Medicare Coverage Policy ~ NCDs

Hyperbaric Oxygen Therapy in Treatment of Hypoxic Wounds and Diabetic Wounds of the Lower Extremities (#CAG-00060N)

Technology Assessment

Hyperbaric Oxygen Therapy in Treatment of Hypoxic Wounds

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Background on rapid response reports

"Rapid Response Reports (RRR)" are abbreviated evidence reports conducted to meet the quick turnaround needs of the Centers for Medicare and Medicaid Services (CMS) in their evaluation of requests for coverage NCDs. The purpose of evidence reports produced under the Agency for Healthcare Research and Quality (AHRQ)'s Evidence-based Practice Center (EPC) program is to summarize information from relevant studies addressing several well-defined key questions. The scope of an evidence report generally covers prevalence, diagnosis and management of important or common clinical problems. Evidence reports, RRRs in particular, focus on data from clinical studies on human subjects who have the condition of interest. Detailed evaluation of the pathophysiology and mechanism of action of treatments is beyond the scope of RRRs. Most importantly, evidence reports do not make specific recommendations on the use of diagnostic tests or treatments. Users of these reports may utilize additional information in the decision making process. While a conventional evidence report takes about one year to complete, the turnaround time for an average RRR is about 6 to 8 weeks. The shortened duration necessitate tradeoffs for the amount of literature that can be assessed and synthesized in the timeframe.

Background on hyperbaric oxygen therapy

In hyperbaric oxygen.(HBO)therapy, patients breathe 100% oxygen at elevated pressure, typically at 2 to 2.5 atmospheric absolute (ATA). Wounds often have reduced oxygen supply (hypoxia) which impairs leukocyte

bacteriocidal activities and wound healing. The benefit of HBO is based on the premise that raising tissue oxygen levels will enhance wound healing ability. Adjunctive HBO therapy is used in the management of a variety of disorders such as refractory wounds, gas gangrene, necrotizing infections, radiation injuries and chronic osteomyelitis.

HBO is administered either in a monoplace or a multiplace chamber. A monoplace chamber accommodates only a single patient, the chamber is pressurized to about 2 to 2.5 ATA with 100% oxygen. A multiplace chamber can accommodate several patients and/or health care personnel. The chamber is compressed with air to 2 to 2.5 ATA while the patient breathes 100% oxygen via head tent, face mask, or endotracheal tube. In either case, the arterial partial pressure of oxygen will approach 1,500 mmHg.

Potential risks for patients undergoing therapy with HBO include pressure related traumas (e.g., barotraumatic otitis, pneumothorax) and adverse effects due to oxygen toxicity (e.g., myopia, seizures). Some patients may experience claustrophobia due to the confined space of the treatment chambers. Most adverse events are self-limiting and resolve after termination of therapy. Patients with barotraumatic otitis may require the placement of tympanostomy tubes. Some centers routinely insert tympanostomy tubes prophylactically. Serious, life-threatening events are probably rare, but not well quantified.

Request by CMS

The Centers for Medicare and Medicaid Services (CMS) requested assistance from the Agency for Healthcare Research and Quality (AHRQ) to perform an assessment on the use of hyperbaric oxygen (HBO) for treatment of hypoxic wounds.

The following nine diagnostic specific wounds (acute and non-acute conditions) are currently covered by existing Medicare policy on the use of HBO as an adjunctive therapy:

1. Acute traumatic peripheral ischemia
2. Crush injuries and suturing of severed limbs (acute)
3. Acute peripheral arterial insufficiency
4. Compromised skin grafts (acute)
5. Osteoradionecrosis
6. Soft tissue radionecrosis
7. Gas gangrene (acute)
8. Progressive necrotizing infections
9. Chronic refractory osteomyelitis

CMS also requested an evaluation of the use of topical hyperbaric oxygen (THO) therapy in the treatment of hypoxic wounds of the extremities and torso. Topical hyperbaric oxygen systems deliver oxygen at high pressures directly to the site of the wound, typically 50 mm Hg intermittent pressure for hypoxic wounds of the extremities and 22 mm Hg for the treatment of hypoxic wounds to the torso. At present, Medicare has a *Non-Coverage* policy for THO.

The New England Medical Center (NEMC) Evidence based Practice Center (EPC) was asked to evaluate the evidence on the use of HBO. CMS requested

a review of the literature relevant to the following questions:

1. Is there sufficient objective evidence that the use of HBO, as adjunctive therapy to standard wound care, aids in wound healing?
    - Chronic refractory wounds
    - Wound conditions covered under current Medicare Policy.
2. At what point in treatment should HBO therapy be introduced?
3. What other treatment modalities must be employed along with HBO therapy in order to maximize therapeutic benefits?
4. Wounds are generally classified based on diagnosis. Could wounds be classified based on a level of "hypoxia" rather than diagnostic specific (such as diabetic)?
5. Are there useful criteria to determine when an individual is likely to benefit from HBO therapy or when an individual will be non-responsive to HBO therapy?
6. Are there absolute contraindications when considering HBO therapy in mono-place or multi-place chambers?
7. Which method of measuring tissue oxygen is most reliable and lends itself to standardization?

