment allocation. The trials had substantial methodologic and statistical heterogeneity. The outcome of interest was dichotomous, presence or absence of signs or symptoms indicative of neurologic injury at 4 to 6 weeks after study inclusion. Two of the 6 RCTs found that HBOT reduced the likelihood of neurologic sequelae at 1 month and 4 others did not find a significant effect. A pooled analysis of the 6 trials did not find a significant effect of HBOT on neurologic injury. Reviewers concluded that there was insufficient evidence to determine whether HBOT reduces the risk of adverse neurologic outcomes after carbon monoxide poisoning. Quality of the evidence was deemed very low, using the GRADE system.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Buckley et al (2011)[10]	Jun 2010	6	Nonpregnant 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: hyperbaric oxygen therapy; OR: odds ratio; RCT: randomized controlled trial.

Nonrandomized Comparative Studies

Nakajima et al (2020) conducted a retrospective cohort study comparing the effect of HBOT versus control (no HBOT) on mortality and morbidity in patients with carbon monoxide poisoning.[11] The median number of HBOT sessions was 3 (range, 2 to 5). After propensity score matching of study participants (N=4068) the study found no significant difference between groups in in-hospital mortality (mean rate difference, -0.4%; 95% CI, -1.0 to 0.2%). Results were consistent across subgroups according to severity of carbon monoxide poisoning, age and number of HBOT sessions. However, the study found HBOT associated with lower rates of depressed mental status (mean difference, -3.2%; 95% CI, -4.9% to -1.5%) and reduced activities of daily living (mean difference, -5.3%; 95% CI, -7.8% to -2.7%) relative to no HBOT.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Carbon Monoxide Poisoning

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

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

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

Comparators of interest include 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.

Review of Evidence

Systematic Reviews

Bennett et al (2016) published a Cochrane review on HBOT for late radiation tissue injury (see Table 4).[12] Reviewers identified 14 RCTs. There was a moderate level of evidence for 2 pooled analyses. In a pooled analysis of 3 studies, a significantly higher proportion of patients with osteoradionecrosis achieved complete mucosal cover after HBOT compared with control treatments, and in a pooled analysis of 2 trials, a significantly lower risk of wound dehiscence after surgery to repair mandibular osteoradionecrosis with HBOT than with control treatments was reported. A single trial found a significantly higher likelihood of successful healing with HBOT than with antibiotics for tooth extraction in irradiated jaws (absolute risk reduction, 25%; p=.02). There were insufficient data to conduct meta-analyses on other outcomes.

Borabet al (2017) published a systematic review focusing on the use of HBOT to treat the subgroup of patients with late radiation tissue injury who had skin necrosis (see Table 4).[13] 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.[14] Ten prospective case series and comparative studies were identified. Qualitative summaries of outcomes were provided, but pooled analyses were not performed. Outcomes of interest included osteonecrosis and dental implant survival (see Table 4). Other outcomes of interest included salivary gland function and QOL, which are discussed in the Radiotherapy Adverse Events section.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2016)[12]	Dec 2015	14	Patients with late radiation tissue injury (including necrosis) and	753	RCTs	• Pooled analyses of 3 trials of patients with osteoradionecrosis (n=246) found a higher rate of

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
			patients treated with large-dose radiotherapy likely to induce early necrosis			complete mucosal cover after HBOT vs. control (RR, 1.3; 95% CI, 1.1 to 1.5) • Pooled analyses of 2 trials (n=264) found a lower risk of wound dehiscence following surgery to repair mandibular osteoradionecrosis in patients treated with HBOT vs control (RR, 4.2; 95% CI, 1.1 to 16.8)
Borab et al (2017)[13]	May 2016	8	Patients with radiation-induced skin necrosis	720	Observational cohort and case series	• Adding across the studies, 80% reported complete healing and 86% reported symptom improvement • Studies had no comparators
Ravi et al (2017)[14]	Dec 2016	10	Patients who received radiotherapy for head and neck cancer	375	Prospective case series and prospective comparative studies	• Osteonecrosis prevention: 1 case series and 1 comparative study (n=77) reported low osteonecrosis rates with HBOT • 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; HBOT: hyperbaric oxygen therapy; RCT: randomized controlled trial; RR: relative risk.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Radionecrosis, Osteoradionecrosis, and Treatment of Irradiated Jaw

A Cochrane review of RCTs found that HBOT improved some radionecrosis and osteoradionecrosis outcomes and resulted in better outcomes before tooth extraction in an irradiated jaw. Observational studies focused on skin necrosis and reported high rates of healing with HBOT, though with no comparators, interpretation of results is limited. Prospective observational studies using HBOT for treatment on patients with head and neck cancer receiving HBOT, have reported low osteonecrosis rates and inconsistent results for dental implant survival. The number of RCTs evaluating HBOT for these indications, especially in irradiated jaws, is limited.

Systemic Hyperbaric Oxygen Therapy for Chronic Refractory Osteomyelitis

Clinical Context and Therapy Purpose

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

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

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.

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

Savvidou et al (2018) conducted a qualitative systematic review of HBOT as an adjunctive treatment of chronic osteomyelitis.[15] 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.[16] Follow-up data were available on 34 patients who had received a mean of 35 adjunctive HBOT sessions (range, 6 to 99 sessions). Of the 26 patients with at least 24 months of follow-up after treatment, 81% (21/26) remained drainage-free. At 60 months of follow-up, 80% (12/15), and at 84 months, 63% (5/8) remained drainage-free.

Davis et al (1986) reviewed outcomes for 38 patients with chronic refractory osteomyelitis treated at another U.S. institution.[17] Patients received HBOT until the bone was fully recovered with healthy vascular tissue; this resulted in a mean of 48 daily treatments (range, 8 to 103 treatments). After a mean post-treatment follow-up of 34 months, 34 (89%) of 38 patients remained clinically free of infection (i.e., drainage-free and no tenderness, pain, or cellulitis). Success rates from several smaller case series (N range, 13 to 15 patients), all conducted in Taiwan (1998 through 2000), ranged from 79% to 92%.[18,19,20] A high percentage of refractory patients in these series had successful outcomes.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Chronic Refractory Osteomyelitis

Only case series data are available; no RCTs or comparative nonrandomized trials were identified. Case series tended to find high rates of successful outcomes in patients with chronic refractory osteomyelitis treated with HBOT. However, controlled studies are needed to determine conclusively that HBOT improves health outcomes in patients with chronic refractory osteomyelitis compared with other interventions.

Systemic Hyperbaric Oxygen Therapy for Acute Thermal Burns

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

In 2004, a Cochrane review assessed HBOT for thermal burns (see Table 5).[21] Two RCTs were identified, published in 1974 and 1997. Sample sizes were 16 and 125. Both trials were judged by reviewers to have poor methodologic quality. Reviewers concluded that the evidence was insufficient to permit conclusions on whether HBOT improves health outcomes in patients with acute thermal burns. No additional trials have been identified in updated literature searches.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Villanueva et al (2009)[21]	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 • 1 trial (N=16) reported shorter healing times (19.7 days vs. 43.8 days; p<.001) with HBOT vs control, and an RR for failed graft without HBOT of 2.0 (95% CI, 0.5 to 8.0)

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

Section Summary: Systemic Hyperbaric Oxygen Therapy for Acute Thermal Burns

A Cochrane review identified 2 RCTs on HBOT for thermal burns. Both were judged to have poor methodologic quality. There is insufficient evidence from well-conducted controlled studies to permit conclusions on the impact of HBOT on health outcomes in patients with acute thermal burns.

Systemic Hyperbaric Oxygen Therapy for Acute Surgical and Traumatic Wounds

Clinical Context and Therapy Purpose

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

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

Populations

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

Review of Evidence

A Cochrane review of RCTs on HBOT for acute surgical and traumatic wounds was published by Eskes et al (2013) (see Table 6).[22] HBOT was administered at pressures above 1 atmosphere (atm). To be included, studies had to compare HBOT with a different intervention or compare 2 HBOT regimens; also, studies had to measure wound healing objectively. Four RCTs met reviewers' inclusion criteria. Trials ranged in size from 10 to 135 participants. Due to differences among trials regarding patient population, comparison intervention, and outcome measurement, results could not be pooled. The primary outcome examined by Cochrane reviewers (wound healing) was not reported in either of the 2 trials comparing HBOT with usual care and was not reported in the trial comparing HBOT with dexamethasone or heparin. Complete wound healing was reported in the RCT comparing active HBOT with sham HBOT. In this study (n=36), there was a statistically higher rate of wound healing in the group, though the time point for outcome measurement in this trial was unclear. Also, there was no statistically significant difference between groups in the mean time to wound healing.

A systematic review of studies on HBOT for acute wounds, published by Dauwe et al (2014), included RCTs and controlled nonrandomized studies (see Table 6).[23] Reviewers included 8 studies, with sample sizes ranging from 5 to 125 patients. Four studies were randomized, 3 were prospective observational studies, and 1 was a retrospective observational study. As in the Eskes et al (2013) systematic review, data were not pooled. Reviewers noted that 7 of the 8 studies reported statistically significant findings for their primary endpoints, but the endpoints differed among studies (e.g., graft survival, hospital length of stay, wound size). Moreover, the studies were heterogenous 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.[24] Among 16 controlled studies comparing routine therapy to HBOT, healing and survival rates ranged from 35.0% to 86.5% and 77.9% to 100%, respectively. Among a subset of studies assessing skin flaps post-mastectomy, the overall therapeutic efficacy rate was 62.5%. Several studies suggested higher success rates when HBOT is initiated as soon as possible following surgery. Limitations of this analysis include heterogeneity in treatment protocols, wound sites and etiologies, and underlying comorbidities. The authors acknowledge that the therapeutic efficacy of HBOT in compromised skin flaps needs to be validated in future randomized, controlled studies but encourage shared decision-making in the absence of Level I evidence.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Eskes et al (2013)[22]	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 • A small trial (N=36) reported patients receiving HBOT had significantly higher

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
						wound healing rate vs. sham; however, no difference in time to healing
Dauwe et al (2014)[23]	Oct 2012	8	Patients with acute wounds, grafts, and flaps	256	RCTs and nonrandomized studies	• HBOT may augment healing of acute wounds • Not indicated for routine wound management
Zhou et al (2014)[24]	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 • Initiation of HBOT within 72 hours is associated with improved outcomes

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

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

Two systematic reviews identified 4 RCTs; 1 of the reviews also included nonrandomized studies. One systematic review identified 16 small Chinese controlled studies on the use of HBOT for compromised skin grafts and flaps. Heterogeneity among studies, (eg, in patient population, treatment regimen, comparison group, outcomes) prevented pooling of study findings and limited the ability to draw definitive conclusions about the impact of HBOT on health outcomes in patients with acute and traumatic wounds. Additional evidence from high-quality RCTs is needed.

Systemic Hyperbaric Oxygen Therapy for Bisphosphonate-Related Osteonecrosis of the Jaw

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

An unblinded RCT by Freiberger et al (2012) evaluated the use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw (see Tables 7 and 8).[25] The investigators did a per-protocol analysis (actual treatment received) due to crossovers between the treatment groups. Participants were evaluated at 3, 6, 12, and 18 months. At 3 months, significantly more patients receiving HBOT as an adjunct to standard care experienced improvements in lesion size and number compared with patients receiving only standard care. When the change from baseline to 6, 12, or 18 months was examined, there were no statistically significant differences between groups in the proportion of patients with improvement or in the proportion of those who healed completely at any time point. This trial had a number of methodologic limitations (e.g., unblinded, crossover, per-protocol analysis rather than intention-to-treat). A disadvantage of the per-protocol analysis is that randomization is not preserved, and the 2 groups may differ on characteristics that affect outcomes.

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

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

ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; NR: not reported.
[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 8. Results of Trials Assessing HBOT for Bisphosphonate-Related Osteonecrosis of the Jaw

Study (Year)	Improved, % (n) 3 Months	Between-Group P-Value	18 Months	Between-Group P-Value	Healed, % (n) 3 Months	Between-Group P-Value	Between-Group P-Value
Freiberger et al (2012)[25],	46		46		46		
HBOT	68.0 (25)	.03	58.3 (12)	.31	36.0 (25)	.04	1.0
Control	35.0 (20)		33.3 (6)		10.0 (20)		

HBOT: hyperbaric oxygen therapy.

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

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

to 2 years). Additional evidence from RCTs is needed to permit conclusions on the impact of HBOT on health outcomes in patients with bisphosphonate-related osteonecrosis of the jaw.

Systemic Hyperbaric Oxygen Therapy for Necrotizing Soft Tissue Infections

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

A Cochrane review by Levett et al (2015) evaluated the literature on HBOT as adjunctive therapy for necrotizing fasciitis.[26] 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).[27] Ten studies assessed to have critical (very high) risk of bias were excluded from meta-analyses. Pooled results from the remaining 21 studies found HBOT associated with a reduced risk of in-hospital mortality (OR, 0.44; 95% CI, 0.33 to 0.58; I^2=8%), but the duration of follow-up for mortality was not reported. Results were consistent when studies were stratified according to moderate (5 studies; OR, 0.39; 95% CI, 0.28 to 0.55; I^2=0%) and serious (high) risk of bias (16 studies; OR, 0.51; 95% CI, 0.33 to 0.80; I^2=17%). Publication bias favoring HBOT was present for this outcome based on funnel plot analysis. For other outcomes, including major amputation and length of hospital stay, there were no statistically significant differences between HBOT use and non-use. Evidence on adjunctive HBOT and the need for surgical debridement was mixed. One study with a low/moderate risk of bias reported a higher number of debridements with HBOT use versus non-use (mean difference, 1.8; 95% CI, 1.15 to 2.45), but the mean difference between HBOT use and non-use in a pooled analysis of 5

studies with methodological flaws was not statistically significant (mean difference, 0.63; 95% CI, -0.49 to 1.75).

Section Summary: Systemic Hyperbaric Oxygen Therapy for Necrotizing Soft Tissue Infections
No RCTs have evaluated HBOT for necrotizing soft tissue infection. A systematic review of retrospective cohort studies with methodological limitations suggested that HBOT use may reduce the risk of in-hospital mortality, but these results were subject to publication bias.

Systemic Hyperbaric Oxygen Therapy for Acute Coronary Syndrome
Clinical Context and Therapy Purpose
The purpose of systemic HBOT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with acute coronary syndrome.

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

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

Interventions
The therapy being considered is systemic HBOT.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
A Cochrane review by Bennett et al (2015) identified 6 trials (N=665) evaluating HBOT for acute coronary syndrome (see Table 9).[28] Included studies were published between 1973 and 2007. All studies included patients with acute myocardial infarction; a study also included individuals with unstable angina. Additionally, all trials used HBOT, administered between 2 and 3 ATA, for 30 to 120-minute sessions, as an adjunct to standard care. Control interventions varied; only a trial described using a sham therapy to blind participants to treatment group allocation. In a pooled analysis of data from 5 trials, there was a significantly lower risk of mortality in patients who received HBOT

compared with a control intervention. Due to the variability of outcome reporting across studies, few other pooled analyses could be conducted. Three trials reported outcomes related to left ventricular function. One did not find a statistically significant improvement in contraction with HBOT, while 2 trials showed left ventricular ejection fraction improved significantly with HBOT. Reviewers noted that, although some evidence from small trials correlated HBOT with a lower risk of death, larger trials with high-quality methods were needed to determine which patients, if any, could be expected to derive benefit from HBOT.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2015)[28]	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 vs. the control (RR, 0.58; 95% CI, 0.36 to 0.92) • 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: hyperbaric oxygen therapy; LVEF: left ventricular ejection fracture; MD: mean difference; RCT: randomized controlled trial; RR: relative risk.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Acute Coronary Syndrome

A Cochrane review of 6 RCTs found insufficient evidence that HBOT is safe and effective for acute coronary syndrome. One pooled analysis of data from 5 RCTs found a significantly lower rate of death with HBOT than with a comparison intervention; however, larger, higher-quality trials are needed. Three trials measuring left ventricular function report inconsistent results.

