Hyperbaric Oxygen Therapy in Treatment of Hypoxic Wounds

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Background

Hyperbaric oxygen (HBO) therapy is achieved by having the patient breathe 100% oxygen at greater than normal atmospheric (sea level) pressure. Wounds are often hypoxic and hypoxia impairs leukocyte bacteriocidal activities and wound healing. The benefit of HBO is based on the premise that raising tissue oxygen level will therefore enhance the wound healing ability. Adjunctive HBO therapy is used extensively in the management of a variety of disorders ranging from refractory wounds to standard medical and surgical care. The clinical effects of HBO therapy differ for the varying conditions treated.

Potential risks for patients undergoing therapy with HBO include myopia, barotraumatic otitis, pneumothorax, and 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. Some patients with barotraumatic otitis may require the placement of tympanostomy tubes. Serious, life-threatening events are probably rare but not well quantified.

The Center 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.

CMS received a request to evaluate HBO therapy as a treatment for non-diagnostic-specific wounds based on the pathophysiology of wound healing aided by standard wound care and adjunctive HBO therapy. 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 (acute)
2. Crush injuries and suturing of severed limbs (acute)
3. Acute peripheral arterial insufficiency (acute)
4. Compromised skin grafts (acute)
5. Osteoradionecrosis
6. Soft tissue radionecrosis
7. Gas gangrene (acute)
8. Progressive necrotizing infections
9. Chronic refractory osteomyelitis

CMS would like to know whether the current literature supports expanding coverage to include the use of HBO therapy in hypoxic wounds.

CMS also received a request for coverage from Advanced Hyperbaric Technologies, Inc. for the use of topical hyperbaric oxygen (THO) therapy pulsed at 50mmHg intermittent pressure for hypoxic wounds of the extremities and delivered at 22mmHg 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 determine the state of current evidence on the use of HBO as an adjunctive therapy for the treatment of hypoxic wounds. Specific questions that CMS would like to address include:

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 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 are 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 throughout large populations?

The NEMC EPC was also asked to summarized 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 consists of technology assessment and original investigation reports. 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 also conducted a Medline literature search to identify human 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.

For THO, we reviewed the material from Advanced Hyperbaric Technologies, Inc. provided to us by AHRQ. We also conducted a literature search in Medline 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.

Study selection

In this evidence report, we considered only published articles that reported original data, and published in English language, included at least

5 human subjects, evaluated the use of HBO or THO for wound care, and reported clinical outcomes. We accepted randomized controlled trials (RCT), non-randomized comparison studies, and case series.

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

Summary of Technology Assessment Reports

1. Technology Assessment (Blue Cross and Blue Shield Association), August 1999

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 including diabetic and non-diabetic ulcers consists of two RCTs of 30 and 70 patients (Doctor 1992; Faglia 1996), respectively, and two non-randomized controlled trials (Baroni 1987, Zamboni 1997) involving 28 and 10 patients, respectively. Another RCT of 16 patients evaluated the effects of HBO therapy in chronic non-healing non-diabetic wounds (Hammarlund 1994). All of these studies reported beneficial results with the use of HBO.

One RCT (Perrins 1967) of 48 patients reported improved survival of split skin grafts when HBO was added to standard surgical management (protocol consisted of HBO at 2 ATA for 2 hours, twice daily for 3 days). There was a 29% increase in graft take in the HBO-treated patients. The

study suggested that HBO treatment might be valuable when extensive raw areas have to be covered.

One well-designed placebo-controlled double-blinded RCT of 36 patients reported the results of HBO treatment in severe crush injures of the limb (Bouachour 1996). 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), Dec 1999

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 only of one prospective study of 28 patients (Esterhal 1987). HBO was administered at 2 ATA for 2 hours and 6 days per week showed no statistical significant difference in the complete healing rates between HBO-

treated and control patients (79% versus 90%). Among the control group, 13 of 14 patients (90%) who did not receive HBO treatment achieved complete healing. In addition, HBO therapy was reported to have no beneficial effect 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 nercotizing 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 adjunctive HBO treatment did not reduce mortality.

This TA found no RCT on clostridial myonecrosis (gas gangrene) and HBO therapy. Seventeen different clinical series enrolled in 903 patients were identified in this report and all patients were treated with a combination of surgical debridement, antibiotic therapy and HBO. The total reported mortality rate across the series was 22%. They also compared five case series of 118 patients treated without HBO and stated the total mortality rate across the series was 51%. However, their averages were not weighted by the study size and may be biased.

3. Technology Assessment (Blue Cross and Blue Shield Association), Dec 1999

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 not part of the wound categories.

4. Hyperbaric Oxygen Therapy (November 2000 Australia)

MSAC applications 1018-1020 assessment report

The report evaluates the safety and efficacy of HBO for thermal burns, diabetic wounds including diabetic gangrene and diabetic foot ulcers, non-diabetic wounds and decubitus (or pressure) ulcer, soft tissue infections including necrotizing fasciitis, Fournier's gangrene, and necrotizing arachnidism, actinomycosis, soft tissue radionecrosis, osteomyelitis, osteoradionecrosis, skin graft survival, multiple sclerosis and cerebral palsy, cardiovascular conditions including acute myocardial infarctions, cerebrovascular disease, and peripheral obstructive arterial disease (POAD), soft tissue injuries including acute ankle sprains and crush injuries, facial paralysis (Bell's palsy), cluster and migraine

headaches, Legg-Calve-Perthes disease (necrosis of the femoral head, especially prevalent in children), sudden deafness and acoustic trauma, Crohn's disease, osteoporosis, cancer and carbon monoxide poisoning.

Topics in the Australian report that are relevant to our evidence report include the following six conditions: diabetic and non-diabetic wounds, necrotizing soft tissue infections, osteomyelitis, osteoradionecrosis, skin graft survival, soft tissue injuries, and crush injuries.

