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Medical Policy Manual

Topic: Hyperbaric Oxygen Pressurization (HBO)

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Section: Medicine

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hyperbaric oxygen therapy (HBO) is a technique of delivering higher pressures of oxygen to the tissues. Two methods of administration are available, systemic and topical.

Systemic HBO

In systemic or large chamber hyperbaric oxygen, the patient is entirely enclosed in a pressure chamber and breathes oxygen at a pressure greater than 1 atmosphere (atm, the pressure of oxygen at sea level). Thus, this technique relies on systemic circulation to deliver highly oxygenated blood to the target site, typically a wound. In addition, systemic hyperbaric oxygen therapy can be used to treat systemic illness, such as air or gas embolism, carbon monoxide poisoning, clostridial gas gangrene, etc. 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.

Mild Hyperbaric Oxygen Therapy

Oxygen therapy delivered via soft-sided chambers is referred to as mild hyperbaric oxygen therapy. While this implies that these chambers provide HBO therapy, the therapy is not considered hyperbaric as

they provide pressurization of only about 4.5 psi, compared with true HBO therapy which is defined as pressurization of 20.5 psi or higher.

Topical Oxygen Therapy

Topical Hyperbaric Oxygen Therapy

Topical hyperbaric oxygen 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. This 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.

Topical hyperbaric oxygen devices consist of an appliance to enclose the wound area (frequently an extremity) and a source of oxygen; conventional oxygen tanks may be used. Topical hyperbaric oxygen therapy may be performed in the office, clinic, or may be self-administered by well-trained patients in the home. Typically, the therapy is offered for 90 minutes per day for 4 consecutive days. After a 3-day break, the cycle may be repeated. The regimen may last for 8 to 10 weeks.

Topical Normobaric Oxygen Therapy

Devices that deliver topical oxygen to a wound at normal atmospheric pressure (normobaric) are not considered hyperbaric oxygen therapy. These devices may also be called low dose tissue oxygenation systems. An example of a normobaric oxygen delivery system is the TransCu O2™, a small handheld device with an attached cannula. According to the manufacturer, the TransCu O2 is "intended for use with wound dressings to treat the following: skin ulcerations due to diabetes, venous stasis, post-surgical infections and gangrenous lesions; pressure ulcers; infected residual limbs; skin grafts; burns; and frostbite." The device concentrates room air to 99.9% oxygen which is delivered via the cannula which is placed under the wound dressing.

Regulatory Status

The following are examples of oxygen therapy devices:

In February 1999, the Numobag™ Kit (Numotech, Inc; Woodland Hills, CA) for application of topical hyperbaric therapy was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices.

In August 2009, the TransCu O2 (Electrochemical Oxygen Concepts, Inc.) was cleared for marketing by the FDA through the 510(k) process as substantially equivalent to existing devices.

There are numerous FDA-approved hyperbaric oxygen chambers. In May 2005, the ATA Monoplace Hyperbaric System (ATA Hyperbaric Chamber Manufacturing, Inc.) was cleared for marketing by the FDA through the 510(k) process. The FDA determined that this device was substantially equivalent to existing hyperbaric devices.

MEDICAL POLICY CRITERIA

I. Topical hyperbaric and topical normobaric oxygen therapies are considered **investigational**.

II. Systemic hyperbaric oxygen therapy

A. Systemic hyperbaric oxygenation ($HBO_{2)}$ services must comply with the following guidelines which are consistent with the Undersea and Hyperbaric Medical Society criteria:

1. Patient must breathe 100% oxygen intermittently or continuously while the pressure of the treatment chamber is increased above one atmosphere absolute
2. Systemic hyperbaric oxygen pressurization should be at least 1.4 atmospheres absolute (atm abs) (20.5 psi)
3. Treatment is provided in a hospital or clinic setting.

B. Oxygen therapy that does not meet the above criteria (II.A.1-3) is considered **investigational**, including but not limited to the following:

1. Mild hyperbaric oxygen chambers (< 1.4 atm abs/20.5 psi)
2. In-home hyperbaric oxygen therapy

C. Systemic hyperbaric oxygen pressurization (i.e., 100% oxygen delivered within a chamber at a pressure of at least 1.4 atm abs) may be considered **medically necessary** in the treatment of any of the following conditions:

1. Acute carbon monoxide poisoning
   **Recommended treatment review threshold*: 5 treatments
2. Acute traumatic ischemia (ie, reperfusion injury, crush injury, compartment syndrome)
   **Recommended treatment review threshold:*
   - Reperfusion injury – 1 treatment
   - Crush injury – 12 treatments (3 times per day for 2 days, then twice a day for 2 days, then daily for 2 days)
   - Compartment syndrome – 3 treatments (twice a day for 1 day, then 1 treatment on day 2)
3. Chronic refractory osteomyelitis
   **Recommended treatment review threshold*: 40 treatments
4. Cyanide poisoning, acute
   **Recommended treatment review threshold for carbon monoxide poisoning complicated by cyanide poisoning*: 5 treatments
5. Decompression sickness
   **Recommended treatment review threshold*: 10 treatments
6. Gas or air embolism, acute
   **Recommended treatment review threshold*: 10 treatments
7. Gas gangrene (i.e., clostridial myositis and myonecrosis)
   **Recommended treatment review threshold*: 10 treatments