Systemic Hyperbaric Oxygen Therapy for Acute Ischemic Stroke

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

observe outcomes. Therefore, 6 months to 1 year or more of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

In a Cochrane systematic review of RCTs, Bennett et al (2014) evaluated HBOT for acute ischemic stroke (see Table 10).[29] Reviewers identified 11 RCTs (N=705) that compared HBOT with sham HBOT or no treatment. Reviewers could pool study findings for only 1 outcome (mortality at 3 to 6 months), and no difference was detected between the treatment groups for that outcome. There was heterogeneity in the participants enrolled and in the clinical and functional outcomes measured across the studies.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2014)[29]	Apr 2014	11	Patients with acute ischemic stroke, defined as sudden neurologic deficit of vascular origin for which hemorrhage was excluded by CT or MRI	705	RCTs	Pooled analyses of 4 trials (n=144) found no difference in mortality at 3 to 6 mo (RR, 0.97; 95% CI, 0.34 to 2.75)

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

Section Summary: Systemic Hyperbaric Oxygen Therapy for Acute Ischemic Stroke

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

Systemic Hyperbaric Oxygen Therapy for Motor Dysfunction Associated with Stroke

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Efrati et al (2013) published an RCT evaluating HBOT for the treatment of neurologic deficiencies associated with a history of stroke (see Tables 11 and 12).[30] Patients in the treatment group were evaluated at baseline and 2 months. For patients in the delayed treatment control group, outcomes were evaluated at 4 months after crossing over and receiving HBOT. Outcome measures included the National Institutes of Health Stroke Scale, which was measured by physicians blinded to the treatment group, and several patient-reported QOL and functional status measures. At the 2-month follow-up, there was a statistically significant improvement in function in the HBOT group compared with the control group, as measured by the National Institutes of Health Stroke Scale, QOL scales, and the ability to perform activities of daily living. These differences in outcome measures were accompanied by improvements in single-photon emission computed tomography imaging in the regions affected by stroke. For the delayed treatment control group, there was a statistically significant improvement in function after HBOT compared with before HBOT. This RCT raises the possibility that HBOT may induce improvements in function and QOL for post-stroke patients with motor deficits. However, the results are not definitive, as the RCT was small and enrolled a heterogeneous group of post-stroke patients. The trial was not double-blind and most outcome measures, except for National Institutes of Health Stroke Scale, were patient-reported and prone to the placebo effect. Also, there was a high total dropout rate (20%) at the 2-month follow-up. Larger, double-blind studies with longer follow-up are needed to corroborate these results.

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

Study (Year)	Countries	Sites	Dates	Participants	Treatment Active (n=30)	Comparator (n=29)
Efrati et al (2013)[30]	Israel	1	2008-2010	Patients ≥18 y with ischemic or hemorrhagic stroke 6 to 36 mo prior to inclusion with ≥1 motor dysfunction	• Hyperbaric oxygen • 100% oxygen at 2 ATA • 40 times over 2 mo	Same as active, delayed after 2 mo

ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy.

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

Study (Year)	National Institutes of Health Stroke Scale			Activities of Daily Living[a]		
	Baseline	2 Months	Between-Group P-Value	Baseline	2 Months	Between-Group P-Value
Efrati et al (2013)[30]	50	50		50	50	
Mean HBOT (SD)	8.5 (3.6)	5.5 (3.6)	.004	16.1 (6.5)	12.8 (7.3)	.02
Mean control (SD)	8.7 (4.1)	8.3 (4.3)		17.4 (9.5)	17.5 (9.5)	

HBOT: hyperbaric oxygen; SD: standard deviation.
[a] Activities of Daily Living: 16 functions scored across a range whether patient was independent to did not perform at all. Range: 0 (best) to 51 (worst).

Section Summary: Systemic Hyperbaric Oxygen Therapy for Motor Dysfunction Associated With Stroke

One crossover RCT evaluated HBOT in patients with a recent history of stroke. The RCT reported better outcomes at 2 months with HBOT than with delayed treatment. However, the trial had a number of methodologic limitations, making it difficult to draw conclusions about the efficacy of HBOT for this indication. Double-blind RCTs that address potential bias in subjective outcomes and studies with adequate follow-up are needed.

Systemic Hyperbaric Oxygen Therapy for Bell Palsy

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with Bell palsy.

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Holland et al (2012) published a Cochrane review evaluating HBOT in adults with moderate-to-severe Bell palsy.[31] The literature search, conducted through January 2012, identified 1 RCT with 79 participants, but this trial did not meet reviewers' prespecified selection standards because the outcome assessor was not blinded to treatment allocation. The trial was therefore excluded with no further analysis.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Bell Palsy

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

Systemic Hyperbaric Oxygen Therapy for Traumatic Brain Injury

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with TBI.

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

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

Table 13. Brain Injury Assessment Scales Outcome Measures

Outcome	Description	Administration	Scoring	MCID
Glasgow Coma Scale (GCS)	Assesses impairment of conscious level in response to stimuli	Physician-administered	Likert-type scale; lower numbers, more severe TBI: • eye opening (0 [not testable]–4) • verbal response (0–5) • motor response (0–6) Total Score: • Severe: ≤ 8	NR

Outcome	Description	Administration	Scoring	MCID
			• Moderate: 9–12 • Mild: 13–15	
Glasgow Outcome Scale (GOS)	Categorizes outcomes of patients after TBI	Physician-administered	1. Death 2. Persistent vegetative state: minimal responsiveness 3. Severe disability: conscious but disabled; dependent on others for daily support 4. Moderate disability: disabled but independent; can work in sheltered setting 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) • Total score range: 17–85 • PTSD cut point score for DoD screening: 31–33	• Response to treatment: ≥ 5 points • 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 • Score range: 0–84 • 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; TBI: traumatic brain injury.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

A meta-analysis by Wang et al (2016) assessed HBOT for TBI (see Table 14).[32] Eight studies (N=519) met the eligibility criteria. HBOT protocols varied across studies in the levels of oxygen and the length and frequency of treatments. The primary outcome was change in the Glasgow Coma Scale score. A pooled analysis of 2 studies found a significantly greater improvement in the mean Glasgow Coma Scale score in the HBOT group compared with control groups. Mortality (a secondary outcome) was reported in 3 of the 8 studies. Pooled analysis of these 3 studies found a significantly lower overall mortality rate in the HBOT group than in the control group.

Another systematic review, by Crawford et al (2016), did not conduct pooled analyses (see Table 14).[33] Reviewers identified 12 RCTs evaluating HBOT for patients with TBI. Using the Scottish

Intercollegiate Guidelines Network (SIGN) 50 criteria, 8 trials were rated acceptable and 4 rated low. Four trials, all rated as having acceptable quality, addressed patients with mild TBI and compared HBOT with sham. None found statistically significant differences between groups on outcomes (i.e., postconcussive symptom severity, psychological outcomes). Seven trials evaluated HBOT for the acute treatment of patients with moderate-to-severe TBI. Four were rated as acceptable quality and 3 as low quality. Study protocols and outcomes varied and none used a sham control. Three acceptable quality studies with standard care controls reported the Glasgow Outcome Scale score and mortality rate. In 2 of them, outcomes were better with HBOT than with standard care; in the third study, outcomes did not differ significantly.

A Cochrane review by Bennett et al (2012) evaluated HBOT as adjunctive therapy for acute TBI (see Table 14).[34] Reviewers identified 7 RCTs comparing a standard intensive treatment regimen with the same treatment regimen plus HBOT. Reviewers did not include studies with interventions in specialized acute care settings. The HBOT regimens varied among studies; e.g., the total number of individual sessions varied from 3 to 40. None of the trials used sham treatment or blinded staff treating patients, and only 1 had blinding of outcome assessment. Allocation concealment was inadequate in all studies. The primary outcomes of the review were mortality and functional outcomes. A pooled analysis of data from 4 trials showed that adding HBOT to standard care decreased mortality, but did not improve functional outcome at final follow-up. The unfavorable functional outcome was commonly defined as a Glasgow Outcome Scale score of 1, 2, or 3, which are described as "dead," "vegetative state," or "severely disabled," respectively. Studies were generally small and judged to have a substantial risk of bias.

The systematic review and pooled analysis by Hart et al (2019) evaluated HBOT for mild traumatic brain injury (mTBI)-associated post-concussive symptoms (PCS) and posttraumatic stress disorder (PTSD).[35] Data were aggregated from 4 Department of Defense (DoD) studies that included participant-level data on 254 patients assigned to either HBOT or sham intervention. An additional 3 studies with summary-level participant data were summarized (n=135). The authors assessed changes from baseline to post-intervention on PCS, PTSD, and neuropsychological measures (Table 14). The DoD data analyses indicated improvements with HBOT for PCS, measured by the Rivermead Total Score. Statistically significant improvements were seen for PTSD based on the PTSD Checklist Total Score, as well as for verbal memory based on the California Verbal Learning Test (CVLT) -II Trial 1-5 Free Recall.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Hart et al (2019)[35]		7 (4 by DoD)	Patients (primarily US Service personnel) with mild traumatic brain injury	389		DoD Analysis: • Improvement in mean Rivermead Total Score (-2.3 points; 95% CI, -5.6 to 1.0; p=.18) • Improvement in mean PTSD Checklist Total Score (-2.7 points; 95% CI, -5.8 to 0.4; p=.089) • 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)[32]	Dec 2014	8	Patients with mild or severe traumatic brain injury	519	RCTs and 2-arm prospective studies	• Pooled analyses of 2 trials (n=120) found significant improvements in GCS score

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
						change (3.1; 95% CI, 2.3 to 3.9) in HBOT vs. control • Pooled analyses of 3 trials (n=263) found lower risk of mortality among patients treated with HBOT vs. controls (OR, 0.3; 95% CI, 0.2 to 0.6)
Crawford et al (2017)[33]	Aug 2014	12	Military and civilian patients with traumatic brain injury		RCTs	• Pooled analyses not performed • Among 3 trials with GCS outcomes, 2 reported improvements with HBOT and 1 found no difference • 4 trials assessed as acceptable quality did not find significant differences in symptom severity or psychological outcomes
Bennett et al (2012)[34]	Mar 2012	7	Patients with acute traumatic brain injury following blunt trauma	571	RCTs	• Pooled analyses of 4 trials (n=385) found that adding HBOT to standard care decreased mortality vs standard care alone (RR, 0.7; 95% CI, 0.5 to 0.9) • 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; CVLT: California Verbal Learning Test; DoD: Department of Defense; GCS: Glasgow Coma Scale; HBOT: hyperbaric oxygen therapy; OR: odds ratio; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; RR: relative risk.

Clinical Trials

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,[36] was the first to include post-intervention follow-up beyond 3 to 6 months. Hart et al (2019) described BIMA, which assessed HBOT for U.S. service members with mTBI.[37] BIMA was initially planned for a 12-month follow-up, but was amended to include PCS and PTSD, QOL, pain, depression, anxiety, and alcohol use assessments at 24 and 36 months. Investigators saw no significant differences at 24 or 36 months between the HBOT and sham groups, and group mean scores had returned to near pre-intervention values. Churchill et al (2019) reported on the chamber- and protocol-related adverse events (AEs) in the HOPPS and BIMA trials.[38] 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.[39] 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.[40] 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 trial 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 Hyperbaric Oxygen Therapy 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 overlap in RCTs included in the reviews. There is a lack of consistent evidence from well-conducted trials that HBOT improves the health outcome for patients with TBI.

Systemic Hyperbaric Oxygen Therapy for Inflammatory Bowel Disease

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with IBD.

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

A systematic review by McCurdy et al (2022) examined the evidence on HBOT for a range of IBD phenotypes (Crohn disease, ulcerative colitis; see Table 15).[41] The review was not limited by study design, and included 3 small RCTs (N=40)[42,43,44] 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[43] and one[42] 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.[44] Quality assessment of the included studies judged 2 of the 3 included RCTs to be at high risk of bias. Study authors concluded that although HBOT was associated with high response rates across phenotypes, high-quality evidence was very limited, and well-designed RCTs are needed to confirm the effect of HBOT in patients with IBD.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Response Rate (95% CI)
McCurdy et al (2022)[41]	Nov 2020	19	Patients with various IBD phenotypes	• Ulcerative colitis (n=383); • Crohn disease (n=250) • Perianal fistula (n=118) • Enterocutaneous fistula (n=21) • Inflammatory pouch disorders (n=60) • Dermatologic manifestation of IBD (n=12)	• 3 RCTs • 16 case series	• Ulcerative colitis (5 studies): 86% (66% to 95%) • Crohn disease (2 studies): 86% (81% to 90%) • Perianal fistula (10 studies): 75% (66% to 83%) • Pouch disorder (2 studies): 65% (52% to 76%) • Enterocutaneous fistula (3 studies): 85% (61% to 95%)

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

Section Summary: Systemic Hyperbaric Oxygen Therapy 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 (eg, attrition, reporting bias).

Systemic Hyperbaric Oxygen Therapy for Idiopathic Sudden Sensorineural Hearing Loss

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with ISSNHL.

Interventions

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

Comparators
Comparators of interest include medical therapy. Medications prescribed for ISSNHL may include systemic and intratympanic steroids, 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.

Review of Evidence
Systematic Reviews
A Cochrane review by Bennett et al (2012) on HBOT for ISSNHL and/or tinnitus identified 7 RCTs (N=392; see Table 16).[45] Treatment of tinnitus is covered in evidence review 8.01.39. Studies were small and generally of poor quality. Randomization procedures were only described in 1 study, and only 1 study stated they blinded participants to treatment group assignment using sham therapy. Six studies included time-based entry criteria for hearing loss and/or tinnitus (48 hours in 3 studies, 2 weeks in 2 studies, 6 months in 1 study). The dose of oxygen per treatment session and the treatment protocols varied across studies (eg, the total number of treatment sessions ranged from 10 to 25). All trials reported the change in hearing following treatment, but specific outcomes varied. Two trials reported the proportion of participants with more than 50% and more than 25% return of hearing at the end of therapy. A pooled analysis of these studies did not find a statistically significant difference in outcomes between the HBOT and the control groups at the level of 50% or higher but did find a significantly higher rate of improvement at the level of 25% or higher (see Table 16). A pooled analysis of 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, the 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.[46] Randomized clinical trials and nonrandomized studies were included. The main outcomes considered were complete hearing recovery, any hearing recovery, and absolute hearing gain. Nineteen studies (3 randomized and 16 nonrandomized) with a total of 2401 patients (mean age, 45.4 years; 55.3% female) were included. In the HBOT+MT group, rates of complete hearing recovery and any hearing recovery were 264/897 (29.4%) and 621/919 (67.6%), respectively, and in the MT alone group were 241/1167 (20.7%) and 585/1194 (49.0%), respectively. Pooled HBOT+MT also showed favorable pooled results from random-effects models for both complete hearing recovery (OR, 1.61; 95% CI, 1.05 to 2.44) and any hearing recovery (OR, 1.43; 95% CI, 1.20 to 1.67). The study was limited by the following: (1) differences in clinical and methodological characteristics of selected studies, (2) considerable

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

A third systematic review, conducted by Joshua et al (2021)[47] 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 audometric gain, was significantly higher with HBOT compared with control based on pooled analysis of 2 studies (OR, 4.32; 95% CI, 1.60 to 11.68; I^2=0%). Limitations of these results include the fact that the included studies were judged to have moderate (2 studies) and high (1 study) risk of bias and the small number of participants in both HBOT (n=88) and medical treatment (n=62) groups.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2012)[45]	May 2012	7	Patients with idiopathic SSNHL and/or tinnitus	392	RCTs	• Pooled analyses of 2 RCTs (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) • Pooled analyses of 4 trials (n=169) found a significantly greater mean improvement in hearing over all frequencies with HBOT vs. control (mean difference, 15.6 dB; 95% CI, 1.5 to 29.8 dB)
Rhee et al (2018)[46]	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 to 2.44) and for hearing recovery (pooled OR, 1.43; CI: 1.20 to 1.67)
Joshua et al (2021)[47]	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; HBOT: hyperbaric oxygen therapy; MT: medical therapy; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SSNHL: sudden sensorineural hearing loss.