The NEMC EPC was also asked to summarize the evidence on the use of THO.

Methods

Literature search

We conducted a systematic review of published literature to evaluate the effect of HBO on wound care. The literature search included original clinical studies and systematic reviews or technology assessments published on HBO. We identified original investigations on this topic from the references of the recently published technology assessment (TA) reports provided by AHRQ and additional systematic reviews we found on this topic. We updated the literature used in these TAs by conducting a Medline search for articles published between mid-1998 to August 2001. Because we relied on the bibliographies of other reports for studies published prior to 1998 and some of these reports excluded case series studies, a full systematic literature search of case series studies published before 1998 on some topics was beyond the scope of this methodology. We supplemented the literature search with case series and other studies suggested by expert peer reviewers. We searched for human subject studies published in English language on HBO for wound care using search terms of "hyperbaric oxygen" and "wound$ or injur$." This search yielded 159 citations. We also searched for articles that measured tissue oxygen levels or hypoxia in conjunction with HBO therapy; this search yielded 149 citations.

For THO, we reviewed the material from Advanced Hyperbaric Technologies, Inc. provided to us by AHRQ. We also conducted a literature search in Medline between 1966 and August 2001 for additional English language articles on the use of THO in human using search terms of "topical", "hyperbaric", and "oxygen." This search yielded 32 citations.

Selection of primary studies

To assess the primary data for this evidence report, we considered only

published articles that report original data, include at least 5 human subjects, evaluate the use of HBO or THO for wound care, and report clinical outcomes. Acceptable clinical outcomes include, but are not restricted to, mortality, amputation, wound healing, duration of hospitalization, and infection control. We included randomized controlled trials (RCT), non-randomized comparison studies, and case series. Conference reports that did not provide primary data, animal studies and review articles were excluded.

Reporting of results

We assessed the characteristics of the original research articles, their results, and relevance to CMS questions. We extracted the following data from each original study and summarized this information in evidence tables:

- Patient demographics
- Description of the conditions, diagnostic criteria, wound duration
- Measurements of tissue oxygen level around wound
- Study design
- Description of hyperbaric oxygen regimen
- Side effects of treatment
- Major clinical outcomes

There were several non-randomized prospective controlled trials. In some of these non-randomized trials, patients who refused HBO because of claustrophobia or patients with contraindications served as controls. Most studies were retrospective reviews of patient series and compare results of patients treated with HBO and those without HBO. This group of retrospective studies was labeled as "retrospective comparison." Most studies did not report specific diagnostic criteria for the underlying conditions. For these studies, we entered "clinical" under the "diagnostic criteria" column in the evidence tables.

RESULTS

The results in this section correspond to the data presented in Evidence Tables 1-4.

Listed in the rows of Evidence Table 1 are six TAs and one systematic review. The columns listed the indications assessed in the report. Each cell represents the type of study and the number of studies evaluated for the specific indication in a particular report, as well as a qualitative indication of the effect of HBO therapy (see table footnote for additional details). TAs evaluating the same indication used mostly the same primary studies, the difference being the inclusion criteria applied.

Evidence Table 2 presents the data for individual studies. A separate table was produced for each of the indications requested by CMS. Within each of the indications, the studies are ordered by the highest methodological rigor studies first (randomized trials). Case series reports appear last. Within each of the methodological categories, studies are ordered chronologically by their publication year.

Evidence Table 3 presents THO data following the same presentation format as in Evidence Table 2 except that there are no separate indications. Evidence Table 4 presents studies that measured tissue oxygen level.

Technology Assessments (Table 1)

1. Technology Assessment (Blue Cross and Blue Shield Association)

Hyperbaric Oxygen Therapy for Wound Healing - Part 1

This TA evaluated the efficacy of HBO therapy in promoting wound healing in: 1) chronic non-healing wounds, 2) compromised skin grafts or flaps, and 3) acute traumatic peripheral ischemia.

The evidence on chronic non-healing wounds comprised two RCTs of 30 and 70 patients, and two non-randomized controlled trials of 28 and 10 patients. Another RCT of 16 patients evaluated the effects of HBO therapy in chronic non-healing non-diabetic wounds. All of these studies reported beneficial results with the use of HBO.

