

Hyperbaric Oxygen Pressurization (HBO)

Policy Number:

MM.02.012

Line(s) of Business:

HMO; PPO; QUEST Integration

Section:

Medicine

Place(s) of Service:

Outpatient; Inpatient

Original Effective Date:

04/15/2006

Current Effective Date:

09/01/2018

I. Description

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

For individuals with wounds, burns or infections who receive topical HBOT, the evidence includes a systematic review, case series, and a randomized controlled trial (RCT). Relevant outcomes are overall survival, 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 single small RCT (N=28) was not included in the review and the uncontrolled studies do not provide sufficient data that topical HBOT is efficacious. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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. One of the 2 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 a meaningful improvement in the net health outcome.

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

However, 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 carbon monoxide poisoning. Thus, based on clinical input and guideline support, this indication may be considered medically necessary.

For individuals who have 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 prior to tooth extraction in an irradiated jaw. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have 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 the effects of the technology on health outcomes.

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

For individuals who have acute thermal burns who receive systemic HBOT, the evidence includes a systematic review of 2 RCTs. Relevant outcomes are overall survival, symptoms, and change in disease status. Only 2 RCTs were identified and both were judged to have poor methodologic quality. Evidence from well-conducted controlled trials is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute surgical and traumatic wounds who receive systemic HBOT, the evidence includes RCTs, controlled nonrandomized studies, and systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. Four RCTs were identified. There was considerable heterogeneity across trials (eg, patient population, comparison group, treatment regimen, outcomes). This heterogeneity prevented pooling of study findings and limits the ability to draw conclusions about the impact of HBOT on health outcomes for patients with acute surgical and traumatic wounds. Additional evidence from high-quality RCTs is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have bisphosphonate-related osteonecrosis of the jaw who receive systemic HBOT, the evidence includes 1 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 the effects of the technology on health outcomes.

For individuals who have necrotizing soft tissue infections who receive systemic HBOT, the evidence includes systematic reviews and a retrospective cohort study. Relevant outcomes are overall survival, symptoms, and change in disease status. A Cochrane review did not identify any RCTs. Another systematic review identified a retrospective cohort study, which did not find better outcomes after HBOT than after standard care without HBOT in patients with necrotizing soft tissue infections. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals who have acute ischemic stroke who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. Cochrane reviewers could only pool data for 1 outcome (mortality at 3-6 months) and for that outcome there was no significant difference between active and sham HBOT treatments. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have motor dysfunction associated with stroke who receive systemic HBOT, the evidence includes 1 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 draw conclusions about the efficacy of HBOT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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 the effects of the technology on health outcomes.

For individuals who have traumatic brain injury who receive systemic HBOT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, symptoms, change in disease status, and functional outcomes. RCTs were heterogeneous in terms of intervention protocols, patient populations, and outcomes reported. Systematic reviews conducted pooled analyses only on a minority of the published RCTs and these findings were mixed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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. Only 1 small RCT has been published, and this study did not find a significant improvement in health outcomes when HBOT was added to standard medical therapy. A systematic review of RCTs and observational studies found a high rate of bias in the literature due to attrition and reporting bias. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with idiopathic sudden sensorineural hearing loss who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms, change in disease status, and functional outcomes. A Cochrane review with pooled analysis of 2 RCTs did not find a statistically significant difference in outcomes between the HBOT and the control groups in hearing for all frequencies at a level greater than 50%, but did find a statistical difference at a level greater than 25%. An RCT published after the review reported no differences in hearing between groups at 4 different frequencies. The RCTs had methodologic limitations. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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 a control condition and no difference in longer term pain or other outcomes (eg, swelling). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have autism spectrum disorder who receive systemic HBOT, the evidence includes 1 RCT and a systematic review. Relevant outcomes are symptoms and functional outcomes. A Cochrane review identified 1 RCT on HBOT for autism spectrum disorder and this trial did not find significantly better parental-assessed or clinician-assessed outcomes with HBOT than with sham. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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 HBO treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have vascular dementia who receive systemic HBOT, the evidence includes 1 RCT and a systematic review. Relevant outcomes are symptoms and functional outcomes. The Cochrane review identified only 1 RCT with methodologic limitations. Well-conducted controlled trials are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 were identified, but pooled analyses were not possible due to heterogeneity in treatment regimens and outcomes measured. One systematic review concluded that more RCTs would be needed. The 2 RCTs identified had inconsistent findings. One reported no short-term benefit with HBOT, but some benefits 12 months after radiotherapy; the other did not find a significant benefit of HBOT at 12-month follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have idiopathic femoral neck necrosis who receive systemic HBOT, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCT had a small sample and only reported short-term (ie, 6-week) outcomes. Larger well-conducted RCTs reporting longer term outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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 1 pooled analysis including 3 of the 11 trials, Meta-analysis of 3 RCTs found significantly greater relief of migraine symptoms with HBOT than a comparator intervention within 45 minutes of treatment. Longer term data are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have herpes zoster who receive systemic HBOT, the evidence includes 1 RCT. Relevant outcomes are symptoms and change in disease status. The RCT was unblinded and only reported short-term (ie, 6-week) outcomes. Additional well-conducted RCTs with longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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, both reported positive effects of HBOT on tender points and pain. However, the trials had relatively small samples and methodologic limitations (eg, 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 the effects of the technology on health outcomes.

For individuals who have 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 the effects of the technology on health outcomes.

For individuals who have cancer and are undergoing chemotherapy who receive systemic HBOT, the evidence includes 1 RCT and a systematic review. Relevant outcomes are overall survival and change in disease status. While the systematic review reported improvements in tumor control in patients with head and neck cancer who received HBOT, the adverse events accompanying the treatment

(eg, radiation tissue injury, seizures) were significant. The single RCT did not find a significant difference in survival for cancer patients who received HBOT prior to chemotherapy compared with usual care. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

Hyperbaric oxygen therapy (HBOT) is a technique for delivering higher pressures of oxygen to tissue. Two methods of administration are available. In systemic or large hyperbaric oxygen chamber, 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.

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.

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

II. Criteria/Guidelines

- A. Systemic hyperbaric oxygen pressurization is covered (subject to Limitations and Administrative Guidelines) for treatment of the following conditions:
1. Non-healing wounds of the lower extremities in patients with type 1 or type 2 diabetes and who meet all of the following criteria:
 - a. Patient has a wound classified as Wagner grade 3 or higher as defined in the table below:

Grade Number	Description
0	No open lesion
1	Superficial ulcer without penetration to deeper layers

2	Ulcer penetrates to tendon, bone, or joint
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
4	Wet or dry gangrene in the toes or forefoot
5	Gangrene involves the whole foot or such a percentage that no local procedures are possible and amputation (at least at below the knee level) is indicated

- b. Patient has no measurable signs of healing after a 30-day course of standard wound therapy which includes the following:
- i. The following standard wound treatment measures have been accomplished for all chronic ulcers and complex wounds:
 - a. Evaluation of wound with documentation of measurements (length, width and depth) at baseline and at least weekly by a licensed medical professional.
 - b. Debridement of necrotic tissue, if present
 - c. Treatment of infection, if present
 - d. Management of diabetes mellitus, if applicable
 - e. Evaluation and management of peripheral artery disease, if applicable
 - ii. The following standard wound treatment measures have been accomplished for chronic ulcers:
 - a. For stage III or IV pressure ulcer:
 1. The patient has been appropriately turned and positioned; and
 2. The patient has used a support surface for pressure ulcers on the posterior trunk or pelvis (pressure reducing mattress or pad), (a support surface is not required if the ulcer is not on the trunk or pelvis); and
 3. Moisture and incontinence have been appropriately managed.
 - b. For neuropathic ulcer
 1. Patient's diabetes is managed by a physician who is responsible for diagnosing and treating the diabetes through a comprehensive plan of care.
 2. Reduction in pressure on a foot ulcer has been accomplished with appropriate modalities.
 - c. For venous insufficiency ulcer:
 1. Compression bandages and/or garments have been consistently applied, and
 2. Leg elevation and ambulation have been encouraged.
2. Acute traumatic ischemia e.g. crush injuries, reperfusion injury, compartment syndrome
 3. Decompression sickness
 4. Gas embolism, acute
 5. Cyanide poisoning, acute

6. Acute carbon monoxide poisoning
 7. Gas gangrene (i.e., clostridial myonecrosis)
 8. Profound anemia with exceptional blood loss: only when blood transfusion is impossible or must be delayed
 9. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) or osteoradionecrosis
 10. Pre- and post-treatment for patients undergoing non-implant related dental surgery (including tooth extraction) of an irradiated jaw
 - a. The patient has had prior radiation to the head or neck and has received greater than or equal to a cumulative dose of 60 gray of radiation.
 11. Chronic osteomyelitis refractory to conventional medical and surgical management
- B. A treatment plan must be submitted for wounds, osteoradionecrosis, soft tissue radiation necrosis and chronic refractory osteomyelitis.
- C. Wounds, osteoradionecrosis, and soft tissue radiation necrosis must be evaluated and documented by the treating physician for signs of healing after every 15 treatments or every 14 days of treatment (whichever comes first).
- D. Continued treatment with HBO therapy is covered if signs of healing have been demonstrated and documented in the medical record.