In their qualitative systematic review, Eryigit et al (2018) assessed the effectiveness of HBOT to treat patients with ISSNHL.[48] Sixteen clinical trials were included, with a total of 1759 operative ears, 580 of which received HBOT. All patients also received steroid treatment—either systemic, intravenous, or intratympanic injection. Most studies found that patients with severe or profound hearing loss who received steroids (any route of administration) plus HBOT saw statistically significant improvements (specified p-value range across studies: .0014 to .012), whereas those with a lower level of hearing loss

did not see these improvements. Several studies reported no significant difference between case and control groups, but the studies that broke down the results by levels of hearing loss all showed that profound (or severe and profound) loss benefited from the addition of HBOT to steroid treatment.

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.[49] Study characteristics are summarized in Table 17.

Table 17. Characteristics of Trials Assessing HBOT for ISSNHL

Study (Year)	Countries	Sites	Dates	Participants	Interventions HBOT (n=60)	Oral Steroids (n=55)	HBOT + Oral Steroids (n=56)
Cavaliere et al (2022)[49]	Italy	Single-center	Feb 2016-Dec 2019	Adults with unilateral and/or bilateral ISSNHL onset within the last 30 days, unknown cause of hearing loss, and normal Eustachian tube function	HBOT 2.5 ATA; 90 min per session for 10 sessions total over 15 days	Oral prednisone 1 mg/kg per day (maximum dose of 60 mg/day) for 12-14 consecutive days	HBOT + oral prednisone

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

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

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

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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Cavaliere et al (2022)[49]			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	1, 2. Duration of follow-up (20 days) insufficient to assess benefit and harms

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
				clinically significant difference	

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

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

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Cavaliere et al (2022)[49]	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 Hyperbaric Oxygen Therapy for Idiopathic Sudden Sensorineural Hearing Loss

A Cochrane review of RCTs had mixed findings from studies that included individuals with tinnitus. Some outcomes (i.e., improvement in hearing of all frequencies, >25% return of hearing) were better with HBOT than with a control intervention, but more than 50% return of hearing did not differ significantly between groups. There was important variability in the patients enrolled in the studies. A subsequent systematic review had similarly limited conclusions due to the inclusion of non-randomized studies. A third review that had stricter inclusion criteria found HBOT increased 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 to or an improvement on existing therapies in individuals with delayed-onset muscle soreness.

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

In a Cochrane review, Bennett et al (2005; updated 2010) identified 9 small RCTs on HBOT for delayed-onset muscle soreness and closed soft tissue injury (see Table 20).[50] Included trials were published between 1996 and 2003. Methodologic quality was assessed as fair to high. Pooled analysis showed significantly higher pain in the group receiving HBOT compared with control. There were no between-group differences in long-term pain outcomes or other measures (e.g., swelling, muscle strength).

Table 20. Systematic Reviews of Trials Assessing HBOT for DOMS

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2010)[50]	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 • 7 DOMS trials, pooled: significantly higher pain at 48 and 72 h in HBOT group, 0.9 (95% CI, 0.09 to 1.7); no differences in long-term pain, swelling, or muscle strength

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

Section Summary: Systemic Hyperbaric Oxygen Therapy for Delayed-Onset Muscle Soreness

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

Systemic Hyperbaric Oxygen Therapy for Autism Spectrum Disorder

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

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

Review of Evidence

A Cochrane review by Xiong et al (2016) identified 1 RCT evaluating systemic HBOT for people with autism spectrum disorder that met eligibility criteria (see Table 21).[51] 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).[52] The primary outcome measures were change in Autism Treatment Evaluation Checklist and Clinical Global Impression scores, evaluated separately by clinicians and parents. There were no statistically significant differences between groups for either primary outcome. 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 21. Systematic Reviews of Trials Assessing HBOT for Autism Spectrum Disorder

Study (Year)	Literature Search	Studies	Participants	N	Design	Results Mean Difference
Xiong et al (2016)[51]	Dec 2015	1	Children aged 3-9 y with autism spectrum disorder	60	RCT	• Parental assessed ATEC: 1.2 (95% CI, -2.2 to 4.6) • Clinician assessed ATEC: 1.5 (95% CI, -1.3 to 4.5)

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

In their controlled trial, Rizzato et al (2018) examined the effect of HBOT on children diagnosed with autism.[53] 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 Hyperbaric Oxygen Therapy for Autism Spectrum Disorder

A Cochrane review identified a single small low-quality RCT on HBOT for autism spectrum disorder, and that trial did not find significantly improved outcomes with HBOT versus sham. A subsequent controlled trial reached the same conclusion, stating results do not support the use of HBOT for autism spectrum disorder.

Systemic Hyperbaric Oxygen Therapy for Cerebral Palsy

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with CP.

Interventions
The therapy being considered is systemic HBOT.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
Two published RCTs were identified on use of HBOT for CP (see Tables 22 and 23). Lacey et al (2012) published a double-blind RCT that included 49 children ages 3 to 8 years with spastic CP.[54] Participants were randomized to 40 treatments with HBOT or hyperbaric air to simulate 21% oxygen at room air. The primary efficacy outcome was change in the Gross Motor Function Measure global score. The trial was stopped early due to futility when an interim analysis indicated that there was less than a 2% likelihood that a statistically significant difference between groups would be found.

Collet et al (2001) randomized 111 children with CP to 40 treatments over a 2-month period of HBOT or slightly pressurized room air.[55] Investigators found similar improvements in outcomes such as gross motor function and activities of daily living in both treatment groups.

An observational study by Long et al (2017) evaluated the effects of HBOT as a treatment for sleep disorders in children with CP (N=71).[56] Children, ages 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 22. Characteristics of Randomized Trials Assessing HBOT for Cerebral Palsy

Study (Year)	Countries	Sites	Dates	Participants	Treatment Active	Comparator
Lacey et al (2012)[54]	United States	2	2005-2009	Children age 3-8 y with spastic CP	• n=25 • Hyperbaric oxygen	• n=24 • Hyperbaric air

Study (Year)	Countries	Sites	Dates	Participants	Treatment Active	Comparator
					• 100% oxygen at 1.5 ATA • 40 times over 2 mo	• 14% oxygen at 1.5 ATA • 40 times over 2 mo
Collet et al (2001)[55]	Canada	17	NR	Children age 3-12 y with CP	• n=57 • Hyperbaric oxygen • 100% oxygen at 1.75 ATA • 40 times over 2 mo	• n=54 • Slightly pressurized air • 100% oxygen at 1.3 ATA • 40 times over 2 mo

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

Table 23. 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)[54]	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)[55]			Mean Change, PEDI Self Care	
HBOT	2.9 (1.9 to 3.9)	-0.4 (-1.7 to 0.9)	2.8 (1.6 to 4.0)	0.1 (-1.8 to 2.0)
Slight pressure	3.0 (2.1 to 3.9)		2.7 (1.3 to 4.0)	

CI: confidence interval; GMFM: Gross Motor Function Measure; HBAT: hyperbaric air therapy; HBOT: hyperbaric oxygen therapy; PEDI: Pediatric Evaluation of Disability Inventory.
[a] Positive score represents improvement in function from baseline.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Cerebral Palsy

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

Systemic Hyperbaric Oxygen Therapy for Vascular Dementia

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with vascular dementia.

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

The general outcomes of interest are symptoms and functional outcomes. The existing literature evaluating systemic HBOT as a treatment for vascular dementia reported follow-up at 12 weeks.

However, longer follow-up is necessary to fully observe outcomes. Therefore, at least 1 year of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

A Cochrane review (2012) identified a small RCT evaluating HBOT for vascular dementia (see Table 24).[57] 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 24. Systematic Reviews of Trials Assessing HBOT for Vascular Dementia

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Xiao et al (2012)[57]	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) • 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: hyperbaric oxygen therapy; HDS: Hasegawa's Dementia Rating Scale; MMSE: Mini-Mental State Examination; RCT: randomized controlled trial; WMD: weighted mean difference.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Vascular Dementia

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

Systemic Hyperbaric Oxygen Therapy for Radiotherapy Adverse Events

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

Comparators of interest include medication. Medications to treat cardiovascular and pulmonary adverse events (e.g., pentoxifylline), gastrointestinal toxicity (e.g., amifostine, antidiarrheals), radiation-induced emesis (5-HT3), radiation cystitis (e.g., phenazopyridine, oxybutynin, and flavoxate), and sexual dysfunction (eg, sildenafil and tadalafil) may be prescribed. Systemic HBOT may be used as an adjunct to these comparators.

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

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

Review of Evidence

Systematic Reviews

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 25).[14] 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.[58] The review included 20 studies, only one of which was an RCT; the remaining studies were cohort studies. The number of HBOT sessions ranged widely from 1 to 179 (mean or median number of sessions was not reported). The review broadly assessed cystitis response across studies, generally based on the absence of hematuria. Complete response was achieved in a weighted mean of 63.6% of patients receiving HBOT (range, 20% to 100%) while 35.2% of patients showed no response. In 11 studies reporting follow-up greater than 1 year, recurrence ranged from 0% to 40.7%. Other pooled outcomes were not reported.

Table 25. Systematic Reviews of Studies Assessing HBOT for Radiotherapy Adverse Events

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Ravi et al (2017)[14]	Dec 2016	10	Patients who have received RT for head and neck cancer	375	Prospective case series and prospective comparative studies	• Salivary gland function: 2 case series (n=96) reported that patients receiving HBOT experienced improvements in salivary flow rates • QOL: 3 case series (n=106) administered various QOL

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
						instruments (eg, SF-36, EORTC, HADS), reporting that many subsets of the questionnaires (eg, swallowing, pain, salivary quantity) showed significant improvements with HBOT
Villeirs et al (2020)[58]	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; HBOT: hyperbaric oxygen therapy; QOL: quality of life; RCT: randomized controlled trial; RT: radiotherapy; SF-36: 36-Item Short-Form Health Survey.

Randomized Controlled Trials

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.[59] Fifty-eight patients with arm lymphedema (at least a 15% increase in arm volume) following cancer treatment were randomized in a 2:1 ratio to HBOT (n=38) or usual care without HBOT (n=20). Fifty-three patients had baseline assessments, and 46 (79%) of 58 had 12-month assessments. At the 12-month follow-up, there was no statistically significant difference in the change from baseline in arm volume. Median change from baseline was -2.9% in the treatment group and -0.3% in the control group. The study protocol defined response as at least an 8% reduction in arm volume relative to the contralateral arm. By this definition, 9 (30%) of 30 patients in the HBOT group were considered responders compared with 3 (19%) of 16 in the control group (p=not significant). Other outcomes (eg, QOL scores on the 36-Item Short-Form Health Survey [SF-36]) also did not differ significantly between groups.

A phase 2/3 RCT by Oscarsson et al (2019) not included in the Villiers systematic review assessed HBOT for late radiation-induced cystitis in adult cancer patients who had received pelvic radiotherapy.[60] Eighty-seven patients were randomized to either HBOT (n=42) or standard care (n=45). Eight patients withdrew consent directly after randomization, so 79 were included in the intention-to-treat analysis. The primary outcome was change in the urinary domain of the Expanded Prostate Index Composite Score, which is a patient-reported outcome measurement tool with 12 questions covering a range of urinary tract symptoms; each answer is given on a Likert scale, and the totals are calculated on a 0 to 100 score. A post hoc analysis determined the minimal clinically important difference to be 9 points. Patients were required to have a baseline score of less than 80 to participate in the study. Patients in the HBOT group received 30 to 40 treatments within 60 to 80 days. No study-specific treatment was administered to the standard care group. The trial included 4 visits, and at the fourth visit, the mean Expanded Prostate Index Composite urinary total score in the HBOT group had increased by 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: Systemic Hyperbaric Oxygen Therapy 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 to or an improvement on existing therapies in individuals with idiopathic femoral neck necrosis.

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

A double-blind RCT evaluating HBOT for the treatment of femoral head necrosis was published by Camporesi et al (2010) (see Tables 26 and 27).[61] 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 ($p<.001$) 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 26. Characteristics of Trials Assessing HBOT for Femoral Neck Necrosis

Study (Year)	Countries	Sites	Dates	Participants	Treatment Active (n=10)	Comparator (n=10)
Camporesi et al (2010)[61]	United States	1	NR	Patients with unilateral femoral neck necrosis	• HBOT • 100% oxygen at 2.5 ATA • 30 sessions over 6 wk	• Hyperbaric air • 30 sessions over 6 wk

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

Table 27. 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)[61]				
HBOT	7.5 (4.0-20.0)	NS	20.0 (15.0-20.0)	<.001
HBAT	4.0 (3.0-6.0)		3.0 (0.0-5.0)	

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

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

Systemic Hyperbaric Oxygen Therapy for Migraine Headache

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with migraine headache.

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

A Cochrane review by Bennett et al (2015) identified 11 RCTs (N=209) comparing the effectiveness of systemic HBOT for preventing or treating migraine headache or cluster headaches with another treatment or a sham control see Table 28).[62] A pooled analysis of 3 trials focusing on migraine headaches (n=58) found a statistically significant increase in the proportion of patients with substantial relief of migraine within 45 minutes of HBOT. No other pooled analyses were conducted due to variability in outcomes reported across trials. The meta-analysis did not report data on treatment effectiveness beyond the immediate post-treatment period, and the methodologic quality of selected trials was moderate to low (e.g., randomization was not well-described in any trial).

Table 28. Systematic Reviews of Trials Assessing HBOT for Migraine or Cluster Headaches

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2015)[62]	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) • No evidence that HBOT can prevent migraine, reduce nausea or vomiting, or reduce the need for rescue medication

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

Section Summary: Systemic Hyperbaric Oxygen Therapy for Migraine

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

Systemic Hyperbaric Oxygen Therapy for Herpes Zoster

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with herpes zoster.

Interventions

The therapy being considered is systemic HBOT.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
Peng et al (2012) in China published an RCT evaluating HBOT for herpes zoster (see Tables 29 and 30).[63] 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. Patients receiving HBOT experienced significantly improved outcomes compared with patients receiving medication alone. Limitations of the trial included a lack of blinding and long-term follow-up.

Table 29. Characteristics of Trials Assessing HBOT for Herpes Zoster

Study (Year)	Countries	Sites	Dates	Participants	Treatment Active (n=36)	Comparator (n=32)
Peng et al (2012)[63]	China	NR	2008-2010	Patients diagnosed with herpes zoster within 2 wk	• HBOT • 100% oxygen at 2.2 ATA • 2 sessions/day for 5 d • Thirty 120-min sessions; plus medications that the control group received	Medication alone, including antiviral, nerve nutritive, pain relief, and antidepressives

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

Table 30. 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	Posttreatment
Peng et al (2012)[63]	68	68	68	68	68
Mean HBOT and medication (SD)	97.2%	2.8 (1.5)	11.1 (4.0)	8.0 (1.8)	1.8 (2.7)
Mean medication alone (SD)	81.3%	3.3 (1.4)	13.9 (4.3)	8.1 (1.7)	3.5 (4.1)

HBOT: hyperbaric oxygen therapy; NPRS: Numeric Pain Rating Scale; SD: standard deviation.
[a] Calculation: (number cases with healing + number cases with improvement)/(total number cases × 100).
[b] Between-group difference p<.05.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Herpes Zoster

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

Systemic Hyperbaric Oxygen Therapy for Fibromyalgia

Clinical Context and Therapy Purpose

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

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

Populations

The relevant population of interest is individuals with fibromyalgia.

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

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

Efrati et al (2015) published an RCT that included 60 symptomatic women who had fibromyalgia for at least 2 years (see Tables 31 and 32).[64] Patients were randomized to an immediate 2-month course of HBOT or delayed HBOT after 2 months. Forty-eight (80%) of 60 patients completed the trial. After the initial 2 months, outcomes including a number of tender points, pain threshold, and QOL (SF-36) were significantly improved in the immediate treatment group than in the delayed treatment group. After the delayed treatment group had undergone HBOT, outcomes were significantly improved compared with scores in the 2 months before HBOT treatment. These findings are not only

consistent with the clinical benefit of HBOT but also with a placebo effect. A sham control trial is needed to confirm the efficacy of HBOT in the treatment of fibromyalgia and other conditions where primary endpoints are pain and other subjective outcomes.