The evidence on split skin grafts comprised one RCT of 48 patients reported improved survival of split skin grafts when HBO was added to standard surgical management. The study suggested that HBO treatment might be valuable when extensive raw areas have to be covered.

The evidence on crush injuries of the limb comprised one well-designed placebo-controlled double-blinded RCT of 36 patients. A favorable effect was found for adjunctive HBO in reducing the number of surgical procedures and improving the incidence of complete wound healing as compared to placebo patients.

We did not review acute thermal burn data that was presented in this TA since it is not within the scope of our topics.

2. Technology Assessment (Blue Cross and Blue Shield Association)

Hyperbaric Oxygen Therapy for Wound Healing - Part II

This TA evaluated the evidence of the efficacy of HBO therapy for severe infectious wounds that included chronic refractory osteomyelitis, clostridial myonecrosis (gas gangrene), and necrotizing soft-tissue infections.

The evidence on adjunctive HBO and chronic refractory osteomyelitis consists of only one prospective study of 28 patients, which found no statistically significant benefit for HBO on the healing outcome, the speed of healing, the recurrence of infection, or the length of hospitalization.

Four non-randomized comparison studies were identified on the use of HBO therapy for necrotizing soft tissue infections. Two reports (n=29 and n=26) observed a favorable and statistically significant effect on survival when HBO was added to surgical and medical management. Two other studies (n=54 and n=37) found that adjunctive HBO treatment did not reduce mortality.

This TA found no RCTs of HBO therapy on clostridial myonecrosis (gas gangrene). Seventeen different case series that enrolled a total of 903 patients were identified. All patients were treated with a combination of surgical debridement, antibiotic therapy and HBO. The overall reported mortality rate across the series was 22%. The authors of the TA compared

this result with five case series of 118 patients treated without HBO and stated the total mortality rate across the untreated patients was 51%. These averages were not weighted by the study size. A major flaw of this approach is that regimens including HBO therapy were not directly compared to regimens that did not include HBO in the studies, and there may be many differences between the case series other than the addition of HBO that could account for the difference in mortality.

3. Technology Assessment (Blue Cross and Blue Shield Association)

Hyperbaric Oxygen Therapy for Wound Healing - Part III

Part III of the BCBSA's TA evaluated acute traumatic brain injury, spinal cord injury, chronic refractory perineal Crohn's disease, and brown recluse spider bites. We did not review the studies examined in this TA because these topics are outside the scope of this report.

4. Hyperbaric Oxygen Therapy

MSAC applications 1018-1020 assessment report (Australia)

The MSAC technology assessment evaluated the safety and efficacy of HBO for diabetic and non-diabetic wounds, necrotizing soft tissue infections, osteomyelitis, osteoradionecrosis, skin graft survival, soft tissue injuries, crush injuries and other topics not relevant to our report. The MSAC report included only prospective and controlled studies.

1. Diabetic and non-diabetic wounds: Two RCTs and three non-randomized comparative studies were identified for diabetic wounds including diabetic gangrene and diabetic foot ulcers. The MSAC report concluded that HBO is effective in promoting wound healing, and reducing the length of hospital stays and the likelihood of major amputations in patients with diabetic wounds. There may also be cost savings associated with these treatment benefits. Only one RCT on non-diabetic wounds (n=16) was identified. It found that HBO was associated with decreases in the area of chronic non-diabetic wounds. However, the study included only a small number of relatively tightly selected subjects and examined only one outcome measure.

2. Necrotizing soft tissue infections: Six studies on necrotizing soft tissue infections including necrotizing fasciitis and Fournier's gangrene, and the prevention and treatment of osteoradionecrosis were identified and there was some indication that HBO improved survival. However, one study reported that the number of operations was increased in the intervention group.

3. Osteomyelitis: A single study on osteomyelitis showed that HBO did not produce a statically significant improvement over the comparison therapy in length of hospital stay, clinical outcome and recurrence.

4. Osteoradionecrosis: One study provides some evidence that HBO is more efficacious than penicillin in the prevention of osteoradionecrosis. Another study provided some evidence of the efficacy of HBO in the treatment of osteoradionecrosis.

5. Skin graft survival: Two RCTs on skin graft survival were identified. HBO may well demonstrate a beneficial effect on the survival of split skin grafts

and myocutaneous flaps, but the results are difficult to interpret in light of the failure of the studies to adequately describe the patient population and comparison interventions. The outcome measures were also poorly described. A single study found that HBO benefited patients with crush injuries of the lower limbs, although this benefit was mainly reported in terms of decreasing surgical intervention rather than decrease healing time.