1. Two RCTs and three non-randomized comparative studies were identified for diabetic wounds including diabetic gangrene and diabetic foot ulcers. The Australian report concluded that HBO is effective in promoting wound healing, and reduced 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 recruited 16 patients 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. 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. 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. 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. 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. 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 (April 1998)

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 and 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 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 four RCTs met our purpose in this evaluation. There were two RCTs on osteoradionecrosis, one double-blinded study that recruited 12 patients reported a significant reduction in healing time in the HBO group, and the other study 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 would 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, they concluded that there is no convincing evidence that HBO is of benefit for the treatment of osteoradionecrosis, burns, skin grafts

or crush injury. However, there may be a physiological rationale for HBO to be efficacious for conditions involving hypoxia such as osteoradionecrosis and wound healing.

7. A systematic review 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.

Summary of studies with original data

For completeness, we evaluated one more condition, chronic non-healing (diabetic and non-diabetic wounds). For the following ten conditions, we found a total of 8 RCTs, 16 non-randomized comparison studies, and 18 case series.

1. Acute traumatic peripheral ischemia

We found no study on this topic.

2. Crush injuries and suturing of severed limbs

Only one study, a RCT on crush injury (Bouachour 1996) including 36 patients (18 HBO and 18 control) was found. HBO treatments were typically given at 2.5 ATA for 90 minutes, twice daily for six days in a mutiplace 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 effect due to HBO was no mentioned.

3. Acute peripheral arterial insufficiency

We found no study on this topic.

4. Compromised skin grafts

Two studies, both RCT (Marx 1995, Perrins 1967) on skin grafts, were found. HBO treatments were typically given either for a total of 20 sessions or twice daily for three 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, as well as clearly defined diagnostic criteria of the underlying conditions. Tissue oxygen level around the wound was not measured in these studies. They concluded that HBO, improved survival of skin grafts and reducing wound infection and wound dehiscence in crush injury. There was no reporting of adverse effects in either study.

5. Osteoradionecrosis

Two RCT_s and one case series on osteoradionecrosis (Marx 1985,

Tobey 1979, McKenzie 1993) were found. HBO treatments were typically given at 2.0 to 2.5 ATA for a total of 20 sessions. Tissue oxygen level around the wound was not measured in these studies.

Clinical signs and symptoms, rate of osteoradionecrosis, and X-ray were measured in two trials and persistent mucosal and sutaneous coverage were measured in the case series.

Two trials did not provide detailed information about the patients' characteristics such as age, sex. They concluded that HBO treatment reduced the rate of osteoradionecrosis. The RCTs provided no reporting of adverse effect. The case series reported one case of transient minor blurring of vision.

6. Soft tissue radionecrosis

We found no study on this topic.

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 criteria for

wound evaluation. Mortality was used as outcome measures in most of the studies. The rates of clinical improvement, infection controlled and amputation were also evaluated. HBO regimen was used at 2 to 3 ATA and the number of sessions ranged from 4 to 44. Each session usually lasting for 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 of 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 attributed to seizure was reported in a study of 88 patients (Darke 1977). One case of fatal pneumothorax was reported in one study of 30 patients (Tonjum 1980). Other adverse effects include earaches and barotraumatic otitis.

8. Progressive necrotizing infections

Six non-randomized and three case-series studies that evaluated the use of HBO in nercotizing 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 (typical session last for 90 minutes) but two studies did not report the data about 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, 3 case series found increased recovery rate and reduced mortality.

None of the studies reported data on adverse events.

9. Chronic refractory osteomyelitis

One non-randomized controlled trial (Esterhai 1987) and one case series (Davis 1986) that evaluated the use of HBO in one 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.

Recurrence of infection, length of hospital, wound healing, and number and type of operations were measured in necrotizing fasciitis.

One non-randomized controlled trials revealed that 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 3 required tympanostomy tubes.

10. Chronic non-healing wounds (diabetic and non-diabetic ulcers)

Two RCTs (Faglia 1996, Doctor 1992) and 4 non-randomized studies (Faglia 1998, Zamboni 1997, Baroni 1987, Oriani 1990) on diabetic wounds that evaluated the use of HBO were identified.

Tissue oxygen level around the wound was measured in three studies (Faglia, 1998, Zamboni 1997, Faglia, 1996) but this was not used as inclusion criteria for HBO treatment. HBO was generally given at 2 to 2.8 ATA for 5 days/week (typical session last for 45 to 90 minutes).

Anatomic clinical features of ulceronecrotic lesion, wound surface area, complete healing, rate amputations and hospital stay were used to measure outcomes in diabetic and non-diabetic wounds.

The studies concluded that HBO is beneficial in the management of diabetic and non-diabetic wounds. They found that HBO significantly reduced wound size when compare with standard wound care alone and had a higher rate of complete healing as well as a decreased in major amputation rate in diabetic wounds (Baroni 1987, Zamboni 1997, Faglia 1998, Oriani 1990).

Only one study reported adverse effects due to HBO therapy, a case of barotraumatic otitis (Faglia 1996).

There was one study on 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 multiplace chamber (typical session last for 90 minutes).

The wound area was scanned into a computer and measured in the non-diabetic wounds.

The study found that HBO significantly reduced wound surface area decreased at 6-week endpoint when compare with control group and concluded that HBO is beneficial in the management of non-diabetic wounds. There was no reporting of adverse effects.

Because of limited data on non-diabetic ulcer, we are not able to conclude whether diabetic and non-diabetic ulcers should be viewed differently.

C. Topical hyperbaric oxygen studies

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 involved diabetic foot ulcers, necrotic gangrenous wounds, human bite infections, infected meningomyelocele, rheumatoid arthritis ulcers, burns and other infected leg and foot ulcers.