Yildiz et al (2004) assessed 50 patients with fibromyalgia (see Tables 31 and 32).[65] On an alternating basis, patients were assigned to HBOT or a control group. After HBOT treatment, the mean standard deviation, number of tender points, and mean visual analog scale scores were improved in patients receiving HBOT compared with controls. It is unclear whether the control group received a sham intervention that would minimize any placebo effect (i.e., whether the control intervention was delivered in a hyperbaric chamber). The authors stated that the trial was double-blind, but did not provide details of patient blinding.

Table 31. Characteristics of Trials Assessing HBOT for Fibromyalgia

Study (Year)	Countries	Sites	Dates	Participants	Treatment Active	Comparator
Efrati et al (2015)[64]	Israel	1	2010-2012	Patients with fibromyalgia based on: (1) widespread pain and (2) at least 11 of 18 tender points	• n=24 • HBOT • 100% oxygen at 2 ATA • 1 session/day for 5 d • Forty 90-min sessions	• n=26 • No treatment for 2 mo, then same treatment as the active group
Yildiz et al (2004)[65]	Turkey	NR	NR	Patients meeting ACR criteria for fibromyalgia, with persistent symptoms despite medical therapy and PT	• n=26 • HBOT • 100% oxygen at 2.4 ATA • 1 session/day for 5 d • Fifteen 90-min sessions	• n=24 • Air • 1 ATA • 1 session/day for 5 d • Fifteen 90-minute sessions

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

Table 32. Results of Trials Assessing HBOT for Fibromyalgia

Study (Year)	Tender Points Baseline	After HBOT	Between-Group P-Value	Pain Threshold Baseline	After HBOT	Between-Group P-Value
Efrati et al(2015)[64]	50			50		
Mean HBOT (SD)	17.3 (1.4)	8.9 (6.0)	<.001	0.5 (1.2)	1.7 (0.8)	<.001
Mean control (SD)	17.7 (0.7)	17.2 (1.1)		0.7 (0.5)	0.6 (0.5)	
Yildiz et al (2004)[65]	50			50		
Mean HBOT (SD)	15.0 (1.5)	6.0 (1.2)	<.001	0.7 (0.1)	1.3 (0.1)	<.001
Mean air (SD)	15.3 (1.2)	12.5 (1.1)		0.7 (0.1)	0.8 (0.1)	

HBOT: hyperbaric oxygen therapy; SD: standard deviation.

Section Summary: Systemic Hyperbaric Oxygen Therapy for Fibromyalgia

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

Systemic Hyperbaric Oxygen Therapy for Multiple Sclerosis

Clinical Context and Therapy Purpose

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

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

Populations
The relevant population of interest is individuals with MS.

Interventions
The therapy being considered is systemic HBOT.

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
Bennett et al (2010) published a systematic review on the use of HBOT for treatment of MS (see Table 33).[66] 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 33. Systematic Reviews of Trials Assessing HBOT for Multiple Sclerosis

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2010)[66]	Jul 2009	9	Patients with multiple sclerosis, at any state or course of the condition	504	RCT	EDSS score difference between groups: • At 4-wk follow-up: 0.07 (95% CI, -0.09 to 0.23) • At 6-mo 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 Hyperbaric Oxygen Therapy for Multiple Sclerosis

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

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

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is systemic HBOT.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

In a Cochrane review (2005),[67] which was updated in 2012,[68] Bennett et al (2012) identified 19 randomized and quasi-randomized trials (N=2286) comparing outcomes following radiotherapy with and without HBOT in patients with solid tumors (see Table 34). The latest trial identified in the Cochrane search was published in 1999. Reviewers did not find any ongoing RCTs in this area. Results from the review reported that HBOT given with radiotherapy might be useful in tumor control in head and neck cancer. However, reviewers expressed caution because significant adverse events, such as severe radiation tissue injury (relative risk, 2.3; p<.001) and seizures (relative risk, 6.8; p=.03) occurred more frequently in patients treated with HBOT.

Table 34. 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)[68]	Sep 2017	19, some including multiple cancer sites	• Head and neck: 10 trials • Uterine: 7 trials • Urinary bladder: 5 trials • Bronchus: 1 trial • Rectum: 1 trial • Brain: 1 trial • Esophagus: 1 trial	2286	RCT and quasi-RCT	Head and neck: • 1-y mortality: RR, 0.8 (p=.03) • 5-year mortality: RR, 0.8 (p=.03) • 5-y recurrence: RR, 0.8 (p=.01) Uterine: • 2-y recurrence: RR, 0.6 (p=.04)

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

In an RCT of 32 patients, Heys et al (2006) found no increase in 5-year survival for patients treated with HBOT to increase tumor vascularity before chemotherapy for locally advanced breast carcinoma.[69]

Section Summary: Systemic Hyperbaric Oxygen Therapy for Tumor Sensitization During Cancer Treatment: Radiotherapy or Chemotherapy

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

Other Indications

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

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

- refractory mycoses;
- acute peripheral arterial insufficiency;
- in vitro fertilization; or
- mental illness.

Summary of Evidence

For individuals with wounds, burns or infections who receive topical hyperbaric oxygen therapy (HBOT), the evidence includes a systematic review, case series, and a randomized controlled trial (RCT). Relevant outcomes are overall survival (OS), symptoms, change in disease status, and functional outcomes. The systematic review identified 3 RCTs including patients with sacral pressure ulcers, ischial pressure ulcers, and refractory venous ulcers. All trials reported that healing improved significantly after HBOT than after standard of care. Pooling of results was not possible due to heterogeneity in patient populations and treatment regimens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with chronic diabetic ulcers who receive systemic HBOT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms and change in disease status. Meta-analyses of RCTs found significantly higher diabetic ulcer healing rates with HBOT than with control conditions. Two of the 3 meta-analyses found that HBOT was associated with a significantly lower rate of major amputation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with carbon monoxide poisoning who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are OS and symptoms. A meta-analysis in a Cochrane review of low-quality RCT data did not find HBOT to be associated with a significantly lower risk of neurologic deficits after carbon monoxide poisoning. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals with acute thermal burns who receive systemic HBOT, the evidence includes a systematic review of 2 RCTs. Relevant outcomes are OS, symptoms, and change in disease status. Both RCTs were judged to have poor methodologic quality. Evidence from well-conducted controlled trials is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with acute surgical and traumatic wounds who receive systemic HBOT, the evidence includes RCTs, controlled nonrandomized studies, and systematic reviews. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. There was considerable heterogeneity across the 4 RCTs identified (eg, patient population, comparison group, treatment regimen,

outcomes). This heterogeneity prevented pooling of trial findings and limits the ability to definitively conclude the impact of HBOT on health outcomes for patients with acute surgical and traumatic wounds. Additional evidence from high-quality RCTs is needed. A systematic review of controlled Chinese studies suggests HBOT may increase the survival rate of compromised skin grafts and flaps when initiated within 72 hours; however, risk of bias in the original Chinese publications cannot be evaluated. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with bisphosphonate-related osteonecrosis of the jaw who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and change in disease status. The RCT was unblinded and reported initial benefits at 3-month follow-up; however, there were no significant benefits of HBOT for most health outcomes compared with standard care in the long-term (6 months to 2 years). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with acute coronary syndrome who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. A Cochrane review identified 6 RCTs. There were 2 pooled analyses, 1 found significantly lower rates of death with HBOT and the other reported inconsistent results in left ventricular function. Additional RCT data are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with motor dysfunction associated with stroke who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and functional outcomes. The RCT, which used a crossover design, found better outcomes with HBOT at 2 months than with delayed treatment. However, the trial had a number of methodologic limitations (eg, lack of patient blinding, heterogeneous population, high dropout rate) that make it difficult to evaluate the efficacy of HBOT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with traumatic brain injury who receive systemic HBOT, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, change in disease status, and functional outcomes. RCTs were heterogeneous regarding intervention protocols, patient populations, and outcomes reported. Systematic reviews conducted pooled analyses only on a

minority of the published RCTs, and these findings were inconsistent. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

For individuals with autism spectrum disorder who receive systemic HBOT, the evidence includes an RCT and a systematic review. Relevant outcomes are symptoms and functional outcomes. A Cochrane review identified a single RCT on HBOT for autism spectrum disorder and this trial did not find significantly better parental-assessed or clinician-assessed outcomes with HBOT compared with sham. A subsequent controlled trial reached the same conclusion. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cerebral palsy who receive systemic HBOT, the evidence includes 2 RCTs and an observational study. Relevant outcomes are symptoms and functional outcomes. One RCT was stopped early due to futility, and the other did not find significantly better outcomes with HBOT than with a sham intervention. The observational study focused on sleep disorders in children with cerebral palsy and reported improvements with the HBOT treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals with radiotherapy adverse events who receive systemic HBOT, the evidence includes RCTs, nonrandomized comparator trials, case series, and systematic reviews. Relevant outcomes are

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

For individuals with idiopathic femoral neck necrosis who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCT, which had a small sample, only reported short-term (i.e., 6-week) outcomes. Larger well-conducted RCTs reporting longer-term outcomes are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a migraine who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The Cochrane review conducted a pooled analysis including 3 of the 11 trials. Meta-analysis of these 3 RCTs found significantly greater relief of migraine symptoms with HBOT than with a comparator intervention within 45 minutes of treatment. Longer-term data are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with herpes zoster who receive systemic HBOT, the evidence includes an RCT. Relevant outcomes are symptoms and change in disease status. The RCT was unblinded and only reported short-term (i.e., 6-week) outcomes. Additional well-conducted RCTs with longer follow-up are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with fibromyalgia who receive systemic HBOT, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Only 2 RCTs were identified, and both reported positive effects of HBOT on tender points and pain. However, the trials had relatively small samples and methodologic limitations (e.g., quasi-randomization, no or uncertain sham control for a condition with subjective outcomes susceptible to a placebo effect). Moreover, the HBOT protocols varied. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Supplemental Information

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

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

2024 Input

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

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

Further details from clinical input are included in the Appendix.

2023 Input

Clinical input was sought to help determine whether the use of systemic hyperbaric oxygen therapy (HBOT) in individuals with acute surgical or traumatic wounds and compromised skin grafts or flaps would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 2 specialty society-level responses.

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

Further details from clinical input are included in the Appendix.

2010 Input

In response to requests, input was received from 6 physician specialty societies and 5 academic medical centers while this policy was under review in 2010. Clinical input varied by condition. There was consensus that topical hyperbaric oxygen therapy (HBOT) and systemic HBOT for autism spectrum disorder and headache/migraine are investigational. There was also wide support for adding acute carbon monoxide poisoning, compromised skin grafts or flaps, chronic refractory osteomyelitis, and necrotizing soft tissue infections to the list of medically necessary indications for HBOT. Several reviewers acknowledged that there is a paucity of clinical trials on HBOT for compromised skin grafts/flaps, necrotizing soft tissue infections, and chronic refractory osteomyelitis. These reviewers commented on the support from basic science, animal studies, and retrospective case series, as well as lack of effective alternative treatments for these conditions. Based on the available evidence and clinical input, acute carbon monoxide poisoning and chronic refractory osteomyelitis were changed in 2010 to medically necessary indications for HBOT. However, despite the clinical input and given the limited published evidence, compromised skin grafts and flaps and necrotizing soft tissue infections are still considered investigational.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a U.S. professional society, an international society with U.S. representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to

guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Otolaryngology - Head and Neck Surgery

In 2019, the American Academy of Otolaryngology-Head and Neck Surgery updated clinical guidelines on the treatment of sudden sensorineural hearing loss (SSNHL).[70] 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 SSNHL."
- "Clinicians may offer, or refer to a physician who can offer, hyperbaric oxygen therapy (HBOT) combined with steroid therapy as salvage within 1 months of onset of SSNHL."

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.

American College of Cardiology/American Heart Association

In 2024, the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines published a Guideline for the Management of Lower Extremity PAD.[2] The Guideline was developed in collaboration with and endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Podiatric Medical Association, Association of Black Cardiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, Society of Interventional Radiology, and Vascular & Endovascular Surgery Society. The Guideline included the following statements relevant to this evidence review:

- "Beyond wound care, hyperbaric oxygen therapy has been studied in the context of wound healing for CLTI as an adjunctive therapy to revascularization and may have a limited role in this population."
- "Hyperbaric oxygen therapy may be considered as an adjunctive therapy to revascularization for wound healing in the context of CLTI (chronic limb threatening ischemia) and diabetic foot ulcers."

American College of Cardiology/American Stroke Association

In 2019 the American Heart Association and American Stroke Association updated the guidelines for early management of acute ischemic stroke.[71] The guidelines were endorsed by the Society for Academic Emergency Medicine, the Neurocritical Care Society, the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons. The Guideline included the following statements relevant to this evidence review:

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

Society of Vascular Surgery et al

In 2016, the Society of Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine published guidelines on the management of the diabetic foot.[72] According to the guidelines, for diabetic foot ulcers that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, adjunctive therapy such as HBOT is recommended (grade 1B). Also, for diabetic foot ulcers with

adequate perfusion that fail to respond to 4 to 6 weeks of conservative management, HBOT is suggested (grade 2B).

Undersea and Hyperbaric Medical Society

In 2015, the Undersea and Hyperbaric Medical Society (UHMS) published guidelines on the use of HBOT for treating diabetic foot ulcers.[73] Recommendations in the current version include:

- Suggest against using HBOT in patients with "Wagner Grade 2 or lower diabetic foot ulcers..."
- Suggest adding HBOT in patients with "Wagner Grade 3 or higher diabetic foot ulcers that have not shown significant improvement after 30 days of [standard of care] therapy..."
- Suggest "adding acute post-operative hyperbaric oxygen therapy to the standard of care" in patients with "Wagner Grade 3 or higher diabetic foot ulcers" who have just had foot surgery related to their diabetic ulcers.

The 2023 UHMS Hyperbaric Oxygen Therapy Indications (15th edition) included the following indications as recommended:[1]

1. Air or Gas Embolism
2. Arterial insufficiencies: Central Retinal Artery Occlusion; Hyperbaric Oxygen Therapy for Selected Problem Wounds
3. Carbon Monoxide Poisoning and carbon monoxide complicated by cyanide poisoning
4. Clostridial Myonecrosis (Gas Gangrene)
5. Acute Traumatic Ischemias
6. Decompression Sickness
7. Severe anemia
8. Intracranial abscess
9. Necrotizing soft tissue infections
10. Refractory osteomyelitis
11. Delayed radiation injury (soft tissue and bony necrosis)
12. Compromised grafts and flaps
13. Acute thermal burn injury
14. Sudden Sensorineural hearing loss
15. Avascular Necrosis (Aseptic Osteonecrosis).

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

In 2003 (updated in 2017), the Centers for Medicare & Medicaid added Medicare coverage of HBOT for diabetic wounds of the lower extremities meeting certain criteria. As of the current coverage statement, Medicare coverage is provided for HBOT administered in a chamber for the following conditions[74]:

1. "Acute carbon monoxide intoxication,
2. Decompression illness,
3. Gas embolism,
4. Gas gangrene,
5. Acute traumatic peripheral ischemia. HBO therapy is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.
6. Crush injuries and suturing of severed limbs. As in the previous conditions, HBO therapy would be an adjunctive treatment when loss of function, limb, or life is threatened.
7. Progressive necrotizing infections (necrotizing fasciitis),
8. Acute peripheral arterial insufficiency,

9. Preparation and preservation of compromised skin grafts (not for primary management of wounds),
10. Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management,
11. Osteoradionecrosis as an adjunct to conventional treatment,
12. Soft tissue radionecrosis as an adjunct to conventional treatment,
13. Cyanide poisoning,
14. Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment,
15. Diabetic wounds of the lower extremities in patients who meet the following 3 criteria:
    a. You have type I or type II diabetes and has a lower extremity wound that is due to diabetes;
    b. You have a wound classified as Wagner grade III or higher; and
    c. You have failed an adequate course of standard wound therapy."

The use of HBO therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30-days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes: 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 the administration of HBO therapy. Continued treatment with HBO therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment."

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 35.