III. Limitations

- A. The use of HBO is not covered for other indications because it is not known to be effective in improving health outcomes. This includes, but is not limited to:
1. Acute arterial peripheral insufficiency
 2. Acute coronary syndromes and as an adjunct to coronary interventions, including but not limited to percutaneous coronary interventions and cardiopulmonary bypass
 3. Acute ischemic stroke
 4. Acute osteomyelitis, refractory to standard medical management
 5. Acute surgical and traumatic wounds
 6. Acute thermal burns
 7. Autism spectrum disorders
 8. Bell's palsy
 9. Bisphosphonate-related osteonecrosis of the jaw
 10. Bone grafts
 11. Brown recluse spider bites
 12. Carbon tetrachloride poisoning, acute
 13. Cerebral edema, acute
 14. Cerebral palsy
 15. Cerebrovascular disease, acute (thrombotic or embolic) or chronic
 16. Chronic arm lymphedema following radiotherapy for cancer
 17. Chronic wounds, other than those in patients with diabetes who meet the criteria specified above in II.A.1
 18. Compromised skin grafts or flaps
 19. Delayed onset muscle soreness

20. Demyelinating diseases, (e.g., multiple sclerosis, amyotrophic lateral sclerosis)
21. Early treatment (beginning at completion of radiation therapy) to reduce adverse effects of radiation therapy; and
22. Fibromyalgia
23. Fracture healing
24. Herpes zoster;
25. Hydrogen sulfide poisoning
26. Idiopathic femoral neck necrosis
27. In vitro fertilization
28. Inflammatory bowel disease (Crohn disease or ulcerative colitis)
29. Intra-abdominal and intracranial abscesses
30. Lepromatous leprosy
31. Meningitis
32. Mental illness (i.e., post-traumatic stress disorder, generalized anxiety disorder, depression)
33. Migraine
34. Motor dysfunction associated with stroke;
35. Necrotizing soft-tissue infections
36. Pseudomembranous colitis (antimicrobial agent-induced colitis)
37. Pyoderma gangrenosum
38. Radiation myelitis,
39. Radiation-induced injury in the head and neck excluding radiation-induced soft tissue necrosis or osteoradionecrosis
40. Refractory mycoses: mucormycosis, actinomycosis, canidiobolus coronato
41. Retinal artery insufficiency, acute
42. Retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment
43. Sickle cell crisis and/or hematuria
44. Spinal cord injury
45. Traumatic brain injury
46. Tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy
47. Vascular dementia

B. Topical hyperbaric oxygen therapy is not a covered benefit.

IV. Administrative Guidelines

- A. Precertification is required for wounds, osteoradionecrosis, soft tissue radiation necrosis and chronic refractory osteomyelitis. To precertify, please complete [HMSA's Precertification Request](#) and mail or fax the form, or use iExchange as indicated.
- B. A treatment plan must be submitted for wounds, osteoradionecrosis, soft tissue radiation necrosis and chronic refractory osteomyelitis.
- C. Documentation of previous medical and surgical interventions including outcomes must be submitted.

- D. For continuation of therapy, documentation from the medical record showing objective signs of wound healing from wounds, osteoradionecrosis, soft tissue radiation necrosis and chronic refractory osteomyelitis must be submitted.

CPT code	Description
99183	Physician attendance and supervision of hyperbaric oxygen therapy, per session
Facility code	Description
413	Respiratory services – hyperbaric oxygen therapy
270	Med/Surg supplies and devices – general classification (for oxygen)
G0277	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval

Click on link below for ICD-10 codes: [See attached code list](#)

V. Scientific Background

This policy has been updated regularly with a search of the MEDLINE database. The most recent literature search was conducted through November 6, 2017.

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

TOPICAL HYPERBARIC OXYGEN FOR WOUNDS, BURNS, OR INFECTIONS

In 2017, de Smet et al conducted a systematic review of various oxygen therapies (oxygen dressing therapy, topical oxygen therapy, hyperbaric oxygen therapy [HBOT], inspired oxygen therapy).³ Three RCTs evaluating topical oxygen therapy for chronic wound healing were identified (see Table 1). One RCT (N=100) administered treatment for 20 minutes 3 times per day for 12 days to the treatment group and standard care to the control group. The number of patients experiencing complete wound healing, defined as complete epithelialization of the wound without drainage, was 16 in the experimental group and 1 in the control group ($p<0.001$). Two of the RCTs, which had overlapping populations with refractory venous ulcers ($n=83$ in one and $n=132$ in the other) administered treatment for 180 minutes 2 times per day for 12 weeks to the treatment group and conventional compression dressing to the control group. In all trials, patients in the treatment group experienced significantly higher proportions of healed ulcers and significantly faster healing times.

A small RCT (1988) not included in the systematic review that included 28 patients with diabetic foot ulcers who were assigned to topical hyperbaric oxygen therapy (HBOT) plus standard wound care or to standard wound care alone. Changes in ulcer size and depth did not differ between the 2 groups following 2 weeks of treatment.

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) ³	Feb 2016	3	<ul style="list-style-type: none"> • Stage II-IV sacral or ischial pressure ulcers (1 RCT) • Refractory venous ulcers (2 RCTs) 	315 ³ (83-132)	RCT	<ul style="list-style-type: none"> • 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 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

The original evidence review on systemic HBOT was based entirely on the 1996 guidelines published by the Undersea and Hyperbaric Medical Society (UHMS); it was subsequently revised in 1999 based on 3 TEC Assessments. The TEC Assessments had conclusions similar to UHMS, except, in contrast to the UHMS guidelines, TEC stated that there was insufficient evidence to conclude that HBOT improved the net health outcome for compromised skin grafts, acute thermal burns, chronic refractory osteomyelitis, necrotizing soft tissue infections, and brown recluse spider bites.

Literature updates have focused on identifying RCTs and meta-analyses of RCTs.

Chronic Diabetic Ulcers

An updated Cochrane review of RCTs on HBO treatment for chronic wounds was published by Kranke and colleagues in 2015 (see Table 2). Reviewers identified 12 RCTs (total N=577 participants) that compared the effect of HBOT on chronic wound healing with an alternative treatment approach that did not use HBOT. Ten of the 12 trials evaluated HBOT in patients with diabetes (N=531). The trials were assessed as moderate quality using the GRADE system. HBOT regimens varied across studies, ranging from 3.0 atmospheres absolute (ATA) for 45 minutes to 2.2 ATA for 120 minutes. In a pooled analysis of data from 5 trials, a significantly higher proportion of ulcers had healed at the end of treatment (ie, 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 2016 systematic review by Elraiyah et al evaluated adjunctive therapies (HBOT, arterial pumps, and pharmacologic agents) used to treat diabetic foot ulcers (see Table 2). 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	5 7 7	RCTs	<ul style="list-style-type: none"> • 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	1 5 2 6	RCTs, cohort	<ul style="list-style-type: none"> • 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)

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

Section Summary: Chronic Diabetic Ulcers

Multiple RCTs and systematic reviews have been published. Seven RCTs were common in the 2 systematic reviews. 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.

Carbon Monoxide Poisoning

A 2011 Cochrane review by Buckley et al included 6 RCTs evaluating HBOT for carbon monoxide poisoning (see Table 3). 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
Buckleylet al (2011) ¹⁰	Jun 2010	6	Nonpregnant adults with acute carbon monoxide poisoning	1361	RCTs	<ul style="list-style-type: none"> • 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.