8. Non-healing diabetic wounds of the lower extremities as an adjunct to ongoing conventional wound care in patients who meet **all** of the following 3 criteria:

   a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes

   b. Patient has a wound classified as Wagner grade 3 or higher

      Wagner classification

Grade 0	No open lesion
Grade 1	Superficial ulcer without penetration to deeper layers
Grade 2	Ulcer penetrates to tendon, bone, or joint
Grade 3	Lesion has penetrated deeper than grade 2 and there is abscess, osteomyelitis, pyarthrosis, plantar space abscess, or infection of the tendon and tendon sheaths
Grade 4	Wet or dry gangrene in the toes or forefoot
Grade 5	Gangrene involves the whole foot or such a percentage that no local procedures are possible and amputation (at least at the below the knee level) is indicated

   c. Patient has no measurable signs of healing after 30 days of an adequate course of standard wound therapy including **all** of the following:

      i. Assessment of vascular status and correction of any vascular problems in the affected limb if possible

      ii. Optimal glycemic control

      iii. Optimal nutritional status

      iv. Topical wound treatment (eg, saline, hydrogels, hydrocolloids, alginates) with maintenance of a clean, moist bed of granulation tissue

      v. Debridement to remove devitalized tissue, any technique

      vi. Pressure reduction or offloading

      vii. Treatment to resolve infection (eg, antibiotics)

   **Recommended treatment review threshold*: 30 treatments (one or two treatments daily)

9. Pre- and post-treatment for patients undergoing dental surgery (non-implant-related) of an irradiated jaw

10. Profound anemia with exceptional blood loss: only when blood transfusion is impossible or must be delayed

    **Recommended treatment review threshold*: HBO treatment should be continued with taper of both time and frequency until red blood cells have been satisfactorily replaced by patient regeneration or the patient can undergo transfusion.

11. Soft-tissue radiation necrosis (e.g., radiation enteritis, cystitis, proctitis) and

osteoradionecrosis

**Recommended treatment review threshold for mandibular osteoradionecrosis*: 60 treatments

*Treatment thresholds at which utilization management review for the continued need for HBO_2 should be evaluated based on The Undersea and Hyperbaric Medical Society's 2008 Hyperbaric Oxygen Therapy Committee recommendations.

D. Hyperbaric oxygen pressurization is considered **investigational** for all other indications, including but not limited to the treatment of the following conditions:

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 osteomyelitis
4. Acute thermal burns
5. Arthritis, rheumatoid and osteoarthritis
6. Autism spectrum disorders
7. Avascular necrosis
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. Cerebellar hypoperfusion
14. Cerebral edema, acute
15. Cerebral palsy
16. Cerebrovascular disease, acute (thrombotic or embolic) or chronic
17. Chronic fatigue syndrome
18. Complex regional pain syndrome (also called causalgia and reflex sympathetic dystrophy syndrome)
19. Compromised skin grafts or flaps
20. Delayed onset muscle soreness
21. Dementia, all types
22. Demyelinating diseases, e.g., multiple sclerosis, amyotrophic lateral sclerosis
23. Depression
24. Early treatment (beginning at completion of radiation therapy) to reduce adverse effects of radiation therapy
25. Femoral neck necrosis, idiopathic
26. Fibromyalgia
27. Fracture healing and fracture non-union treatment
28 Frostbite

29. Headache prevention and/or treatment of symptoms, including but not limited to migraine and cluster headaches
30. Hepatitis
31. Herpes zoster
32. Hydrogen sulfide poisoning
33. Idiopathic sudden sensorineural hearing loss
34. In vitro fertilization
35. Intra-abdominal and intracranial abscesses
36. Lepromatous leprosy
37. Lyme Disease
38. Lymphedema, chronic
39. Meningitis
40. Multiple chemical sensitivity
41. Necrotizing soft tissue infections
42. Ophthalmologic conditions
    a. Age-related macular degeneration
    b. Glaucoma
    c. Keratoendotheliosis
    d. Retinal artery insufficiency, acute
    e. Retinal detachment
    f. Retinopathy, adjunct to sclera buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment
43. Osteoporosis
44. Parkinson's disease
45. Pseudomembranous colitis (antimicrobial agent-induced colitis)
46. Pulmonary emphysema
47. Pyoderma gangrenosum
48. Radiation myelitis;
49. Radiation –induced injury in the head and neck
50. Refractory mycoses: mucormycosis, actinomycosis, Conidiobolus coronato
51. Retinal artery insufficiency, acute
52. Retinopathy, adjunct to scleral buckling procedures in patients with sickle cell peripheral retinopathy and retinal detachment
53. Severe or refractory Crohn's disease
54. Sickle cell crisis and/or hematuria
55. Spinal cord injury;
56. Stroke
    a. Acute ischemic stroke

b. Stroke-related motor dysfunction

57. Tinnitus
58. Traumatic brain injury
59. Tumor sensitization for cancer treatments, including but not limited to, radiotherapy or chemotherapy
60. Viral encephalitis and viral encephalopathy
61. Wounds: all wounds that do not meet the criteria in II.C.8., including but not limited to the following:
    a. Acute surgical wounds
    b. Arterial insufficiency ulcers
    c. Decubitus ulcers
    d. Non-diabetic cutaneous ulcers
    e. Non-infected wounds (Wagner grade I or II)
    f. Pressure sores
    g. Ulcers caused by atherosclerotic vascular disease
    h. Ulcers caused by peripheral vascular disease
    i. Venous stasis ulcers

SCIENTIFIC EVIDENCE

Topical Hyperbaric Oxygen

Due to their different methods of delivery, topical and systemic hyperbaric oxygen are distinct technologies such that they must be examined separately.[1] There is minimal published literature regarding topical hyperbaric oxygen therapy. In 1984, Heng and colleagues published a controlled study of topical hyperbaric oxygen therapy in 6 patients with 27 ulcers compared to no treatment in 5 patients with 10 ulcers.[2] Although a greater improvement was noted in the treated group, the results were calculated according to the number of ulcers rather than based on individual patients. Leslie and colleagues reported on a trial that randomly assigned 18 patients with diabetic foot ulcers to receive either topical hyperbaric oxygen therapy plus standard wound care or standard wound care alone.[3] Changes in ulcer size and depth did not differ between the 2 groups. Other studies consist of anecdotal reports or uncontrolled case series.[4]

Systemic Hyperbaric Oxygen (HBO)

<u>In-home Hyperbaric Oxygen</u>

A position statement from the National Board of Diving & Hyperbaric Medical Technology on in-home HBO therapy has been published on the Web site for The Undersea and Hyperbaric Medicine Society (UHMS).[5] The statement indicates that in-home HBO therapy “is inherently unsafe and cannot be condoned.” This position is based on concern for the safety and well-being of patients as well as those

people in proximity to the HBO therapy delivery system because in-home provision of HBO therapy is likely to:

- Bypass otherwise mandatory federal, state, and local codes related to design, construction, installation, and operation of these devices; and
- Occur without adequate physician oversight and the operational support of appropriately qualified HBO providers.