Table 35. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02407028	Hyperbaric Oxygen Brain Injury Treatment (HOBIT) Trial	200	Jun 2027
NCT04975867	Targeted Temperature Management Combined With Hyperbaric Oxygen Therapy in Acute Severe Carbon Monoxide Poisoning: Multicenter Randomized Controlled Clinical Trial (TTM-COHB Trial)	46	Jul 2025
NCT05289700	Multicentric, Double-blind, Randomised Controlled Trial of Hyperbaric-oxygen Therapy (HBOT) Versus Placebo for Treating Vaso-Occlusive Crisis (VOC) in Sickle Cell Disease (SCD) After 8 Years Old	100	Mar 2025
Unpublished			
NCT04193722	The Effect of Hyperbaric Oxygen Therapy on Breast Cancer Patients With Late Radiation Toxicity	189	May 2023

NCT: national clinical trial.

Appendix 1

2024 Clinical Input

Objective

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

Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS)
- Undersea and Hyperbaric Medical Society (UHMS)

Ratings

Clinical Indication	Respondent	Identified by	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome: Yes or No	NO: High 5	NO: Intermediate 4	NO: 3	NO: 2	NO: Low 1	YES: Low 1	YES: Intermediate 2	YES: 3	YES: 4	YES: High 5	Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice: Yes or No	NO: High 5	NO: Intermediate 4	NO: 3	NO: 2	NO: Low 1	YES: Low 1	YES: Intermediate 2	YES: 3	YES: 4	YES: High 5
Systemic hyperbaric oxygen therapy for individuals with necrotizing soft tissue infections	UHMS		YES									■		YES									■	
Systemic hyperbaric oxygen therapy for individuals with idiopathic sudden sensorineural hearing loss	UHMS		YES									■		YES									■	
Systemic hyperbaric oxygen therapy for individuals with idiopathic sudden sensorineural hearing loss	AAO-HNS		YES										■	YES										■
Systemic hyperbaric oxygen therapy for individuals with central retinal artery occlusion	UHMS		YES									■		YES									■	
Systemic hyperbaric oxygen therapy for individuals with acute peripheral artery insufficiency	UHMS		YES										■	YES										■

AAO-HNS: American Academy of Otolaryngology – Head and Neck Surgery; UHMS: Undersea and Hyperbaric Medical Society.

Respondent Profile

#	Specialty Society Name of Organization	Clinical Specialty
1	American Academy of Otolaryngology – Head and Neck Surgery	Otolaryngology – Head and Neck Surgery
2	Undersea and Hyperbaric Medical Society	Undersea and Hyperbaric Medicine

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	NO		NO		NO		NO	
2	NO		NO		NO		NO	

Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Clinical Input Responses

Question 1a: We are seeking your rationale on whether using systemic HBOT in individuals necrotizing soft tissue infections provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience.
Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome.
- Specific outcomes that are clinically meaningful.
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication.
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	No response
2	Necrotizing soft tissue infection (NSTI) is a set of disorders characterized by a rapidly progressive infection with necrosis or gangrene. This term includes but is not limited to necrotizing fasciitis, Founier's gangrene, Ludwig's angina, and infections can be both monomicrobial or polymicrobial (Steven and Bryant, 2017 PMID: 29211672). While incidence is low, NSTI is associated with a high morbidity and mortality in spite of current standards of care including surgical source control and antibiotics. Mortality is estimated between 16-33%, and limb loss was found to be 26% of patients with limb involvement in one study (Anaya and Patchen Dellenger, 2007 PMID: 17278065). The rationale for hyperbaric oxygen therapy (HBOT) is that it decreases local tissue edema via vasoconstriction and increases tissue oxygen tension. These effects may limit bacterial proliferation as well as improve antibiotic efficacy, immune system response, and overall tissue survival (Jallali, Hons, Eng et al, 2005 PMID: 24786980). Inclusion criteria for using HBOT in NSTI includes high clinical suspicion with supportive imaging or identification of necrotic tissue in the operating room. Additional supportive criteria include evidence of immune system dysfunction (i.e., sepsis) or comorbidities such as diabetes. The only true exclusion criteria for HBOT is untreated pneumothorax. Clinical signs of instability may be a relative contraindication for HBOT, especially for patients who cannot be safely transported, or those requiring high oxygen requirements between treatments who are at risk of developing pulmonary oxygen toxicity. Patients with goals of comfort-focused care should also be considered for exclusion. The decision to treat HBOT should be made on a case-by-case basis. Several meta-analysis and retrospective cohort studies show that hyperbaric oxygen therapy is beneficial in necrotizing soft tissue infections. Patients treated with hyperbaric oxygen demonstrate improvements in mortality rates, amputation rates, and quality of life. As noted in the 15th edition of the Undersea and Hyperbaric Medical Society Hyperbaric Medicine Indications Manual, a study by Wilkinson and Doolette looking at hyperbaric oxygen therapy and necrotizing soft tissue infections showed that hyperbaric oxygen therapy increased survival with an odds ratio of 8.9 and a number of 3 needed to treat to benefit. Specific outcomes that are clinically meaningful (and have been shown to be improved with hyperbaric oxygen therapy). - Mortality - Number of required surgical procedures - Amputations and therefore quality of life years - Length of hospital stay - Discharge destination (home vs acute care facility) Clinical Case Example: A 60-year-old female with a past medical history significant for diabetes mellitus underwent disarticulation of her right lower extremity. She then developed a necrotizing soft tissue infection at the surgical site which

#	Rationale
	tracked up into her pelvis. The wound dehisced and an extensive amount of devitalized tissue was noted along with a sinus tract that went down to bone, likely caused by a necrotizing infection. She received broad spectrum antibiotics and surgical debridement. With her underlying diabetes and the fact this necrotizing soft tissue infection had spread into her pelvis, her mortality risk was high. She received hyperbaric oxygen therapy emergently and then routinely as an adjunct to the antibiotics and surgical debridement. The patient survived this serious infection, and after undergoing a total of 20 hyperbaric treatments, the sinus tract to the bone closed. Her wound bed at the surgical site epithelialized and she underwent a skin graft to close the wound.

Question 1b. What key clinical features are used to identify individuals with necrotizing soft tissue infections most likely to benefit from systemic HBOT? Are there any unique considerations based on wound characteristics, site and depth of infection, or time to treatment delivery?

#	Rationale
1	No response.
2	Patients with high clinical suspicion for necrotizing fasciitis who have received broad spectrum antibiotics with either performed or planned therapeutic and diagnostic surgical debridement should be considered for HBO2. Note: while frozen section soft-tissue biopsy may be the gold standard of diagnosis, this may not be feasible in practice and may delay treatment leading to worsened outcomes. Therefore, high clinical suspicion and/or direct visualization of stigmata of necrotizing fasciitis through surgery remain the most important factors to decision to employ HBOT. Significant clinical features that are most likely to benefit from treatment with hyperbaric oxygen therapy for necrotizing soft tissue infections include immunocompromised patients, patients with peripheral arterial disease, patients with truncal necrotizing soft tissue infections, diabetic patients, and patients with Fournier's gangrene. Patients with comorbidities such as diabetes or peripheral vascular disease may especially benefit from HBOT to limit infection spread and initiate wound healing, given that many patients incur large surgical wounds to achieve adequate source control. Additionally, those with infection sites that are difficult to control due to a high bioburden such as the genital/rectal (Fournier's) or in the head/neck (Ludwig's) may also have a higher potential for clinical benefit. ALL patients with necrotizing soft tissue infections should be considered for hyperbaric oxygen therapy as an adjunctive treatment in conjunction with surgical debridement and antibiotics. Amputation rates and mortality rates are higher in patients with necrotizing soft tissue infections who do not receive hyperbaric oxygen therapy as part of their treatment. There are no unique clinical considerations based on the wound characteristics, site and/or depth of infection or time to treatment. By their very nature, necrotizing soft tissue infections are life and limb threatening and they spread very rapidly. Therefore, it is important to treat these patients as quickly as possible with hyperbaric oxygen therapy in addition to surgical debridement and antibiotics.

Question 1c. Please describe any contraindications for systemic HBOT in patients with necrotizing soft tissue infections.

#	Rationale
1	No response.
2	• Untreated pneumothorax is the only absolute contraindication for hyperbaric oxygen therapy, but HBOT can be provided after a chest tube is placed. • Patients unsuitable or too unstable for hyperbaric oxygen therapy at their specific institution § Note: Some facilities have robust critical care capabilities for treatment extremely unstable patients while others are unable to safely treat such patients, capabilities will vary with individual facilities and training/comfort of individual practitioners. Programs vary widely in their ability to manage critically ill patients.

Question 1d. Please provide any additional comments about the clinical context or specific clinical pathways for the necrotizing soft tissue infections indication and/or any key citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight..

#	Rationale
1	No response.
2	It is imperative that necrotizing soft tissue infections be treated as a medical urgency/emergency. Delaying the emergency initiation of HBOT treatments for insurance authorization increases the likelihood of limb loss and death. We urge BCBS not to require prior authorization prior to the initiation of HBOT for this emergency indication. While guidelines may exist to help guide the treatment pressure, duration and/or frequency of HBOT, the details of HBOT administration should be left to the hyperbaric clinician who must weigh the specific clinical/patient factors, coordination with other clinical interventions, and local technical capabilities. Thus, HBOT treatment profiles should always be based on clinical judgement. It is understood that the term "hyperbaric oxygen therapy" in this document always refers to treatment at pressures greater than 1.4 atmospheres absolute, administered in a hard-sided hyperbaric chamber that meets applicable safety standards. Key points: 1. Necrotizing soft tissue infections (NSTIs) are rare, rapidly spreading infections within soft tissue compartments with a high mortality and morbidity in the absence of aggressive intervention. 2. Hyperbaric oxygen treatment adjunctive to surgery and antibiotic therapy reduces odds of dying during the sentinel event and reduces risk for major amputations. 3. Diagnosis of necrotizing fasciitis can be difficult and initially may appear visually to involve nothing more than a minor abrasion, boil, insect bite or injection site. 4. The causative organisms may be polymicrobial aerobic, anaerobic, or mixed flora bacteria. Comorbidities including diabetes mellitus and immune suppression are not only included in diagnosing but increases risk of morbidity and mortality. Fournier angrene is a particularly common form of necrotizing fasciitis of the groin region found in diabetics. 5. Tissue oxygen tensions greater than 250mmHg are required to halt the alpha toxin production of clostridial infection. This level of tissue oxygen tension can only be achieved with HBOT treatment. (It should be noted that Group A streptococcus produces a toxin similar to the alpha toxin of Clostridium myonecrosis infections.) Key Citations • Soh, C. R., Pietrobon, R., Freiberger, J. J., Chew, S. T., Rajgor, D., Gandhi, M., Shah, J., & Moon, R. E. (2012). Hyperbaric oxygen therapy in necrotising soft tissue infections: a study of patients in the United States Nationwide Inpatient Sample. Intensive Care Medicine, 38(7), 1143–1151. https://doi.org/10.1007/S00134-012-2558-4 (PMID 22527074) - this retrospective analysis of 45,913 patients in the National Inpatient Sample (NIS) from 1988 to 2009 showed inpatient hyperbaric oxygen was associated with a statistically significant reduction in mortality (OR 0.49, 95 % CI 0.29-0.83). https://doi.org/10.1007/S00134-012-2558-4 (PMID 22527074) • Hedetoft et al. BMJ Open 2020. Retrospective analysis of a Danish cohort with 1527 patients between 2005-2018 found that hyperbaric oxygen was associated with decreased 30-day mortality (OR 0.54, 95% CI 0.33 to 0.91, p=0.02) and 90-day mortality (OR 0.61, 95% CI 0.39 to 0.97, p=0.03) when compared with standard therapy alone. PMID: 3681348 • Huang et al. World Journal of Emergency Surgery 2023. A recent systematic review and meta-analysis including a total of 49,152 patients from 23 non-randomized studies spanning three decades (1990-2022) found an association between patients treated with hyperbaric oxygen for necrotizing soft tissue infections and a reduced risk of mortality, RR 0.52 (95% CI 0.40-0.68, p=0.03) PMID: 36966323 • Toppen et al. Plos One 2024. Retrospective analysis of the National Inpatient Sample Database including 60,481 patients from 2012-2020 throughout the United States admitted for necrotizing fasciitis who underwent surgery found that, after adjusting for differences between groups, an association existed between hyperbaric oxygen therapy and improved mortality (Adjusted Odds Ratio (AOR) 0.22, 95% CI 0.09-0.53, P<0.001) and lower risk of amputation (AOR 0.73, 95% CI 0.55-0.96, P = 0.03). They also found that hyperbaric oxygen patients had lower risk of non-home discharges (AOR 0.79, 95%CI 0.65-0.96). (PMID: 38512943) • Wilkson, Doolette. JAMA Surgery 2004. Retrospective review of 44 patients undergoing hyperbaric oxygen therapy as adjunctive therapy to surgery and antibiotics demonstrated increased survival

#	Rationale
	rate (OR 8.9) with a number needed to treat of 3. This level of clinical response and low number needed to treat is rarely seen in the medical field. • Faunø Thrane, J., & Ovesen, T. (2019). Scarce evidence of efficacy of hyperbaric oxygen therapy in necrotizing soft tissue infection: a systematic review. Infectious Diseases, 51(7), 485–492. https://doi.org/10.1080/23744235.2019.1597983. PMID: 30985236

Question 2a. We are seeking your rationale on whether using systemic HBOT in individuals idiopathic sudden sensorineural hearing loss provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience.
Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	There are several randomized controlled trials and a Cochrane review from 2021 that show some benefit of hyperbaric oxygen therapy (HBOT) as either primary or salvage therapy for sudden sensorineural hearing loss. As such, the 2019 American Academy of Otolaryngology clinical practice guideline on sudden sensorineural hearing loss reserves HBOT as an option when combined with steroid therapy in SSNHL as primary therapy within 2 weeks of onset of symptoms and as salvage therapy when used within 4 weeks of onset, with potentially more benefit notes in cases of severe to profound loss. The is the official Key Action Statement #9, which pertains to this issue: STATEMENT 9a. INITIAL THERAPY WITH HYPERBARIC OXYGEN THERAPY: Clinicians may offer, or refer to a clinician who can offer, hyperbaric oxygen therapy (HBOT) combined with steroid therapy within 2 weeks of onset of SSNHL. Option based on systematic reviews of RCTs with a balance between benefit and harm. STATEMENT 9b. SALVAGE THERAPY WITH HYPERBARIC OXYGEN THERAPY: Clinicians may offer, or refer to a clinician who can offer, HBOT combined with steroid therapy as salvage within 1 month of onset of SSNHL. Option based on systematic reviews of RCTs and new RCTs with a balance of benefit and harm. Since 2019, four prospective RCTs comparing HBOT + steroids vs steroids alone have also been published.[2-5] A systematic review and meta-analysis published in 2021 (Jama Otolaryngology) of three of these clinical trials reported significant benefit of HBOT as adjuvant therapy over control treatments, with a mean gain of 10.4 dB (95% CI 6.3 to 14.6) over control groups (steroids alone). They reported the odds of hearing recovery was 4.3 times greater (95% CI 1.6 to 11.7; I^2=0%) in patients who had HBOT compared to controls. Of note, the 3 studies pooled together showed 0% interstudy statistical heterogeneity, which was an improvement from prior systematic reviews that were especially heterogeneous in their inclusion criteria and study design. None of these three clinical trials were included in the 2019 clinical practice guideline update. A 2021 RCT of 136 patients comparing steroids alone vs steroids + HBOT also reported an improved success rate (defined as $\geq$15 dB improvement in pure tone average) of the HBOT/steroids group (60.6%, N = 40/66) compared to steroids alone (42.9%, N = 30/70), p<.05. Given these findings, it would be prudent to continue to offer HBOT as an option for the treatment of SSNHL in the adjuvant or salvage setting, consistent with the 2019 clinical practice guideline. References: 1. Chandrasekhar SS, Tsai Do BS, Schwartz SR, et al. Clinical Practice Guideline: Sudden Hearing Loss (Update). Otolaryngol Head Neck Surg. Aug 2019; 161(1_suppl): S1-S45. PMID 31369359 2. Krajcovicova Z, Melus V, Zigo R, et al. Efficacy of hyperbaric oxygen therapy as a supplementary therapy of sudden sensorineural hearing loss in the Slovak Republic. Undersea Hyperb Med. 2018; 45(3): 363-370. PMID 30028922 3. Khater A, El-Anwar MW, Nofal AA, et al. Sudden Sensorineural Hearing Loss: Comparative Study of Different Treatment Modalities. Int Arch Otorhinolaryngol. Jul 2018; 22(3): 245-249. PMID 29983762

