Hyperbaric Oxygen Therapy

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which medical services should attract funding under Medicare.

This report was prepared by the Medicare Services Advisory Committee (MSAC) with the assistance of Dr Elmer Villanueva, Dr Renea Johnston, Ms Ornella Clavisi, Ms Elizabeth Burrows, Ms Vivienne Bernath, Ms Meera Rajendran, Mr Jason Wasiak, Dr Paul Fennessy and Associate Professor Jeremy Anderson, Centre for Clinical Effectiveness, Monash Institute of Public Health, Monash University and Mr Anthony Harris and Ms Karen Yong, Health Economics Unit, Monash University. The report was endorsed by the Commonwealth Minister for Health and Aged Care on 9 February 2001.

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Hyperbaric oxygen therapy (HBOT) involves the intermittent inhalation of 100 per cent oxygen in chambers pressurised above one atmosphere absolute. The treatment duration and number of sessions required depend on the reason for HBOT. Each treatment duration can vary from 45 to 300 minutes, although most treatments are in excess of 90 minutes, for a variable number of sessions.

This report evaluates the safety and effectiveness of HBOT for the following indications: thermal burns; diabetic wounds including diabetic gangrene and diabetic foot ulcers; non-diabetic wounds and decubitus (or pressure) ulcers; soft tissue infections including necrotising fasciitis, Fournier's gangrene, and necrotising 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.

Medicare Services Advisory Committee – role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. The medical literature available on the technology is searched and the evidence assessed and classified according to the National Health and Medical Research Council (NHMRC) four-point hierarchy of evidence. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of hyperbaric oxygen therapy

Safety

Potential risks for patients undergoing therapy with hyperbaric oxygen are myopia, barotrauma, claustrophobia or oxygen toxicity. Estimates of incidence are uncertain, although most adverse events are self-limiting and resolve after termination of therapy. Serious, life-threatening events are rare.

Published guidelines seek to provide industry-wide acceptance of recommendations and requirements for the safe operation of hyperbaric facilities. Staffing levels, training, and qualifications are explicitly provided by these documents.

Effectiveness

Thermal burns

The identified studies were disparate in their research designs, varied in their populations, inconsistent in their therapies, and conflicting in their outcomes and conclusions. Overall, there is little firm evidence and a lack of well-conducted studies to support the use of hyperbaric oxygen therapy for thermal burns.

Diabetic wounds

The similar characteristics of the collected studies and their statistical homogeneity provided some confidence in the effects of HBOT on specific outcomes. Major amputations were less likely in diabetic patients with chronic ulceronecrotic lesions who were exposed to HBOT compared to those receiving comparison therapies only. For these patients there was some indication that HBOT promoted wound healing and reduced length of hospital stay, but also increased the risk of minor amputations. These last few outcomes represent inferences drawn on a smaller population group, with wide margins of error, and further studies are required. These results, in the light of low uptake rates of the technology for this particular indication, generally indicate there is potential for this technology in the treatment of diabetic wounds.

Non-diabetic wounds

There is some indication that exposure to 100 percent oxygen in a hyperbaric chamber for lengths up to a month was associated with decreases in the area of chronic, non-diabetic wounds. However, the evidence comes from just one study which included small numbers of relatively tightly-selected subjects and examined only one outcome measure. More studies in different settings, examining more varied outcomes (eg. absolute wound healing) are required to provide more generalisable evidence of a treatment effect.

Necrotising soft tissue infections: general

Overall, there was some indication that HBOT improved survival in patients with necrotising soft tissue infections. However, one study indicated the number of operations was increased in the intervention group. The studies addressing these conditions looked at different populations of patients and their research designs were dissimilar. This made it difficult to quantify the effects of HBOT. However, any final judgment should be reserved until more conclusive evidence is available.

Necrotising soft tissue infections: necrotising fasciitis

The studies collected looked at different populations, the sample sizes were small, and information about the HBOT intervention was inadequate. The studies presented little firm evidence to support the use of hyperbaric oxygen therapy for necrotising fasciitis.

Necrotising soft tissue infections: Fournier's gangrene

A single study suggests patients with Fournier's gangrene will benefit from exposure to HBOT. However, there is some concern about the possibility of systematic differences

affecting the outcome. More rigorous studies in different settings and examining more varied outcomes are required to provide more generalisable evidence to confirm a positive effect.

Osteomyelitis

The regime of HBOT reported in the single identified study does not seem to be beneficial to patients diagnosed with osteomyelitis in terms of their length of hospital stay, the treatment successes and the risk of recurrence following therapy. However this regime is atypical in several respects of HBOT regimes used for other indications, calling into question the extent to which the findings may be generalisable.

Osteoradionecrosis: prevention

A single study provides some evidence that exposure to HBOT is more efficacious than penicillin in the prevention of osteoradionecrosis in this population of patients. The patient sample is representative of the potential target population to which inferences are to be applied.

Osteoradionecrosis: treatment

One study provides some evidence of the efficacy of HBOT in the treatment of osteoradionecrosis. More evidence from properly randomised clinical trials focussing on other outcomes will be needed to determine the effectiveness of HBOT for this indication.

Skin graft survival

Exposure to HBOT may well demonstrate a beneficial effect on the survival of split skin grafts and myocutaneous flaps, but the studies identified possess serious flaws that strictly limit their generalisability. Results are difficult to interpret in the light of the failure of the studies to adequately describe their patient populations and comparison interventions, and the limited and poorly-described outcomes they measured.

Multiple sclerosis

The studies do not consistently demonstrate any beneficial effect of HBOT on clinical outcomes of multiple sclerosis. There is little evidence to support the use of HBOT for this indication at this time.

Cardiovascular disease conditions: acute myocardial infarction

There is no firm evidence to support the use of HBOT for acute myocardial infarction. The studies that examine this issue either do not find beneficial effects on major end-points or suffer from flaws in design. There is some indication that HBOT used in conjunction with thrombolytic therapy may be beneficial in pain relief although more studies are needed to arrive at a firm and generalisable conclusion.

Cardiovascular disease conditions: cerebrovascular disease

The collected evidence examines only a small number of clinical outcomes. In these end-points, the effectiveness of exposure to HBO is conflicting. There is evidence of small improvements in functional status, but these are seen a year after therapy is initiated. Whether these changes are scale-independent is questionable. Of potential concern is the

evidence that exposure to HBO may be no better than placebo or sham therapy. The review concluded that no firm and generalisable evidence is available to support the use of HBOT for cerebrovascular disease at this time.

Cardiovascular disease conditions: peripheral obstructive arterial disease

A single, small trial provides little evidence of benefit. Some of the methodology used during the trial and the conclusions drawn from it are cause for concern. The study provided no evidence of the efficacy of HBOT for peripheral obstructive arterial disease.

Soft tissue injuries: acute ankle sprains

A single study provided no evidence to support the use of HBOT for acute ankle sprains.

Soft tissue injuries: crush injuries

A single study found that exposure to HBOT benefited patients with crush injuries of the lower limbs, although this benefit was mainly reported in terms of decreasing surgical interventions rather than decreased healing time. Studies examining a broader range of outcomes in larger populations are required to generate firmer and more generalisable conclusions.

Cluster headaches

There is some evidence of a beneficial effect on pain relief and physiochemical outcomes in patients with some forms of cluster headache exposed to HBOT. Concerns about the methodology of the studies and their quality strictly limit their usefulness. These concerns included small sample sizes, inadequate masking, and inability to control for temporal or measurement bias. The Hawthorne effect, in which responses by participants are affected because they know they are being studied, is also an important consideration. Only one of the studies measured clinically relevant outcomes. More rigorous studies in different settings and examining more varied outcomes in bigger groups of patients are required to provide firmer and more generalisable evidence of effect. At this time, the evidence found is insufficient to support the use of HBOT in cluster headaches.

Migraine headaches

Exposure to HBO seems to provide pain relief for migraine headaches. However, more studies in different settings and examining more varied outcomes in larger groups of patients are required to provide further conclusive evidence of a firm and generalisable effect.

Facial paralysis

A single report provided some evidence of the benefit of exposure to HBO for subjects with moderate to severe forms of facial paralysis of less than one week duration. Replication of this study to other settings and an examination of other outcomes are required to come to firm and generalisable conclusions.

Sudden deafness and acoustic trauma

The studies provided conflicting evidence of the efficacy of HBOT in the management of sudden deafness and acoustic trauma. Problems with methodology were common in

the identified studies. Until more rigorous evidence is collected, the use of HBOT in the management of these conditions cannot be supported on the basis of the current inconsistent results.

Cancer: head and neck

The identified studies were disparate in their research designs, varied in their populations, discrepant in their therapies, and conflicting in their outcomes and conclusions. Overall, there is a lack of well-conducted studies to support the use of hyperbaric oxygen therapy for head and neck cancer and there is little firm evidence of a beneficial effect.

Cancer: cervix

The studies failed to provide enough evidence to come to firm conclusions about the effectiveness of exposure to HBO in conjunction with radiotherapy for cervical cancer. Any conclusions reached from these studies would need to take into consideration the disparity in intervention and comparison protocols, poor methodological descriptions, and substantial *post-hoc* comparisons.

Cancer: bladder

There are conflicting results about the survival benefit afforded by exposure to HBOT in conjunction with radiotherapy for bladder cancer. The lack of methodological rigour, the variations in protocols, and inadequate descriptions of populations make it difficult to arrive at a global assessment of effectiveness.

Cancer: lymphomas

A single study provides some evidence of the efficacy of HBOT in the treatment of lymphomas. The validity of the end-points used is unclear. The generation of evidence from properly randomised clinical trials that focus on other outcomes is needed to support or refute the effectiveness of HBOT for this indication.

Cancer: lung

A single study provides little evidence of the effect of HBOT in the treatment of lung cancer. More studies in different settings and examining more varied outcomes are required to reach more generalisable evidence of effect.