Section Summary: Carbon Monoxide Poisoning

A Cochrane review identified 6 RCTs, the majority of which did not find a significant effect of HBOT on health outcomes. In addition, a pooled analysis of RCT data did not find a significant effect of HBOT on neurologic injuries and the quality of the evidence was considered very low.

Radionecrosis, Osteoradionecrosis, and Treatment of Irradiated Jaw

In 2016, Bennett et al published a Cochrane review on HBOT for late radiation tissue injury. 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 than with control treatments, and in a pooled analysis of 2 trials a significantly lower risk of wound dehiscence after surgery to repair mandibular osteoradionecrosis with HBOT than with control treatments was reported. A single trial found a significantly higher likelihood of successful healing with HBOT than with antibiotics for tooth extraction in irradiated jaws (absolute risk reduction, 25%; $p=0.02$). There were insufficient data to conduct meta-analyses on other outcomes.

In 2017, Borab et al published a systematic review focusing on the use of HBOT to treat the subgroup of patients with late radiation tissue injury had skin necrosis (see Table 4). 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.

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

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2016) ¹¹	Dec 2015	14	Patients with late radiation tissue injury (including necrosis) and patients treated with large-dose radiotherapy likely to induce early necrosis	753	RCTs	<ul style="list-style-type: none"> • Pooled analyses of 3 trials of patients with osteoradionecrosis (n=246) found a higher rate of complete mucosal cover after HBOT vs control (RR=1.3; 95% CI, 1.1 to 1.5) • 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) ¹²	May 2016	8	Patients with radiation-induced skin necrosis	720	Observational cohort and case series	<ul style="list-style-type: none"> • Adding across the studies, 80% reported complete healing and 86% reported symptom improvement • Studies had no comparators
Ravi et al (2017) ¹³	Dec 2016	10	Patients who received radiotherapy for head and neck cancer	375	Prospective case series and prospective comparative studies	<ul style="list-style-type: none"> • 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: 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.

Chronic Refractory Osteomyelitis

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

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

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

Section Summary: Chronic Refractory Osteomyelitis

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

Acute Thermal Burns

In 2004, a Cochrane review assessed HBOT for thermal burns (see Table 5). Two RCTs were identified, published in 1974 and 1997. Sample sizes were 16 and 125. Both of these were judged by reviewers to have poor methodologic quality. Reviewers concluded that the evidence was insufficient to permit conclusions on whether HBOT improves health outcomes in patients with acute thermal burns. No additional trials were identified when the Cochrane reviewers conducted an updated literature search in 2009 (the 2004 publication date continues to be used).

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Villanueva et al (2009) ¹⁹	Jun 2009	5	Patients with thermal injuries to the epidermis, subcutaneous tissues, vessels, nerve, tendons, or bone	141	RCTs	<ul style="list-style-type: none"> • 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; $p < 0.001$) 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: 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.

Acute surgical and traumatic wounds

In 2013 an updated Cochrane review of RCTs on HBO therapy for acute wounds (e.g., surgical wounds, lacerations, traumatic wounds, and animal bites) was published by Eskes and colleagues (see Table 6). HBOT was administered at pressures above 1 atmosphere (atm). To be included, studies needed to compare HBO with a different intervention or compare 2 HBO regimens; in addition, studies needed to objectively measure wound healing. A total of 7 potentially relevant studies were identified; 3 of these met the review's inclusion criteria. The 3 studies ranged in size from 36 to 135 participants. Due to differences among studies in terms of patient population, comparison intervention, outcome measurement, etc., study results could not be pooled. The primary outcome examined by Cochrane reviewers, wound healing, was not reported in either of the 2 trials comparing HBO to usual care and was not reported in the 1 trial comparing HBO to dexamethasone or heparin. Complete wound healing was reported in the 1 RCT comparing active HBO to sham HBO. In this small study (n=36), there was a statistically higher rate of wound healing in the HBO group; the time point for outcome measurement in this study was unclear. In the sham-controlled study there was not a statistically significant difference between groups in the mean time to wound healing.

Another 2014 systematic review of studies on HBO for acute wounds, published by Dauwe and colleagues included randomized and non-randomized controlled studies (see Table 6). The review included 8 studies, with sample sizes ranging from 5 to 125 patients. Four studies were randomized, 3 were prospective non-randomized controlled studies and 1 was a retrospective non-randomized controlled study. As in the Eskes systematic review, data were not pooled. The authors noted that 7 of the 8 studies reported achieving statistical significance in their primary endpoints, but the endpoints differed among studies e.g. graft survival, length of hospital stay, wound size. Moreover, the studies were heterogeneous in terms of treatment regimens, patient indications (e.g., burns, face lifts), and study designs, making it difficult to draw conclusions about the effect of HBO on acute wound treatment.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Eskes et al (2013) ²⁰	Aug 2013	4	Patients with acute wounds (skin injuries occurring due to surgery or trauma)	229	RCTs	<ul style="list-style-type: none"> • 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 wound healing rate vs sham; however, no difference in time to healing
Dauwe et al (2014) ²¹	Oct 2012	8	Patients with acute wounds, grafts, and flaps	256	RCTs and nonrandomized studies	<ul style="list-style-type: none"> • HBOT may augment healing of acute wounds • Not indicated for routine wound management

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

Section Summary: Acute Surgical and Traumatic Wounds

Two systematic reviews identified 4 RCTs; one of the reviews also included nonrandomized studies. Heterogeneity among studies (eg, in patient population, treatment regimen, comparison group, outcomes) prevented pooling of study findings and limits the ability to draw conclusions

about the impact of HBOT on health outcomes in patients with acute and traumatic wounds. Additional evidence from high-quality RCTs is needed.

Bisphosphonate-Related Osteonecrosis of the Jaw

An unblinded RCT by Freiburger et al (2012) evaluated use of HBOT as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw (see Tables 7 and 8). The investigators did a per-protocol analysis (actual treatment received) because of the relatively large degree of crossover. Participants were evaluated at 3, 6, 12, and 18 months. 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 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 (eg, 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) ²²	United States	NR ^a	2006-2010	Patients with bisphosphonate-related osteonecrosis of the jaw	<ul style="list-style-type: none"> 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; RCT: randomized controlled trial.

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

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

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

HBOT: hyperbaric oxygen.

Section Summary: Bisphosphonate-Related Osteonecrosis of the Jaw

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

Necrotizing Soft Tissue Infections

A 2015 Cochrane review by Levett et al evaluated the literature on HBOT as adjunctive therapy for necrotizing fasciitis. No RCTs were identified. Previously, in 2005, a systematic review by Jallali et

al identified only a few retrospective studies with small sample sizes. Findings from these studies were inconsistent. A 2009 retrospective cohort study compared outcomes in 48 patients at 1 center who received adjunctive HBOT for necrotizing soft tissue infections to those in 30 patients at a different center who did not receive HBOT. There was no significant difference in the mortality rate between the 2 groups (8% [4/48] in the HBOT group vs 13% [4/30] in the non-HBOT group; $p=0.48$). The median number of days in the intensive care unit and the median number of days in the hospital also did not differ significantly between groups. There was a higher median number of débridement procedures per person in the HBOT group (3.0) than in the non-HBOT group (2.0; $p=0.03$).

Section Summary: Necrotizing Soft Tissue Infections

No RCTs have evaluated HBOT for necrotizing soft tissue infection. A retrospective cohort study did not find a difference in outcomes after HBOT or standard care.

Acute Coronary Syndrome

A 2015 Cochrane review by Bennett et al identified 6 trials (total N=665 patients) evaluating HBOT for acute coronary syndrome (see Table 9). 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 rate of death in patients who received HBOT compared with a control intervention. Due to the variability of outcome reporting across studies, few other pooled analyses could be conducted. Three trials reported outcomes related to left ventricular function. One did not find a statistically significant improvement in contraction with HBOT, while 2 trials showed left ventricular ejection fraction improved significantly with HBOT. Reviewers noted that, although some evidence from small trials correlated HBOT with a lower risk of death, larger trials with high-quality methods were needed to determine which patients, if any, could be expected to derive benefit from HBOT.