THO regimen was used at 1.03-1.04 ATA for most studies, but it differed in session duration. Three studies had treatment sessions lasting 90 minutes, other studies had treatment duration of 20 minutes to 12 hours. No studies measured tissue oxygen level as part of the evaluation.

Bacterial cultures, wound complete healing, clinical improvement, recurrent ulceration, amputation, length of hospital stay, return to functional status, complications, and costs were used to measure outcomes. 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 shorten hospitalization and earlier return to functional status (Lehman 1985). They also found that THO is effective in stimulating angiogenesis, granulation and epithelium

formation and marked inhibition of bacterial growth (Heng 2000, Fisher 1969). However, two studies found that there is no significant difference between THO and control groups in the treatment of lower extremity ulcers (Landau 1998, Leslie 1998).

No adverse effects from the use of THO were noted or reported in the 12 studies.

Answers to specific questions

- *Is there sufficient objective evidence that the use of HBO, as 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 and non-randomized comparative studies (not including case series) evaluated in this rapid response report addressing the topic.

1. Acute traumatic peripheral ischemia (no study)
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 (no study)

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)

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.

- *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 wound. 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 have begun immediately upon hospitalization or after initial wound debridement.

- *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.

- *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 to use measured tissue hypoxia as a criteria to determine whether adjunctive HBO treatments might be efficacious in reducing the mortality and morbidities. 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.

- *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?*

No study we analyzed attempted to address this question. All studies reported summary data of patients and did not stratify their results by potential predictors of response.

- *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. In one study, a patient died as a result of the seizure. One fatality due to pneumothorax was reported in a case series of 30 patients. The need to provide emergency care during HBO treatment suggests that multi-place chambers may provide a safer treatment modality.

- *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. 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.

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Evidence tables

Table 1. Technology Assessment Reports Examined

Name Year Organization/ Country	Title	Indications										
		Chronic non-healing wound (diabetes and nondiabetis)	Acute traumatic peripheral ischemia	Crush injuries	Acute peripheral arterial insufficiency	Skin grafts	Osteo-radionecrosis	Soft tissue radionecrosis	Gas gangrene	Narcotizing infections	Chronic Osteomyelitis	Other unrelated conditions
BC/BS TEC 1 August 1999 USA	Hyperbaric Oxygen Therapy for Wound Healing-Part I	3 R 2 N	1 R			1 R						2 R 5 N
		+	+			–						
BC/BS TEC II August 1999 USA	Hyperbaric Oxygen Therapy for Wound Healing-Part II								4 N 17 C	4 N	1 N	
									+	+/-	–	
BC/BS TEC III August 1999 USA	Hyperbaric Oxygen Therapy for Wound Healing-Part III											
MSAC applications assessment report Nov 2000 Australia	Hyperbaric Oxygen Therapy	3 R 3 N				2 R	1 R 1 N			6 N	1 N	31 R 14 N 1 C
		+				–	–			+/-	–	

Table 1. Technology Assessment Reports Examined (continued)

Name Year Organization/ Country	Title	Indications										
		Chronic non healing wound (diabetes and nondiabetes)	Acute traumatic peripheral ischemia	Crush injuries	Acute peripheral arterial insufficiency	Skin grafts	Osteo-radionecrosis	Soft tissue radionecrosis	Gas gangrene	Necrotizing infections	Chronic Osteomyelitis	Other unrelated conditions
Saunders April 2000 USA	Hyperbaric oxygen therapy in the management of carbon monoxide poisoning, osteoradionecrosis, burns, skin grafts and crush injury			1 R		1 R	2 R					9 R
				+		+	+					
Mason 1999 USA	A systematic review of foot ulcer in patients with type 2 diabetes mellitus II: treatment	2 R										
		+										
Alberta April 1998 Canada	Hyperbaric Oxygen Treatment in Alberta	2 R 2 N		1 R		1 R 1 C	2 N 2 C		1 N	3 N 3 C	1 N 1 C	10 N
		+		+		+	+		+	+	+/-	

Abbreviation: R = randomized controlled trials
N = non-randomized comparison studies
C = case series
+ = significant effect
- = no effect
+/- = conflicting results

Table 2

1. Acute traumatic peripheral ischemia (no study)
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 (no study)
7. Soft tissue gangrene (4 non-randomized comparison, 13 case series)
8. Progressive necrotizing infections (6 non-randomized comparison, 3 case series)
9. Chronic refractory osteomyelitis (1 non-randomized comparison, 1 case series)
10. Chronic non-healing wounds (diabetic ulcers: 2 RCT, 4 non-randomized comparison; non-diabetic ulcers: 1 non-randomized comparison)

1. Acute traumatic peripheral ischemia (no study)

2. Crush injuries and suturing of severed limbs

Part I

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Bouachour 1996 France	36 18 HBO 18 Control	Mean age: HBO 46y (16 sd) Control 52y (21 sd)	RCT, double-blinded, placebo-controlled	Within 6 hour of injury	Type II or III, Gustillo classification depending on soft-tissue injury.	Y Miniature Clark electrode

Part II

Author, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Bouachour 1996 France	HBO 2.5 ATA, 90 minutes twice daily for six days. Placebo 1.1 ATA of air. Multiplace chamber.	Wound healing, major surgery, time of healing, length of stay	ND	Complete healing HBO: 17; Control: 10 $p<0.01$ New surgical procedures HBO: 1; Control: 6; $p<0.05$

3. Acute peripheral arterial insufficiency (no study)

4. Compromised skin grafts

Part I

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Marx 1995 USA *Unable to retrieved article*	160 80 HBO 80 Control	ND	RCT	ND	Patients requiring tissue flaps in tissues radiated to a dose greater than 6400cGy.	N
Perrins 1967 UK	48 24 HBO 24 control	ND (infants excluded)	RCT	NA	Clinical	N