Cancer: neuroblastoma

While this study provides some evidence of the effect of HBOT in the treatment of neuroblastoma, the use of this technology cannot be supported until more rigorous evidence is collected.

Carbon monoxide poisoning

A Cochrane systematic review failed to demonstrate a significant reduction in neurologic sequelae following HBOT for carbon monoxide poisoning. Additional rigorous studies are required to examine the efficacy of HBOT on other outcomes and in distinct patient subsets.

No available evidence

No evidence was collected for the following indications: necrotising arachnidism, actinomycosis, soft tissue radionecrosis, cerebral palsy, Crohn's disease, Legg-Calve-Perthes disease, and osteoporosis.

The following indications were not formally evaluated as the Supporting Committee agreed they have little clinical acceptance and/or have been minimally reported in the literature: cyanide poisoning, head trauma, cerebral oedema, acquired brain injury, cognitive impairment, senile dementia, glaucoma, keratoendotheliosis, HIV infection, anaemia from exceptional blood loss, insulin dependent diabetes mellitus, facial neuritis, arthritis, spinal injuries and non-union of fractures.

Indications not reviewed in this report

HBOT is widely accepted as standard clinical care for decompression illness, gas gangrene air and gas embolism. There are limited alternative treatment options for these life-threatening conditions. Therefore, MSAC did not review the evidence for the effectiveness of HBOT in them, particularly as much of the relevant literature was published many years ago.

Cost effectiveness

Based on a cost per course of treatment of $6,941 and the evidence of the review of its effectiveness, it seems monoplace HBOT could be cost-effective in the treatment of diabetic wounds, and necrotising soft tissue infections and could save resources in those treatments. For osteoradionecrosis, HBOT may cost an estimated $28,480 per case avoided. It needs to be recognised however that the true cost of monoplace HBOT may be considerably different from this depending on how the facility is staffed and operated, and that there is considerable uncertainty surrounding the true effectiveness of HBOT and associated health cost offsets in these indications.

Recommendations

MSAC recommended that public funding for hyperbaric oxygen therapy should be supported for hyperbaric oxygen therapy (HBOT) administered in either a multiplace or monoplace chamber, as appropriate, for the following indications:

- decompression illness, gas gangrene, air or gas embolism. HBOT is widely accepted as standard clinical care in the management of these life-threatening conditions for which there are limited alternative treatment options;

- diabetic wounds including diabetic gangrene and diabetic foot ulcers. There is evidence that HBOT 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; and

- necrotising soft tissue infections including necrotising fasciitis and Fournier's gangrene, and the prevention and treatment of osteoradionecrosis. These are serious conditions in which HBOT provides a non-invasive treatment option which may have a beneficial effect and offer cost savings. Further studies are required to provide

more conclusive evidence of an effect but are difficult to undertake due to the ethical and practical constraints of conducting trials in these conditions. Public funding should be continued for HBOT use in these conditions until conclusive evidence becomes available that indicates it is not effective or that other treatments are preferable and more cost-effective.

Since there is currently insufficient evidence pertaining to HBOT use in the following indications, MSAC recommended that public funding should not be supported for HBOT administered in either a multiplace or monoplace chamber, for:

- thermal burns, non-diabetic wounds and decubitus (or pressure) ulcers, necrotising arachnidism, actinomycosis, soft tissue radionecrosis, osteomyelitis, 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, carbon monoxide poisoning, cyanide poisoning, head trauma, cerebral oedema, acquired brain injury, cognitive impairment, senile dementia, glaucoma, keratoendotheliosis, HIV infection, anaemia from exceptional blood loss, insulin- dependent diabetes mellitus, facial neuritis, arthritis, spinal injuries and non-union of fractures.

MSAC has not considered safety standards for HBOT services administered in either multiplace or monoplace chambers, in detail, but endorses a standard for facilities, staffing and training which meets that in development by Standards Australia.

Introduction

The Medicare Services Advisory Committee (MSAC) evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer affairs and health administration.

The Hyperbaric Oxygen Therapy (HBOT) Supporting Committee of MSAC (membership at Appendix B) has supervised a systematic review of the use of hyperbaric oxygen therapy for the following indications: thermal burns; diabetic wounds; non-diabetic wounds; nectrotising soft tissue infections including necrotising fasciitis, Fournier's gangrene, and necrotising arachnidism; osteomyelitis; osteoradionecrosis and soft tissue radionecrosis; survival of skin grafts and flaps; multiple sclerosis; cardiovascular conditions including acute myocardial infarctions, cerebrovascular disease, and peripheral obstructive arterial disease; soft tissue injuries including acute ankle sprains and crush injuries; cluster and migraine headaches; facial paralysis; sudden deafness and acoustic trauma; neoplastic conditions including cancers of the head and neck, cervic, bladder, lung, and lymphomas and neuroblastomas; carbon monoxide poisoning; actinomycosis; Crohn's disease; Legg-Calve-Perthes disease; and osteoporosis.

This report summarises the assessment of current evidence for the use of hyperbaric oxygen therapy in these indications.

Background

Hyperbaric oxygen therapy

This evaluation was undertaken in response to an application for assessment of adjunctive hyperbaric oxygen therapy delivered in monoplace-only facilities, which is currently ineligible for funding under the Australian Medicare Benefits Scheme (see Current Reimbursement Arrangement, pg 5). However, the scope of the review was broadened to consider all indications for hyperbaric oxygen therapy identified in the initial search, although in most cases it is used as an adjunctive treatment only.

Evidence from studies on hyperbaric oxygen therapy delivered in either monoplace or multiplace systems was evaluated and no attempt was made to perform a comparative assessment of the two types of delivery systems. This was done because, according to expert clinical opinion, the therapeutic effect is the same regardless of the delivery system. The higher pressures that multiplace chambers can deliver was not an issue in the evaluation as the majority of treatments are administered at less than 3ATA.

No comparative studies of efficacy or safety in monoplace and multiplace systems were found. However, there are marked regional variations in the delivery system used, which are reflected in the literature. Australian clinical practice and expertise is primarily in the use of multiplace chambers because the majority of the long-established hyperbaric facilities have multiplace chambers only. In contrast, clinical practice in the United States is primarily monoplace-based as many facilities, including those used for intensive care patients, are equipped solely with monoplace chambers.

The procedure

Hyperbaric oxygen therapy (HBOT) involves the intermittent inhalation of 100 per cent oxygen in chambers pressurised above one atmosphere absolute (ATA).[1,2] An ATA is defined as the atmospheric pressure at sea level and is equivalent to 101.3 kiloPascals (kPa) or about 14.7 pounds per square inch.

Exposure to hyperbaric oxygen (HBO) is measured by the pressures used in single-treatment exposures to HBO and the number of treatment sessions. Tolerance to therapy is dependent on both these parameters. In general, HBOT is well-tolerated if pressures do not exceed three ATA (approximately 300 kPa) and lasts less than two hours. Depending on the reason for HBOT, treatment duration can vary from 45 to 300 minutes, although most treatments are in excess of 90 minutes, for a variable number of sessions.[1-4]

Treatment with HBO is administered in two types of chambers – monoplace and multiplace chambers. A monoplace chamber accommodates a single patient and is the most common type of chamber in use worldwide.[3] It can be pressurised with either 100 percent oxygen or with air, in which case oxygen is delivered to the patient via a mask, hood or endotracheal tube. The smaller size of the chamber translates to relative portability and lower cost, but imposes limits on ready access to the patient. The risk of fire is increased in oxygen chambers due to the pure oxygen used to fill the chamber.[4]

Multiplace chambers can accommodate several occupants, including observers, and medical and support personnel. Instead of 100 percent oxygen, the chamber is pressurised with air, while subjects undergoing therapy breathe pure oxygen through masks, hoods, or endotracheal tubes. The chamber's larger size allows personnel to enter and move about with relative ease in order to deal with acute problems. The risk of fire is also reduced due to the administration of pure oxygen through patient-specific devices.[4]

Intended purpose

As a large number of indications for hyperbaric oxygen therapy was identified in the initial literature search, a decision was made by the Supporting Committee to exclude from evaluation those indications for which HBOT is widely accepted as the clinical standard of care and those that have little clinical acceptance, or have been minimally reported in the literature. Those indications considered standards of care and not evaluated were decompression illness, gas embolism and gas gangrene.

The indications chosen for evaluation by the Supporting Committee were: thermal burns; diabetic wounds including diabetic gangrene and diabetic foot ulcers; non-diabetic wounds and decubitus (or pressure) ulcers; soft tissue infections including necrotising fasciitis, Fournier's gangrene, and necrotising 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.

The indications excluded from evaluation because they have little clinical acceptance, and/or have been minimally reported in the literature are: cyanide poisoning, head trauma, cerebral oedema, acquired brain injury, cognitive impairment, senile dementia, glaucoma, keratoendotheliosis, HIV infection, anaemia from exceptional blood loss, insulin dependent diabetes mellitus, facial neuritis, arthritis, spinal injuries and non-union of fractures.

Clinical need

Brief prevalence data for some of the indications examined in this report are shown in Table 1. No reliable Australian estimates are available for Fournier's gangrene, necrotising arachnidism, osteoradionecrosis, acute ankle sprains, sudden deafness and acoustic trauma, radionecrosis, cerebral palsy, Crohn's disease, and Legg-Calve-Perthes disease.

Table 1 Measures of disease burden for selected conditions.