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

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2015) ²⁶	Jun 2010	6	Adults with acute coronary syndrome, with or without S-T segment elevation	665	RCTs	<ul style="list-style-type: none"> • 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 fraction; MD: mean difference; RCT: randomized controlled trial; RR: relative risk.

Section Summary: 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.

Acute Ischemic Stroke

In a 2014 Cochrane systematic review of RCTs, Bennett et al evaluated HBOT for acute ischemic stroke (see Table 10). Reviewers identified 11 RCTs (total N=705 participants) that compared HBOT with sham HBOT or no treatment. Reviewers could only pool study findings for 1 outcome (mortality at 3-6 months) and no difference was detected between the treatment groups for that outcome.

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) ²⁷	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: Acute Ischemic Stroke

A Cochrane review of RCTs conducted 1 pooled analysis (4 RCTs), which found no significant difference in mortality at 3 to 6 months when patients with acute ischemic stroke were treated with HBOT or a sham intervention. Additional RCT data is needed to permit conclusions on the impact of HBOT on the health outcome in patients with acute ischemic stroke.

Motor Dysfunction Associated With Stroke

In 2013, Efrati et al published an RCT evaluating HBOT for treatment of neurologic deficiencies associated with a history of stroke (see Tables 11 and 12). Patients in the treatment group were evaluated at baseline and 2 months. For patients in the delayed treatment control group, outcomes were evaluated at 4 months after crossing over and receiving HBOT. Outcome measures included the National Institutes of Health Stroke Scale (NIHSS), which was measured by physicians blinded to treatment group, and several patient-reported (QOL) and functional status measures.

At the 2-month follow-up, there was statistically significant improvement in function in the HBOT group than in the control group, as measured by the NIHSS, QOL scales, and the ability to perform activities of daily living (ADLs). These differences in outcome measures were accompanied by improvements in single-photon emission computed tomography imaging in the regions affected by stroke. For the delayed treatment control group, there was a statistically significant improvement in function after HBOT compared with before HBOT. This RCT raises the possibility that HBOT may induce improvements in function and QOL for poststroke patients with motor

deficits. However, the results are not definitive, as the RCT was small and enrolled a heterogeneous group of poststroke patients. It was not double-blind and most outcome measures, except for NIHSS, were patient-reported and thus prone to the placebo effect. Also, there was a high total dropout rate (20%) at the 2-month follow-up. Therefore, larger, double-blind studies with longer follow-up are needed to corroborate these results.

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

Study (Year)	Countries	Sites	Dates	Participants	Treatment	
					Active (n=30)	Comparator (n=29)
Efrati et al (2013) ²⁸	Israel	1	2008-2010	Patients ≥18 y with ischemic or hemorrhagic stroke 6 to 36 mo prior to inclusion with ≥1 motor dysfunction	<ul style="list-style-type: none"> 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) ²⁸	50	50		50	50	
Mean HBOT (SD)	8.5 (3.6)	5.5 (3.6)	0.004	16.1 (6.5)	12.8 (7.3)	0.02
Mean control (SD)	8.7 (4.1)	8.3 (4.3)		17.4 (9.5)	17.5 (9.5)	

HBOT: hyperbaric oxygen; SD: standard deviation.

^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: Motor Dysfunction Associated With Stroke

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

Bell Palsy

In 2012, Holland et al published a Cochrane review evaluating HBOT in adults moderate-to-severe with Bell palsy. 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: Bell Palsy

There is a lack of evidence on 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.

Traumatic Brain Injury

A 2016 meta-analysis by Wang et al addressed HBOT for treatment of traumatic brain injury (TBI see Table 14). Eight studies (total N=519 participants) met the eligibility criteria. HBOT protocols varied across studies in the levels of oxygen and the length and frequency of treatments. The primary outcome was change in the Glasgow Coma Scale (GCS) score. A pooled analysis of 2 studies found a significantly greater improvement in the mean GCS score in the HBOT than 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 2016 systematic review, by Crawford et al, did not conduct pooled analyses (see Table 13). Reviewers identified 12 RCTs evaluating HBOT for patients with TBI. Using 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 (ie, postconcussive symptom severity, psychological outcomes). Seven trials evaluated HBOT for acute treatment of patients with moderate-to-severe TBI. Four were rated as acceptable quality and 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 (GOS) score and mortality rate. In 2 of these, outcomes were better with HBOT than standard care; in the third study, outcomes did not differ significantly.

Previously, in 2012, a Cochrane review by Bennett et al evaluated HBOT as adjunctive therapy for acute TBI (see Table 13). Reviewers identified 7 RCTs (total N=571 participants) 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; eg, 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 GOS score of 1, 2, or 3, which are described as “dead,” “vegetative state,” or “severely disabled,” respectively. Studies were generally small and judged to have substantial risk of bias.

In addition, several trials on mild TBI in military populations have been published; they did not find significant benefits of HBOT compared with sham treatment.³¹⁻³³ For example, in 2015, Miller et al evaluated HBOT in 72 military service members with continuing symptoms at least 4 months after mild TBI. Patients were randomized to 40 daily HBOT sessions at 1.5 atm, 40 sham sessions consisting of room air at 1.2 atm, or standard care with no hyperbaric chamber sessions. The primary outcome was change in Rivermead Post-Concussion Symptoms Questionnaire (RPQ) score. A cutoff of 15% improvement was deemed clinically important, which translates to a change score of at least 2 points on the RPQ-3 subscale. The proportion of patients who met this prespecified change on the RPQ-3 was 52% in the HBOT group, 33% in the sham group, and 25% in the standard care-only group. The difference between rates in the HBOT and sham groups was not statistically significant ($p=0.24$). None of the secondary outcomes significantly favored the HBOT group. A criticism of this study, as well as the other military population studies, was that

patient response in the sham group was not due to a placebo effect but to an intervention effect of slightly increased atmospheric pressure (1.2 atm). Other researchers have noted that room air delivered at 1.2 atm would not be considered an acceptable therapeutic dose for any indication, and especially for a condition with persistent symptoms like postconcussive syndrome.

Table 13. Systematic Reviews of Trials Assessing HBOT for Traumatic Brain Injury

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Wang et al (2016) ³⁰	Dec 2014	8	Patients with mild or severe traumatic brain injury	519	RCTs and 2-arm prospective studies	<ul style="list-style-type: none"> • Pooled analyses of 2 trials (n=120) found significant improvements in GCS score change (3.1; 95% CI, 2.3 to 3.9) in HBOT vs control • 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 (2016) ³¹	Aug 2014	12	Military and civilian patients with traumatic brain injury		RCTs	<ul style="list-style-type: none"> • 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) ³²	Mar 2012	7	Patients with acute traumatic brain injury following blunt trauma	571	RCTs	<ul style="list-style-type: none"> • 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; GCS: Glasgow Coma Scale; HBOT: hyperbaric oxygen therapy; OR: odds ratio; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; RR: relative risk.

Section Summary: Traumatic Brain Injury

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

Inflammatory Bowel Disease

A 2014 systematic review by Dulai et al examined the evidence on HBOT for inflammatory bowel disease (Crohn disease, ulcerative colitis; see Table 14). One RCT identified was published in 2013;

it was open-label and included 18 patients with ulcerative colitis. Patients were randomized to standard medical therapy only (n=8) or medical therapy plus HBOT (n=10). The hyperbaric oxygen intervention consisted of 90 minutes of treatment at 2.4 atm, 5 days a week for 6 weeks (total of 30 sessions). The primary outcome was the Mayo score, which has a potential range of 0 to 12, consisting of 4 components (bleeding, stool frequency, physician assessment, and endoscopic appearance) rated from 0 to 3, and added to the final score. Patients with a score of 6 or more are considered to have moderate-to-severe active disease. At follow-up, there was no significant difference between groups in the Mayo score; the median score at 6 months was 0.5 in the HBOT group and 3 in the control group (p value not reported). In addition, there were no significant differences in any secondary outcomes, including laboratory tests and fecal weight. This small study may have been underpowered. Overall, reviewers found that the selected studies had a high risk of bias, particularly in the areas of attrition and reporting bias.