Chronic Wounds

An updated Cochrane review of randomized controlled trials (RCTs) on HBO treatment for chronic wounds was published by Kranke and colleagues in 2012.[6] The authors identified 9 RCTs with a total of 471 participants that compared the effect of HBO on chronic wound healing compared to an alternative treatment approach that did not use HBO. Eight of the 9 trials included in the review evaluated HBO therapy in patients with diabetes. The remaining trial addressed HBO for patients with venous ulcers; that study had only 16 participants and the comparator treatment was not specified. In a pooled analysis of data from 3 trials, a significantly higher proportion of ulcers had healed at the end of the treatment period (6 weeks) in the group receiving HBO compared to the group not receiving HBO (RR: 5.20: 95% CI: 1.25 to 21.7). Pooled analyses, however, did not find significant differences between groups in the proportion of ulcers healed in the HBO versus non-HBO-treated groups at 6 months (2 trials) or 12 months (3 trials). There were insufficient data to conduct pooled analyses of studies evaluating HBO for treating patients with chronic wounds who did not have diabetes. The most recently published trial conducted with diabetic patients was double-blind and included 75 diabetic patients with chronic wounds who had failed at least 2 months of treatment at a diabetic foot clinic.[7] After 12 months, the healing rate was 61% in the hyperbaric oxygen group and 27% in the sham hyperbaric group; this difference was statistically significant, p=0.009.

Published clinical trial data is insufficient to determine the effectiveness of HBO for wounds that are not related to diabetes. The UHMS does not include these wounds in their list of indications for HBO, noting the lack of available evidence.[8] As shown in studies of adjunctive HBO for treatment of severe diabetic lower extremity ulcers, this treatment is well suited to randomized, controlled comparative trials. In spite of this, only 1 small (n=16) randomized, controlled trial was found for non-diabetic wounds.[9] This trial is too small and short-term to be reliable.

Acute Surgical and Traumatic Wounds

A 2011 Cochrane review analyzed randomized controlled trials comparing either HBO with a different intervention, or two HBO regimens for acute wounds (e.g., surgical wounds, lacerations, traumatic wounds and animal bites).[10] The three studies that met inclusion criteria ranged in size from 36 to 135 subjects. Reported outcomes were mixed. Meta-analysis of pooled data was not possible due to differences among studies with respect to patient characteristics, interventions studied, and outcome measures. Also identified was a high potential for bias due to insufficient disclosure of randomization methods and selective reporting of outcome data. Findings of individual studies were mixed. The authors concluded that there is insufficient high-quality data on the effect of HBO therapy on treatment of acute wounds. Therefore, HBO is considered investigational for the treatment of these wounds.

Other Investigational Indications

The original policy on systemic hyperbaric oxygen was based entirely on the 1996 guidelines published by the UHMS and was subsequently revised in 1999 with 3 BlueCross BlueShield Association

Technology Evaluation Center (TEC) Assessments.[11-13] The TEC assessment conclusions were similar to UHMS, except, in contrast to the UHMS guidelines, they concluded that there was insufficient evidence to conclude that hyperbaric oxygen treatment improved the net health outcome for the following indications:

- compromised skin grafts
- acute thermal burns
- chronic refractory osteomyelitis
- necrotizing soft tissue infections
- brown recluse spider bites

The TEC Assessments also concluded that there was insufficient evidence to permit conclusions on the use of HBO for the treatment of brain injury, spinal cord injury, and Crohn's disease, indications not addressed by UHMS Guidelines. Two randomized controlled trials (RCTs) on traumatic brain injury were identified, and both suggested that functional outcomes were not improved with HBO. The evidence on use of HBO for spinal cord injury or severe or refractory Crohn's disease was primarily limited to small uncontrolled studies. There was also 1 case-controlled report on Crohn's disease that reported intermediate outcomes only.

The following sections summarize literature on systemic hyperbaric oxygen treatment for other investigational indications.

Acute Coronary Syndromes

A 2012 Cochrane review by Bennett and colleagues identified 6 trials with a total of 665 patients evaluating HBO for acute coronary syndrome.[14] All of the studies included patients with acute myocardial infarction (MI); one study also included individuals presenting with unstable angina. Additionally, all trials used HBO as an adjunct to standard care. Control interventions varied; only 1 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 HBO compared to a control intervention (RR: 0.58: 0.36 to 0.92). Due to variability of outcome reporting in the studies, few other pooled analyses could be conducted. A pooled analysis of data from 3 trials on improvements in left ventricular function did not find a statistically significant benefit of HBO treatment (RR: 0.09; 95% CI: 0.01 to 1.4). The authors noted that, although there is some evidence from small trials that HBO treatment is associated with a lower risk of death, larger trials with high methodologic quality are needed in order to determine which patients, if any, can be expected to derive benefit from HBO. Therefore, HBO is considered investigational in the treatment of acute coronary syndromes.

Amyotrophic Lateral Sclerosis

No randomized trials were found evaluating HBO for the treatment of amyotrophic lateral sclerosis. Therefore, HBO is considered investigational for this indication.