Condition	Hospital Separations	Deaths	Years of Potential Life Lost	References
Thermal burns	6,063*#	34†¶	609†¶	5, 6
Diabetic foot Amputations**	972‡# 2,800§#			7
Non-diabetic wounds	780‡#			7
Necrotising fasciitis	108‡#			7
Actinomycosis	174‡#			7
Problem Wounds Osteomyelitis Skin grafts	 2,225‡# 35,780‡#			 7 7
Cardiovascular disease conditions Acute myocardial infarction Cerebrovascular disease Peripheral obstructive arterial disease	 28,632‡# 24,976‡#	 29,051§# 12,133§# 411†¶	 65,448†¶ 24,114†¶ 2,528†¶	 6-8 6-8 6
Crush injuries	1,153‡#			7
Multiple sclerosis		36†¶	586†¶	6
Cluster and migraine headaches	16,015‡#			7
Facial paralysis	654‡#			7
Osteoporosis		24†¶	146†¶	6
Carbon monoxide poisoning	568‡#			7

* 1995-1996 data.

† 1996 data.

‡ 1997-1998 data.

§ 1997 data

\# National estimates

¶ Victorian estimates

** Prevalence estimated as 25 per 1,000 population. Incidence estimated as 1.1 per 1,000 population. Both figures are 1998 national rates. (Colagiuri S, Colagiuri R, Ward J. National Diabetes Strategy and Implemenation Plan. Canberra: Diabetes Australia, 1998.)

Existing procedures and comparators

In this review, exposure to HBO is compared to procedures not using HBO, including standard or conventional therapy (variously defined), normobaric oxygen, or placebo procedures. The effectiveness of one HBOT protocol against another is not examined.

Marketing status of the device

The Hyox monoplace unit was listed on the Australian Register of Therapeutic Goods (ARTG) on 27 July 1995 as AUST L 53179 (TGAIN approval No. 66805). Multiplace chamber, as fixed installations, are exempted from listing on the ARTG.

Current reimbursement arrangement

Medicare Benefits Schedule item numbers 13020, 13025, 13030 cover hyperbaric oxygen therapy performed in a comprehensive hyperbaric medicine facility.[9] There are also two item numbers (18022 and 18026) which cover administration of an anaesthetic during hyperbaric therapy where the medical practitioner is or is not confined in the chamber (including the administration of oxygen).

For the purposes of these items, a comprehensive hyperbaric medicine facility is defined in the Schedule as "a separate hospital area that, on a 24 hour basis:

(a) is equipped and staffed so that it is capable of providing to a patient:
- hyperbaric oxygen therapy at a treatment pressure of at least 2.8 atmospheric pressure absolute (180 kPa gauge pressure); and
- mechanical ventilation and invasive cardiovascular monitoring within a multiplace chamber for the duration of the hyperbaric treatment.

(b) is supported by:
- at least one specialist anaesthetist, consultant physician or medical practitioner who holds the Diploma of Diving and Hyperbaric Medicine of the South Pacific Underwater Medicine Society (SPUMS) who is rostered and immediately available to the hyperbaric facility during normal working hours;
- a registered medical practitioner who is present in the hospital and immediately available to the facility at all times when patients are being treated at the hyperbaric facility; and
- a registered nurse with specific training in hyperbaric patient care to the published standards of the Hyperbaric Technicians and Nurses Association who is present during hyperbaric oxygen therapy.

(c) has defined admission and discharge policies."

There is also a regulation (Regulation 14 of the *Health Insurance Regulations 1975)* precluding payment of Medicare benefits for professional services rendered in relation to the use of hyperbaric oxygen therapy in the treatment of multiple sclerosis.

Medicare benefit payments were limited to services performed in comprehensive hyperbaric medical facilities because of concerns about standards of patient selection and management and staff supervision and training in monoplace-only hyperbaric facilities which were managed by health professionals other than medical practitioners.

An industry based code of practice, the Hyperbaric Oxygen Therapy Facilities Industry Guidelines (HOTFIG)[10], has recently been developed which addresses treatment protocols, staffing, safety standards and industry training and certification in both monoplace and multiplace facilities. This is a consensus document developed by the Australian & New Zealand Hyperbaric Medicine Group (a subcommittee of SPUMS), the Special Interest Group in Diving and Hyperbaric Medicine of the Australian and New Zealand College of Anaesthetists, the Hyperbaric Technicians and Nurses Association Australia, and industry representatives. An Australian standard based on these guidelines is also under development by Standards Australia Committee SF46. A draft, "DR 00249 Work in compressed air and hyperbaric facilities - Part 2: Hyperbaric oxygen treatment facilities" was published for comment on 1 September 2000 and is available from Standards Australia at http://www.standards.com.au/.

The most comprehensive Australian data available on HBOT services are self-reported data collated by the Hyperbaric Technicians and Nurses Association (HTNA). These data are mainly from the six public hospital hyperbaric units and two other chambers which are used for naval and commercial diving injuries. The 1998/99 figures also include data from two major private hospital units. Annual figures for the past three years are at Table 2, and the number and percentage of patients by indication are at Table 3. No data are available for HBOT services provided by stand-alone private clinics.

Table 2 Australian hyperbaric unit data

Indication	Patients treated		
	1996/97	1997/98	1998/99
Decompression illness	342	322	289
Radiation tissue injury	144	202	260
Problem wound healing	140	183	280
Carbon monoxide poisoning	136	135	106
Osteomyelitis	41	56	63
Acute ischaemic wound	36	48	50
Necrotising fasciitis	33	27	39
Gas gangrene	13	9	9
Spider bite	11	13	12
Other electives	101	72	90
Other emergencies	77	42	91
Total patients	1090	1141	1289
Total treatments	11785	13553	16796

Table 3 1998 – 1999 self-reported data from Australian hyperbaric units by indication

Indication	No of Patients	% of Total Patients (N=1289)
Decompression illness	289	22.3
Osteoradionecrosis	146	11.3
established ORN	114	8.8
prophylactic ORN	32	2.5
Soft tissue radionecrosis	114	8.8
established	106	8.2
prophylactic	8	0.6
Carbon monoxide poisoning	106	8.2
Diabetic ulcers	100	7.7
Vascular ulcers	98	7.6
Refractory osteomyelitis	63	4.9
Other problem wounds	41	3.2
Necrotising fasciitis	39	3.0
Surgical wound incisions – problem wound	30	2.3
Compromised flaps and grafts	24	1.9
Crush injury	18	1.4
Acute gas embolism – diving	18	1.4
Smoke inhalation	14	1.1
Retinal arterial/ vein occlusion	14	1.1
Other ocular ischaemic pathology	12	0.9
Spider bite	12	0.9
Other bubble injury	10	0.8
Clostridial myonecrosis	9	0.7
Acute gas embolism – Iatrogenic	7	0.5
Cystoid macular oedema	7	0.5
Compartment syndrome	6	0.5
Decubitus ulcers	5	0.4
Frostbite	4	0.3
Acute hearing loss	4	0.3
Thermal burns	2	0.2
Radiation problem wound	2	0.2
Temporal arteritis	1	0.1
Myonecrosis	1	0.1
Malignant otitis externa	1	0.1
Tinnitus	1	0.1

Approach to assessment

Review of literature

This review follows methods outlined in the Cochrane Collaboration Handbook[11] appropriately modified to deal with observational studies.

Literature search

The medical literature was searched to identify relevant studies and reviews for the period between 1966 and 1999. Table 4 lists the electronic databases used in the search.

Table 4 Electronic databases (including edition) used in the review.

Database	Period Covered
Best Evidence (Ovid)	1991 to 1999
Biological Abstracts (Ovid)	1985 to October 1999
CINAHL (Ovid)	1982 to October 1999
Cochrane Library including: the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness, and the Cochrane Controlled Trials Register	Issue 4, 1999
EMBASE (Ovid)	1988 to October 1999
HealthSTAR	1975 to October 1999
Medline (Ovid)	1966 to November 1999
National Guidelines Clearinghouse	November 1999
Nursing Collection (Ovid)	1995 to September 1999

A two-stage search strategy was employed. The first stage attempted to retrieve a subset of articles focusing on HBOT, regardless of indication. The search terms used are given in table 5.

Table 5 Search terms used to identify citations for the first stage of literature retrieval*

hyperbar$†
hbo$
multiplace chamber
monoplace chamber

Terms were searched as text words. A medical subject heading (MeSH) term search was conducted, if allowed by the database.

† Represents wildcard.

The second stage of literature retrieval focused on individual indications for HBOT. The search terms given in Table 5 were combined with terms specific for each indication (Table 6).

Table 6 Indication-specific search terms used to identify citations for the second stage of literature retrieval.

Indication	Search terms*
Thermal burns	burns, burn$†
Diabetic wounds	diabetic foot, diabetes mellitus, wounds and injuries, diabetic gangrene, gangrene, amputation, diabet$, wound$, ulcer$
Non-diabetic wounds and decubitus ulcers	wounds and injuries, decubitus ulcer, pressure sore, bed sore, bed ulcer
Necrotising soft tissue infections (narcotising fasciitis, arachnidism, Fournier's gangrene)	necrotizing fasciitis, arachnidism, arachnida, spider bite, Fournier's gangrene, Fournier$
Actinomycosis	actinomycosis
Cardiovascular disease conditions (AMI, CVD, POAD)	cardiovascular disease, stroke, cerebrovascular disorders, vascular diseases, physiologic neovascularization, angiogenesis
Radiation necrosis	radiation injuries, radiotherapy, radiation sickness, radiation necrosis
Osteoradionecrosis	osteoradionecrosis
Osteomyelitis	osteomyelitis
Skin graft survival	skin transplantation, surgical flaps, graft survival, dermoplasty, plastic surgery
Soft tissue injuries	orthopedics, orthopedic procedures, athletic injuries, sports, sports medicine, fractures, compartment syndromes, sport injur$, Volkman$
Multiple sclerosis and cerebral palsy	multiple sclerosis, cerebral palsy, spastic diplegia, Little's disease
Facial paralysis	facial paralysis, Bell's palsy
Cluster and migraine headaches	headache, cluster headache, migraine, vascular headache
Legg-Calve-Perthes disease	Legg-Perthes disease, Legg$
Sudden deafness and acoustic trauma	sudden deafness, acoustic trauma, noise-induced hearing loss
Crohn's disease	Crohn disease, Crohn$
Osteoporosis	osteoporosis
Cancer therapy	neoplasms, cancer
Carbon monoxide poisoning	carbon monoxide, CO

* Terms were searched as text words. A medical subject heading (MeSH) term search was conducted, if allowed by the database. American English spellings were used in the first instance, with UK English spelling variations included.