Table 14. Systematic Reviews of Studies Assessing HBOT for Inflammatory Bowel Disease

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Dulai et al (2014) ³⁷	Dec 2013	17	Patients with ulcerative colitis or Crohn disease	<ul style="list-style-type: none"> • Ulcerative colitis (n=327); • Crohn disease (n=286) 	<ul style="list-style-type: none"> • 11 case reports • 3 case series • 2 case-control • 1 RCT 	<ul style="list-style-type: none"> • Overall HBOT response rate across studies: 86% • 1 RCT (N=18) reported no difference in outcomes among patients with ulcerative colitis treated with HBOT vs HBOT plus medical therapy

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

Section Summary: Inflammatory Bowel Disease

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

Idiopathic Sudden Sensorineural Hearing Loss

A 2012 Cochrane review by Bennett et al on HBOT for idiopathic sudden sensorineural hearing loss (ISSNHL) and tinnitus identified 7 RCTs (total N=392; see Table 15). Studies were small and generally of poor quality. All trials included patients with ISSNHL with and/or without tinnitus; 2 trials also included patients with tinnitus in the absence of ISSNHL. Randomization procedures were only described in 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 10-25).

All trials reported on change in hearing following treatment; but specific outcomes varied. Two trials reported the proportion of participants with greater than 50% 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 15). A pooled analysis of 4 trials found a significantly greater mean improvement in hearing over all frequencies with HBOT compared with control. Reviewers stated that, due to methodologic shortcomings of the trials and the modest number of patients, results of the meta-analysis should be interpreted cautiously; they did not recommend use of HBOT for treating ISSNHL.

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

Table 15. Systematic Reviews of Trials Assessing HBOT for Idiopathic Sudden Sensorineural Hearing Loss

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2012) ⁴⁰	May 2012	7	Patients with idiopathic sudden sensorineural hearing loss and/or tinnitus	392	RCTs	<ul style="list-style-type: none"> • Pooled analyses of 2 studies (n=114) showed HBOT did not result in >50% improvement in pure tone average threshold (RR=1.5; 95% CI, 0.9 to 2.8), but was able to achieve >25% improvement (RR=1.4; 95% CI, 1.1 to 1.8) • 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)

CI: confidence interval; HBOT: hyperbaric oxygen therapy; RR: relative risk.

Section Summary: Idiopathic Sudden Sensorineural Hearing Loss

A Cochrane review of RCTs had mixed findings. Some outcomes (ie, 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. The Cochrane reviewers noted methodologic imitations and variability across published studies. An RCT published after the review including patients with ISSNHL found no differences in HBOT treatment compared with steroid injections in mean hearing thresholds at 0.25, 0.5, 1, and 4 kHz; however, a significant difference was detected at the 2-kHz level.

Delayed-Onset Muscle Soreness

In a 2005 Cochrane review, Bennett et al identified 7 small RCTs on HBOT for delayed-onset muscle soreness. Pooled analysis showed significantly higher pain at 48 and 72 hours in the group

receiving HBOT compared with a control condition. There were no between-group differences in long-term pain outcomes or other measures (eg, swelling, muscle strength).

Table 16. Systematic Reviews of Trials Assessing HBOT for DOMS

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2010) ⁴²	Feb 2010	9	Patients with acute closed soft tissue injuries or DOMS	219	RCTs	<ul style="list-style-type: none"> • 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.

Section Summary: 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).

Autism Spectrum Disorder

A 2016 Cochrane review by Xiong et al identified 1 RCT evaluating systemic HBOT for people with autism spectrum disorder who met reviewers' eligibility criteria (see Table 17). Criteria included a hyperbaric oxygen intervention using 100% oxygen at more than 1 atm. The trial, published by Sampanthaviat (2012), was considered low-quality evidence as assessed by the GRADE approach. The trial randomized 60 children with autism to receive 20 one-hour sessions with HBOT or sham air (n=30 per group). The primary outcome measures were change in Autism Treatment Evaluation Checklist (ATEC) and Clinical Global Impression scores, evaluated separately by clinicians and parents. There were no statistically significant differences between groups for any primary outcomes. For example, posttreatment clinician-assessed mean scores on ATEC were 52.4 in the HBOT group and 52.9 in the sham air group.

Table 17. 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) ⁴³	Dec 2015	1	Children aged 3-9 y with autism spectrum disorder	60	RCT	<ul style="list-style-type: none"> • 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.

Section Summary: 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.

Cerebral Palsy

Two published RCTs were identified on HBOT for cerebral palsy (see Tables 18 and 19). In 2012, Lacey et al published a double-blind RCT that included 49 children ages 3 to 8 years with spastic cerebral palsy. Participants were randomized to 40 treatments with HBOT (n=25) or hyperbaric air to simulate 21% oxygen at room air (n=24). The primary efficacy outcome was change in the Gross Motor Function Measure (GMFM-88) global score after the 8-week treatment period. The 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. Previously, Collet et al (2001) randomized 111 children with cerebral palsy to 40 treatments over a 2-month period of HBOT (n=57) or slightly pressurized room air (n=54). Reviewers found HBOT produced similar improvements in outcomes such as gross motor function and ADLs in both groups as slightly pressurized air.

In 2017, an observational study by Long et al evaluated the effects of HBOT as a treatment for sleep disorders in children with cerebral palsy (N=71). Children, aged 2 to 6 years, underwent 60-minute sessions of 100% oxygen, at 1.6 ATA, for 15 to 20 sessions total. Results showed improvements in average time to fall asleep, average hours of sleep duration, and an average number of night awakenings after 10 HBOT sessions compared with pretreatment.

Table 18. Characteristics of Trials Assessing HBOT for Cerebral Palsy

Study (Year)	Countries	Sites	Dates	Participants	Treatment	
					Active	Comparator
Lacey et al (2012) ⁴⁵	United States	2	2005-2009	Children aged 3-8 y with spastic CP	<ul style="list-style-type: none"> • n=25 • Hyperbaric oxygen • 100% oxygen at 1.5 ATA • 40 times over 2 mo 	<ul style="list-style-type: none"> • n=24 • Hyperbaric air • 14% oxygen at 1.5 ATA • 40 times over 2 mo
Collet et al (2001) ⁴⁶	Canada	17	NR	Children aged 3-2 y with CP	<ul style="list-style-type: none"> • n=57 • Hyperbaric oxygen • 100% oxygen at 1.75 ATA • 40 times over 2 mo 	<ul style="list-style-type: none"> • 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 19. 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) ⁴⁵	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) ⁴⁶			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; HBOT: hyperbaric oxygen; PEDI: Pediatric Evaluation of Disability Inventory.

^a Positive score represents improvement in function from baseline.

Section Summary: Cerebral Palsy

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

Vascular Dementia

A 2012 Cochrane review identified 1 small RCT evaluating HBOT for vascular dementia (see Table 20). This 2009 RCT study, 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 as assessed by the Mini-Mental State Examination. 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 20. Systematic Reviews of Trials Assessing HBOT for Vascular Dementia

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Xiao et al (2012) ⁴⁸	Dec 2011	1	Patients with vascular dementia, according to DSM- IV criteria	64	RCT	<ul style="list-style-type: none"> • 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; WMD: weighted mean difference.

Section Summary: Vascular Dementia

A Cochrane review identified 1 RCT judged to be of poor quality. This trial provides insufficient evidence to permit conclusions on the impact of HBOT on health outcomes in patients with vascular dementia.