Based on the above data, MSAC recommended that public funding for HBO should be provided, in either a multiplace or monoplace chamber, for: diabetic wounds, necrotizing soft tissue infections, and the prevention and treatment of osteoradionecrosis. The report concluded that HBO should not be supported for: non-diabetic wounds, soft tissue radionecrosis, osteomyelitis, skin graft survival and soft tissue injuries including crush injuries.

5. Hyperbaric oxygen treatment in Alberta -Technology Assessment Report

The Alberta report evaluated evidence of HBO treatment and the potential impact on health care costs of a second HBO facility in the province. Conditions this report evaluated that are relevant to our review include gas gangrene, osteoradionecrosis, necrotizing soft tissue infections, lower wound extremities, and compromised skin grafts and flaps. Using systemic review and cost analysis, the report concluded that HBO is efficacious for osteoradionecrosis, diabetic leg ulcers, and gas gangrene. The report also concluded that while some reports suggest a possible use of HBO for soft tissue radiation injuries and necrotizing soft tissue infections, the available evidence appears insufficient to support its routine use in treatment of these conditions. The report concluded that the available evidence does not support the routine use of HBO for refractory osteomyelitis, compromised skin grafts/flaps, and ischemic traumatic peripheral injuries (e.g. crush injury, compartment syndrome).

6. Hyperbaric Oxygen Therapy in the management of Carbon Monoxide Poisoning, Osteoradionecrosis, Burns, Skin Grafts and Crush Injury Birmingham, April 2000

This review focused on five conditions and identified 13 RCTs, six on carbon monoxide poisoning, two on osteoradionecrosis, three on burn, one on skin grafts and one on crush injury. Only the RCTs on osteoradionecrosis, skin grafts and crush injury are relevant to our report. There were two RCTs on osteoradionecrosis, one a double-blinded study that recruited 12 patients and reported a significant reduction in healing time in the HBO group, and the other a study that that recruited 74 patients and reported no effect. One RCT on skin grafts and flaps was identified. In patients with major soft-tissue surgery this study found significant improvements in wound dehiscence, infection and healing time in the HBO group. One RCT on crush injury was identified which reported a significant effect on wound healing particularly in patients over 40 years old.

Overall, this report concluded that there is no convincing evidence that HBO is of benefit for the treatment of osteoradionecrosis, burns, skin grafts or crush injury. However, they commented that there might be a physiological rationale for HBO to be efficacious for conditions involving hypoxia such as osteoradionecrosis and wound healing.

7. A systematic review (Mason, 1999) of foot ulcer in patients with

Type 2 diabetes mellitus. II: treatment

This systematic review assessed the value of HBO for foot ulcers in patients with Type-2 diabetes mellitus. Two RCTs were identified. The first RCT included 70 patients with severe infected diabetic foot ulcers and compared usual care versus usual care plus daily 90-minute sessions of HBO at 2.2-2.5 atmospheres. Participants either had full thickness gangrene or abscess or a large infected ulcer that had not healed after 30 days. After 10 weeks, rates of major amputation were significantly lower in the intervention group. In another RCT of 30 patients with chronic infected foot ulcers compared usual treatment versus usual treatment plus four treatments of HBO over 2 weeks. The risk of major amputation was lower in the intervention group but not significantly.

Evaluation of Original Studies (Table 2)

This section contains an independent evaluation of clinical studies on HBO. Most of these studies reviewed in detail in this section have already been identified in one or more of the TA reports produced by other groups.

1. **Acute traumatic peripheral ischemia**
   We identified a single study on acute traumatic peripheral ischemia. This study by Mathieu (1990) was a case series of 23 patients with post-traumatic limb ischemia. HBO treatments were given at 2.5 ATA. Tissue oxygen level were measured under three successive conditions: the patient breathing normal air, the patient breathing normobaric pure oxygen by facial mask, and the patient breathing pure oxygen at 2.5 ATA. Transcutaneous oxygen levels were measured by the use of a miniature Clark electrode. The overall sensitivity and specificity for predicting the limb's final outcome, when the ratio of Pt_cO_2 in traumatized and non-traumatized limb is < 0.40 at 2.5 ATA of pure oxygen, are 100% and 94% respectively. The study concluded that comparison between transcutaneous oxygen measurements in normal and at 2.5 ATA hyperbaric pure oxygen is a reliable test to predict final outcome in post-traumatic limb ischemia. The capability of hyperbaric oxygen therapy to improve recovery in the borderline cases needs further study. There was no reporting of adverse events in this study.

2. **Crush injuries and suturing of severed limbs**
   Only one study, an RCT on crush injury (Bouachour 1996) which included 36 patients (18 HBO and 18 control) was found. HBO treatments were typically given at 2.5 ATA for 90 minutes, twice daily for 6 days in a multiplace chamber. Wound healing, major surgery, time of healing and length of stay in the hospital were evaluated. Tissue oxygen level around the wound was measured in the study but this was not used as inclusion criteria for HBO treatment. The study concluded that HBO improved complete healing rates and reducing wound infection and wound dehiscence in crush injury. Adverse effects due to HBO were not mentioned.