† Represents wildcard.

Electronic searching included the Internet sites of the following health technology assessment groups:

- International Society of Technology Assessment in Health Care;[12]
- International Network of Agencies for Health Technology Assessment[13](and 28 member organisations, see Appendix F);
- British Columbia Office of Health Technology Assessment (Canada);[14]
- German Health Technology Assessment Project;[15]
- Center for Medical Technology Assessment (Sweden);[16]
- Scottish Health Purchasing Information Centre (Scotland);[17]

- Medical Technology and Practice Patterns Institute (USA);[18]
- NIH Office of Medical Applications of Research (USA);[19]
- Office of Technology Assessment Archive (USA);[20]
- RAND Corporation (USA);[21]
- University Health Systems Consortium (USA);[22]and
- the Veterans Affairs Technology Assessment Program (USA).[23]

Other Internet sites are listed in Appendix H.

Access to the Database of Randomised Controlled Trials in Diving and Hyperbaric Medicine (DORCTHIM) and a number of publications were made available by members of the MSAC Supporting Committee. Some publications were acquired from health technology assessment agencies and professional organisations. Textbooks and book chapters were assessed. Reference lists of publications were scanned and relevant citations retrieved.

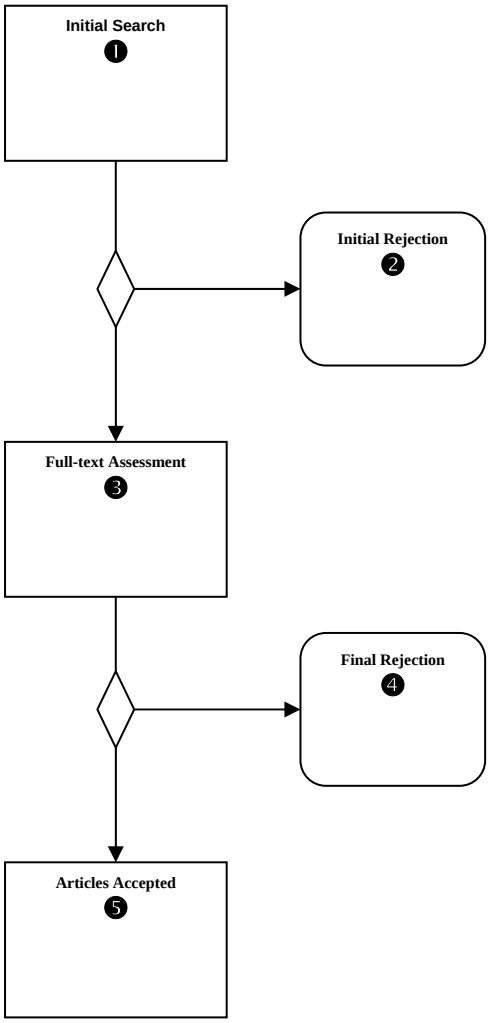
Inclusion and exclusion criteria

Collected citations were filtered through a multi-level review involving a team with skills in clinical medicine, public health, health information, basic science, and clinical epidemiology. Articles were excluded if they met the following criteria:

- focus was not one of the indications determined by the Supporting Committee;
- therapy was not HBO in a monoplace or multiplace chamber;
- uncontrolled studies or those that did not have a comparison group;
- articles that included data presented in later studies; and
- publications in a language other than English.

Figure 1 outlines the process of article selection and exclusion. An initial assessment of the abstracts of collected citations selected out articles that did not meet the selection criteria. Ambiguous or uncertain citations proceeded to the next stage. From an initial search of 5,477 articles, 5,300 were rejected, leaving 177 articles to be assessed in full-text form. Full text articles from the remaining citations were retrieved and assessed further. A final decision was made to reject articles based on a thorough reading of the complete article. Only the studies that successfully passed this process are discussed further. In this review, 80 studies were assessed to have met inclusion and exclusion criteria.

Phase of Search



Indication	❶	❷	❸	❹	❺
Thermal burns	113	104	9	1	8
Diabetic wounds	111	104	7	2	5
Non-diabetic wounds	1,283	1,281	2	1	1
Necrotising soft tissue infections	116	102	14	8	6
Actinomycosis	8	8	0	0	0
Skin graft survival	170	168	2	0	2
Cardiovascular disease conditions	1,334	1,326	8	3	5
Radiation necrosis	231	224	7	7	0
Osteoradionecrosis	136	130	6	4	2
Osteomyelitis	132	130	2	1	1
Soft tissue injuries	790	784	6	4	2
Multiple sclerosis and cerebral palsy	114	93	21	4	17
Facial paralysis	7	4	3	2	1
Cluster and migraine headaches	71	62	9	5	4
Legg-Calve-Perthes disease	2	2	0	0	0
Sudden deafness and acoustic trauma	31	21	10	6	4
Crohn's disease	19	19	0	0	0
Osteoporosis	3	3	0	0	0
Cancer	806	735	71	49	22
Carbon monoxide poisoning	389	360	29	12	4
Total	5,866	5,660	206	109	84

Figure 1 Outline of search, retrieval, and selection process. Table at right shows the number of citations at each phase of the procedure.

Data extraction

The review extracted data from accepted articles using a standardised instrument created for this assessment. Two independent reviewers examined each article. Discrepancies in evaluation were discussed and resolved through consensus.

Assessment of quality

All accepted articles underwent an assessment of study quality based on criteria that focus on important aspects of study design (Table 7).[24,25]

Table 7 Domains and levels used in the assessment of methodologic quality.

Randomisation	
Adequate	Adequate measures to conceal allocations such as central randomisation; serially numbered, opaque, sealed envelopes; or other descriptions that contain convincing elements of concealment
Unclear	Unclearly concealed trials in which the author failed to describe the method of concealment with enough detail to determine its validity
Inadequate	Method of allocation is not concealed, such as alternation methods or the use of case numbers
None	No randomisation method was employed
Masking	Masking strategy applied (triple, double, etc.)
Losses to Follow-up	Losses specified.

The review assessed evidence presented in the selected studies and classified it according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence (Table 8).[26]

Table 8 Designation of levels of evidence.

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

Source: NHMRC[26]

Assessment of heterogeneity

The review used a two-stage process to examine the heterogeneity of treatment effects. Firstly, the clinical and epidemiological attributes of the identified research in each indication category were examined to establish whether they were sufficiently similar to justify further analysis. If this was the case the second stage of assessment of heterogeneity moved on to statistical analysis. The review used the Cochran Q statistic[27] to test the hypothesis that the reported treatment effects for each indication were equal. The Q statistic is known to have low power in detecting heterogeneity.[28] For this reason, the review specified a Type I error rate of ten percent ($\alpha = 0.10$) for this test,[29] and examined Galbraith diagrams[30] and L'Abbé plots[31] generated from the extracted data. All statistical analyses were performed using Stata version 6.0 (Stata Corporation, College Station, Texas, USA).

Conduct of meta-analysis

When the degree of homogeneity was acceptable on statistical and clinical grounds, summary estimates of odds ratios and weighted mean differences was derived using a random-effects model.[32] The review checked the robustness of the summary estimate by performing sensitivity analyses. Standard statistical convention was followed and a Type I error (the probability of detecting a difference when one is not present) was assumed for all analyses at five percent ($\alpha = 0.05$).

Expert advice

A supporting committee with expertise in hyperbaric medicine, neurology, sports medicine, plastic surgery and radiation oncology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

Adverse events

Potential risks for patients undergoing therapy with HBO are listed in Table 9. Most available data on adverse events are retrospective case series; properly designed and conducted studies are lacking. This suggests that estimates of incidence are uncertain, although the nature of the event might be recognised.

Table 9 Adverse events associated with exposure to hyperbaric oxygen.

Myopia	Claustrophobia
Barotrauma	Decompression illness
Oxygen toxicity	

The most common adverse events associated with the procedure include middle ear barotrauma and reversible myopia.[1,2,4] The first occurs in about 2% of subjects. Measures to prevent or treat this condition have been studied with some recommendations currently available.[33,34]

Progressive myopia is associated with prolonged, daily exposure to HBO[35-37] and is more common in higher pressures. Spontaneous reversal usually occurs within a few days to several weeks after therapy is discontinued. There is some evidence that extending the number of exposures to more than 100 increases the risk of irreversible changes to the refractive media of the lens or to the development of new cataracts.[1,2] In an observational study published in Sweden, 24 of 25 patients (mean age of about 65 years) undergoing at least 150 hourly sessions of HBOT for persistent leg ulcers developed myopia of one diopter or more. The mean change in refraction was 3.0 diopters. Of 15 subjects with clear lens nuclei before treatment, seven developed cataracts with definite increases in the turbidity of the lens nucleus. More than half developed these changes within six months of exposure to HBOT. Termination of therapy did not lead to a reversal of changes to the lens.[37] While some patients may require extended exposure to HBOT, which is dependent on several factors, it is uncommon for the number of sessions to exceed 60 treatment sessions (usually 90 minutes at 2.4 ATA) in Australian clinical practice.

Claustrophobia may induce anxiety when patients are placed in the confines of the treatment chamber. Mild sedatives may assist in the continuation of therapy.

Oxygen toxicity may be manifested as pulmonary or neurologic changes and are often a major cause for concern. Seizures have been estimated to occur at a rate of about 0.01 percent[1] but do not seem to produce residual effects.