Radiotherapy Adverse Effects

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

In 2010, Spiegelberg et al conducted a systematic review of studies on HBOT to prevent or treat radiotherapy-induced head and neck injuries associated with treatment of malignant tumors (see Table 21). Reviewers identified 20 studies. Protocols and conclusions varied across the studies. Eight studies included control groups; their sample sizes ranged from 19 to 78 subjects. Four studies with a control group concluded that HBOT was effective; the other 4 did not. Reviewers noted a paucity of RCTs; they did not state how many RCTs, because studies were only identified only as prospective or retrospective. In 2017, Ravi et al conducted a systematic review assessing the effect of HBOT on patients with head and neck cancer who had received radiotherapy (see Table 21).¹³ Pooled analyses were not performed; however, summary results were discussed for the following outcomes: salivary gland function, osteonecrosis prevention, dental implant survival, and

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

Table 21. Systematic Reviews of Studies Assessing HBOT for Radiotherapy Adverse Events

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Spiegelberg et al (2010) ⁴⁹	Jun 2009	20	Patients who have received RT for malignant tumors in the head and neck	695	Prospective and retrospective studies	<ul style="list-style-type: none"> • Due to the heterogeneity among studies, pooled analysis was not possible • 8 studies had control groups and 4 concluded that HBOT was effective and 4 concluded that HBOT was not
Ravi et al (2017) ¹³	Dec 2016	10	Patients who have received RT for head and neck cancer	375	Prospective case series and prospective comparative studies	<ul style="list-style-type: none"> • Salivary gland function: 2 case series (n=96) reported that patients receiving HBOT experienced improvements in salivary flow rates • Quality of life: 3 case series (n=106) administered various QOL instruments (eg, SF-36, EORTC, HADS), reporting that many subsets of the questionnaires (eg, swallowing, pain, salivary quantity) showed significant improvements with HBOT

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

Several RCTs were identified in literature searches. A 2009 trial by Teguh et al, included in the reviews, evaluated 17 patients with oropharyngeal or nasopharyngeal cancer who were treated with radiotherapy; the trial was conducted in The Netherlands. HBOT was used to prevent adverse events following radiotherapy. Eight patients were randomized to 30 sessions of HBOT, beginning within 2 days of completing radiotherapy, and 9 patients to no additional treatment. QOL outcomes were assessed, and the primary outcome was xerostomia at 1 year. QOL measures did not differ significantly between groups in the acute phase (first 3 months). For example, 1 month after treatment, the mean visual analog scale (VAS) score for xerostomia (0-to-10 scale) was 5 in the HBOT group and 6 in the control group. However, at 1 year, there was a statistically significant difference between groups in several outcomes. For example, the mean QOL score for swallowing (0-to-100 scale) was 7 in the HBOT group and 40 in the control group ($p < 0.001$). The trial is limited by its small sample size and wide fluctuations over the follow-up period in QOL ratings.

In a trial not included in the reviews, Gothard et al (2010) in the U.K. published findings of an RCT using HBOT for arm lymphedema occurring after radiotherapy for cancer. Fifty-eight patients with arm lymphedema (at least 15% increase in arm volume) following cancer treatment were randomized in a 2:1 ratio to HBOT (n=38) or to usual care without HBOT (n=20). Fifty-three

patients had baseline assessments and 46 (79%) of 58 had 12-month assessments. At the 12-month follow-up, there was no statistically significant difference in the change from baseline in arm volume. Median change from baseline was -2.9% in the treatment group and -0.3% in the control group. The study protocol defined response as at least an 8% reduction in arm volume relative to the contralateral arm. By this definition, 9 (30%) of 30 of patients in the HBOT group were considered responders compared with 3 (19%) of 16 in the control group ($p=NS$). Other outcomes (eg, QOL scores on the 36-Item Short-Form Health Survey [SF-36]) also did not differ significantly between groups.

Section Summary: Radiotherapy Adverse Effects

A systematic review noted a lack of RCTs evaluating HBOT for radiotherapy adverse effects. One review focused on salivary gland function, osteonecrosis prevention, dental implant survival, and QOL. The available RCTs had mixed findings. One found no short-term benefit and some benefits of HBOT 12 months after radiotherapy, while the other did not find a significant benefit of HBOT 12 months after radiotherapy. An RCT not included in the reviews focused on arm lymphedema; it found no significant differences between study groups.

Idiopathic Femoral Neck Necrosis

A double-blind RCT evaluating HBOT for treatment of femoral head necrosis was published in 2010 by Camporesi et al (see Tables 22 and 23). The trial included 20 adults with idiopathic unilateral femoral head necrosis. Patients received HBOT or a sham treatment of hyperbaric air ($n=10$). Mean severity of pain on a 0-to-10 scale was significantly lower in the HBOT group than in the control group after 30 sessions ($p<0.001$) but not after 10 or 20 sessions. (The article 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, were 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 22. 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) ⁵²	United States	1	NR	Patients with unilateral femoral neck necrosis	<ul style="list-style-type: none"> Hyperbaric oxygen 100% oxygen at 2.5 ATA 30 sessions over 6 wk 	<ul style="list-style-type: none"> Hyperbaric air 30 sessions over 6 wk

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

Table 23. 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) ⁵²				
HBOT	7.5 (4.0-20.0)	NS	20.0 (15.0-20.0)	<0.001
HBAT	4.0 (3.0-6.0)		3.0 (0.0-5.0)	

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

Section Summary: 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.

Migraine

A 2015 Cochrane review by Bennett et al identified 11 RCTs (total N=209 patients) comparing the effectiveness of systemic HBOT for preventing or treating migraine headache or cluster headaches with another treatment or a sham control (see Table 24). A pooled analysis of 3 trials (n=58 patients) 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 posttreatment period, and the methodologic quality of selected trials was moderate to low (eg, randomization was not well-described in any trial).

Table 24. Systematic Reviews of Trials Assessing HBOT for Migraine or Cluster Headaches

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2015) ⁵³	Jun 2015	11	Patients with migraine or cluster headaches	209	RCT	<ul style="list-style-type: none"> 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 need for rescue medication

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

Section Summary: Migraine

A Cochrane review identified 11 RCTs on HBOT for migraine headache. However, only 1 pooled analysis was conducted including 3 of the 11 trials. Pooled analysis found significantly greater relief of migraine symptoms with HBOT than a comparator intervention within 45 minutes of treatment. Limitations included availability of outcomes specific to the immediate posttreatment period, variability of outcomes across trials, and generally low methodologic quality of trials.

Herpes Zoster

In 2012, Peng et al in China published an RCT evaluating HBOT for herpes zoster (see Tables 25 and 26). Sixty-eight patients with herpes zoster were randomized to HBOT with medication or medication treatment alone. The following outcomes were measured after 3 weeks of treatment: therapeutic efficacy, days to blister resolution, days to scar formation, and pain. Patient receiving HBOT experienced significantly improved outcomes compared with patients receiving medication alone. Limitations of the trial included a lack of blinding and long-term follow-up.

Table 25. 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) ⁵⁴	China	NR	2008-2010	Patients diagnosed with herpes zoster within 2 wk	<ul style="list-style-type: none"> • Hyperbaric oxygen • 100% oxygen at 2.2 ATA • 2 sessions/day for 5 d • Thirty 120-min sessions; plus medications that control group received 	Medication alone, including: antiviral, nerve nutritive, pain relief, and antidepressives
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ATA: atmospheres absolute; HBOT: hyperbaric oxygen therapy; NR: not reported.

Table 26. 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) ⁵⁴	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.

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

^b Between-group difference $p < 0.05$.

Section Summary: Herpes Zoster

One RCT was identified. Only short-term outcomes were reported. Outcomes at the end of the treatment period were significantly better in the HBOT group compared with the medication group. Limitations include lack of blinding and long-term outcomes.

Fibromyalgia

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

In 2015, Efrati et al published an RCT that included 60 symptomatic women who had fibromyalgia for at least 2 years (see Tables 27 and 28). Patients were randomized to an immediate 2-month course of HBOT or delayed HBOT after 2 months. Forty-eight (80%) of 60 patients completed the trial. After the initial 2 months, outcomes including a number of tender points, pain threshold, and QOL (SF-36) were significantly improved in the immediate treatment group than in the delayed treatment group. After the delayed treatment group had undergone HBOT, outcomes were significantly improved compared with scores in the 2 months before HBOT treatment. These findings are not only consistent with a clinical benefit of HBOT, but also with a placebo effect. A sham control trial is needed to confirm the efficacy of HBOT in the treatment of fibromyalgia and other conditions where primary end points are pain and other subjective outcomes.