#	Rationale
	4. Cho I, Lee HM, Choi SW, et al. Comparison of Two Different Treatment Protocols Using Systemic and Intratympanic Steroids with and without Hyperbaric Oxygen Therapy in Patients with Severe to Profound Idiopathic Sudden Sensorineural Hearing Loss: A Randomized Controlled Trial. Audiol Neurootol. 2018; 23(4): 199-207. PMID 30380530 5. Tong B, Niu K, Ku W, et al. Comparison of Therapeutic Results with/without Additional Hyperbaric Oxygen Therapy in Idiopathic Sudden Sensorineural Hearing Loss: A Randomized Prospective Study. Audiol Neurootol. 2021; 26(1): 11-16. PMID 32535600 Additionally, in regards to the 3rd bullet point, physicians should have the option to request coverage for their patients when appropriate and when medically necessary.
2	ISSNHL is an abrupt loss of hearing, typically unilaterally, without a definitive or identifiable cause upon investigation, as is the case for 90% of sudden sensorineural hearing loss patients. The degree of hearing loss is typically defined as a loss of 30 decibels or more across 3 contiguous frequencies on audiogram. Hearing loss can significantly affect the ability of patients to work, maintain social connections, and be safely mobile. Further, the hearing loss initially occurring on one side can occur subsequently on the contralateral side in the future. The exact etiology of ISSHL has not been elucidated but of the major proposed mechanisms may be mitigated by HBOT. One of the proposed mechanisms is an acute ischemic process which causes decreased oxygen delivery to the cochlea, which has a high metabolism and high O2 requirement, but sparse vascularity. Direct vascular supply is minimal, especially to the Organ of Corti. Tissue oxygenation to the structures within the cochlea occurs via oxygen diffusion from cochlear capillary networks into the perilymph and the cortilymph. The perilymph is the primary oxygen source for these intracochlear structures. In patients with ISSHL, the perilymph O2 tension is decreased from normal. Hyperbaric oxygen (HBOT) corrects that deficit and increases O2 tension. Another suggested etiology is an auto-inflammatory cascade that attacks the inner ear apparatus, including the hair cells within the cochlear duct, semi-circular canals, utricle, and saccule resulting in hearing loss. In 2020, Liu et al. described the occurrence of an inflammatory response in ISSHL that expressed Toll-like receptor (TLR) 4, nuclear factor (NF)-KB, and tumor necrosis factor (TNF). They elucidated that TLR4, NF-KB, and TNF-were upregulated in ISSHL patients compared to healthy control subjects. They demonstrated with statistical significance that HBOT suppressed the inflammatory response caused by TLR4 and NF-KB and subsequently alleviated the hearing loss in ISSHL. Among the physiological mechanisms of action of HBOT in treating indicated conditions is the contravening of inflammatory cascades, such as seen in the established treatment by HBOT of carbon monoxide toxicity, ischemia reperfusion injury, and decompression sickness. A third suggested etiology is a viral infection. Viral infections, particularly significant ones such as CMV, HSV, seasonal viruses (influenza), and recently SARS CoV-2 (COVID-19), can cause inflammation and edema of the vestibulocochlear nerve which can subsequently damage the nerve, or the viral infection can directly damage the inner ear structures resulting in sudden sensorineural hearing loss. In this case, HBOT may have the same inflammatory contravening mechanism of action as seen in auto-inflammatory conditions, as well as the vasoconstriction effect that reduces edema. Clinical scenario: A 53 year-old male patient with history of hypertension and anxiety was diagnosed with idiopathic sudden sensorineural hearing loss on his left ear. He had associated dizziness that resolved over time, but the hearing loss worsened in the meantime and was debilitating. He had a trial of oral prednisone with taper and intratympanic dexamethasone injection thereafter with minimal response. The patient received 20 HBOT at 2.4 ATA for 2 hours per session. After 15 HBOTs, the patient noticed significant improvement in his hearing, but his audiogram revealed incomplete normalization of his hearing on the left side in the high frequency range. His audiogram results after additional 5 HBOT showed continued improvement in his hearing without plateau. After 20 HBOT, the patient felt that his hearing was back to normal and HBOT was stopped.

Question 2b: What key clinical features are used to identify individuals with idiopathic sudden sensorineural hearing loss most likely to benefit from systemic HBOT? Are there any unique considerations based on degree of hearing loss or time post symptom onset?

#	Rationale
1	Anyone with audiometrically diagnosed sudden sensorineural hearing loss is a potential candidate for HBOT as adjuvant therapy or salvage therapy.
2	Patient selection for HBOT in ISSHL: There are no unique considerations based on degree of hearing loss (or persistent tinnitus). Even patients treated after 3 months have improved in response to HBOT and thus should be offered HBOT if ISSHL symptoms (hearing loss and/or tinnitus) have not completely resolved with conventional therapy (such as oral and/or intratympanic steroid treatment).

Question 2c. Please describe any contraindications for systemic HBOT in patients with idiopathic sudden sensorineural hearing loss.

#	Rationale
1	Relative contraindications include those with severe anxiety/claustrophobia and those with eustachian tube dysfunction with resultant severe otalgia from dives. Additionally, patients with pulmonary fibrosis may not do well after coming out of HBOT. It is best avoided in such cases as well as in COPD. It becomes very hard to wean such patients off of HBOT.
2	The only absolute contraindication for hyperbaric oxygen therapy is untreated pneumothorax. HBOT can be provided once a chest tube is placed.

Question 2d. Please provide any additional comments about the clinical context or specific clinical pathways for the idiopathic sudden sensorineural hearing loss indication and/or any key citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight..

#	Rationale
1	See references in 2a, above.
2	It is imperative that ISSHL be treated as a medical urgency/emergency. Delaying the emergency initiation of HBOT treatment while waiting for insurance authorization may reduce the likelihood of benefit. We urge BCBS not to require prior authorization prior to the initiation of HBOT for this emergency indication. While guidelines may exist to help guide the treatment pressure, duration and/or frequency of HBOT, the details of HBOT administration should be left to the hyperbaric clinician who must weigh the specific clinical/patient factors, coordination with other clinical interventions, and local technical capabilities. Thus, HBOT treatment profiles should always be based on clinical judgement. It is understood that the term "hyperbaric oxygen therapy" in this document always refers to treatment at pressures greater than 1.4 atmospheres absolute, administered in a hard-sided hyperbaric chamber that meets applicable safety standards. The primary goal of treatment in ISSNHL is to improve hearing on repeat audiogram. This can be measured by overall detection thresholds, pure-tone average, or speech/word recognition scoring. Improvements in dizziness or vertigo symptoms may also be monitored clinically. Though a multitude of medical therapies have been employed in treating idiopathic sudden sensorineural hearing loss (ISSHL), including thrombolytics, antivirals, antioxidants, and vasodilators, only two have been shown to be clinically effective and have been given the highest recommendation by the American Academy of Otolaryngology in the Guidelines for the Treatment of ISSHL: Steroids (oral and/or intratympanic injection) and hyperbaric oxygen (HBOT). The American Academy of Otolaryngology – Head and Neck Surgery Foundation published in 2012 their Clinical Practice Guidelines for Sudden Hearing Loss with the recommendation that HBOT therapy be utilized within three months of symptom onset. However, substantive improvement in symptoms have been reported among patients treated with HBOT after six months or greater of delay. A Cochrane systematic meta-analysis review of the literature investigating the three most widely used therapies for ISSHL using steroids, vasodilators and HBOT, only HBOT received a positive, objective, critical review (Cochrane Review, 2010) and the conclusion that "for people with acute ISSHL, the application of HBOT significantly improved hearing," compared to corticosteroid and vasodilator therapies. Several controlled trials studies have demonstrated that the combined treatment of concomitant HBOT and corticosteroids produced even better outcome with a greater degree of hearing improvement. In

#	Rationale

aggregate, four Cochrane Reviews in 2005, 2007, 2010, and 2012 demonstrate the preponderance of the evidence of beneficial outcomes when ISSHL is treated using HBOT therapy.

Because patients treated after more than 3 months of onset have benefitted from HBOT, because HBOT is safe, because hearing loss represents a life changing debility, and because there are no other proven therapies if steroids fail, HBOT is warranted even if patients present later than 3 months. We acknowledge that the longer the delay to starting HBOT, the greater the number of HBOT treatments will likely be needed to achieve benefit.
The number of HBOT treatments necessary for ISSHL cannot be predicted because of significant variability between patients affected and the uncertainties around pathophysiology. A treatment course of only 7 sessions has been successful at recovering hearing loss but as many as 24 sessions may be necessary. Progress is typically slow and only incremental. As long as progress is made, HBOT treatments should continue. A reasonable expectation would be that the hearing loss is likely to reach optimal recovery within 30 HBOT treatments.

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#	Rationale
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Question 3a. We are seeking your rationale on whether using systemic HBOT in individuals central retinal artery occlusion provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience.
Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	No response
2	Central retinal artery occlusion (CRAO) is a relatively rare yet devastating diagnosis. It has a poor prognosis for spontaneous recovery with only 22% of patients improving spontaneously in the absence of a patent cilioretinal artery (Hayreh, 2004). Factors which influence outcome include the length of time of occlusion prior to HBOT treatment, the anatomical site of the occlusion, and the presence of a patent cilioretinal artery. The diagnosis of central retinal artery occlusion is typically and reliably made with a fundoscopic exam. Advanced diagnostic studies can confirm CRAO but are not required for the diagnosis.

#	Rationale
	Several treatments for CRAO have been tried including ocular massage, anterior chamber paracentesis, fibrinolysis, and ocular pressure lowering agents. However, none of these have been shown in experimental models to demonstrate improved outcomes compared to control. Thus, the current standard therapy for CRAO is of almost no benefit. Hyperbaric oxygen therapy (HBOT) is able to supply 100% of the retinal oxygen needs through the choroidal circulation (Patz, 1955). This allows for continuing oxygenation while awaiting retinal vessel recanalization. The FDA has added Central Retinal Artery Occlusion to the list of cleared indications for hyperbaric oxygen therapy. It is pertinent to note that central retinal artery occlusion is a rare diagnosis (1 in 100,000) and only about 10% of hyperbaric departments offer emergency services. Given these two considerations, a prospective, blinded trial with a statistically sufficient number of patients is unlikely to be performed, and it can be argued that, given the low benefit of standard therapy, it is unethical to withhold HBOT. Many case series have shown a clear benefit from HBOT. However, there is one negative study that should be mentioned for completeness, The Effects of Hyperbaric Oxygen Therapy in patients with Central Retinal Artery Occlusion: a Retrospective Study, Systematic Review, and Meta-Analysis by Rosignoli, et al. The authors analyzed only three prior publications in their "meta-analysis", one of which was quite old, despite the fact that several more recent studies could have been included which would have strengthened the outcomes in favor of HBOT. The authors also included a retrospective review of a small number of CRAO cases from their own institution (15 patients that received hyperbaric oxygen and 33 patients that did not receive HBOT). The patients had a wide range of elapsed time from onset to hyperbaric treatment (18 hours +/- 10 hours), the HBOT treated patients had a higher than normal rate of complications such as otic barotrauma (e.g. 20% vs. the norm of 10%), and HBOT was stopped after the first treatment if there was no obvious improvement in vision. Both the meta-analysis and the clinical care were substandard. This clinical protocol can be used as an example of poor clinical use of HBOT since most practitioners recommend that at least 2-3 HBOT treatments be performed before making the determination that HBOT has not been beneficial, particularly given the challenges involved in objectively measuring incremental improvement in cases of near blindness. The primary outcome is an improvement in visual acuity. The patients' visual acuity should be assessed at least daily although visual acuity may need to be assessed by near-cards (rather than a wall chart). Relevant Scenario: 78yo male ● Sudden onset of painless and near complete vision loss to the right eye ● Presented to ED emergency department within 12 hours of onset ● Seen by ophthalmology and diagnosed with CRAO ● Treated at 2.8 ATA for 80 minutes of 100% oxygen x 1 followed by TT9 2.4 ATA for 90 minutes of 100% oxygen x BID for 5 days - total number of treatment = 10 ● Discharged as plateau reached, vision improvement noted by patient was significant and, "close to what it was prior to the vision loss"

Question 3b. What key clinical features are used to identify individuals with central retinal artery occlusion most likely to benefit from systemic HBOT? Are there any unique considerations based on time since symptom onset or site and etiology of arterial occlusion?

#	Rationale
1	No response
2	Although the Undersea and Hyperbaric Medical Society Committee reports recommends treatment if the patient presents within 24 hours of onset (Murphy-Lavoie H, Butler F, Hagan C, 2023) many successful cases have been reported in which treatment began outside that window, in some cases, up to weeks later (Chiago, et al, 2023, W.X., 2018). Although all studies demonstrate that the outcome of HBOT is improved with early treatment, given the safety of HBOT, the lack of successful alternative medical treatments, the debilitating impact of vision loss, and the challenges faced in getting a patient to a hyperbaric facility, we do not support a specific time cutoff after which HBOT should not be tried for CRAO. There are some related clinical syndromes for which HBOT should be offered. For example, there is literature to support the use of hyperbaric oxygen for branch retinal artery occlusion (Murphy-Lavoie, Butler, Hagan, 2023). Although these patients generally tend to have a better prognosis than those with a central retinal

#	Rationale
	artery occlusion, there are situations where HBOT should be offered to patients with a branch retinal artery occlusion. This includes patients who may already have complete or near complete blindness in the contralateral eye. Another unusual phenomenon that may respond to hyperbaric oxygen is visual loss associated with Susac's Syndrome. This is a rare disorder thought to be an autoimmune endotheliopathy causing vascular injury and deposition of thrombotic material in the lumen of small vessels. This diagnosis is typically made by MRI in conjunction with fluorescence angiography. Previous literature has documented other treatments that have been tried such as steroids, anticoagulation, and IVIG. There are some case reports demonstrating use of hyperbaric oxygen that has greatly improved the visual acuity in these patients. (Li, et al, 1996; Meca-Lallana et al, 1999; Navarro, G., Bains, R. 2020). Also, a rare complication associated with CaHA cosmetic filler injection is central retinal artery occlusion, likely due to embolism. There has been one case report showing significant improvement after HBO was used in this patient (Hsiao, SF, Huang YH., 2014).

Question 3c. Please describe any contraindications for systemic HBOT in patients with central retinal artery occlusion.

#	Rationale
1	No response
2	The only absolute contraindication would be an untreated pneumothorax. Patients can be treated with HBOT after chest tube placement. The presence of ocular gas (used to stabilize the retina from prior retinal detachment) is not an absolute contraindication to hyperbaric oxygen treatments. Retinal gas is spontaneously absorbed. We recommend discussion with ophthalmology regarding risk vs. benefit of proceeding with HBOT.

Question 3d. Please provide in the box below any additional comments about the clinical context or specific clinical pathways for the central retinal artery occlusion indication and/or any key citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight.