Operational safety guidelines and recommendations

Hyperbaric Oxygen Therapy Facilities Industry Guidelines (HOTFIG)

Guidelines published under the auspices of the Hyperbaric Technicians and Nurses Association (HTNA) were released in August 1998, although preliminary work started as

early as 1995. The guidelines – known as HOTFIG[10] – were developed to provide industry-wide codes of practice and involved representatives from the Australia and New Zealand Hyperbaric Medicine Group (ANZHMG), HTNA technicians, HTNA nurses, and suppliers and operators of hyperbaric chambers.

HOTFIG was envisaged to be a consensus document with industry-wide acceptance and sought to provide recommendations and requirements for the safe operation of hyperbaric facilities. To wit: "All of [HOTFIG] will comply with the world's best practice." In August 1999, HTNA released amendments to the original document. The major sections are discussed below.

Hyperbaric facility

It was recommended that consideration be given to proper access, fire protection, emergency procedures, and patient support. Issues relating to the treatment chamber include advice about the pressure vessel, viewports, doors, penetrators, fixtures and furniture, and other physical structures.

Operational systems and preventive maintenance

Recommendations for monoplace and multiplace chambers are given separately, although proposals are shared between the two. Various aspects of operation discussed in the document include air pressurisation encompassing air purity, monitoring and storage; breathing gas systems including oxygen supply and gas analysis; environmental conditioning; communications; patient monitoring; and lighting, electrical, and fire suppression systems.

HOTFIG recommends that established written procedures be in place for regular preventive maintenance of the hyperbaric system and its ancillary equipment. Emergency protocols should likewise be established and regularly reviewed. Some emergency situations identified by HOTFIG include loss of primary pressurising gas, loss of primary oxygen source, rapid changes in chamber pressures, fire, and patient states including oxygen toxicity seizures, cardiac arrest, barotrauma, pneumothorax claustrophobia or acute anxiety and accidental extubation.

Personnel

HOTFIG recommendations for staffing of hyperbaric facilities focus on three aspects: general concerns, training and qualifications, and minimum staffing levels.

General concerns include recommendations for hazard identification and risk assessment, and determination of appropriate staffing. The following qualified personnel be available:

- medical director – a physician with special knowledge in the diagnosis, treatment and assessment of disorders treated with HBO and having special training or experience in the management of clinical hyperbaric medical problems;

- consultant hyperbaric physician – a physician with training and experience in hyperbaric medicine who is able to prescribe HBOT and is medically accountable for the safety of patients and staff. Minimum requirements are completion of an

approved course (two weeks minimum), six months full time (or equivalent) supervised training in a recognised hospital with a consultant hyperbaric physician, and possession of a Diploma in Diving and Hyperbaric Medicine administered by SPUMS or equivalent;

- hyperbaric physician – a physician with training and experience in hyperbaric medicine who is able to prescribe HBOT and is medically accountable for the safety of patients and staff. Minimum requirements are less than those for a consultant hyperbaric physician and include full registration as a medical practitioner by the appropriate Medical Registration Board and successful completion of an introductory course in hyperbaric medicine;

- hyperbaric attendant – a person who has successfully completed a course to a level at or exceeding hyperbaric attendant qualifications as provided by the Hyperbaric Nurses Courses in Australia. An "inside" attendant should be medically fit to enter the chamber with a skill set reflective of the needs of the patients undergoing treatment. The "outside" attendant need not be medically fit to enter the chamber unless emergency protocols require such entry.

- chamber operators – monoplace operators and hyperbaric technical officers are personnel who have completed training courses, the minimum standards of which are suggested in HOTFIG.

A general outline of staff qualifications is given in Table 10.

Table 10 Minimum staff qualifications suggested by HOTFIG.[10]

Staff	Qualification	Training	Experience	Patient Type*	Comments
Medical Staff					
Consultant hyperbaric physician	Diploma in hyperbaric medicine	Diploma course	12 months	All	
Hyperbaric physician	Registered medical doctor	Introductory course in HBOT	Desirable	P1	Have communication link to a consultant hyperbaric physician
Inside Attendant					
Critical care trained	Minimum standards as set in HOTFIG	5 days	20 hours	All	Critical care experience and fitness to dive
No critical care training	Minimum standards as set in HOTFIG	5 days	20 hours	P1 or P2	Fitness to dive
Outside Attendant					
Critical care trained	Minimum standards as set in HOTFIG	5 days	20 hours	All	Critical care experience and optional fitness to dive
No critical care training	Minimum standards as set in HOTFIG	5 days	20 hours	P1 or P2	Optional fitness to dive
Chamber Operators					
Hyperbaric technical officer	Hyperbaric technical officer	Minimum standards as set in HOTFIG	50 cycles of occupied chambers	All	
Monoplace operators	First aid and oxygen resuscitation	Minimum standards as set in HOTFIG	Work experience	P1 or P2	Doctor available in three minutes

*HOTFIG patient type classification: P1 = elective / non-medical intervention patients, P2 = patients requiring adjunctive medical intervention, P3 = critically ill patients. The medical director of the hyperbaric facility has responsibility for patient classification.

HOTFIG also recommends that minimum staffing levels be appropriately determined based on the following factors: type of chamber, type and number of patients, treatment parameters, and backup and emergency management resources. Table 11 summarises HOTFIG recommendations.

Table 11 Minimum staffing levels by chamber type suggested by HOTFIG.[10]

Staff	Patient Type*	Monoplace	Multiplace	
			Single Lock	Multilock
Hyperbaric Physician	All	Consultant hyperbaric physician		
	P1	Hyperbaric physician		
Inside Attendant	P1 or P2	Not required	Patient attendant – fit for pressure	
	P3	Not required	Patient attendant – critical care trained and fit for pressure	
Outside Attendant†	P1	Patient attendant	Not required	Patient attendant – fit for pressure
	P2	Patient attendant		Patient attendant – fit for pressure
	P3	Patient attendant – critical care trained	Patient attendant – fit for pressure	
Chamber Operator†‡	P1 or P2	Monoplace operator	Hyperbaric Technical Officer	
	P3	Hyperbaric Technical Officer		

* HOTFIG patient type classification: P1 = elective / non-medical intervention patients, P2 = patients requiring adjunctive medical intervention, P3 = critically ill patients. The medical director of the hyperbaric facility has responsibility for patient classification.

† The outside attendant and chamber operator can be the same person. However, at least one other person needs to be in the area during treatments.

‡ During any monoplace therapy, a ratio of two chambers to one operator is the maximum allowed by HOTFIG.

Undersea and Hyperbaric Medicine Society (UHMS)

Guidelines for clinical hyperbaric facilities are available in the 1999 Committee Report of the Undersea and Hyperbaric Medicine Society.[1] The report was cited as informing the creation of HOTFIG. General guidelines appear as summaries of an earlier report by the UHMS Operations Committee.

Clinical hyperbaric facility operations

UHMS recommends that clinical departments be hospital-based with available 24-hour service. The Society recommends that treatment be limited to those indications approved by the Society. Quality improvement programs should include technical and nursing indicators and utilisation points.

Education of clinical hyperbaric staff

Practicing physicians should hold unrestricted licenses and be Board-eligible or Certified in a recognised medical or surgical specialty. Nursing staff should likewise be licensed to provide care. Technical staff are required to hold basic life support certification and possess advanced education and experience relative to their positions. The Society recommends that physicians, nurses, and technicians complete an approved course in introductory hyperbaric medicine.

Staffing of clinical hyperbaric facilities

UHMS recommends that a minimum of two hyperbaric physicians be on the staff of any full-time clinical hyperbaric medicine program, with one qualifying and assuming the duties of Medical Director. A minimum of one certified hyperbaric nurse or certified hyperbaric technician should be on duty in the clinical area at all times when a patient is receiving treatment.

Is it effective?

The review assessed the effectiveness of HBOT separately according to indication. Each assessment starts with a description of the included studies. Any subsequent statistical pooling of results occurred only when clinical, epidemiologic, and statistical evidence suggested no heterogeneity of treatment effects was present. Otherwise, a simple, descriptive explanation of results was performed.

The pertinent characteristics of accepted studies are summarised in the evidence tables at Appendix C.

Thermal burns

Eight studies were retrieved from the published literature. A brief description of each study is given in Table 12.

Table 12 Descriptive characteristics of included studies focusing on the use of HBOT in thermal burns.*

First Author and Year of publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Brannen 1997[38]	II	RCT	USA	?‡	125	?	I=50:12 C=44:19
Niezgoda 1997[39]	II	RCT	USA	?	12	?	7:5
Hammarlund 1991[40]	III-2	Comparative study	Sweden	?	9	26 (24-29)§	9:0
Cianci 1990[41]	III-2	Comparative study	USA	Jan 1982 to Jul 1987	21	I=28 (9) C=29 (8.3)	?
Gorman 1988[42]	III-3	Comparative study with historical controls	Australia	T=Jul 1986 to Jun 1988 C=Jan 1983 to Jun 1986	180	I=34.2 (14.9) C=38.6 (17.2)	?
Niu 1987[43]	III-2	Comparative study	Taiwan	After 1981	875	I=27 (2-82)§ C=26 (7/12-80)	?
Waisbren 1982[44]	III-2	Comparative study	USA	?	72	I=35.2 (15.0)# C=35.6 (14.8)	?
Hart 1974[45]	II	RCT	USA	Nov 1972 to Jan 1974	16	I=21.62 C=21.31	14:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Median of total population. Figures in parentheses are ranges.

Figures in parentheses are assumed to be standard deviations. Authors did not provide enough information for a definite conclusion.

The studies were published over a period of 23 years and were conducted in four countries (with a majority conducted in the USA). The sample sizes ranged from as small as nine to as large as 875. Three of the studies were randomised controlled trials

(RCT).[38,39,45] The most recent studies failed to give a summary of the ages of participants,[38,39] while half of the studies[41-44] did not report sex ratios.