Part II

Author, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Marx 1995 USA	Comparison therapy plus HBO for 20 sessions prior to surgery, then 10 sessions after surgery. Chamber type not reported.	Wound infection, wound dehiscence, delayed wound healing	ND	Wound infection HBO: 5; Control: 19 P=0.001 Wound dehiscence HBO: 9; Control: 38 P=0.001 Delayed wound healing HBO: 9; Control: 44
Perrins 1967 UK	HBO 2 ATA 2 hours on evening of operation and twice daily for three days in a Vicker's clinical transparent pressure chamber	Survival of patch and sheet grafts	ND	Improved survival of skin grafts HBO: 84.2% Control: 62.7%; P<0.01

5. Osteoradionecrosis

Part I

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Marx 1985 USA	74 37 HBO 37 penicillin	No data on age, gender. Patients with indications for removal of one or more teeth in a segment of the mandible that had received >6000 Rads.	RCT, not blinded	Irradiated bone at risk >6 months and <15 years after exposure	Socket wounds which had failed to heal after tooth removal.	N
Tobey 1979 USA	12 HBO unknown controls	ND	RCT, double-blinded	NA	Clinical	N
McKenzie 1993 Canada	26	Median age 56y (28 - 80) 19 M, 7 F	Case series	ND	Strict criteria of Marx et al.	N

Part II

Author, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Marx 1985 USA	HBO 2.4 ATA for 90 minutes, 20 sessions prior, and ten post tooth removal, one session daily for five to six days a week. Chamber type not reported.	Rate of osteoradionecrosis	ND	Rate of osteoradionecrosis HBOT: 5.4% Control: 30%
Tobey 1979 USA	HBO 2.0 ATA for two hours per day, five days per week for eight weeks. Comparator as above but 1.2 ATA. Chamber type not reported.	X-ray, clinical signs and symptoms.	ND	"Significant improvement in HBO group." This is a preliminary report, full analysis of the study apparently never published.
McKenzie 1993 Canada	HBO was delivered at 2.5 ATA, with 100% oxygen for 90 min per drive. Multiplace chamber.	Persistent mucosal and cutaneous coverage	1 case of transient minor blurring of vision	21 of 26 patients improved following HBO as part of treatment regime; 13 of 26 met strict criteria for resolution of disease

6. Soft tissue radionecrosis (no study)

7. Gas gangrene

Retrospective comparison studies: Part I

Authors, year of publication, country	N	Patient demographics	Wound duration	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Gibson 1986 New Zealand	46 29 HBO 12 Control	Age: 16-83y Trauma (n=17) Surgical (n=21) Spontaneous (n=8) Diabetes (n=11)	NA	Clinical and bacteriologic	N
Hitchcock 1975 USA	33 19 HBO 14 Control	Mean age: 52y (15-84)	NA	Clinical and Bacteriologic Gas gangrene infections of the small intestine, colon and rectum	N
Schweigel 1973 Canada	43 7 HBO 36 Control	Gas gangrene due to: Abd surgeries (n=19) Compound fracture (n=42) Other surgeries (n=10)	ND	Clinical and bacteriologic	N
Jackson 1973 Canada	24 15 HBO 9 Control	Posttraumatic =18 Postoperative =6	NA	Clinical and bacteriologic	N

Retrospective comparison studies: Part II

Authors, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Gibson 1986 New Zealand	Average of 4.5 treatments over a two-day period. Monoplace chamber.	Mortality	ND	Mortality: HBO: 9/29 (31) % Control: 7/12 (58%); P<0.05
Hitchcock 1975 USA	A tight-fitting oronasal mask equipped with a demand valve. The bottom time is two hours at 3 ATA	Mortality	ND	Mortality HBO: 7/19 (37%) Control: 7/14 (50%)
Schweigel 1973 Israel	ND	Mortality	ND	No quantitative results reported. "Fewer deaths reported among patients treated with HBO compared to those with HBO compared to those not treated with HBO"
Jackson 1973 Canada	5 sessions at 90 min each, up to 3.0 atm over a 30-hour period Chamber use did not report	Mortality, amputation	ND	Mortality HBO: 4/15 (27%) Control: 5/9 (56%) Amputation (among survivors) HBO: 2/11 Control: 3/4

Case series: Part I

Authors year of publication, country	N	Patient demographics	Wound duration	Diagnostic criteria
Rudge 1993 USA	77	Mean age: 33y (10d - 81y)	NA	Clinical and bacteriological Clostridial Myonecrosis
Trivedi 1990 India	15	13 adults (12 M and 1 F) 2 children (both males)	NA	A swab was taken for smear and anaerobic culture from the wound after inspection
Hirn 1988 Finland	32	Mean age: 55y (17–84) 21 M, 11 F	NA	On the basis of the clinical appearance of the patient and presence of gram-positive rods on a smear
Unsworth 1984 Australia	73	Age 5-85y	NA	Clinical
Hart 1983 USA	139	Mean age: 38y (7-84) 95 M, 44 F	NA	Bacteriologic culture and/or histologic studies of tissues removed
Guidi 1981 Italy	21	No age or gender data	NA	History, clinical evaluation of wound area, X-ray studies, bacteriological findings

Case series, Part I (continued)

Authors year of publication, country	N	Patient demographics	Wound duration	Diagnostic criteria
Tonjum 1980 Norway	30	Mean age 51y (13-83) 23 M, 7 F 12 patients with diabetes	Mean 13 days (13 hours to 8 weeks)	Patients' general condition on admission classified into three stages of serverity: Stage I- mild (1); Stage II – toxic (18); Stage III – moribund (11)
Skiles 1978 USA	33	Age: 24-83y	NA	Clinical history, physical findings and Gram's stain
Fowler 1977 USA	9	ND	NA	Clinical
Darke 1977 UK	88	Mean age: ~54y (10-90) M:F 2.5:1 Diabetes (n=20) 23 %	Less than 24 hours and up to 28 days	Clostridial infection: patients presented with infection and had a positive culture of pathogenic clostridia form the wound or blood. Non-clostridial infection: patients with infection, spreading gangrene and usually gas formation demonstrable clinically or radiologically.
Holland 1975 UK	49	Age: ~10-80y	NA	Clinical evidence and smears of wound secretions demonstrating gram-positive rods
Hart 1974 USA	44	Age: 7-73y	NA	Pathologic examination of debrided tissue and culture of clostridia
Roding 1972 Netherlands	130	ND	NA	Clinical and bacteriologic