Autism Spectrum Disorders

A 2012 systematic review of evidence on hyperbaric oxygen therapy for treatment of children with autism identified two RCTs with a total of 89 participants.[15] One of the two RCTs found better outcomes after hyperbaric oxygen compared with placebo treatment, and the other did not find significant differences in outcomes. The author concluded that additional sham-controlled trials with

rigorous methodology are needed in order to draw conclusions about the efficacy of HBO for treating autism. A 2012 review article also concluded that, although studies to date suggest that HBO is safe and potentially effective, additional studies are warranted.[16] In particular, it was recommended that future studies use standardized behavioral measurement tools and also assess physiological biomarkers.

- One of the above two RCTs was by Rossignol and colleagues.[17] This study was a double-blind RCT including 62 children, ages 2-7, meeting DSM-IV criteria for autistic disorder. The active treatment was hyperbaric treatment at 1.3 atmospheres (atm) and 24% oxygen in a hyperbaric chamber. (This regimen differs from standard HBO treatment which uses 100% oxygen and a pressure of at least 1.4 atm). The other group received a sham treatment consisting of 1.03 atm and ambient air (21% oxygen). Both groups received 40 sessions of active or sham treatment lasting 60 minutes each over a period of 4 weeks. The equipment, procedures, etc. in the two groups were as similar as possible to maintain blinding. The investigators, participants, parents and clinic staff were blinded to treatment group. Only the hyperbaric technician, who had no role in outcome assessment, was aware of group assignment. After completion of the 4-week study, families with children in the control group were offered the active intervention. When asked at the end of the study, there was no significant difference in the ability of parents to correctly guess the group assignment of their child.

  The outcomes were change compared to baseline after 4 weeks on the following scales: Aberrant Behavior Checklist (ABC) total score and 5 subscales; Autism Treatment Evaluation Checklist (ATEC) total score and 4 subscales; and Clinical Global Impression-Improvement (CGI) overall functioning score and 18 subscales. P values of <0.05 were considered statistically significant; there was no adjustment for multiple comparisons. The analysis included all children who completed at least one complete session. Of the 33 children assigned to active treatment, 30 were included in the analysis and 29 completed all 40 treatments. Of the 29 children assigned to the control treatment, 26 completed all 40 sessions and were included in the analysis.

  There was no significant between-group improvement on the ABC total score, any of the ABC subscales, or on the ATEC total score. Compared to the control group, the treatment group had a significant improvement in 1 of 4 subscales of the ATEC, the sensory/cognitive awareness subscale. The change from baseline on this subscale was a mean of 16.5 in the treatment group and a mean of 5.4 in the control group, a difference of 11.1 ($p=0.037$). (Note: due to an administrative error, baseline ATEC was not collected at one site, and thus data were not available for 23 children in the treatment group and 21 children in the control group). On the physician-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 (very much improved) or 2 (much improved) compared to 2/26 (8%) in the control group ($p=0.047$). On the parental-rated CGI total score, 9/30 (30%) children in the treatment group had a score of 1 or 2 compared to 4/26 (15%) in the control group ($p=0.22$, not statistically significant). (The exact numbers receiving scores of 1 vs. 2 were not reported). Change in mean CGI scores were also reported, but this may be a less appropriate way to analyze these data. Among the parental-rated CGI subscales, significantly more children were rated as improved in the treatment group compared to control on 2 out of 18 subscales, receptive language ($p=0.017$) and eye contact ($p=0.032$).

  A key limitation of this study was that the authors reported only outcomes at 4 weeks, directly after completion of the intervention. It is not known whether there are any long-term effects. Additional follow-up data cannot be obtained because members of the control group crossed over to the intervention after 4 weeks. Other limitations included lack of adjustment for multiple comparisons and unclear clinical significance of the statistically significant outcomes. The Undersea and Hyperbaric Medical Society (UHMS) issued a position paper after publication of the Rossignol et al.

study stating that they still did not recommend routine treatment of autism with HBO.[18]

- A 2012 RCT published after the systematic reviews randomly assigned 60 children with autism to receive 20 one-hour sessions with HBO or sham air treatment (n=30 per group).[19] The primary outcome measures were change in the ATEC and CGI, evaluated separately by clinicians and parents. There were no statistically significant differences between groups on any of the primary outcomes. For example, post-treatment clinician-assessed mean scores on the ATEC were 52.4 in the HBO group and 52.9 in the sham air group.

In summary, there is insufficient evidence from rigorous randomized controlled trials that hyperbaric oxygen (HBO) improves health outcomes for patients with autism spectrum disorder; therefore, HBO therapy for this indication is considered investigational.

Bell's Palsy

In 2012, Holland and colleagues published a Cochrane review evaluating HBO treatment in adults with Bell's palsy.[20] The authors identified one RCT with 79 participants, and this study did not meet the Cochrane review methodologic standards because the outcome assessor was not blinded to treatment allocation. Therefore, the evidence is insufficient to permit conclusions and HBO is considered investigational for the treatment of Bell's palsy.

Bisphosphonate-related Osteonecrosis of the Jaw

An unblinded RCT was published by Freiberger and colleagues in 2012 on use of HBO as an adjunct therapy for patients with bisphosphonate-related osteonecrosis of the jaw.[21] Forty-nine patients were randomly assigned to HBO in addition to standard care (n=22) or standard care alone (n=27). Five patients in the standard care group received HBO treatment and 1 patient assigned to the HBO group declined HBO. The investigators decided to do 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. Data were available on 46 patients, 25 received HBO in addition to standard care and 21 received standard care alone. The primary outcome measure was change in oral lesion size or number. When change from baseline to last available follow-up was examined, 17 of 25 (68%) of HBO-treated patients had improvement in oral lesion size or number compared to 8 of 21 (38%) in the standard care group, p=0.043. When change from baseline to 6, 12 or 18 months was examined, there was not a statistically significant difference between groups in the proportion of patients with improvement. In addition, the proportion of patients who healed completely did not differ significantly between groups at any time point. This single trial does not report consistent findings of benefit across outcome measures. It also has a number of methodologic limitations, e.g., unblinded, cross-over, and analysis performed on a *per-protocol* basis rather than intention to treat. A disadvantage of the *per-protocol* analysis is that randomization is not preserved, and the two groups may differ on characteristics that affect outcomes. As a result, this trial is insufficient to conclude that HBO improves health outcomes for patients with bisphosphonate-related osteonecrosis of the jaw.