3. **Acute peripheral arterial insufficiency**
   We found no studies on this topic.

4. **Compromised skin grafts**
   Two studies, both RCTs (Marx 1995, Perrins 1967), were found on skin grafts. HBO treatments were typically given either for a total of 20

sessions or twice daily for 3 days. The number of wound infections, dehiscence, and delayed wound healing as well as survival of patch grafts and sheet grafts, were measured.

These studies did not provide detailed information about the patients' characteristics such as age, sex, and wound duration, or clearly defined diagnostic criteria of the underlying conditions. Tissue oxygen levels around the wound were not measured in these studies. The authors concluded that HBO improved survival of skin grafts and reduced wound infection and wound dehiscence in crush injury. There was no reporting of adverse effects in either study.

5. **Osteoradionecrosis**
Two RCTs and one case series on osteoradionecrosis (Marx 1985, Tobey 1979, McKenzie 1993) were found. HBO treatments were typically given at 2 to 2.5 ATA for a total of 20 sessions. Tissue oxygen levels around the wound were not measured in these studies.

Clinical signs and symptoms and X-ray examinations were performed to evaluate each patient's progress in the two trials. Persistent mucosal and cutaneous coverage of the wound was used as the outcome in the case series. Two of the trials did not provide detailed information about the patients' characteristics such as age and sex.

The authors of the studies concluded that HBO treatment reduced the rate of osteoradionecrosis. The RCTs provided no reporting of adverse effects. The case series reported one case of transient minor blurring of vision.

6. **Soft tissue radionecrosis**
We found no controlled studies (randomized or non randomized) on soft tissue radionecrosis alone; however, the patients in the study by Marx et al. (1995) required skin grafts to treat soft tissue radionecrosis. The study by Marx et al. is discussed in the previous section on compromised skin grafts. Several case series have been published on the use of HBO in soft tissue radionecrosis (Mathews, 1999, Warren 1997, Woo, 1997, Neovius, 1997, Feldmeier, 1995, Bevers, 1995, Weiss, 1994, Norkool, 1993, Feldmeier, 1993, Williams, 1992, Nakada, 1992, Rijkmans, 1989, Ferguson, 1987). All of these studies reported a beneficial effect of the treatment regimen, which included HBO, for this condition. One study compared the patients to historical controls (Neovius, 1997); in this study a greater number of patients healed without surgical intervention in the HBO group, but the authors do not calculate whether this difference is statistically significant. In several of the studies, patients had failed to heal using standard treatments before the trial of HBO (Mathews, 1999, Neovius, 1997, Norkool, 1993, Williams, 1992).

7. **Gas gangrene**
Seventeen studies on gas gangrene were identified, 4 retrospective comparison studies and 13 case series. The number of patients in these series varied from 9 to 139 and included both children and adults. None of the studies measured tissue oxygen levels or used hypoxia as a criteria for wound evaluation. Mortality was used as an outcome measure in most of the studies. The rates of clinical improvement, infections and amputation were also evaluated. The HBO regimen used

was 2 to 3 ATA for 4 to 44 sessions. Each session usually lasted 90 minutes.

Most authors commented that adjunctive HBO was therapeutically beneficial. However, because of the non-comparative nature of case series, it is difficult to assess the therapeutic effects of HBO reliably. The reported mortality rates in these studies ranged from 11% to 52%.

Six case series reported adverse events attributed to HBO. A total of 23 patients with seizures attributed to oxygen toxicity were reported in five studies involving 322 patients. One death occurred in a study of 88 patients. This patient had an uncontrolled seizure and died 2 hours after decompression. This patient was also reported to be severely toxemic and infection was due to an anaerobic streptococcus (Darke 1977). One pneumothorax was reported in one study of 30 patients (Tonjum 1980). Another case of "oxygen toxicity" was reported in the same study (Tonjum 1980) but the details were not reported. This patient died with pulmonary embolism, pneumonia and peritonitis. Other adverse effects included earaches and barotraumatic otitis.

8. **Progressive necrotizing infections**
Six non-randomized and three case-series studies that evaluated the use of HBO in necrotizing fasciitis were identified. (Hollabaugh 1998, Shupak 1995, Sawin 1994, Brown 1994, Barzilai 1985, Risenman 1990, Korhonen 1988, Eltoral 1986, Gozal 1986). HBO was generally given at 2 to 3 ATA for 5 to 7 sessions (a typical session last for 90 minutes) but two studies did not report how the HBO was given. None of the studies measured tissue oxygen levels or used hypoxia as criteria for wound evaluation.