#	Rationale
1	No response
2	It is imperative that CRAO be treated as a medical urgency/emergency. Delaying the emergency initiation of HBOT treatments for insurance authorization increases the likelihood of vision loss. We urge BCBS not to require prior authorization prior to the initiation of HBOT for this emergency indication. While guidelines may exist to help guide the treatment pressure, duration and/or frequency of HBOT, the details of HBOT administration should be left to the hyperbaric clinician who must weigh the specific clinical/patient factors, coordination with other clinical interventions, and local technical capabilities. Thus, HBOT treatment profiles should always be based on clinical judgement. It is understood that the term "hyperbaric oxygen therapy" in this document always refers to treatment at pressures greater than 1.4 atmospheres absolute, administered in a hard-sided hyperbaric chamber that meets applicable safety standards. Retinal Detachment should NOT be a contraindication to HBOT for CRAO. The 78-year-old man described in the clinical scenario was completely blind in the right eye except for one small quadrant in which he could determine only dark vs light. He explained to the clinician that it was difficult to imagine living with this loss of sight and that he had recently lost his wife. His quality of life was looking very bleak. After his first treatment, he was able to visualize and count fingers in front of his affected eye. He continued with treatment for 5 days, twice a day for a total of 10 treatments, after which he completely regained vision in the affected eye. Being able to restore someone's sight is extremely clinically significant and supports the use of HBOT, particularly given the fac that, "Individuals with vision impairment are…more likely to experience restrictions in their independence, mobility, and educational achievement, as well as an increased risk of falls, fractures, injuries, poor mental health, cognitive deficits, and social isolation." (National Academies of Sciences,

#	Rationale

Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on Public Health Approaches to Reduce Vision Impairment and Promote Eye Health; Welp A, Woodbury RB, McCoy MA, et al., editors. Making Eye Health a Population Health Imperative: Vision for Tomorrow. Washington (DC): National Academies Press (US); 2016 Sep 15. 3, The Impact of Vision Loss. Available from: https://www.ncbi.nlm.nih.gov/books/NBK402367.)

A clinically significant outcome for patients with central retinal artery occlusion is greater than or equal to a logMAR of 0.3 improvement in visual acuity on a log scale. This scale is used in leu of a Snellen Chart as patients tend to have profound vision loss and many are unable to read any lines on the Snellen Chart. Multiple prior research trials have shown improved outcomes using hyperbaric oxygen for this diagnosis. One large review of historical research showed a mean improvement of 65% (306 patients) in patients treated with hyperbaric oxygen (Murphy-Lavoie, Butler, Hagan, 2012). In a more recent study of 123 patients treated with HBO compared to 23 controls, patients treated with HBO had a mean improvement of 0.5logMAR (Rozenberg, et al, 2022). A second retrospective review of 128 patients that underwent HBO also demonstrated statistically significant improvement using HBO with a logMAR of 0.526. There have also been two smaller case series recently with improvement of 57% (0.5 logMAR) and 72% (5 lines improvement on Snellen Chart) respectively (St Peter et al, 2023; Masters et al, 2019). "Clinical plateau" may be defined as no meaningful improvement after 2-3 consecutive HBOT treatments.

Any improvement in vision, especially for those with professions dependent on their vision in both eyes and for those with poor vision in the contralateral eye. HBOT can improve vision loss in CRAO 65% of the time.

CRAO patients should be evaluated for stroke. However, given the emergent nature of CRAO, HBOT should NOT be delayed for CRAO while other etiologies are ruled out. HBOT treatments should continue until a clinical plateau is reached or until the retinal artery re-cannulates. Some studies indicate that this may be up to 2-3 weeks post-insult (Chiabo, et al, 2023).

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#	Rationale
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Question 4a. We are seeking your rationale on whether using systemic HBOT in individuals with acute peripheral artery insufficiency provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience.
Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	No response
2	• Acute arterial Insufficiencies (AAI) are interruptions, complete or partial, of perfusion that put the tissues distal to the interruption at risk loss of function or dying. AAIs span a variety of conditions including central retinal artery occlusion, arterial thrombosis, end-stage peripheral artery disease, sludging in the microcirculation, coronary artery occlusion, skeletal muscle-compartment syndrome, drug induced vasoconstriction, traumatic arterial interruptions, trash syndrome, failed amputations and iatrogenic causes from too tight bandaging, swelling after casting, vessel constriction-narrowing as a consequence of over stretching, and severing in association with surgery.

#	Rationale
	• The unifying finding in the acute periphery artery insufficiency syndromes is tissue hypoxia associated with some form of injury. Tissue hypoxia subsequently leads to ischemia and edema. • AAIs leading to death of tissue or loss of function are costly. For example, amputations associated with critical limb ischemia cost about $115,000 while managing diabetic foot ulcers was $8.78 billion annually in the years spanning 2006-2010 (Ruder, Kate, Diabetic foot infections and amputations are all too common—Here's what could Move the Needle, J Am Med Assoc, 2024; 331(12):998-1000). Greater than 50% amputation, infection and/or functional loss in leg crush injuries occurs in those patients that require revascularization because of AAI. (Gustilo, J Trauma 1981). Pathophysiology of AAIs • Oxygen as well as other substances are required for tissue survival. Of all the agents in blood, oxygen is the most critical for tissue function and survival. All oxygen transfer to tissues occurs in the microcirculation s at the capillary level. Ordinarily 97.5 percent of the oxygen to tissues is carried by the red blood cell (RBC). Of all the blood flow passing through the capillary, the RBC is the most flow dependent. This is because of the mass of RBC in contrast to physically dissolved substances in the plasma such as glucose, hormones, vitamins, minerals, antibiotics, etc. • AAIs have a spectrum of "golden periods," that is, the times to mitigate the problem that vary from tissue to tissue. Time frames range from a few minutes with neuro tissues, to a couple of hours for muscle, to a day or two for skin and bone and even longer for relatively avascular connective tissues, cartilage, and adnexal structures. • Death of appendage tissues occurs at the level where AAI is severe enough that tissues die, do not heal, and/or are unable to control infection. Demarcation depends on adequate perfusion to the level of the AAI. Without adequate perfusion, demarcation does not occur and more proximal levels of amputation are required. In addition, with AAI, at the level of the amputation, the site does not heal. For this indication, due to the diverse clinical presentation of this condition, we thought a series of actual cases would be useful [6 CASES PRESENTED WITH PHOTO DOCUMENTATION]

Question 4b. What patient selection criteria are used to identify individuals with acute peripheral artery insufficiency most likely to benefit from systemic HBOT? Are there any unique considerations based on time since symptom onset or site, etiology, and nature of injury (e.g., ischemic occlusion from traumatic injury, thrombosis, embolism)?

#	Rationale
1	No response
2	It is imperative that acute arterial insufficiency be treated as a medical urgency/emergency. Delaying the emergency initiation of HBOT treatments for insurance authorization increases the likelihood of tissue loss and even death. We urge BCBS not to require prior authorization prior to the initiation of HBOT for this emergency indication. While guidelines may exist to help guide the treatment pressure, duration and/or frequency of HBOT, the details of HBOT administration should be left to the hyperbaric clinician who must weigh the specific clinical/patient factors, coordination with other clinical interventions, and local technical capabilities. Thus, HBOT treatment profiles should always be based on clinical judgement. It is understood that the term "hyperbaric oxygen therapy" in this document always refers to treatment at pressures greater than 1.4 atmospheres absolute, administered in a hard-sided hyperbaric chamber that meets applicable safety standards. HBOT should be started as soon as possible, particularly for threatened flaps and grafts. Clinical assessments and judgement are crucial in making the decision of whether or not to use HBOT. Transcutaneous oxygen measurements should not be required since performing TCOM may not be possible depending on the location of tissue (e.g., penis), and the risk of additional damage from the heated electrode. In most cases, ischemia is clinically obvious to the naked eye (see cases provided). Because of the variability of presentation in this category, it is not possible to make hard rules regarding the cut off period for providing HBOT. Another reason not to put a strict restriction on the time frame to initiate HBOT therapy is because the injury and the manifestation of the injury may take days to weeks to make itself apparent. For example, in the

#	Rationale
	case of vasopressor or frostbite-induced ischemia, the injury may occur, but the patient cannot be treated due to extant circumstances such as remote locations or being in such a critical state that transfer to the hyperbaric chamber cannot be facilitated. Tissue recovery has been documented even after many days/weeks of delay.

Question 4c. Please describe any contraindications for systemic HBOT in patients with acute peripheral artery insufficiency.

#	Rationale
1	No response
2	• Untreated pneumothorax is the only absolute contraindication for hyperbaric oxygen therapy, but HBOT can be provided after a chest tube is placed. • Patients unsuitable or too unstable for hyperbaric oxygen therapy at their specific institution § Note: Some facilities have robust critical care capabilities for treatment extremely unstable patients while others are unable to safely treat such patients, capabilities will vary with individual facilities and training/comfort of individual practitioners. Programs vary widely in their ability to manage critically ill patients.

Question 4d. Please provide in the box below any additional comments about the clinical context or specific clinical pathways for the acute peripheral artery insufficiency indication and/or any key citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight.

#	Rationale
1	No response
2	The physics and physiology of systemic hyperbaric oxygen therapy (HBO) are well defined. HBOT can increase plasma and tissue fluid oxygen tensions 10-fold. The result is the oxygen carrying capacity of blood is increased and approaches a level that meets the normal oxygen extraction through the capillary network. Also, diffusion through relative barriers such as edema fluid, suppuration, cicatrix, biofilms, nonviable bone, cartilage, and relatively avascular connective tissues is significantly improved. Additionally, hyperoxygenation of serum leads to vasoconstriction of some vessels in peripheral circulation while still maintaining adequate oxygenation, leading to reduction in edema with resultant decreased diffusion distances for oxygen to travel and reduced external pressure on microcirculation. In the tissues that are ischemic/necrotic, HBOT augments tissue demarcation through its angiogenesis effects and assists in managing infection through improved WBC oxidative killing as well as some bactericidal and bacteriostatic effects on some microorganisms. The role of HBOT is adjunctive to surgery (when indicated) and medical management. HBOT can make the difference between tissue survival and loss. If re-establishment of pulsatile blood flow is not possible, then the ability of hyperbaric oxygen to maintain tissue viability until angiogenesis/new collateral blood flow will minimize tissue loss and associated problems. Key Citations: 1. Bouachour, G., et al. "Hyperbaric oxygen therapy in the management of crush injuries: a randomized double-blind placebo-controlled clinical trial." Journal of Trauma and Acute Care Surgery 41.2 (1996): 333-339. PMID: 8760546 2. Nakamura, Hideharu, et al. "Changes in skin perfusion pressure after hyperbaric oxygen therapy following revascularization in patients with critical limb ischemia: a preliminary study." The International Journal of Lower Extremity Wounds 19.1 (2020): 57-62. PMID: 31478408 3. Strauss, Michael B. "The role of hyperbaric oxygen for acute traumatic ischemias." Undersea & Hyperbaric Medicine 49.2 (2022). PMID: 35580490 4. Suen, Nien Hsiu, et al. "Case Report of Efficacy of Skin Perfusion After Hyperbaric Oxygen Therapy Following Peripheral Tissue Injury due to Usage of Inotropes and Vasopressors." Clinical and Experimental Emergency Medicine (2024). PMID: 38368879 5. Kwee, Esmee, et al. "Adjunctive hyperbaric oxygen therapy in the management of severe lower limb soft tissue injuries: a systematic review." European Journal of Trauma and Emergency Surgery (2024): 1-8 PMID: 38386077

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2023 Clinical Input

Objective

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

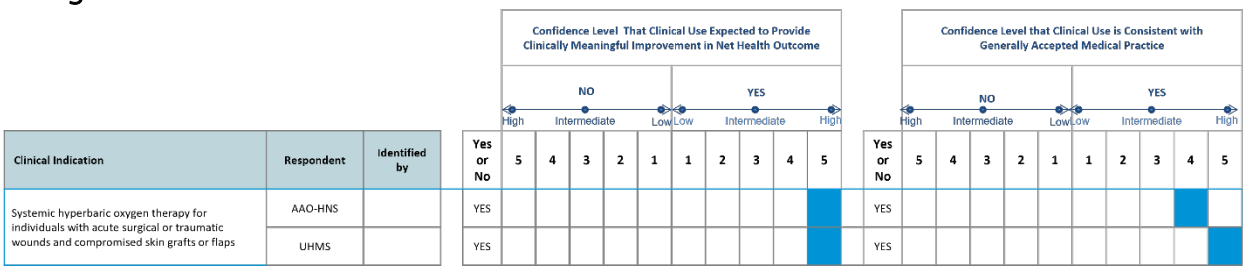
Respondents

Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS)
- Undersea and Hyperbaric Medical Society (UHMS)

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.
** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Ratings



Clinical Indication	Respondent	Identified by	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome: Yes or No	NO: High 5	NO: Intermediate 4	NO: Intermediate 3	NO: Intermediate 2	NO: Low 1	YES: Low 1	YES: Intermediate 2	YES: Intermediate 3	YES: Intermediate 4	YES: High 5	Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice: Yes or No	NO: High 5	NO: Intermediate 4	NO: Intermediate 3	NO: Intermediate 2	NO: Low 1	YES: Low 1	YES: Intermediate 2	YES: Intermediate 3	YES: Intermediate 4	YES: High 5
Systemic hyperbaric oxygen therapy for individuals with acute surgical or traumatic wounds and compromised skin grafts or flaps	AAO-HNS		YES										■	YES									■	
	UHMS		YES										■	YES										■

AAO-HNS: American Academy of Otolaryngology – Head and Neck Surgery; UHMS: Undersea and Hyperbaric Medical Society.

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Respondent Profile

#	Specialty Society Name of Organization	Clinical Specialty
1	American Academy of Otolaryngology – Head and Neck Surgery	Otolaryngology – Head and Neck Surgery
2	Undersea and Hyperbaric Medical Society	Undersea and Hyperbaric Medicine

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	NO		NO		NO		NO	
2	NO		NO		NO		NO	

Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response.

Clinical Input Responses

Question 1. We are seeking your rationale on whether using systemic HBOT in individuals with compromised skin grafts or flaps provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	We believe that using systemic hyperbaric oxygen (HBO) treatment with compromised skin grafts and flaps can provide a clinically meaningful improvement in cases where wound healing is compromised. Hyperbaric

#	Rationale
	oxygen treatment is known to increase fibroblast function, collagen synthesis, enhance angiogenesis, and improve skin flap circulation.[1] Grafts (avascular tissue that relies on receiving bed of tissue for oxygenation), and flaps (have inherent blood supply) are instrumental in improving functional outcomes and quality of life in patients who need reconstructive or plastic surgery. Not all surgical grafts/flaps are successful with vascular compromise and edema leading to failure. This amounts to a waste of surgical efforts and need for costly recurrent surgical interventions as well as decrease in patient satisfaction and overall quality of life. Hyperbaric hyperoxia benefits these at-risk flaps/grafts by decreasing hypoxia, and enhancing collagen deposition, fibroblast function, stimulating angiogenesis, decreasing vasogenic edema (increase oxygen delivery in the setting of vasoconstriction) and inhibiting ischemia-reperfusion injury.[2] Indication for hyperbaric oxygen treatment for skin grafts and flaps includes different settings, particularly where there is concern for vascular compromise or insufficiency. Additionally, areas of previous radiation exposure have decreased vascularization and compromised wound healing. Reperfusion injuries and thermal burns with skin grafts are also indications for hyperbaric oxygen treatment.[3] The goal of hyperbaric oxygen treatment is to preserve the tissue at risk, thus minimizing morbidity and maximizing the reconstructive effect by salvaging the compromised tissue and avoiding additional surgical intervention. Therefore, hyperbaric oxygen therapy may limit the need for repeated surgical debridements and revision reconstructive surgery in some cases. There are many animal studies that demonstrate the beneficial effects of hyperbaric oxygen treatment in compromised tissue and flaps. Similarly, clinical case reports and series support these findings.[4] Unfortunately, there are few prospective clinical studies and no randomized controlled trials. However, this is likely because hyperbaric oxygen treatment is not routinely used in wound healing and that clinicians have increased knowledge in the factors that can influence viability of grafts and flaps. The incidence of compromised flaps appears to be relatively low. Therefore, it makes performing a randomized control trial in this specific patient population very challenging. It should be noted that one of the few randomized controlled trials testing the result of HBO therapy in the head and neck region found statistically significant improvements in wound healing in patients treated for osteonecrosis of the mandible.[5] Clinical scenarios: Choosing the proper patient for hyperbaric oxygen therapy (HBOT) is important to maximize benefit. Flaps should first be evaluated for occlusion in its blood supply with interventional vascular procedures to dislodge or dissolve the offending obstruction. On the other hand, grafts have no vascular supply and should be treated emergently with hyperbaric oxygen without delay. Flap/Grafts after degloving injuries, burns, crush and compartment syndrome, very large flaps and reconstruction in irradiated tissue are ideal for emergent/urgent HBOT. These are already at-risk tissue before flap/graft surgery due to the underlying pathology of hypoxia. It should be noted that normal appearing flaps/grafts after surgery do not need routine hyperbaric hyperoxia. However, in the setting of breast reconstruction, using nipple sparing technique, the nipple is poorly perfused and therefore at high risk of necrosis. This type of surgery should be treated with extreme care and hyperbaric oxygen therapy should be initiated soon after any sign of ischemia or edema leading to hypoxia of the superficial skin. In addition, the use of dermal fillers and inadvertent injection of the material into an artery has also led to hypoxia of the superficial skin. These patients benefit from hyperbaric oxygen to decrease the potential for permanent facial scarring. In the pediatric population, there is abundant clinical experience that supports the use of hyperbaric oxygen in children who are getting staged reconstruction of the penis for hypospadias. The biggest risk to these patients is delay in consultation to hyperbaric medicine for this time-sensitive indication. There are many case series, and retrospective studies that show the benefit of hyperbaric oxygen for flaps/grafts. Kleban and Baynosa wrote a review of these studies, and rationale for hyperbaric oxygen that much of this evaluation is based on. (PMID: 33227840)There is one prospective randomized control trial published in the Lancet, showed level I evidence for HBOT PMID: 4164367. Other studies are level II evidence and consist of a total of almost two thousand patients. There are numerous level IV reports of case series that support the use of HBOT. Clinically meaningful outcomes include improved functionality and quality of life. Decrease in complications overall from surgery, and decreased need for repeat surgery are also important from a cost to insurance companies and medical facilities.
2	Key Supporting Evidence: The UHMS assessed the body of evidence for flaps and grafts according to GRADE. Among 23 comparative clinical trials conducted on compromised flaps or skin grafts in which patients received HBOT vs standard of care published from 1999 to 2011, 15 had data regarding flap/graft