Current evidence is insufficient to determine the safety and efficacy of hyperbaric oxygen (HBO) in the treatment of bisphosphonate-related osteonecrosis of the jaw. Therefore, HBO is considered investigational for this indication.

Cancer Treatment

In a randomized, controlled trial of 32 patients, Heys and colleagues found no increase in 5-year survival in patients treated with HBO prior to chemotherapy for locally advanced breast carcinoma to increase tumor vascularity.[22] This approach is being studied since studies in animal models have suggested that HBO increases tumor vascularity and thus may make chemotherapy more effective. In a Cochrane review, Bennett and colleagues concluded that HBO given with radiotherapy may be useful in tumor control; however, the authors expressed caution since significant adverse effects were common with HBO and indicated further study would be useful.[23]

Current evidence is insufficient to determine the safety and efficacy of hyperbaric oxygen (HBO) in the treatment of cancer of any type and location. Therefore, HBO is considered investigational for this indication.

Cerebral Palsy

In 2012, Lacey and colleagues published a double-blind RCT that included 49 children age 3-8 years with spastic cerebral palsy.[24] Participants were randomized to receive 40 treatments with either HBO (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 study 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. At the time of the interim analysis, there was no significant between-group difference in the post-treatment GMFM-88 global score (p=0.54).

In the largest randomized trial to date, Collet et al. randomly assigned 111 children with cerebral palsy to 40 treatments over a 2-month period of either HBO (n=57) or slightly pressurized room air (n=54). [25] The authors found HBO and slightly pressurized air produced similar improvements in both groups for outcomes such as gross motor function and activities of daily living.

HBO is considered investigational as a treatment for cerebral palsy because it has not been shown to provide additional health benefits in this patient population.

Compromised Skin Grafts and Flaps

In a 2010 Cochrane review, Estes and colleagues found a lack of high quality evidence regarding HBO in the treatment of skin grafts and flaps.[10,26] The authors found one randomized controlled trial (RCT) on skin grafts for burn wounds (n=48) which reported significantly higher graft survival with HBO, and one RCT on flap grafting (n=135) which reported no significant differences in graft survival with HBO compared with dexamethasone or heparin. However, these data are unreliable due to various methodologic limitations such as biased analysis, omitted data, and small size.

In 2006, Friedman and colleagues published a systematic review of literature on use of HBO for treating skin flaps and grafts.[27] No RCTs were found. The authors identified 2 retrospective case series on use of HBO for clinically compromised skin grafts and flaps. The series had sample sizes of 65 and 26, respectively; both were published in the 1980s based on treatment provided in the 1970s and 1980s.

Although the study of hyperbaric oxygen (HBO) therapy goes back several decades, the clinical trial data is limited to noncomparative case series and a single randomized controlled trial. This evidence is insufficient to determine the safety and efficacy of HBO therapy in the treatment of compromised skin grafts and flaps. Therefore, HBO therapy is considered investigational for these indications.

Delayed-Onset Muscle Soreness

In a Cochrane review, Bennett and colleagues concluded that available evidence is insufficient to demonstrate beneficial outcomes with HBO for delayed-onset muscle soreness and closed soft-tissue injury.[28] It was noted that HBO possibly even increases pain initially and further studies are needed. Therefore, use of HBO for this indication is considered investigational.

Dementia

A 2012 Cochrane review identified 1 RCT evaluating HBO for the treatment of vascular dementia.[29] The 2009 study compared HBO plus donepezil to donepezil-only in 64 patients. The HBO and donepezil group had significantly better cognitive function after 12 weeks of treatment, as assessed by the Mini-Mental State Examination. However, the Cochrane investigators judged the trial to be of poor methodologic quality because it was not blinded and the methods of randomization and allocation concealment were not discussed.

The current evidence for hyperbaric oxygen (HBO) therapy as a treatment of dementias of any cause is limited to a single short-term clinical trial on vascular dementia. This evidence is insufficient to permit conclusions about the safety and efficacy of HBO treatment on vascular dementia. No other randomized controlled trials were found for HBO as a treatment of demential from any cause. Due to the lack of sufficient evidence, HBO is considered investigational for treatment of dementias.

Femoral Neck Necrosis, Idiopathic

In 2010, Camporesi and colleagues published the results of a double-blind RCT that evaluated HBO therapy in 20 adult patients with idiopathic unilateral femoral head necrosis.[30] Patients received 30 treatments over 6 weeks with either HBO at 2.5 ATA (n=10) or a sham treatment consisting of hyperbaric air (n=10). The mean severity of pain on a 0-to-10 scale was significantly lower in the HBO group than 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 also reported. At the end of the initial treatment period, extension, abduction and adduction, but not flexion, were significantly greater in the HBO group compared to the control group. Longer-term comparative data were not available because the control group was offered HBO at the end of the initial 6-week treatment period.

The current evidence is limited to a single, small short-term randomized controlled trial. Thus, there is insufficient data on which to draw conclusions about the efficacy of HBO for treating femoral head necrosis, and it is considered investigational for this indication.

Fracture Healing

In 2012, Bennett and colleagues published a Cochrane review on HBO to promote fracture healing and treat non-union fractures.[31] The investigators did not identify any published RCTs on this topic that compared HBO to no treatment, sham treatment, or another intervention and reported bony union as an outcome.