Mortality, length of hospital and ICU stay, duration of antibiotic therapy, healing, and number and type of operations were measured in necrotizing fasciitis.

There were inconsistent findings regarding the survival rates in patients with necrotizing fasciitis. Three studies found that there is no significant difference between HBO and control groups, casting doubt on HBO's effectiveness in reducing patient mortality and morbidity rates (Shupak 1995, Barzilai 1985, Brown 1994). Three other studies found significantly reduced mortality rates in the HBO group (Hollabaugh 1998, Sawin, 1994, Risenman 1990). However, three case series' found increased recovery rate and reduced mortality.

None of these nine studies reported data on adverse events.

9. **Chronic refractory osteomyelitis**
One non-randomized controlled trial (Esterhal 1987) and one case series (Davis 1986) that evaluated the use of HBO on chronic refractory osteomyelitis were identified.

HBO was generally given at 2 and 2.4 ATA for 2 hours and 6 days per week in one study. None of the studies measured tissue oxygen levels or used hypoxia as criteria for wound evaluation.

Outcomes assessed in the studies included recurrence of infection,

length of hospitalization, wound healing, and clinical signs of osteomyelitis.

One non-randomized controlled trial revealed that HBO had no significant effect on the healing outcomes for patients with chronic refractory osteomyelitis (Esterhal 1987). However, the case series found 34 out of 38 patients remained free of clinical signs of osteomyelitis for an average of 34 months. Two patients reported transient vision changes and three patients required tympanostomy tubes.

10. **Chronic non-healing wounds (diabetic and non-diabetic ulcers)**
Two RCTs (Faglia 1996, Doctor 1992) and four non-randomized studies (Faglia 1998, Zamboni 1997, Baroni 1987, Oriani 1990) that evaluated the use of HBO on diabetic wounds were identified.

Tissue oxygen levels around the wound were measured in three studies (Faglia, 1998, Zamboni 1997, Faglia, 1996) but this was not used as an inclusion criteria for HBO treatment nor used for stratification in the analyses. HBO was generally given at 2 to 2.8 ATA for 5 days/week (a typical session last for 45 to 90 minutes).

Outcome measures in studies of diabetic wounds included anatomic clinical features of lesions, wound surface area, complete healing, amputation rate and length of hospital stay. The authors of the studies concluded that HBO is beneficial in the management of diabetic wounds. They found that the use of HBO significantly reduced wound size when compared with standard wound care alone and that the use of HBO was associated with a higher rate of complete healing as well as a decrease in major amputation rates in diabetic wounds (Baroni 1987, Zamboni 1997, Faglia 1998, Oriani 1990).The only adverse event reported was a case of barotraumatic otitis (Faglia 1996) due to HBO therapy.

Only one study included patients with non-diabetic wounds (Hammarlund 1994). Tissue oxygen level around the wound was not measured in the study. HBO was generally given at 2.5 ATA for 5 days/week for total of 30 treatments in a multiplace chamber (a typical session last for 90 minutes). The study found that the use of HBO significantly reduced wound surface area. The wound size decreased at 6-week endpoint when compared with the control group and the investigators concluded that the use of HBO is beneficial in the management of non-diabetic wounds. There was no reporting of adverse effects.

Because the direct evidence base on non-diabetic wounds is limited to a single study of only 16 patients, more research is needed to assess the efficacy of HBO in these patients. The information on the clinical studies of diabetic and non-diabetic wounds is not sufficient to determine whether results in studies on diabetic wounds are generalizable to non-diabetic wounds.

C. Topical Hyperbaric Oxygen Studies (Table 3)

Two RCTs (Leslie 1988, Heng 2001), two non-randomized comparison studies (Lehman 1985, Landau 1998), one prospective cohort (Heng 2000) and seven case series were identified that evaluated the effect of THO on diabetic foot ulcers, necrotic gangrenous wounds, human bite infections, infected

meningomyelocele, rheumatoid arthritis ulcers, burns and other infected leg and foot ulcers.

THO was administered at 1.03-1.04 ATA for most studies, with varying session durations. Three studies had treatment sessions lasting 90 minutes, other studies had treatment sessions of 20 minutes to 12 hours. No studies measured tissue oxygen level as part of the evaluation.