In 2004, Yildiz et al assessed 50 patients with fibromyalgia (see Tables 27 and 28). 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 (ie, 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 27. Characteristics of Trials Assessing HBOT for Fibromyalgia

Study (Year)	Countries	Sites	Dates	Participants	Treatment	
					Active	Comparator

				Treatment		
Efrati et al (2015) ⁵⁵	Israel	1	2010-2012	Patients with fibromyalgia based on: (1) widespread pain and (2) at least 11 of 18 tender points	<ul style="list-style-type: none"> • n=24 • Hyperbaric oxygen • 100% oxygen at 2 ATA • 1 session/day for 5 d • Forty 90-min sessions 	<ul style="list-style-type: none"> • n=26 • No treatment for 2 mo, then same treatment as active group
Yildiz et al (2004) ⁵⁶	Turkey	NR	NR	Patients meeting ACR criteria for fibromyalgia, with persistent symptoms despite medical therapy and PT	<ul style="list-style-type: none"> • n=26 • Hyperbaric oxygen • 100% oxygen at 2.4 ATA • 1 session/day for 5 d • Fifteen 90-min sessions 	<ul style="list-style-type: none"> • 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 28. Results of Trials Assessing HBOT for Fibromyalgia

Study (Year)	Tender Points			Pain Threshold		
	Baseline	After HBOT	Between-Group P Value	Baseline	After HBOT	Between-Group P Value
Efrati et al (2015) ⁵⁵	50			50		
Mean HBOT (SD)	17.3 (1.4)	8.9 (6.0)	<0.001	0.5 (1.2)	1.7 (0.8)	<0.001
Mean control (SD)	17.7 (0.7)	17.2 (1.1)		0.7 (0.5)	0.6 (0.5)	
Yildiz et al (2004) ⁵⁶	50			50		
Mean HBOT (SD)	15.0 (1.5)	6.0 (1.2)	<0.001	0.7 (0.1)	1.3 (0.1)	<0.001
Mean air (SD)	15.3 (1.2)	12.5 (1.1)		0.7 (0.1)	0.8 (0.1)	

HBOT: hyperbaric oxygen therapy.

Section Summary: Fibromyalgia

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

Multiple Sclerosis

A 2004 Cochrane review of RCTs on HBOT for multiple sclerosis was published by Bennett et al and updated in 2010 (see Table 29). The 2010 Cochrane literature search did not identify any new trials since the Cochrane review. Nine RCTs (total N=504 participants) were identified that compared the effects of HBOT with placebo or no treatment. All trials used an initial course of 20 sessions over 4 weeks, although dosages among studies varied from 1.75 ATA for 90 minutes to 2.5 ATA for 90 minutes. The primary outcome of the review was Expanded Disability Status Scale score. A pooled analysis of data from 5 trials (n=271 patients) did not find a significant difference in mean Expanded Disability Status Scale score change after 20 HBOT treatments vs control or after 6 months of follow-up.

Table 29. Systematic Reviews of Trials Assessing HBOT for Multiple Sclerosis

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Bennett et al (2010) ⁵⁷	Jul 2009	9	Patients with multiple sclerosis, at any state or course of the condition	504	RCT	EDSS score difference between groups: <ul style="list-style-type: none"> 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: Multiple Sclerosis

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

Tumor Sensitization During Radiotherapy or Chemotherapy Treatment for Cancer

In a 2005 Cochrane review, which was updated in 2012, Bennett et al identified 19 randomized and quasi-randomized trials (total N=2286 patients) comparing outcomes following radiotherapy with and without HBOT in patients with solid tumors (see Table 30). The latest trial identified in the Cochrane search was published in 1999. Reviewers did not find any ongoing RCTs in this area. Results from the review reported that HBOT given with radiotherapy might be useful in tumor control in head and neck cancer; However, reviewers expressed caution because significant adverse events, such as severe radiation tissue injury (relative risk, 2.3; $p < 0.001$) and seizures (relative risk, 6.8; $p = 0.03$) occurred more frequently in patients treated with HBOT.

Table 30. 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) ⁵⁹	Sep 2008	19, some including multiple cancer sites	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 1-y mortality: RR=0.8 ($p = 0.03$) 5-year mortality: RR=0.8 ($p = 0.03$) 5-y recurrence: RR=0.8 ($p = 0.01$) Uterine: <ul style="list-style-type: none"> 2-y recurrence: RR=0.6 ($p = 0.04$)

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.

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

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 (eg, 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, we could not identify sufficient evidence to support the use of HBOT. Since 2000, there have been no published controlled trials or large case series (ie, ≥ 25 patients) assessing:

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

SUMMARY OF EVIDENCE

For individuals with wounds, burns or infections who receive topical HBOT, the evidence includes a systematic review, case series, and an RCT. Relevant outcomes are overall survival, 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 single small RCT (N=28) was not included in the review and the uncontrolled studies do not provide sufficient data that topical HBOT is efficacious. The evidence is insufficient to determine the effects of the technology on health outcomes.

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. One of the 2 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 a meaningful improvement in the net health outcome.

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

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 a meaningful 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 the effects of the technology on health outcomes.

For individuals with acute thermal burns who receive systemic HBOT, the evidence includes a systematic review of 2 RCTs. Relevant outcomes are overall survival, symptoms, and change in disease status. Only 2 RCTs were identified, and both were judged to have poor methodologic quality. Evidence from well-conducted controlled trials is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with acute surgical and traumatic wounds who receive systemic HBOT, the evidence includes RCTs, controlled nonrandomized studies, and systematic reviews. Relevant outcomes are

overall survival, symptoms, change in disease status, and functional outcomes. There was considerable heterogeneity across the 4 RCTs identified (eg, patient population, comparison group, treatment regimen, outcomes). This heterogeneity prevented pooling of trial findings and limits the ability to conclude the impact of HBOT on health outcomes for patients with acute surgical and traumatic wounds. Additional evidence from high-quality RCTs is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

For individuals with necrotizing soft tissue infections who receive systemic HBOT, the evidence includes systematic reviews and a retrospective cohort study. Relevant outcomes are overall survival, symptoms, and change in disease status. A Cochrane review did not identify any RCTs. Another systematic review identified a retrospective cohort study, which did not find better outcomes after HBOT than after standard care without HBOT in patients with necrotizing soft tissue infections. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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

For individuals with inflammatory bowel disease who receive systemic HBOT, the evidence includes an RCT, observational studies, and a systematic review. Relevant outcomes are symptoms, change in disease status and functional outcomes. One small RCT has been published, and this trial did not find a significant improvement in health outcomes when HBOT was added to standard medical therapy. A systematic review including the RCT and observational studies found a high rate of bias in the literature due to attrition and reporting bias. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with idiopathic sudden sensorineural hearing loss who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms, change in disease status, and functional outcomes. A Cochrane review with pooled analysis of 2 RCTs did not find a statistically significant difference in outcomes between the HBOT and the control groups in hearing for all frequencies at a level greater than 50%, but did find a statistical difference at a level greater than 25%. An RCT published after the review reported no differences in hearing between groups at 4 different frequencies. The RCTs had methodologic limitations. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 (eg, swelling). The evidence is insufficient to determine the effects of the technology on health outcomes.

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. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 were identified, but pooled analyses were not possible due to heterogeneity in treatment regimens and outcomes measured. One systematic review concluded that more RCTs would be needed. The 2 RCTs identified had inconsistent findings. One reported no short-term benefit with HBOT, but some benefits 12 months after radiotherapy; the other did not find a significant benefit of HBOT at 12-month follow-up. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 (ie, 6-week) outcomes. Larger well-conducted RCTs reporting longer term outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

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 (ie, 6-week) outcomes. Additional well-conducted RCTs with longer follow-up are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 (eg, 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 the effects of the technology on health outcomes.

For individuals with multiple sclerosis who receive systemic HBOT, the evidence includes RCTs and a systematic review. Relevant outcomes are symptoms and functional outcomes. A Cochrane review of RCTs did not find a significant difference in Expanded Disability Status Scale scores when

patients with multiple sclerosis were treated with HBOT vs a comparator intervention. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with cancer and are undergoing chemotherapy who receive systemic HBOT, the evidence includes an RCT and a systematic review. Relevant outcomes are overall survival and change in disease status. While the systematic review reported improvements in tumor control in patients with head and neck cancer who received HBOT, the adverse events accompanying the treatment (eg, 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 the effects of the technology on health outcomes.