Note that the studies of Niezgoda *et al.*[39] and Hammarlund *et al.*[40] formed a distinct subset. They were different from the other studies included because they examined the effect of HBOT on burns that were created experimentally, rather than clinically identified burns.

Study quality

All RCTs failed to provide enough detail to assess the adequacy of randomisation (Table 13). There were three studies[39,41,45] that reported masking procedures; two were RCTs and both were double masked. Seven of the eight collected studies reported complete follow-up of participants.[38-44]

Table 13 Methodological quality of included studies focusing on the use of HBOT in thermal burns.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Brannen 1997[38]	RCT	Unclear	Unclear	No losses
Niezgoda 1997[39]	RCT	Unclear	Double masked	No losses
Hammarlund 1991[40]	Comparative study	None	None	No losses
Cianci 1990[41]	Comparative study	None	Single masked	No losses
Gorman 1988[42]	Comparative study with historical controls	None	Unclear	No losses
Niu 1987[43]	Comparative study	None	Unclear	No losses
Waisbren 1982[44]	Comparative study	None	Unclear	No losses
Hart 1974[45]	RCT	Unclear	Double masked	Unclear

* Abbreviation: RCT = randomised controlled trial.

Patient criteria

Table 14 compares the various patient criteria used for enrolment into the identified studies. There were wide variations in the criteria used. Two studies[39,40] recruited healthy volunteers in an experimental setting, two studies[42,45] explicitly specified the extent of burn injury (from 10 to 75 percent total body surface area burned), and another two studies[38,45] only included patients admitted within 24 hours of injury. Three studies[41,43,44] failed to describe the criteria used for enrolment.

Table 14 Patient criteria of included studies focusing on the use of HBOT in thermal burns.

First Author and Year of Publication	Patient Criteria
Brannen 1997[38]	Acutely burned patients admitted within 24 hours of injury.
Niezgoda 1997[39]	Healthy, non-smoking volunteers who tolerate pressurisation. Exclusions: acute sinusitis, otitis media, pneumonia, pregnancy, active cancer, pneumothorax.
Hammarlund 1991[40]	Healthy, non-smoking, male volunteers.
Cianci 1990[41]	Burn patients with injuries representing 19 to 50 percent total body surface area.
Gorman 1988[42]	Burn patients with injuries representing 10 to 75 percent total body surface area.
Niu 1987[43]	Burn patients.* Exclusions: viral infections, untreated pneumothorax, serious otolaryngologic conditions, claustrophobia, septic patients referred from other hospitals.
Waisbren 1982[44]	Burn patients.*
Hart 1974[45]	Patients with thermal burns amounting to between 10 and 50 per cent of the total body surface area admitted within 24 hours of injury. Exclusions: subjects with untreated neoplasms, pneumothorax or profound claustrophobia.

* No additional details given.

Interventions examined

Subjects were exposed to HBOT in different ways in each of the eight identified studies (Table 15). For instance, all studies that stated exposure pressures declared pressures between 2.0 ATA and 3.0 ATA, but these pressures were not standardised across studies. They ranged from 2 ATA[41,45] to 2.4 ATA[39] to 2.5 ATA[43] to 2.8 ATA.[40] In three studies, exposure pressure was not stated.[38, 42, 44]

Table 15 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in thermal burns.*

First Author and Year of Publication	Intervention Group	Comparison Group
Brannen 1997[38]	n=63 Comparison therapy plus treatment in an unstated chamber HBO device using 100% oxygen at 2 ATA for 90 minutes twice a day for at least 10 treatments and a maximum of 1 treatment per percent total body surface area burn.	n=62 Conventional therapy.†
Niezgoda 1997[39]	n=6 Placement in a multiplace HBO chamber using oxygen at 2.4 ATA for 30 minutes twice a day for 3 days.	n=6 Placement in a multiplace HBO chamber using air at 2.4 ATA for 30 minutes twice a day for 3 days.
Hammarlund 1991[40]	n=9 Placement in a multiplace HBO chamber at 1.5, 10.5, and 21.5 hours after injury at approximately 2.8 ATA for 1 hour.	n=9 No treatment.
Cianci 1990[41]	n=10 Comparison therapy plus treatment in a monoplace chamber HBO device at 2 ATA for 90 minutes twice a day. Alpha-tocopherol (400 units) as seizure prophylaxis.	n=11 Burn therapy protocol.†
Gorman 1988[42]	n=67 Comparison therapy plus HBOT.†	n=113 Conventional surgical care.†
Niu 1987[43]	n=266 Comparison therapy plus treatment in a monoplace chamber HBO device. For adults, exposure was to 2.5 ATA for 90-120 minutes, two to three times a day. For children, exposure was to 2 ATA for 60 minutes one to two time a day.	n=609 Colloid, debridement, dressing.
Waisbren 1982[44]	n=36 HBOT not described.	n=36 Therapy not described.
Hart 1974[45]	n=8 Comparison therapy plus treatment in a monoplace HBO chamber with 100% oxygen at 2 ATA for 90 minutes every 8 hours for 24 hours, then every 12 hours until healed.	n=8 Buffered Ringer's lactate, colloid, or blood as needed. Silver sulfadiazine, vitamin B complex three times a day, alpha-tocopherol four times a day, vitamin C, antibiotics for the first 96 hours. Escharotomy or tracheostomy as needed. Sham treatment in a monoplace HBO chamber.

* Abbreviations: ATA = atmosphere absolute, n = sample size

† Therapy not described.

The frequency and duration of exposure were equally variable. In the clinical studies, duration of exposure ranged from 30-90 minutes, while daily to three-times daily exposures were used. Some studies explicitly mentioned maximum exposure times, while others employed HBOT until lesions were healed.

The disparities in intervention protocols were reflected in equally varied comparison protocols. In three studies[39,43,45] comparison therapies were described, but only two

offered ample details. The remaining five studies compared HBOT to "conventional therapy" or some variant of this term. Given the lack of standardised treatment protocols for thermal burn injuries that are universally accepted across institutions in four continents and over two decades, the term "conventional therapy" is insufficiently specific to allow confident comparison across these studies.

Assessment of heterogeneity

Taking into consideration the wide differences in study population, study design, patient criteria, and treatment protocols employed by the eight studies that met eligibility criteria, the review undertook no statistical analysis of heterogeneity and made no attempt to arrive at a statistically pooled effect estimate through meta-analysis.

Review of published clinical experience

The experimental studies of Niezgoda *et al.*[39] and Hammarlund *et al.*[40] found statistically significant effects of HBOT on artificially created, small forearm burns. These studies found that wound exudates were less in subjects exposed to HBO, but the interpretation of this finding was unclear given the different times during which the end point was studied and the small sample sizes across the studies.[39,40] While this evidence supports the biological plausibility of HBOT treatment, it has uncertain clinical significance.

Exposure to HBO was not shown to improve mortality in each of four studies that examined this outcome according to commonly accepted levels of statistical significance.[38,42-44] Length of hospital stay, an end-point examined in three studies, was found to be statistically significantly decreased in only one (Mean ± SD: 28.4 ± 16.1 versus 43.2 ± 19.4 days),[41] although there was some evidence of decreased length of stay in a sub-population of young to middle-aged subjects in another (Mean: 47 versus 59; $p > 0.05$).[43] The third study did not show a difference in length of stay.[38]

A number of studies looked at different aspects of wound healing, although no two studies examined this characteristic in the same way. "Mean healing time" was found to be shorter in patients exposed to HBOT (Mean: 19.7 versus 43.8), although no definition of a "healed" burn was given.[45]

Summary

The identified studies were disparate in their research designs, varied in their populations, inconsistent in their therapies, and conflicting in their outcomes and conclusions. Overall, there is little firm evidence and a lack of well-conducted studies to support the use of hyperbaric oxygen therapy for thermal burns.

Diabetic wounds

Literature focusing on the use of HBOT on all forms of diabetic wounds was sought. However, the strategy only retrieved studies that examined the efficacy of HBOT on diabetic foot ulcers.

Five studies were identified from the published literature. A brief description of each study is given in Table 16. The studies were published over a period of 11 years. Most were performed in Italy.[46-48] The sample sizes varied from 10 to 115. Two studies[47,49]

were RCTs, the rest were comparative studies. Most study participants were males and the mean age of participants was above 50 years.

Table 16 Descriptive characteristics of included studies focusing on the use of HBOT in diabetic wounds.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Faglia 1998[48]	III-2	Comparative study	Italy	1990 to 1993	115	63.4 (9.9)	84:31
Zamboni 1997[50]	III-2	Comparative study	USA	?‡	10	I=63.6 (8.9) C=53.8 (7.8)	I=4:1 C=4:1
Faglia 1996[47]	II	RCT	Italy	Aug 1993 to Aug 1995	68	I=61.7 (10.4) C=65.6 (9.1)	I=27:8 C=21:12
Doctor 1992[49]	II	RCT	India	2 years. No specific dates.	30	I=56.2 (45-70)§ C=59.8 (48-70)	I=3:1 C=2:1
Baroni 1987[46]	III-2	Comparative study	Italy	Jan 1982 to Dec 1984	28	I=57.7 (7.4) C=59.4 (7.6)	I=11:7 C=6:4

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

Study quality

All RCTs failed to provide enough detail to assess the adequacy of randomisation (Table 17). None of the studies provided enough details to assess masking. All of the five collected studies reported complete follow-up of participants.

Table 17 Methodological quality of included studies focusing on the use of HBOT in diabetic wounds

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Faglia 1998[48]	Comparative study	None	Unclear	No losses
Zamboni 1997[50]	Comparative study	None	Unclear†	No losses
Faglia 1996[47]	RCT	Unclear	Unclear†	No losses
Doctor 1992[49]	RCT	Unclear	Unclear	No losses
Baroni 1987[46]	Comparative study	None	Unclear†	No losses

* Abbreviation: RCT = Randomised controlled trial

† A portion of the outcome assessment is reported to be masked. However, neither the nature of the masking nor the extent to which masking is applied is unclear.