Case series: Part II

Author, year of publication, country	HBO Regimen	Outcome measures	Side effects	Major results
Rudge 1993 USA	All patients treated in USAF hyperbaric chambers.(? multiplace)	Mortality, amputation	ND	Survival correlated well with site of infection (P=0.004) and time to HBO (p=0.08)
Trivedi 1990 India	100 % oxygen for 2 hours at approximately 2.5 atm. Each one received a minimum of 3 successive sittings. Vockers monoplace chamber.	Infection control	3 patients had slight earaches during treatments	Within 3-5 sittings, all cases were found to be devoted of clostridial organisms as judged by smear and culture methods
Hirn 1988 Finland	2.5 ATA for 120 minutes. 3 treatments first 24 hours; thereafter continued twice daily until cure. Vockers monoplace chamber.	Mortality	3 patients had convulsions, 3 patients suffered barotrauma	Mortality: 9/32 (28%)
Unsworth 1984 Australia	Five sessions were given in the first 48 hours, each at 2.8 atm for 2 hours, and its use was continued until clinical improvement occurred, in a large walk-in chamber (? Multiplace).	Mortality, amputation clinical improvement	ND	Mortality: 15/73 (22%)
Hart 1983 USA	Monoplace chamber.	Mortality, amputation	8 patients suffered seizures	Mortality: 27/139 (19%) Amputations: 24/139 (17%)

Case series, Part II (continued)

Author, year of publication, country	HBO Regimen	Outcome measures	Side effects	Major results
Guidi 1981 Italy	Each HBO at 2.8 atm lasted for 2 h. Started within 2-3 h after admission or immediately after surgical procedures in a multiplace chamber.	Mortality, amputation, clinical improvement	ND	Mortality: 4/21 (19%) Amputations: 7/21 (33%)
Tonjum 1980 Norway	HBO 3 ATA for 100 min. During the first 24 hours, treatment was given at 8 hours intervals, during the following 2 days at 12 hours intervals, making a total of 7 periods of treatment in a stationary pressure chamber.	Mortality, amputation	One pneumo-thorax. Three patients developed convulsions without sequelae.	Mortality: 9/30 (30%) one death occurred in the patient with pneumothorax, another death in patient with “oxygen toxicity” Amputations: 6/30 (20%)
Skiles 1978 USA	ND	Mortality	Treatment terminated in one patient who developed convulsion	Mortality: 17/33 (52%)
Fowler 1977 USA	HBO at 2.5 to 3 ATA for 90 minutes and then continued every 8 hours for two days, and then every 12 hours for three days (4-11 treatments) in a monoplace chamber	Mortality, amputation	ND	Mortality: 1/9 (11%) Amputations: 3/5 lower extremities cases
Darke 1977 UK	HBO 1.5 to 2 hour were given in a monoplace chamber at 2.5ATA, total exposure of 15-20 hours over 7 days.	Mortality, clinical improvement	8 episodes of convulsions attributed to HBO, one death	Mortality: 28/88 (32%)

Case series, Part II (continued)

Author, year of publication, country	HBO Regimen	Outcome measures	Side effects	Major results
Holland 1975 UK	Five to seven 2 hour of 100% oxygen at 3 ATA. With the first three treatment being completed during the initial 24 hours. Chamber type not reported.	Mortality and morbidity, primary wound closure, organisms recovered	ND	Mortality 13/49 (27%)
Hart 1974 USA	2.5 atm for 90 minutes every 8 hrs for 24 hrs, then twice a day. Multiplace and monoplace chambers.	Mortality	ND	Mortality: 10/44 (23%)
Roding 1972 Netherlands	3 sessions of 2 hours during the first 24 hours, 2 sessions of 2 hours during the second and third 24 hours. Chamber type not reported.	Mortality	ND	Mortality: 29/130 (22%)

8. Progressive necrotizing infections

Retrospective comparison studies: Part I

Authors, year of publication, country	N	Patient demographics	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Hollabaugh 1998 USA	26 14 HBO 12 Control	Mean age: 57y (26 - 87) 10 pts with diabetes (35 %), 9 pts alcohol abuse, 3 pts immunosuppressed	NA	Fournier's gangrene	Clinical	N
Shupak 1995 Israel	37 25 HBO 12 Control	Mean age HBO: 53y (15 sd) 14 M, 11 F Control: 57y (16 sd) 9 M, 3 F	NA	Necrotizing fasciitis	Clinical	N
Sawin 1994 USA	7 4 HBO 3 Control	Mean age: 9 days (3-15) 6 with omphalitis, 1 infected circumcision wound	NA	Neonatal abdominal wall necrotizing fasciitis	Clinical	N
Brown 1994 Canada	54 30 HBO 24 Control	Mean age HBO: 51y (17 sd) 22 M, 8 F Controls: 62y (13 sd) 13 M, 11 F	NA	Major truncal necrotizing infections: necrotizing fasciitis, gas gangrene, Fournier's gangrene	Clinical	N

Retrospective comparison studies: Part I (continued)