REGULATORY STATUS

Several hyperbaric oxygen systems have been approved by the U.S. Food and Drug Administration (FDA), including: Sechrist Monoplace Hyperbaric Oxygen Chamber (Sechrist Industries, 2014); Monoplace Hyperbaric Oxygen Treatment System (Khrunichev State Research & Production, 2006); SI18/D18/T120 Hyperbaric Oxygen Treatment (Fink Engineering, 2003); Vx-400 Topical Hyperbaric Oxygen Chamber (Vascular One, 2002); Topical Sacral Hyperbaric Oxygen Chamber (Topox Therapeutic Rentals, 1992); Topical Hyperbaric Oxygen Chamber (Stephenson Industries, 1986); Hyperbaric Oxygen Gurney (Orthopedic Systems, 1984); Disposable Hyperbaric Oxygen Chamber (Hospitak, 1984); and Hyperbaric Oxygen Chamber (Hyperbaric Oxygen Therapy, 1979).

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

Clinical Input Received through Physician Medical 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.

In response to requests, input was received through 6 Physician Specialty Societies and 5 Academic Medical Centers while this policy was under review in 2010. Clinical input varied by condition. There was universal agreement 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

Undersea and Hyperbaric Medical Society

In 2015, the Undersea and Hyperbaric Medical Society (UHMS) published a guideline on use of HBO for treating foot ulcer. This guideline is scheduled for a revision in 2018. Recommendations are:

- Suggest against using HBOT in patients with “Wagner Grade 2 or lower diabetic foot ulcers....”
 - Where a patient has previously required HBO for a Wagner Grade 3 or higher DFU and is now presenting with another ulcer, it may be advisable to incorporate HBO before the ulcer progresses, but this should be the exception and not the rule. This would be in combination with addressing mechanical offloading, optimizing revascularization, elimination of infection, debriding devitalized tissue, and improving metabolic control.
- 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.

Infectious Disease Society of America

In 2012, the Infectious Disease Society of America published guidelines on the diagnosis and treatment of diabetic foot infections.⁶² The guidelines stated that “for selected diabetic foot wounds that are slow to heal, clinicians might consider using hyperbaric oxygen therapy (strength of evidence: strong; quality of evidence: moderate).”

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.⁶³ 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).

Other Conditions

Undersea and Hyperbaric Medical Society

The 2014 UHMS hyperbaric oxygen therapy indications committee report included the following indications as recommended:

1. Air or Gas Embolism
2. Carbon Monoxide Poisoning and carbon monoxide complicated by cyanide poisoning
3. Clostridial Myositis and Myonecrosis (Gas Gangrene)
4. Crush Injury, Compartment Syndrome and Other Acute Traumatic Ischemias
5. Decompression Sickness
6. Arterial Insufficiencies
7. Severe Anemia
8. Intracranial Abscess
9. Necrotizing Soft Tissue Infections
10. Osteomyelitis (Refractory)
11. Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
12. Compromised Grafts and Flaps
13. Acute Thermal Burn Injury
14. Idiopathic Sudden Sensorineural Hearing Loss.

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

American Academy of Otolaryngology-Head and Neck Surgery

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

Tenth European Consensus Conference on Hyperbaric Medicine

The 10th European Consensus Conference on Hyperbaric Medicine (ECHM) convened in April 2016 to update HBOT indication recommendations.⁶⁹ Evidence was assessed using a modified GRADE system with the DELPHI system for consensus evaluation. Table 31 presents the updated recommendations:

Table 31. Recommendations on Hyperbaric Medicine

Condition	SOR	LOE
Carbon monoxide poisoning	Strong	Moderate
Open fractures with crush injury	Strong	Moderate
Prevention of osteoradionecrosis	Strong	Moderate
Osteoradionecrosis (mandible)	Strong	Moderate
Soft tissue radionecrosis (cystitis, proctitis)	Strong	Moderate
Decompression illness	Strong	Low

Gas embolism	Strong	Low
Anaerobic or mixed bacterial infection	Strong	Low
Sudden deafness	Strong	Moderate
Diabetic foot lesions	Weak	Moderate
Femoral head necrosis	Weak	Moderate
Compromised skin grafts and musculocutaneous flaps	Weak	Low
Central retinal artery occlusion	Weak	Low
Crush injury without fracture	Weak	Low
Osteoradionecrosis (other than mandible)	Weak	Low
Radio-induced lesions of soft tissues	Weak	Low
Radio-induced lesions of soft tissues (preventive)	Weak	Low
Ischemic ulcers	Weak	Low
Refractory chronic osteomyelitis	Weak	Low
Burns, second degree, >20% body surface area	Weak	Low
Pneumatosis cystoides intestinalis	Weak	Low
Neuroblastoma, stage IV	Weak	Low
Brain injury in highly selected patients	Neutral	Low
Radio-induced lesions of larynx	Neutral	Low
Radio-induced lesions of central nervous system	Neutral	Low
Post-vascular procedure reperfusion syndrome	Neutral	Low
Limb replantation	Neutral	Low
Selected non-healing wounds, secondary to systemic process	Neutral	Low
Sickle cell disease	Neutral	Low
Interstitial cystitis	Neutral	Low

Adapted from Mathieu et al (2017).⁶⁹

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

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

Dana Farber/Brigham and Women's Cancer Center

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

Recommendations

Not applicable.

Medicare National Coverage

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

- Acute carbon monoxide intoxication (ICD-9-CM diagnosis 986)
- Decompression illness (ICD-9-CM diagnosis 993.2, 993.3)
- Gas embolism (ICD-9-CM diagnosis 958.0, 999.1)
- Gas gangrene (ICD-9-CM diagnosis 0400)

- 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 (ICD-9-CM diagnosis 902.53, 903.01, 903.1, 904.0, 904.41).
- 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 (ICD-9-CM diagnosis 927.00-927.03, 927.09-927.11, 927.20-927.21, 927.8-927.9, 928.00-928.01, 928.10-928.11, 928.20-928.21, 928.3, 928.8-928.9, 929.0, 929.9, 996.90- 996.99).
- Progressive necrotizing infections (necrotizing fasciitis) (ICD-9-CM diagnosis 728.86)
- Acute peripheral arterial insufficiency (ICD-9-CM diagnosis 444.21, 444.22, 81)
- Preparation and preservation of compromised skin grafts (not for primary management of wounds) (ICD-9CM diagnosis 996.52; excludes artificial skin graft)
- Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management (ICD-9-CM diagnosis 730.10-730.19)
- Osteoradionecrosis as an adjunct to conventional treatment (ICD-9-CM diagnosis 526.89)
- Soft tissue radionecrosis as an adjunct to conventional treatment (ICD-9-CM diagnosis 990)
- Cyanide poisoning (ICD-9-CM diagnosis 987.7, 989.0)
- Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment (ICD-9-CM diagnosis 039.0-039.4, 039.8, 039.9)
- Diabetic wounds of the lower extremities in patients who meet the following three criteria:
 - Patient has type 1 or type 2 diabetes and has a lower extremity wound that is due to diabetes;
 - Patient has a wound classified as Wagner grade III or higher; and
 - Patient has failed an adequate course of standard wound therapy.

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 32. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01659723	Radiation Induced Cystitis Treated With Hyperbaric Oxygen - A Randomized Controlled Trial (RICH-ART)	80	Dec 2017

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03147352	Pro-Treat – Prognosis and Treatment of Necrotizing Soft Tissue Infections: a Prospective Cohort Study	310	Jan 2018
NCT02089594	Hyperbaric Oxygen Therapy Treatment of Chronic Mild Traumatic Brain Injury (mTBI)/Persistent Post-Concussion Syndrome (PCCS)	59	Mar 2019
NCT02714465	Treatment of Adverse Radiation Effects after Gamma Knife Radiosurgery (GKS) by Hyperbaric Oxygen Therapy (HBO)	65	May 2019
NCT03325959	Hyperbaric Oxygen versus Standard Pharmaceutical Therapies for Fibromyalgia Syndrome – Prospective, Randomized, Crossover Clinical Trial	70	Nov 2019
NCT00596180	Hyperbaric Oxygen Therapy and SPECT Brain Imaging in Carbon Monoxide Poisoning	40	Dec 2019
NCT01847755	Phase 1-2 Study of Hyperbaric Treatment of Traumatic Brain Injury	100	Dec 2020
Unpublished			
NCT02085330	Hyperbaric Oxygen Therapy for Mild Cognitive Impairment	60	Feb 2017 (unknown)
NCT01002209	Postoperative Hyperbaric Oxygen Treatments to Reduce Complications in Diabetic Patients Undergoing Vascular Surgery (HODIVA)	112	Oct 2017 (unknown)

NCT: national clinical trial.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

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