#	Rationale
	survival. In those 15 studies, the survival rate was consistently higher in the HBOT group compared to the standard of care group. (Roje, PMID: 18461678). A review article detailed 23 comparative clinical trials that were conducted in China regarding HBOT and compromised flaps or grafts (Chen LS, Zhong JL, Ma ZL. Effect of hyperbaric oxygen on survival of skin flaps in patients receiving skin grafting due to trauma. Chin J Naut Med & Hyperbar Med.2002;9(2):97-98. =No PMID available.) Taking into account the 2 main studies and the results/meta-analysis from the Chinese studies, our judged GRADE is moderate certainty with a weak recommendation for using HBOT in compromised flaps, grafts, meaning that it's use should be contextual. Meaningful Outcomes: Clinically meaningful outcomes include graft survival/take rates (both percentage of grafts that survived and mean graft survival rates). Given the serious consequences for the patient regarding flap or graft failure, which require surgical revision, all patients undergoing flaps and grafts should be considered for HBOT eligibility as part of standard of care for surgical reconstruction.

Question 2. What key clinical features or guidelines are used to identify compromised skin grafts or flaps to best select individuals for salvage treatment with systemic HBOT? Are there any unique considerations based on wound etiology, graft/flap features, or patient comorbidities?

#	Rationale
1	Clinical judgment is required to identify compromised skin grafts or flaps. Graft compromise can become apparent through skin color and texture changes, such as duskiness, epidermolysis, and flap necrosis. Flap compromise can be seen with arterial (pale color, decreased capillary refill, and cool temperature) and venous (warm temperature, purple color, and increased turgor) insufficiency. Flap/Grafts after degloving injuries, burns, crush and compartment syndrome, very large flaps and reconstruction in irradiated tissue are ideal for emergent/urgent HBOT. These are already at-risk tissue before flap/graft surgery due to the underlying pathology of hypoxia. Patients with prior radiation, diabetes, crush/compartment syndrome, and known peripheral vascular disease are all at risk for flap and graft failure. Wound factors can include areas where previous grafts or flaps have failed, if the tissue is in an irradiated area, or if there are diseases that predispose to decreased microcirculation.
2	Clinical Features/Guidelines: Hyperbaric Oxygen Therapy (HBOT) is utilized in the salvage of jeopardized skin grafts or flaps when hypoxia and/or decreased perfusion compromises the viability of the transposed tissue. Failure of the transferred tissue is evidenced by visible ischemic changes such pallor, mottling, tissue color changes or frank necrosis of the overlying skin. This can occur either in the peri-operative period, or potentially a few days later, especially if there is a confounding factor that impeded tenuous blood flow such as edema. If there is any question, hyperbaric oxygen should be started as soon as possible, and should be continued based upon clinical responsiveness. Since this is a complication of reconstructive procedures which are as unique as each patient, prospective RCTs are few and in some scenarios (e.g., hypospadias), RCTs are unethical. Thus, most studies are prospective series. Ischemia of the transferred tissue can sometimes be confirmed by diagnostic testing but testing should not be required prior to HBOT because testing may not be possible to obtain emergently and some methods can further damage tissue. Visual inspection is generally sufficient to identify patients in need of HBOT. Clinicians are expected to confirm that arterial supply to the area has been optimized insofar as feasible, that infection is being adequately controlled either locally or systemically, that devitalized tissue has been debrided when clinically appropriate, that nutritional status is optimized, and that a clean, moist wound bed has been maintained using appropriate dressings. HBOT is utilized during the acute period of flap or graft ischemia and is discontinued when the area stabilizes. Relevant clinical scenarios: Any location in the body where tissue is being moved to provide coverage and which is subsequently noted to be jeopardized is encompassed by the term "compromised flaps and grafts." The most common clinical scenarios are breast reconstruction post cancer treatment (often into irradiated fields), complex hypospadias repairs, rotational flaps to cover traumatic or surgical tissue defects, and skin grafts in burn patients.

#	Rationale
	Clinical impact: The impact of salvaging a compromised flap or graft is immeasurable to the patient who, if HBOT is effective, will: 1) be spared subsequent surgical procedures, 2) have a far more aesthetically pleasing outcome, and 3) not have to sacrifice another less ideal donor tissue when the primary tissue fails. Comorbidities: HBOT always involves a risk/benefit assessment. The few risks of HBOT have an exceedingly low incidence even when relative contraindications exist (e.g., claustrophobia, congestive heart failure, severe asthma, etc.) and these must be weighed against the morbidity and even mortality associated with flap/graft loss, the almost certain need for re-operation in the event of flap failure and the possibility that no alternative tissues can be found with which to create a flap if the initial flap fails (e.g., hypospadias).

Question 3. Please describe any contraindications for systemic HBOT in patients with compromised skin grafts or flaps.

#	Rationale
1	Absolute contraindications to HBOT in a monoplace chamber include untreated pneumothorax, severe COPD, severe CHF, anxiety, claustrophobia; However, multiplace chambers, especially those with critical care capabilities, are able to treat almost all patients except those with moderate-sized untreated pneumothorax. Relative contraindications include pregnancy, implanted devices including pacemakers, history of seizures or claustrophobia, perilymph fistulas, among others. Certain medications such as disulfiram, which blocks superoxide dismutase, which may increase the risk of oxygen toxicity. Concurrent treatment with cisplatin or other chemotherapeutics is a relative contraindication as it can impair the wound healing process.
2	There is only one contraindication to HBOT for any indication and that is untreated pneumothorax. All other contraindication are relative.

Question 4. Do patients with compromised skin grafts or flaps who are undergoing systemic HBOT benefit from adjunctive use of negative pressure wound therapy in the inpatient setting? How are patients selected for combination treatment?

#	Rationale
1	VAC therapy is useful in patients with excessive drainage and need to keep a moist wound bed. Together, these treatments have a cumulative effect on the wound healing, graft, and flap salvage. VAC treatments are generally reserved for open wounds that cannot be closed during the first operation. To our knowledge, there are few or no studies that enumerate criteria for adding negative pressure wound therapy in addition to HBOT. Typically, combination treatment is used for severely compromised wounds that also permit placement of negative pressure wound therapy. It is notably challenging to employ negative pressure wound therapy broadly in the head and neck region due to the regional anatomy.[7]
2	There are no relevant comparative studies that analyze the effect of combined therapy of HBOT and NPWT so this question cannot be answered.

Question 5. Please provide in the box below any additional comments about the clinical context or specific clinical pathways for this topic and/or any key citations (including the PMID) with evidence that demonstrates health outcomes you would like to highlight.

#	Additional Comments
1	An RCT is unlikely due to the abundance of pre-clinical and clinical data that is currently available suggesting HBOT is an important tool in salvaging flaps/grafts. The lack of an RCT should not prevent the use of HBOT since the functional and quality of life outcomes are important to maintain. Large traumatic wounds that could lead to limb amputation can also be avoided if HBOT is utilized. An ideal study would include time from surgery to hints of flap failure to HBOT. Currently, there are no large

#	Additional Comments
	retrospective or prospective studies investigating this time component. It is logical to deduce that early HBOT will lead to better outcomes, and delays in treatment will lead to failure. A controlled clinical study by Perrins looked at 48 patients undergoing graft placement with and without hyperbaric oxygen treatment. Their results demonstrated that 64% of the grafts survived in patients that underwent hyperbaric oxygen treatment versus a 17% survival rate for the control group (p=0.01).[6] Bowersox et al. looked at a series of 105 patients with ischemic skin grafts and flaps. 90% of the patients had risk factors associated with poor prognostic indicators for graft or flap survival. Their results demonstrated that 91% of the skin grafts and 89% of the threatened flaps were salvaged with hyperbaric oxygen treatment.[8] A study by Skeik et al. demonstrated that 75.7% of patients with a failed flap or skin graft showed a positive overall outcome with hyperbaric oxygen treatment.[9]
2	It is important to note that the UHMS does not include acute wounds amongst its indications for HBOT. Thus in an evidence review, it is not appropriate to consider flaps and grafts under the same overarching indication of acute surgical wounds. Additionally, it is not ethical to perform RCTs in some of the relevant clinical scenarios that are known to benefit from HBOT such as penile amputations, limb reimplantations, the reattachment of facial parts or hypospadias repairs since there are no alternative tissues to utilize if the reimplantation fails. In such cases, BCBS is compelled to use the best available evidence which may be case series. Examples of such series include: Hanna, Moneer K. "Complex and Redo Hypospadias Repairs: Management of 402 Patients." Hypospadias Surgery. Springer, Cham, 2022. 855-875; Hanna, Moneer K. "The contribution of preconditioning hyperbaric oxygen for complex re-operative surgery of bladder exstrophy and epispadias. A case study of 11patients." Journal of Pediatric Urology 17.5 (2021): 656-e1. There is sufficient evidence to support the use of HBOT flaps and grafts as a clinical category. Clinically meaningful outcomes include graft survival/take rates (both percentage of grafts that survived and mean graft survival rates). In cases such as the reattachment of the nose, the penis and the nipple (for which there are no prospective, randomized trials) the meaningful nature of graft survival should be self-evident.

Question 6. Is there any key evidence missing from the attached draft Evidence Opinion that demonstrates clinically meaningful improvement in net health outcome?

#	YES / NO	Citations of Missing Evidence
1	YES	Perrins DJ. Influence of hyperbaric oxygen on the survival of split skin grafts. Lancet. 1967;1(7495):868-871. doi:10.1016/s0140-6736(67)91428-6 PMID: 4164367 Kleban S, Baynosa RC. The effect of hyperbaric oxygen on compromised grafts and flaps. Undersea Hyperb Med. 2020;47(4):635-648. doi:10.22462/10.12.2020.13 PMID: 33227840 Bowersox JC, Strauss MB, Hart GB. Clinical experience with hyperbaric oxygen therapy in salvage of ischemic skin flaps and grafts. J Hyperbaric Med 1986;1:141–149 Skeik N, Porten BR, Isaacson E, Seong J, Klosterman DL, Garberich RF, Alexander JQ, Rizvi A, Manunga JM Jr, Cragg A, Graber J, Alden P, Sullivan T. Hyperbaric oxygen treatment outcome for different indications from a single center. Ann Vasc Surg. 2015 Feb;29(2):206-14. doi: 10.1016/j.avsg.2014.07.034. Epub 2014 Oct 13. PMID: 25308240. Bibliography: 1. Friedman HI, Fitzmaurice M, Lefaivre JF, Vecchiolla T, Clarke D. An evidence-based appraisal of the use of hyperbaric oxygen on flaps and grafts. Plast Reconstr Surg. 2006 Jun;117(7 Suppl):175S-190S; discussion 191S-192S. PMID: 16799386 2. Kleban S, Baynosa RC. The effect of hyperbaric oxygen on compromised grafts and flaps. Undersea Hyperb Med. 2020 Fourth Quarter;47(4):635-648. doi: 10.22462/10.12.2020.13. PMID: 33227840. 3. Kindwall EP, Gottlieb LJ, Larson DL. Hyperbaric oxygen therapy in plastic surgery: a review article. Plast Reconstr Surg. 1991 Nov;88(5):898-908. doi: 10.1097/00006534-199111000-00029. PMID: 1924583.

#	YES / NO	Citations of Missing Evidence
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2	YES	In 23 comparative clinical trials conducted in China regarding compromised flaps or skin grafts in which patients received HBOT or standard of care, of which 18 were comparative and 16 were controlled trials, published from 1999 to 2011, 15 had data regarding flap/graft survival. In those 15 studies, the survival rate was consistently higher in the HBOT group compared to the standard of care group. 1. Perrins DJ. PMID: 4164367 2. Roje Z. PMID: 18461678 3. Zhou PMID: 24984315 4. Huang KJ, Chen GX, Li H. Application of hyperbaric oxygenation to ultrathin pediculated skin with subdermal vascular net grafting. Modern Hospital. 2005;5(11):23-24. No PMID available. 5. Xu JJ, Guo JL, Jin XM, et al. Therapeutic efficacy of hyperbaric oxygen in full thickness skin grafts. People's Mil Surg. 2000;43(1):17-18. No PMID available. 6. Chen M, Hao Y, Zhou N, et al. Clinical observation on hyperbaric oxygen in the treatment of survival ratio of skin flaps. Chin Med Herald. 2011;8(12):28-30. No PMID available. 7. Qi Y, Lin SH, Jiang YH, et al. The effect of hyperbaric oxygen therapy in 36 cases of skin flap transplantation. J Rare & Uncom Dis. 2009;16(3): 30-33. No PMID available. 8. Cheng ZT, Hu FF, Zhang CY, et al. Effect of hyperbaric oxygen therapy on blood supply disorder after skin grafting. Chin J of Phys Med and Rehabil. 2008;30(8):560-561. 9. Jiang KP, Pan W. Therapeutic efficacy of hyperbaric oxygen after skin grating. Acta Medicinae Sinica. 2004;17(6):941-942. No PMID available. 10. Xie ZX, Li CY. Changes in arterial inflow after flap grafting under various tensions. J Clin Rehabil Tissue Eng Res. 2007;11(25):5004-5005. No PMID available.* 11. Zhang JB, Chen LZ. Application of hyperbaric oxygen for maxillofacial wound healing after skin grafting. J Modern Stomatol. 2002,16(5):390. No PMID available. 12. Liu H, Yang QJ. An analysis of the therapeutic effect of blood supply insufficiency of injured limb after dissection of the pedicles of abdominal flaps treated with hyperbaric oxygen in 30 cases. Beijing Med. 2006,28(5):284-285. No PMID available. 13. Chen LS, Zhong JL, Ma ZL. Effect of hyperbaric oxygen on survival of skin flaps in patients receiving skin grafting due to trauma. Chin J Naut Med & Hyperbar Med.2002;9(2):97-98.No PMID available.

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Documentation for Clinical Review

Please provide the following documentation:

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

Post Service (in addition to the above, please include the following):

- Treatment report(s)

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

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

Policy History

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

Effective Date	Action
12/01/2025	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status
In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).

4. Professionals, specialists, and experts.
5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.