Outcomes measured in the studies include bacterial cultures, complete wound healing, clinical improvement, recurrent ulceration, amputation, length of hospital stay, return to functional status, complications, and costs. Most studies reported that THO enhanced the complete healing rate on wounds (Fischer 1975, Fischer 1969, Diamond 1982, Heng 2000, Ignacio 1985, Olejniczak 1976, Heng 2001, Landau 2001), led to shorter hospitalization and earlier return to functional status (Lehman 1985). The authors also concluded that THO therapy is effective in stimulating angiogenesis, granulation and epithelium formation and inhibiting bacterial growth (Heng 2000, Fisher 1969). However, two studies found no significant difference between THO and control groups in the treatment of lower extremity ulcers (Landau 1998, Leslie 1998).

Two studied reported that there were no adverse effects from the use of THO. The remaining 10 studies made no mention of adverse effects.

It is difficult to draw conclusions from this collection of heterogeneous studies about whether THO is beneficial for any of the conditions studied. The quality and relevance of these studies are also questionable as seven of these reports were case series and five of the studies were published over 20 years ago. Furthermore, unlike systemic HBO where a large body of supportive basic and clinical research has been conducted, there is no similar body of background research for THO.

D. Studies that Measured Tissue Oxygen Level (Table 4)

One RCT (Faglia 1996), two non-randomized comparison studies (Faglia 1998, Zamboni 1997), and five case series (Mathieu 1990, Wattel 1990, Wattel 1991, Smith 1996, Schirmaer 1996) were identified that measured tissue oxygen level on diabetic wounds, post-traumatic limb ischemia, chronic arterial insufficiency, edematous non-healing extremity wounds and other infected leg and foot ulcers. These studies are summarized in evidence table 4. We were unable to retrieve one potentially relevant study (Mathieu 1993).

HBO was generally given at 2 to 2.8 ATA for 5 days/week (a typical session lasts for 45 to 90 minutes). Tissue oxygen level around the wound was measured in all of these studies by using either a miniature Clark electrode or a Radiometer American TCM2 monitor as part of the evaluation.

Complete wound healing, clinical improvement, amputation, and transcutaneous oxygen levels were the outcomes. None of these studies used hypoxia as inclusion criteria for HBO treatment. All studies reported that HBO treatment enhanced the complete healing rate on wounds (Zamboni 1997, Mathieu 1990, Wattel 1990, Wattel 1991, Smith 1996) significantly reduced edema around the wound (Schirmaer 1996) and decreased the rate of amputations (Faglia 1996, Faglia 1998).

One group of investigators concluded that the PT_cO_2 distal to the wound at 2.5 ATA HBO is a reliable indicator to predict final outcome (healing or no change) (Wattel 1989) and is a useful tool to predict the evolution of diabetic foot ulcers (Wattel 1991). Another study from the same group reported that comparison between transcutaneous oxygen measurements in normal air and at 2.5 ATA HBO is a reliable test to predict final outcome in post-traumatic limb ischemia (Mathieu 1990). Smith et al (1996) reported that elevated peri-wound transcutaneous oxygen measurements at 2.4 ATA and reduced peri-wound oxygen measurements at 1 ATA were associated with a more rapid response to HBO therapy in patients with chronic leg wounds.

However, another study found single $PTcO_2$ measurements were not predictive of changes in peri-wound edema or overall wound severity despite significant correlations between pre-therapy peri-wound PtcO2 measured during O_2 and HBO challenges and changes in wound severity. (Schirmer 1996).

There was no reporting of adverse effects in 8 studies.

Answers to specific questions

1. Is there sufficient objective evidence that the use of HBO, as an adjunctive therapy to standard wound care, aids in wound healing?

- *Chronic refractory wounds*
  Most of the TAs that we reviewed concluded that HBO is a beneficial adjunctive therapy to standard wound care in patients with chronic refractory wounds (progressive necrotizing infections, chronic refractory osteomyelitis). Our assessment of the primary studies on this type of wound concurs with their conclusions.

- *Wound conditions covered under current Medicare Policy.*
  Listed next to each of the conditions is the number of randomized, non-randomized comparative studies and case series studies identified through searches of the literature and suggestions of expert peer reviewers:

  1. Acute traumatic peripheral ischemia (1 case series)
  2. Crush injuries and suturing of severed limbs (1 RCT)
  3. Acute peripheral arterial insufficiency (no study)
  4. Compromised skin grafts (2 RCTs)
  5. Osteoradionecrosis (2 RCTs, 1 case series)
  6. Soft tissue radionecrosis (13 case series)
  7. Gas gangrene (4 non-randomized comparison studies, 13 case series)
  8. Progressive necrotizing infections (6 non-randomized studies, 3 case series)
  9. Chronic refractory osteomyelitis (1 non-randomized study, 1 case series)
  10. Chronic non-healing wounds (diabetic ulcers: 2 RCT, 4 non-randomized study; non diabetic ulcers: 1 non- randomized study)

From the studies that we were able to evaluate, there is sufficient objective

evidence that HBO aids in wound healing for: compromised skin grafts, osteoradionecrosis, gas gangrene, progressive necrotizing infections, and chronic non-healing wounds. There is evidence from case series studies suggesting the beneficial effect of HBO for soft tissue radionecrosis.