Authors, year of publication, country	N	Patient demographics	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Risenman 1990 USA	29 17 HBO (1987-90) 12 Control (1980-87)	Mean age HBO: 60y (14-82); 11 M, 6 F Control: 69y (41-88); 7 M, 5 F. On admission, 1/12 patient in control was in shock vs 5/17 HBO patients, 4 patients (33%) had diabetes mellitus.	ND	Patients with necrotizing fasciitis, gas gangrene, or Fournier's disease	Clinical	N
Barzilai 1985 Israel	11 3 HBO 8 Control	Mean age HBO: 48 (13 sd); 3 M Control: 56 (9 sd); 6 M, 2 F	NA	Necrotizing fasciitis	Clinical	N

Retrospective comparison studies: Part II

Author, year of publication, country	HBO Regimen	Outcome Measures	Side Effects	Major results and comments
Hollabaugh 1998 USA	90 minutes at 2.4 atm Mean duration of HBO 12 days. Chamber type not reported	Mortality	ND	Mortality HBO: 1/14 (7%); Control: 5/12 (42%)
Shupak 1995 Israel	HBO at 2.5 atm, 2 cycles of 45 min each separated by 5 min of air breathing, until improvement. INMI's walk-in chamber.	Mortality and morbidity, and risk factors for grave prognosis	ND	Mortality HBO: 9/25 (36%); Control: 3/12 (25%); p=N.S. Length of hospital stay HBO: 16d ± 6.4; Controls: 20d ±13.8; p=N.S.
Sawin 1994 USA	ND	Mortality	ND	Mortality HBO: 2/4; Control: 0/3
Brown 1994 Canada	HBO administered at 2.5-3 atm 90 min per session, HBO followed each debridement until no evidence of necrosis, 80% of patients received < 5 sessions; 20% of patients received 5-7 sessions. Chamber type not reported.	Mortality, length of hospital and ICU stay, duration of antibiotic therapy and number and type of operations	ND	Mortality HBO: 9/30 (30%); Control: 10/24 (42%); P=NS No significant differences in duration of hospital or ICU stay, or duration of antibiotic therapy.

Retrospective comparison studies: Part II (continued)

Author, year of publication, country	HBO Regimen	Outcome Measures	Side Effects	Major results and comments
Risenman 1990 USA	90 minutes at 2.5 ATA every 8 hours first day, then twice daily for total of 10 treatments. Monoplace chamber	Mortality, debridements	ND	Mortality HBO: 4/17 (23%) Control:8/12 (67%); P<0.025 Mean debridements/patients: HBO: 1.2 per case Control: 3.3 per case; P<0.03
Barzilai 1985 Israel	ND	Mortality	ND	Mortality HBO: 2/3 (66%) Control: 5/8 (62%)

Case series: Part I

Authors year of publication, country	N	Patient demographics	Wound duration	Condition(s)	Diagnostic criteria
Korhonen 1988 Finland	33	Mean age: 51y (24–84) 31 M, 2 F 7 diabetes, 4 alcoholism, 2 immunosuppressed	2-7 days	Fournier's Gangrene	Identification of multiple pathogenic organisms in the primary Gram stain or culture, and systemic toxicity.
Eltorai 1986 USA	9	Age: 44-65y 1 patient with diabetes	NA	Fournier's gangrene	Clinical and bacteriologic
Gozal 1986 Israel	16	Mean age: 51.9y (20-84) 5 patient with diabetes	ND	Necrotizing Fasciitis	Clinical

Case series: Part II

Author, year of publication, country	HBO Regimen	Outcome measures	Side effects	Major results
Korhonen 1988 Finland	2.5 ATA for 120 min. 3 treatments during the first 24 hours; then continued twice daily until clearing of toxic symptoms of clostridial infection. Both Vockers monoplace chamber and multiplace chamber.	Mortality, amputation	ND	Mortality: 3/33 (9%)
Eltorai 1986 USA	Four to 12 (one patient needed 40) sessions of HBO at 2 to 2.5 ATA. Chamber type not reported.	Recovery	ND	All patients recovered
Gozal 1986 Israel	Three HBO session in the first 24 hours and two sessions per day thereafter. Each session consists of 100% oxygen at 2.8 to 3 ATA for 90 min in a multiple hyperbaric chamber.	Mortality	ND	Mortality: rate of 12.5%

9. Chronic refractory osteomyelitis

Part I

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Esterhal 1987 USA	28 14 HBO 14 control	matched by staging system and general health status mean age: 40y (15-74) 19 M, 9 F	Non-randomized controlled trial	Mean 70 months (8-628) (data verified)	Uncomplicated chronic refractory osteomyelitis	Osteomyelitis staging system per Cierny, Mader, and Penninck	N
Davis 1986 USA	38	Mean age: 40y (16-76) 24 M, 14 F	Case series	Average 8.9 y (6-15)	Non-hematogenous osteomyelitis had been present for at least 6 months	Clinical and bacteriological	N

Part II

Authors, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Esterhal 1987 USA	Daily administration for 2 hours at 2 ATA, 6 days per week Chamber type not reported.	time to wound healing, initial clinical outcome, length of hospitalization, recurrence of infection	ND	Treatment failures: HBO: 3/14 Control: 1/14 .
Davis 1986 USA	HBO 2.4 ATA. Chamber type not reported.	Clinical sign of osteomyelitis Free of infection	3 patients required tympanotomy tubes; 2 patients reported transient vision changes	34 of 38 patients remained free of clinical signs of osteomyelitis for an average of 34 months

10. Chronic non-healing wounds

Part I

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Faglia 1996 Italy	70 35 HBO 33 Control	Mean age HBO: 62y (10.4 sd); Control: 54y (7.8 sd) 84 M, 31 F	RCT	ND	Severe infected diabetic foot ulcers	Lesions were classified according to Wagner grading method	Y $TcPO_2$ on admission
Doctor 1992 India	30 Number of subjects in study arms can not be determined	Mean age: HBO: 56y (45-70) M : F = 3 : 1 Control: 60y (48-70) M : F = 2 : 1	RCT	ND	Diabetic patients with chronic foot lesions hospitalized	Clinical	N