Patient criteria

Most studies enrolled consecutive patients. The criteria for inclusion was generally standard across studies — long standing foot gangrene, ulceration or infection in a population of chronic diabetic patients (Table 18). The review made the assumption that the definition of these conditions had not changed significantly between 1987 and 1998.

The method of enrolment and allocation employed in two studies was unusual.[48,50] In these studies, patients who refused HBOT subsequently served as a control group against which the outcomes of the subjects undergoing HBOT were compared. This method of allocation was potentially a source of bias since the control group may have had different

characteristics compared to the treatment group, which may be predictive of outcome independent of allocation.

Table 18 Patient criteria of included studies focusing on the use of HBOT in diabetic wounds.*

First Author and Year of Publication	Patient Criteria
Faglia 1998[48]	Consecutive diabetic patients with foot ulcers seen during enrolment period
Zamboni 1997[50]	Consecutive, insulin-dependent diabetic patients with non-healing lower extremity wounds referred for HBOT. Refusals (n=3) and claustrophobic patients (n=2) served as controls
Faglia 1996[47]	Consecutive patients hospitalised for diabetic foot ulcer. Patients had full-thickness gangrene or abscesses. Subjects with less deep ulcers were included if the ulcer was large, infected, and showed defective healing in 30 days of outpatient therapy. Exclusions: refusal (n=1), stroke death (n=1)
Doctor 1992[49]	All diabetic patients with chronic foot lesions admitted over the enrolment period.
Baroni 1987[46]	All diabetic patients with ulceronecrotic foot lesions seen during the enrolment period.

* Abbreviation: n = sample size

Interventions examined

Three of the five studies[46-48] used similar HBOT protocols that involved a two-phase exposure regimen first described by Baroni and colleagues in 1987.[46] Similar pressures (2.2 to 2.5 ATA) and exposure durations (90 minutes) were used, and two of the three studies reported that subjects were exposed to about 35 HBO sessions on average.[46,47]

The remaining two studies[49,50] used pressures above or below those used in the first group (2 or 3 ATA), and exposure times were half as long or a third longer (45 or 120 minutes).

The comparison procedures used consisted of general measures of surgical, infection and diabetic control, and were similar across studies. Lesions underwent debridement and topical antimicrobials were applied to local dressings. Empirical antibiotic therapy was used in the first instance, with the results of microbiological sensitivity guiding subsequent therapy. For most studies, glycaemic control was achieved using insulin. Table 19 summarises the therapeutic protocols used.

Table 19 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in diabetic wounds.*

First Author and Year of Publication	Intervention Group	Comparison Group
Faglia 1998[48]	n=51 Comparison therapy plus treatment in a multiplace HBO chamber. Two phases: (1) first (antibacterial) phase uses 100% oxygen at 2.5 ATA for 90 minutes daily; (2) second (reparative) phase uses 100% oxygen at 2.2 – 2.4 ATA for 90 minutes, 5 days a week.	n=64 Debridement, topical antimicrobial agents, occlusive dressing. Empirical antibiotic therapy modified following sensitivity results. Diabetic control with insulin. PTCA or CABG, if needed.
Zamboni 1997[50]	n=5 Comparison therapy plus treatment in a monoplace HBO chamber with 100% oxygen at 2 ATA for 120 minutes, 30 sessions 5 days a week.	n=5 Debridement, silver sulfadiazine dressing twice a day for 5 days, and culture-specific antibiotics.
Faglia 1996[47]	n=35 Comparison therapy plus treatment in a multiplace HBO chamber. Two phases: (1) first (antibacterial) phase uses 100% oxygen at 2.5 ATA for 90 minutes daily; (2) second (reparative) phase uses 100% oxygen at 2.2 – 2.4 ATA for 90 minutes, 5 days a week. Mean (SD) number of sessions = 38 (8)	n=33 Debridement, topical antimicrobial agents, occlusive dressing. Empirical antibiotic therapy modified following sensitivity results. Diabetic control with insulin. PTCA or CABG, if needed.
Doctor 1992[49]	n=? Comparison therapy plus treatment in a monoplace HBO chamber with 100% oxygen at 3 ATA for 45 minutes, 4 sittings over 3 weeks.	n=? Regular surgical treatment, incision and drainage, debridement, local dressing with boric acid and bleaching powdered solution, or glycerine acriflavine. Amputation for gangrene or infection above the knee. Cephalosporins, aminoglycosides, and metronidazole with changes made following sensitivity patterns. Diabetic control with insulin
Baroni 1987[46]	n=18 Comparison therapy plus treatment in a multiplace HBO chamber. Two phases: (1) first (antibacterial) phase uses 100% oxygen at 2.8 ATA for 90 minutes daily; (2) second (reparative) phase uses 100% oxygen at 2.5 ATA for 90 minutes. Mean (SD) number of sessions = 34 (21.8)	n=10 Debridement. Diabetic control with insulin.

* Abbreviations: ATA = atmosphere absolute, CABG = coronary artery bypass grafting, n = sample size, PTCA = percutaneous transluminal coronary angioplasty, SD = standard deviation

Assessment of heterogeneity

All the identified studies were sufficiently similar in clinical and epidemiological characteristics to allow statistical analysis of heterogeneity to proceed.

The risk for major amputations was studied by all of the eligible reports. The Cochrane Q statistic failed to detect the presence of heterogeneity ($\chi^2_{df=3} = 0.87$, $p = 0.833$). A L'Abbé plot and Galbraith diagram (Figure 2) of the measures of effect supported this conclusion. Similarly sensitivity analyses performed across simple classifications of the identified studies demonstrated no statistically significant differences in effect sizes. This was the case for sensitivity analyses based on study design (RCTs only: $\chi^2_{df=1} = 0.44$, $p = 0.508$), HBOT protocols used (two-phase protocol: $\chi^2_{df=2} = 0.68$, $p = 0.710$), and recent publication (post-1995: $\chi^2_{df=1} = 0.53$, $p = 0.468$).

Similar results were seen for risk of minor amputations ($p = 0.722$) and wound healing ($p = 0.462$).

In all analyses, the review made the assumption that the study by Doctor *et al.*[49] was successful in establishing balanced groups.

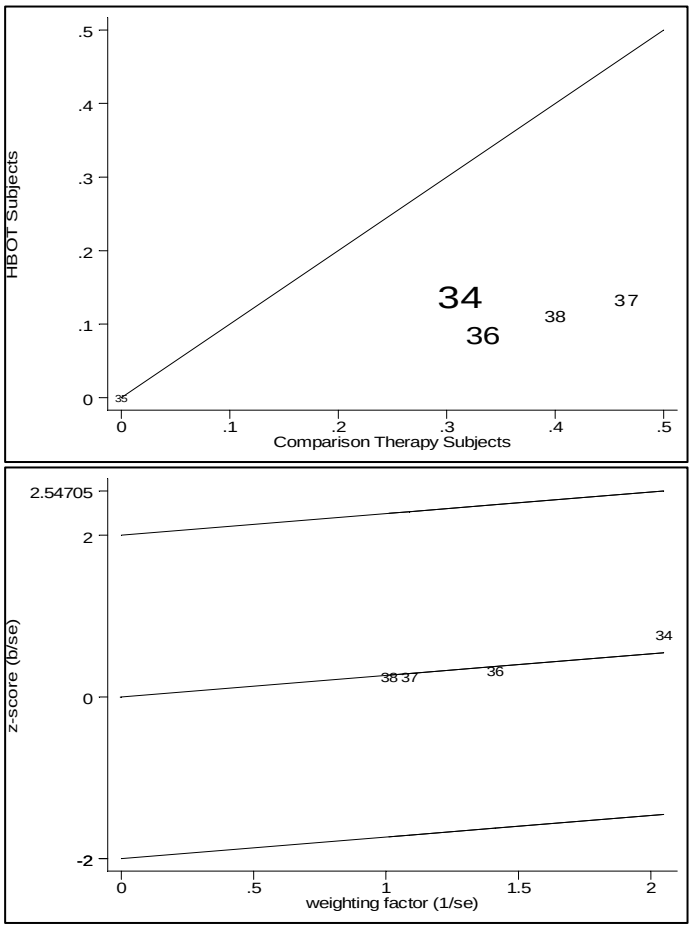


Figure 2. L'Abbé plot (top) and Galbraith diagram (bottom) of subjects undergoing major amputation. Numerical symbols in each of the graphs refer to bibliographic citations found in the text. Sizes of studies in the L'Abbé plot are weighted using the Mantel-Haenszel method.

Pooled results

Given the lack of clinical, epidemiologic and statistical heterogeneity across the identified studies the review proceeded to examine statistically pooled estimates of treatment effect for each of the outcomes with sufficient data to allow this, namely major amputation, minor amputation and wound healing. Each treatment effect was examined from the perspective of both relative and absolute risk.

Risk of major amputation

Major amputation was defined as amputation above the ankle joint. The review examined outcomes for 251 subjects.

The relative risk for major amputation was reduced in all studies, but only reached statistical significance in those conducted by Faglia *et al*.[47,48] The pooled result shows there was a reduction in risk (odds ratio (OR) = 0.25; 95% Confidence Interval (CI) = 0.13, 0.50; $p < 0.0001$) in those patients undergoing HBOT compared to those undergoing comparison therapies (Figure 3). Subjects exposed to HBO were 75 percent less likely to experience major amputations compared to those subjects given the comparison therapies. The study by Zamboni *et al*.[50] was excluded from this pooled estimate of effect because they reported no major amputations.