2. At what point in treatment should HBO therapy be introduced?

The literature provides no guidance on when HBO therapy should be initiated for chronic non-healing wounds. Only two studies that evaluated the effect of HBO on chronic diabetic wounds reported the duration of the wounds prior to treatment, which ranged from at least 6 to 12 months. For acute wounds such as necrotizing faciitis, HBO treatments generally were reported to begin immediately upon hospitalization or after initial wound debridement. In the case series reports on soft tissue radionecrosis, many studies began HBO treatment after failure of a course of standard therapy; however, one study (Mathews, 1999) reported that earlier treatment with HBO led to earlier resolution of cystitis.

3. What other treatment modalities must be employed along with HBO therapy in order to maximize therapeutic benefits?

In all studies, HBO was used as adjunctive therapy in addition to the main treatment modalities of wound debridement and antibiotics.

4. Wounds are generally classified based on diagnosis. Could wounds be classified based on a level of "hypoxia" rather than diagnostic specific (such as diabetic)?

There is insufficient evidence based on the studies we examined to use measured tissue hypoxia as a criteria to determine whether adjunctive HBO treatments might be efficacious in reducing mortality and morbidity. None of the studies evaluated in this report used measured tissue hypoxia as patient inclusion criteria. Only two RCTs (Faglia 1996, Bouachour 1996) and two non-randomized comparison studies (Faglia 1998, Zamboni 1997) reported measurements of transcutaneous tissue oxygen levels. Mean transcutaneous tissue oxygen levels on admission of these studies were: 12mmHg in the HBO group and 35mmHg in the control group (Zamboni 1997), 28mmHg (_13.4) (Faglia 1998), 22mmHg (_10.6) (Faglia 1996), and about 15-19mmHg (Bouachour 1996). These measurements represent averages of the study populations and were not correlated with outcomes of individual patients. Therefore, this information is not useful to guide treatments for individual patients. The large difference in tissue oxygen levels between the HBO group and control group in the Zamboni study also suggests patient selection bias in this non-randomized study that will make interpretation of outcomes difficult.

5. Are there useful criteria to determine when an individual is likely to benefit from HBO therapy or when an individual will be non-responsive to HBO therapy?

Several studies measured whether patients' tissue oxygen level during HBO is predictive of response. One study (Wattel 1990) of 20 patients with chronic arterial insufficiency ulcers (11) and diabetic ulcers (9) reported that wound healing was achieved in all patients who were able to achieve a distal transcutaneous tissue oxygen level of at least 100 mmHg during HBO therapy. Complete healing occurred in 15 of the 20 patients. Two of the authors of this report along with others (Mathieu 1993) reported similar findings in a study of

15 patients in the setting of musculocutaneous flap transplantation.

None of the studies stratified results by any other potential predictors of response.

6. Are there absolute contraindications when considering HBO therapy in mono-place or multi-place chambers?

We found no studies that addressed the issues of efficacy or safety differences between mono-place versus multi-place chambers. Examination of the adverse events reporting from all the studies revealed that oxygen toxicity in the form of seizures was observed up to about 10% of the patients in several studies. One seizure related death occurred in a "severely toxemic" patient who died two hours after an uncontrolled seizure. A patient with pneumothorax was one among several deaths reported in a case series of 30 patients. The pneumothorax was not reported to be the immediate cause of death in this patient. The need to provide emergency care during HBO treatment suggests that multi-place chambers may provide a safer treatment modality although this has not been demonstrated.

7. Which method of measuring tissue oxygen is most reliable and lends itself to standardization throughout large populations?

This question cannot be answered with the studies we reviewed in this report. In our collection of studies, only two RCTs (Faglia 1996, Bouachour 1996) and two non-randomized comparison studies (Faglia 1998, Zamboni 1997) reported transcutaneous measurements of tissue oxygen levels. Three studies evaluated 195 patients with diabetic leg ulcers. The fourth study (Bouachour 1996) involved 36 patients with acute limb injuries and reported that it used the miniature Clarke electrode as the method of transcutaneous measurement. Zamboni (1997) used an instrument from Radiometer America Inc. (TCM3/TINA) and took measurements in noninflamed skin 1cm medially away from the wound edge at the midpoint of the ulcer. The other two reports did not provide specific information about the method of tissue oxygen measurement.

To adequately address this question, a more comprehensive literature search and a set of different inclusion criteria will be required including the use of studies that do not report clinical outcomes.

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