Part II

Author, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Faglia 1996 Italy	100% oxygen at 2.5 ATA In 1st phase, 2.2 - 2.4 ATA in 2nd phase. 90 min daily in 1st phase 5d/wk in 2nd phase. Multiplace chamber.	Vascular procedures, amputation rates	2 subjects with barotraumatic otitis (did not interrupt treatment)	Major amputations HBO: 3/35 (8.6%) Control: 11/33 (33.3%) Risk ratio: 0.26 (0.08-0.84); P=0.016
Doctor 1992 India	4 sessions of HBO over 2 weeks at 3 ATA for 45 min each. Monoplace chamber	Wound cultures, assessment of local wound daily, skin flaps, hospital stay, need for amputation, level of amputation	ND	Above ankle amputations HBO: 2/15, Control: 7/15; P<0.05 Minor (others) amputations HBO: 4/15, Control: 2/15; P=NS Number of positive cultures decreased from baseline of 19 to 3 in HBO; 16 to 12 in control, P<0.05

Non-randomized comparative studies

Part I

Authors, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Faglia 1998 Italy	115 51 HBO 64 Control	Mean age: 63y (10 sd) 84 M, 31 F	Comparative study	ND	Diabetic wounds	Clinical (lesions were classified according to Wagner)	Y (not used as criteria)
Zamboni 1997 USA	10 5 HBO 5 Control	Mean age HBO: 84y (8.9); 4 M, 1 F Control: 54y (7.8); 4 M, 1 F Outpatient setting. There is a trend that the wound size and T_cPO_2 is worse in HBO group but not statistically significant.	Controlled trial Patients who refused HBO treatment served as controls	> 6 months	Chronic lower extremity diabetic wounds	Clinical	Y (not used as criteria) (TCM3/ TINA, Radiometer American Inc)
Baroni 1987 Italy	28 18 HBO 10 Control	HBO: mean age 58y (41-72) 11 M, 7 F Control: mean age 59y (46-75) 6M, 4F	Controlled trial control group subjects refused HBOT for psychological reason	ND	Ulceronecrotic diabetic foot lesions	Clinical and Bacteriological	N

Non-randomized comparative studies: Part I (continued)

Authors, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Oriani 1990 Italy	80 62 HBO 18 Control	Mean age HBO: 53y (12 sd) Control: 58y (8 sd)	Retrospective comparison. Controls consist of patients who refused HBO or contraindication	ND	Diabetic patients with ulceronecrotic lesions	Clinical	N

Non-randomized comparative studies: Part II

Authors, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Faglia 1998 Italy	In the first phase: HBOT at 2.5 ATA, A daily session (90 min for each session). In the second phase: 2.4-2.2 ATA. Chamber type not reported.	Major amputations	ND	Major amputations: HBO: 7/51 Control: 20/64 P=0.012
Zamboni 1997 USA	30 HBO treatments at 2 ATA 2 hr/day, 5 day/wk for 7 weeks Chamber type not reported.	Wound surface area, complete healing, amputations	ND	HBO in conjunction with standard wound care significantly reduced wound size when compare with standard wound care alone (P<0.05). At 4 to 6 month follow-up, the HBO treated patients had a higher rate of compete healing (4/5 versus 1/5), no amputation in either group
Baroni 1987 Italy	100 % oxygen at 2.8 ATA 90 min daily. Multiplace chamber	Amputation, anatomic clinical features of ulceronecrotic lesions	ND	Healing HBO: 16/18 (89%); Control: 1/10 (10%) P=0.001 Amputation HBO: 2/18; Control: 4/10
Oriani 1990 Italy	Initial HBO at 2.8 ATA, then at 2.5 ATA 6 days a week until beginning granulation and then 5 days a week until recovery. Chamber type not reported.	“Recovery”, amputation	ND	“Recovery” HBO: 59/62 (96%) Control: 12/18 (67%) Amputation HBO: 3/62 (5%) Control: 6/18 (33%) P<0.001

2) Non-diabetic ulcers

Part I

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Hammarlund 1994 Sweden	16 8 HBO 8 Control	Median age: 67y (42-75); 9 M, 7 F No large vessel disease as measured by ultrasound Doppler.	RCT, double-blinded, placebo-controlled	More than one year	Non-diabetic leg ulcers. No signs of healing the prior 2 months.	Clinical	N

Part II

Author, year of publication, country	HBO regimen	Outcome measures	Side effects	Major results and comments
Hammarlund 1994 Sweden	HBO: 100 % oxygen at 2.5 ATA, 90 min, 5 days/wk for total of 30 treatments. Multiplace chamber.	The wound area was scanned into a computer and measured.	ND	Mean wound surface area decreased at 6 week endpoint HBO: 35.7 % (±17%) Control: 2.7 % (±11%) $P < 0.001$.

Table 3. Topical hyperbaric oxygen studies

Table 3. Topical hyperbaric oxygen studies – Part I

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue pO_2 (Y/N)
Leslie 1988 USA	28 12 HBO 16 Control	Mean age 49 y (32-71) 16 M, 12 F Both groups were similar in age, clinical characteristics at baseline	RCT	Mean 6.3 wk (1-32)	Diabetic wounds	A well-demarcated foot ulcer, diagnosis of diabetes mellitus, absence of gangrene	N
Heng 2001 USA	40 29 THO 50 Control	THO age 73.8 (SD=6.4) 13 M Control age 75.5 26 M, 1F	RCT	ND	Necroticlgangrenous wounds	Clinical	N
Lehman 1985 USA	43 16 HBO 27 Control	ND	Prospective comparison study (claims to be randomized, but not true)	ND	Human bite infections	Clinical and bacteriologic	N
Landau 1998 Israel	50 15 THO 35 Control	Age: 59 ± 11y Range 38-88 M=28; F=22	Non randomized comparison	9 ± 6.6 month, range 2-70	Chronic diabetic foot ulcers	Clinical	N