Due to the lack of RCTs, it is not possible to conclude whether the use HBO to promote fracture healing improves outcomes; therefore, the use of HBO for this indication is considered investigational.

Headaches

When assessing any treatment focused on pain relief, randomized, placebo-controlled trials are necessary to investigate the extent of any placebo effect and to determine whether any improvement with the treatment exceeds that associated with a placebo.

The following is a summary of the available evidence:

- Migraine headaches

  In a randomized, double-blind, placebo-controlled study of 40 patients, Eftedal and colleagues reported no significant reductions in migraine occurrence with HBO compared to hyperbaric air treatments.[32]

  A Cochrane review by Bennett and colleagues identified RCTs that evaluated the effectiveness of systemic hyperbaric oxygen therapy for preventing or treating migraine headache compared to another treatment or a sham control.[33] Five trials with a total of 103 patients were identified that addressed treatment of acute migraine with HBO. A pooled analysis of 3 trials (total of 43 patients) found a statistically significant increase in the proportion of patients with substantial relief of migraine within 45 minutes of HBO treatment (relative risk [RR],5.97, 95% confidence interval [CI],1.46-24.38, p=0.001). No other pooled analyses were conducted due to variability in the outcomes reported in the trials. The meta-analysis did not report data on treatment effectiveness beyond the immediate post-treatment period, and the methodologic quality of trials was moderate to low, e.g., randomization was not well-described in any trial. There was no evidence that HBO could prevent episodes of migraine headache.

- Cluster headaches

  Two 2008 systematic reviews, including the Cochrane review noted above, reported few studies comparing HBO with sham treatment for cluster headaches.[33,34] Available randomized, placebo-controlled trials measuring effect on symptoms are unreliable due to very small size.[35,36]

Due to the lack of sufficient evidence from well-designed clinical trial, HBO for the treatment of headaches from any cause is considered investigational.

Herpes zoster

In 2012, Peng and colleagues published an RCT evaluating HBO as a treatment of herpes zoster. (64) Sixty-eight patients with herpes zoster diagnosed within the previous 2 weeks were randomized to 30 sessions of HBO therapy (n=36) or medication treatment (n=32). Pharmacotherapy included antiviral, pain, nerve nutritive and antidepressive medication. Therapeutic efficacy was calculated at the end of the 3-week treatment period and included the proportion of patients who were healed (i.e., complete subsidence of pain and rash) or improved (i.e., significant pain relief and rash subsistence). Rates of therapeutic efficacy were 97.2% in the HBO group and 81.3% in the medication group ($p<0.05$). Limitations of the study included a lack of blinding and lack of long-term follow-up.

The evidence from the single randomized controlled trial is insufficient to permit conclusions about the effect of HBO on health outcomes for patients with herpes zoster; therefore, HBO is considered investigational for this indication.

Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL)

A 2012 Cochrane review on HBO for ISSNHL and tinnitus identified 7 trials with a total of 392 participants.[37] The literature search was last assessed as up-to-date in July 2009. All trials included patients with ISSNHL with and/or without tinnitus; two trials also included patients with tinnitus in the absence of ISSNHL. Randomization procedures were only described in one study, and only one study stated they blinded participants to treatment group assignment using sham therapy. Six of the studies included time-based entry criteria for hearing loss and/or tinnitus; this was 48 hours in 3 studies, 2 weeks in 2 studies (for acute presentation) and 6 months in 1 study. The dose of oxygen per treatment session and the treatment protocols varied among studies e.g., the total number of treatment sessions varied from 10 to 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% 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 HBO and control groups (RR: 1.53, 95% CI: 0.86 to 2.78). In contrast, a pooled analysis of two trials reporting the proportion of participants with greater than 25% return of hearing at the end of therapy found a significantly higher rate of improvement after HBO compared to a control intervention (RR: 1.39: 95% CI: 1.05 to 1.84). Moreover, a pooled analysis of four trials found a significantly greater mean improvement in hearing over all frequencies with HBO compared to control (mean difference: 15.6 decibels (dB); 95% CI: 1.5 to 29.8). The authors 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 HBO for treating ISSNHL.

In 2012, Suzuki and colleagues in Japan published findings of a non-randomized controlled trial in 276 consecutive patients with ISSNHL.[38] All patients had been treated with intravenous hydrocortisone. In addition, 174 patients underwent HBO treatment and 102 patients received intratympanic dexamethasone injection. There was no significant difference in most outcomes e.g., cure rate, marked recovery rate and hearing gain (dB) between the groups of patients who received HBO treatment compared to dexamethasone injections. However, at the $p<0.05$ level, the recovery rate (complete, good, or fair recovery) was significantly higher in the dexamethasone injection group than the HBO group (79.4% vs. 68%, respectively $p=0.048$). Limitations of this study were that individuals were not randomized to treatment group, and the authors did not adjust the p value to account for multiple outcome variables.

Due to methodologic limitations and variability among published studies, the evidence is insufficient to draw conclusions about the effect of HBO on health outcomes in patients with ISSNHL. Thus, HBO is considered investigational for treating ISSNHL.

In Vitro Fertilization

Van Voorhis and colleagues reported that HBO was well tolerated in women undergoing ovarian follicular stimulation for in vitro fertilization; however no outcomes were reported. [39] Therefore, current evidence is insufficient to permit conclusions and HBO is considered investigational for this indication.

Necrotizing Soft Tissue Infections

A 2005 systematic review by Jallali and colleagues evaluated the literature on HBO as adjunctive therapy for necrotizing fasciitis.[40] They did not identify any RCTs. There were only a few retrospective

studies with small sample sizes and findings were inconsistent. The authors concluded that more robust evidence is needed before widespread use of HBO is recommended.

A 2009 retrospective cohort study compared outcomes in 48 patients at one center who received adjunctive HBO for necrotizing soft issue infections to those in 30 patients at a different center who did not receive HBO.[41] There was not a significant difference in the mortality rate between the two groups; 4 of 48 (8%) in the HBO group and 4 of 30 (13%) in the non-HBO 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. There was a higher median number of debridement procedures per person in the HBO group, 3.0 compared to 2.0 in the non-HBO group (p=0.03).

Due to the lack of sufficient evidence from well-designed clinical trial, HBO for the treatment of necrotizing soft tissue infections is considered investigational.

Radiotherapy Adverse Effects

In 2010, Spiegelberg and colleagues conducted a systematic review of studies on HBO therapy to prevent or treat radiotherapy-induced head and neck injuries associated with treatment of malignant tumors.[42] The authors identified 20 studies. Eight of the studies included control groups; their sample sizes ranged from 19 to 78 individuals. Four (50%) of the studies with a control group concluded that HBO was effective, and the other 4 did not conclude that the HBO was effective. The authors noted a paucity of RCTs but did not state the number of RCTs identified in their review.

Teguh and colleagues reported on 17 patients with oropharyngeal or nasopharyngeal cancer who were treated with radiation therapy.[43] Eight patients were randomly assigned to receive 30 sessions of HBO, beginning within 2 days of completing radiation therapy, and 9 patients received no additional treatment. All patients were included in the analysis. Quality of life outcomes were assessed and the primary outcome was specified as xerostomia at 1 year. Quality of life 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 HBO group and 6 in the control group. However, at 1 year, there was a statistically significant difference between groups; the mean VAS score for xerostomia was 4 in the HBO group and 7 in the control group (p=0.002). Also at 1 year, the mean quality of life score for swallowing (0-to-100 scale) was 7 in the HBO group and 40 in the control group (p=0.0001). The study is limited by the small sample size and the wide fluctuation over the follow-up period in quality-of-life ratings.

In 2010, Gothard et al. randomized 58 patients with arm lymphedema (at least 15% increase in arm volume) following cancer treatment in a 2:1 ratio to receive HBO (n=38) or usual care without HBO (n=20).[44] Fifty-three patients had baseline assessments and 46/58 (79%) had 12-month assessments. No statistically significant difference was found in the change in arm volume from baseline to 12-month follow-up. The 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. According to this definition, 9 of 30 (30%) patients in the HBO group were considered responders compared with 3 of 16 (19%) in the control group; the difference between groups was not statistically significant. Other outcomes, e.g., quality-of-life scores on the Short-Form (SF)-36, were also similar between groups.

Due to the lack of sufficient evidence from well-designed clinical trial, HBO for the treatment of adverse effects related to radiation therapy is considered investigational.

Stroke

Current evidence is insufficient to permit conclusions about whether HBO improves health outcomes in the treatment of stroke or stoke-related functional limitations. Therefore, HBO is considered investigational for these indications.

The following is a summary of the available evidence:

- Acute Stroke

  In a 2005 Cochrane systematic review, Bennett and colleagues evaluated HBO treatment for acute stroke.[45] The investigators identified 6 RCTs with a total of 283 participants that compared HBO to sham HBO or no treatment. The authors were only able to pool study findings for 1 outcome, the mortality rate at 3-6 months. A pooled analysis of 3 trials found no significant benefit of HBO compared to the control for this outcome. Based on the available evidence, acute ischemic stroke is considered investigational.

  In a 2005 systematic review, Carson and colleagues concluded that current evidence did not demonstrate any benefit with the use of HBO therapy for the treatment of stroke.[46] The authors noted it was undetermined whether there were any benefits with HBO therapy that would outweigh potential harms, and further study was required.

- Stroke-related motor dysfunction

  In 2013, Efrati and colleagues published an RCT evaluating HBO therapy for treatment of neurologic deficiencies associated with a history of stroke.[47] The study included 74 patients with at least 1 motor dysfunction who had an ischemic or hemorrhagic stroke 6-36 months prior to study participation. Participants were randomly assigned to receive 2 months of HBO treatment (40 daily sessions, 5 days per week, n=30) or delayed treatment (n=32). Patients 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 HBO treatment. Twenty-nine of 32 patients (91%) in the delayed treatment group crossed over to the active intervention. Outcome measures included the National Institutes of Health Stroke Scale (NIHSS), which was measured by physicians blinded to treatment group, and several patient-reported quality-of-life and functional status measures.

  At 2 months' follow-up, there was statistically significantly greater improvement in function in the HBO group compared to the control group as measured by the NIHSS, quality-of-life scales and the ability to perform activities of daily living (ADLs). These differences in outcome measures were accompanied by improvements in single-photon emission computed tomography (SPECT) imaging in the regions affected by stroke. For the delayed treatment control group, there was a statistically significant improvement in function after HBO treatment compared to before treatment. This RCT raises the possibility that HBO may induce improvements in function and quality of life for post-stroke patients with motor deficits. However, the results are not definitive for a number of reasons. This RCT is small and enrolled a heterogeneous group of post-stroke patients. The study was not double-blind and the majority of outcome measures, except for the NIHSS, were patient reported and thus prone to the placebo effect. Also, there was a high total dropout rate of 20% at the 2-month follow-up point. Therefore, larger, double-blind studies with longer follow-up are needed to

corroborate these results. Because of these limitations in the evidence, HBO is considered investigational for treating motor dysfunction associated with stroke.