Table 3. Topical hyperbaric oxygen studies – Part I (continued)

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Heng 2000 USA	15	Mean age: 76y (56-92) 8 M, 7 F 11 diabetes	Prospective cohort	ND	Necrotic gangrenous wounds	Unchanged or worsened for 6 or more weeks before THO treatment	N
Fischer 1969 USA	52	Age: 9-84y 2 diabetes	Case series, 6 cases used self control	Months to years	Lesions of the lower extremities	Clinical	N
Fischer 1969 USA	8	Age: 1 to 14 days	Case series	NA	Infected meningomyelocele	Clinical	N
Fischer 1975 USA	30	Age: 8-95y	Case series	15 days to 6 years	Burns, pressure sores, venous stasis ulcers, infected surgical wounds, rheumatoid arthritis ulcers	Clinical	N
Olejniczak 1976 USA	174	93 M, 81 F	Case series	ND	Leg Ulcers due to various etiologies	Clinical	N
Diamond 1982 USA	11	Age: 25-85y 1 diabetes	Case series	ND	Lower extremity Ulcerations	Clinical	N

Table 3. Topical hyperbaric oxygen studies – Part I (continued)

Author, year of publication, country	N	Patient demographics	Study design	Wound duration	Condition(s)	Diagnostic criteria	Measured tissue PO_2 (Y/N)
Ignacio 1985 USA	15	12 diabetes	Case series	ND	Extensive leg and foot ulcers	Clinical	N
Landau 2001 Israel	100	ND	Case series	7 ± 5 months	Diabetic foot ulcers	Clinical	N

Table 3. Topical hyperbaric oxygen studies – Part II

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Author, year of publication, country	THBO regimen	Outcome measures	Side effects	Major results and comments
Leslie 1988 USA	THBO 90 min twice daily with a topical hyperbaric bed chamber which provided humidified 100% oxygen at pressures cycling between 0 and 30 mmHg every 20 secs.	Bacterial cultures, measurements of the ulcers	ND	Ulcer area and changes in ulcer depth revealed no statistically significant differences between treatment groups
Heng 2001 USA	THBO at 1.04 ATA	Wound measurements Histological assessment Cost analysis	ND	Wound healing: THO: 90% Control: 22% The size of ulcers (at 4 weeks) THO: significantly smaller Control: larger
Lehman 1985 USA	50 mmHg 100% oxygen is cycled every 30 seconds for 90 minutes twice daily.	Hospital stay, return to functional status complications	ND	Shorter hospitalization and earlier return to functional status was found in the severe infection subgroup treated with THBO
Landau 1998 Israel	Oxygen 100% was pumped into the bag and the pressure in the chamber was kept to between 20 and 30 mmHg(1.02-1.03 ATM)	Clinical improvement	No side effect	There was no significant clinical difference between the topical hyperbolic oxygen alone or combined with a low power laser. Both methods should be considered in the treatment of chronic diabetic foot ulcers.

Table 3. Topical hyperbaric oxygen studies – Part II (continued)

Author, year of publication, country	THBO regimen	Outcome measures	Side effects	Major results and comments
Heng 2000 USA	Oxygen flow into the bag at the rate of 15 L/min. Pressures at least 10 mm below capillary filling pressures. 4h/day, 4 consecutive days each week, over a 4-week period.	Wound healing (Ulcer size, severity grading of wounds) Costs	ND	22 of 24 ulcers (13 of 15 patients) were healed by 12 weeks.
Fischer 1969 USA	A constant 22 mmHg (1.03 ATA) of pure oxygen at a flow-rate of 2-8 L/min continuously for 4-12 hr/day	Healing of lesions	ND	6 failures out of 52 patients
Fischer 1969 USA	A constant 22 mmHg (1.03 ATA) of pure oxygen at a flow-rate of 1-4 L/min for a total of 10 hr/day	Cessation of cerebrospinal fluid leakage, bacterial growth	ND	Cerebrospinal fluids leakage is stopped as soon as pressurized oxygen was applied. Marked inhibition of bacterial growth Granulation and epithelium formation are stimulated
Fischer 1975 USA	Oxygen at 4L/min at pressure not exceeding 22 mmHg (1.03 ATA) twice daily, each session 2-3 hours.	Healing of lesions	ND	Completed healing of all lesions
Olejniczak 1976 USA	3.4 liters per minute oxygen flow is applied twice a day for 20 min, with pressure in each bag from 0 to 5 mmHg	Complete healing	ND	Compete healing: 33/33 (100%) posttraumatic ulcers 11/11 (100%) varicose veins 87/91 (96%) phlebitis 10/33 (30%) arteriosclerosis ulcers
Diamond 1982 USA	22 mmHg at a flow rate of 4 L/min. All treatments were 90 min, twice a day.	Clinical improvement, bacterial cultures	ND	Total healing in all 11 patients who were refractory to outpatient management.

Table 3. Topical hyperbaric oxygen studies – Part II (continued)

Author, year of publication, country	THBO regimen	Outcome measures	Side effects	Major results and comments
Ignacio 1985 USA	16 to 20 mmHG pressure for 45 min each session using a disposable, inflatable, vinyl sleeve applied twice a day.	Assessment of the vascular integrity, and complete pictorial documentation of the size of the ulcers and the progress of response	ND	Complete healing in 11 of 15 patients (73%).
Landau 2001 Israel	THO was administered by pumping 100% humidified oxygen Into a hyperbaric chamber, 150 min x 2 to 3/week, up to 1.4 atm	Total cured Recurrent ulceration Amputations	No side effect	Cure: 81/100 (81%) Recurrent ulceration: 3/81 (4%) Amputations: 19 THO therapy may be a safe, simple, and inexpensive early adjunctive treatment for patients with chronic diabetic foot ulcers.