Traumatic Brain Injury

A 2012 Cochrane systematic review addressed HBO as adjunctive treatment for traumatic brain injury.[48] The investigators identified 7 RCTs with a total of 571 participants comparing a standard intensive treatment regimen to the same treatment regimen with the addition of HBO. The review did not include studies in which interventions occurred in a specialized acute care setting. The HBO regimens varied among studies; for example, the total number of individual sessions varied from 3 to 30-40. No trial used sham treatment or blinded the staff members who were treating the patients, and only 1 had blinding of outcome assessment. Allocation concealment was inadequate in all of the studies. The primary outcomes of the review were mortality and functional outcomes. A pooled analysis of data from 4 trials that reported this outcome found a statistically significantly greater reduction in mortality when HBO was added to a standard treatment regimen. However, when data from the 4 trials were pooled, the difference in the proportion of patients with an unfavorable functional outcome at final follow-up did not reach statistical significance. Unfavorable outcome was commonly defined as a Glasgow Outcome Score (GOS) of 1, 2 or 3, which are described as 'dead', 'vegetative state' or 'severely disabled'. Studies were generally small and were judged to have substantial risk of bias.

A 2012 sham-controlled double-blind trial evaluating HBO was published after the 2012 Cochrane review.[49] The study included 50 military service members, 48 of whom were male, with combat-related mild traumatic brain injury. Participants were randomized to 30 sessions of HBO over 8 weeks (n=25) or a sham intervention (room air at 1.3 ATA) (n=25). The primary outcome measures were scores on the Immediate Post-Concussive Assessment and Cognitive Testing (ImPACT) and Post-Traumatic Disorder Check List- Military Version (PCL-M) instruments. Patients were evaluated after every 5 treatment sessions and at 6 weeks post-exposure. Forty-eight of 50 participants (96%) completed the study. There were no statistically significant differences on the ImPACT total mean score or the PCL-M composite score at any time point. While the sample size was relatively small, the study was powered to detect clinically significant differences among groups on the cognitive tests.
In summary, a systematic review of small trials with limitations found a mortality reduction with HBO but no significant improvement in patient function among survivors of traumatic brain injury. One additional trial, which was double-blind and sham-controlled trial of HBO treatment in patients with mild traumatic brain injury, did not find a statistically significant benefit with HBO. Thus, the evidence is insufficient that HBO treatment improves health outcomes in patients with traumatic brain injury, and this indication is considered investigational.

Other

No data from well-designed randomized, controlled clinical trials were found that supported HBO therapy for any other investigational indication, including but not limited to refractory mycoses and acute peripheral arterial insufficiency.

Clinical Practice Guidelines and Position Statements

U.S. Food and Drug Administration (FDA)

In 2013, the FDA published a position statement with a warning that HBO has not been proven safe and effective for uses not cleared by the agency.[50] This statement was developed due to numerous complaints from consumers and health care professionals that unproven claims made by some HBO treatment centers may mislead consumers and ultimately endanger their health. The statement included the following conditions for which patients may be unaware that safety and effectiveness of HBO have *not* been established:

- AIDS/HIV
- Alzheimer's Disease
- Asthma
- Bell's Palsy
- Brain Injury
- Cerebral Palsy
- Depression
- Heart Disease
- Hepatitis
- Migraine
- Multiple Sclerosis
- Parkinson's Disease
- Spinal Cord Injury
- Sport's Injury
- Stroke

Undersea and Hyperbaric Medical Society (UHMS)

In 2008, the UHMS updated their list of indications considered *appropriate* for hyperbaric oxygen therapy.[51] These indications are as follows:

- Acute thermal burn injury
- Air or gas embolism
- Arterial insufficiencies (central retinal artery occlusion, enhancement of healing in selected problem wounds)
- Carbon monoxide poisoning and carbon monoxide complicated by cyanide poisoning
- Clostridial myositis and myonecrosis (gas gangrene)
- Crush injury, compartment syndrome, and other acute traumatic ischemias
- Decompression sickness Delayed radiation injury (soft tissue and bony necrosis)
- Intracranial abscess
- Necrotizing soft tissue infections
- Osteomyelitis (refractory)
- Severe anemia
- Skin grafts and flaps (compromised)

A 2010 UHMS position paper reported that most RCTs have failed to show clinical benefit for HBO therapy for multiple sclerosis.[52] "We conclude that, while there is some case for further investigation of possible therapeutic effects in selected sub-groups of patients (well-characterized and preferably early in the disease course) and for the response to prolonged courses of HBO_2T, this case is not strong. At this time, the UHMS cannot recommend the routine treatment of MS with HBO_2T outside appropriate comparative research protocols."

In October 2011, the UHMS Executive Board approved idiopathic sudden sensorineural hearing loss (ISSNHL) as an additional indication.[53] According to treatment guidelines, patients with moderate to profound ISSNHL who present within 14 days of symptom onset should be considered for HBO treatment.

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.[54] 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 [this condition]"

Summary

Hyperbaric oxygen (HBO) therapy has been studied for a wide variety of clinical indications, a majority of which are considered investigational. For the investigational indications discussed in the policy, the evidence is not sufficient to permit conclusions concerning the effects of HBO therapy on final health outcomes. Studies for these indications are limited and often suffer from methodologic limitations which impact the reliability of the reported results. In some cases, no beneficial results were reported, or conflicting results were reported from different studies for the same indication. Well-designed randomized controlled trials are needed to determine whether HBO therapy results in improved health outcomes compared with standard therapies. Therefore, these indications are considered investigational.

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CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	99183	Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session Note: This code is not intended for reporting systemic oxygen therapy in chambers that provide oxygen at less than hyperbaric pressure (eg, “mild hyperbaric” oxygen therapy) which should be reported using code 99199.
	99199	Unlisted special service, procedure or report
HCPCS	A4575	Topical hyperbaric oxygen chamber, disposable

CODES	NUMBER	DESCRIPTION
	C1300	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval
	E0446	Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories NOTE: This code is intended for devices such as the TransCu 02 that deliver oxygen at normal atmospheric pressure under wound dressings; it should not be used to report topical hyperbaric oxygen therapy devices.
	E1399	Durable medical equipment, miscellaneous