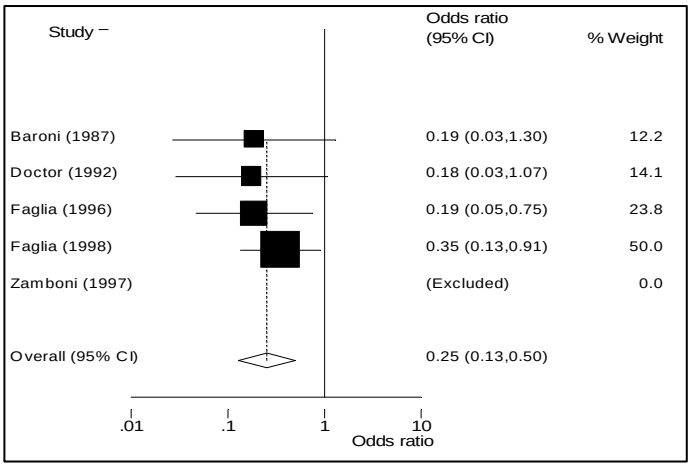


Figure 3. Individual study and pooled results for the relative risk of major amputation following exposure to HBOT compared to comparison therapy.

Figure 4 shows the absolute reduction in risk of major amputation for each of the five studies and for the pooled result. Except for Zamboni *et al*,[50] all other studies reported a decrease in the risk difference associated with HBOT with the studies by Faglia *et al* and Doctor *et al* reaching statistical significance.[47-49] The pooled risk difference indicates that a reduction of 20 percent (95% CI = 11, 30%; $p < 0.0001$) in the number of major amputations is experienced by subjects following exposure to HBOT. One major amputation is prevented for every 5 subjects exposed to HBOT (95% CI = 3.3, 9.1).

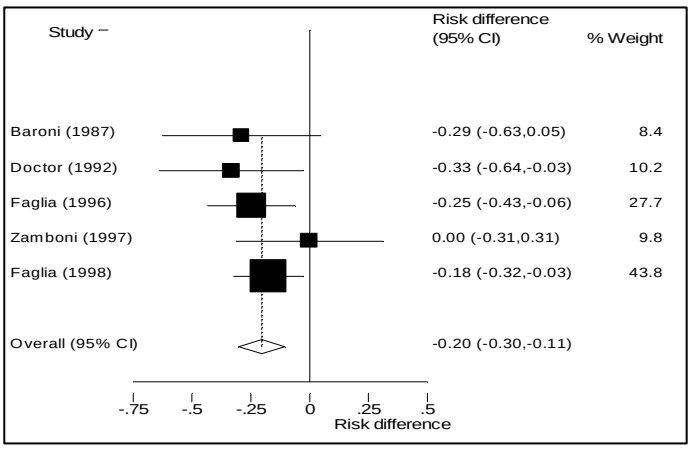


Figure 4. Individual study and pooled results for the absolute risk reduction of major amputation following exposure to HBOT compared to comparison therapy.

A sensitivity analysis that examined results based on study design (ie., two studies[47,49] using a randomised controlled approach), HBOT protocols used (ie., three studies[46-48] using the two-phase protocols), and recent publication (ie., three studies[47,48,50] published after 1995) provided evidence of the robustness of the results (Figure 5), although studies with stronger study designs were more likely to report results that were further from unity.Risk of minor amputation

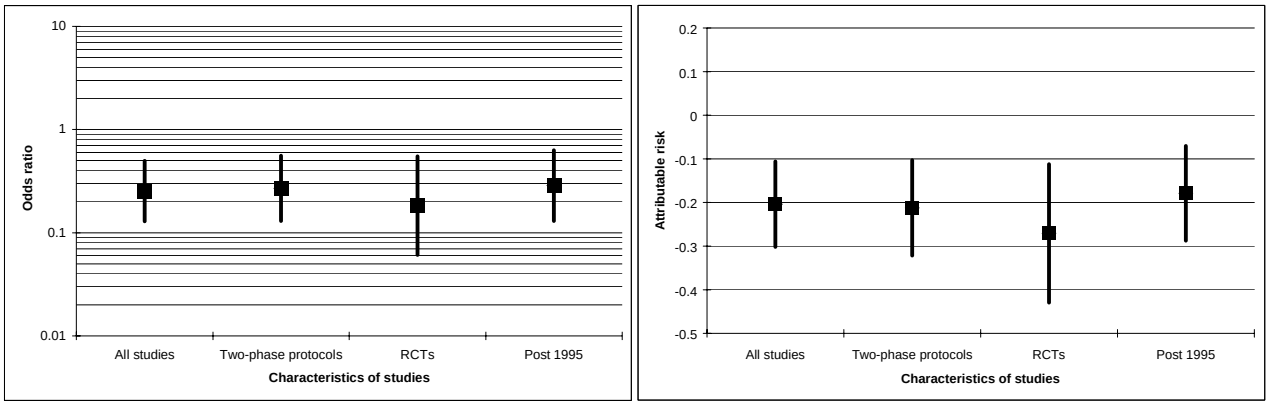


Figure 5. Sensitivity analyses conducted on relative (left) and absolute risks (right) of major amputations following HBOT compared to comparison therapy.

Risk of minor amputation

The review defined minor amputation as amputation of the toe or forefoot and was limited to those performed below the ankle joint. Only three studies reported these outcomes, representing the experience of 155 subjects.[48-50] Excluding the study by Zamboni *et al*,[50] which reported no minor amputations, all other studies reported increases in the risk of minor amputations following HBOT compared to comparison therapies, although none reached commonly accepted levels of statistical significance. The pooled estimate of the odds of minor amputations is 1.76 (95% CI = 0.68, 4.59; p = 0.245). Subjects exposed to HBO were about 75 percent more likely to undergo minor amputations compared to those receiving comparison therapies (Figure 6).

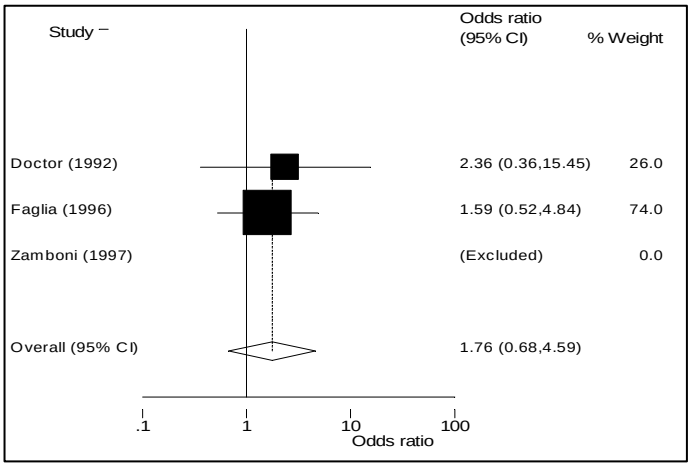


Figure 6. Individual study and pooled results for the relative risk of minor amputation following exposure to HBOT compared to comparison therapy.

Figure 7 shows the absolute difference in the risk of minor amputations for each of the three studies and for the pooled result. Except for the study by Zamboni *et al*,[50] all other studies reported an increase in the absolute risk difference associated with HBOT. The pooled risk difference indicates that an increase of 9 percent (95% CI = -8, 25%; p = .295) in the number of minor amputations is experienced by subjects following exposure to HBOT. For every 11 patients exposed to HBOT, one more will experience a minor amputation than in a comparable group provided comparison therapy.

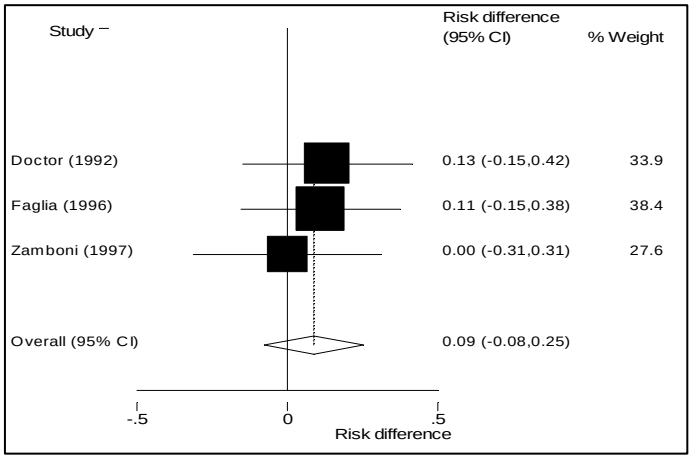


Figure 7. Individual study and pooled results for the absolute risk of minor amputation following exposure to HBOT compared to comparison therapy.

Given the small number of studies, no sensitivity analyses were performed.

Although the identified studies demonstrated that HBOT reduced major amputations, the treatment effect on minor amputations was in the opposite direction. That is, the trend of both the relative and absolute risk of minor amputation was higher in the HBOT group, although neither risk reached commonly accepted levels of statistical significance. A possible explanation is that HBOT subjects preserved their limbs from major amputation because of the efficacy of the intervention, thus making them as a group more liable to minor amputation. If this explanation is valid the increased risk of minor amputation in the HBOT subjects could conceivably be interpreted as a positive outcome. Unfortunately the review could not examine this hypothesis further, since major amputation and minor amputation were not mutually exclusive outcomes.

Wound healing

Two of the five identified studies examined wound healing, although none offered an objective definition of this outcome.[46,50] Altogether, the review considered the experience of only 38 subjects. The small number of patients translated to wide confidence intervals in the estimates of individual and pooled treatment effects, implying a wide margin of error in these estimates. Subjects exposed to HBOT are about 40-times more likely to experience healing of their lesions (OR = 39.39; 95% CI = 5.54, 280.32; $p < 0.0001$) compared to those receiving comparison therapies (Figure 8). Three out of every four patients exposed to HBOT will have their lesions healed compared to comparison therapies.

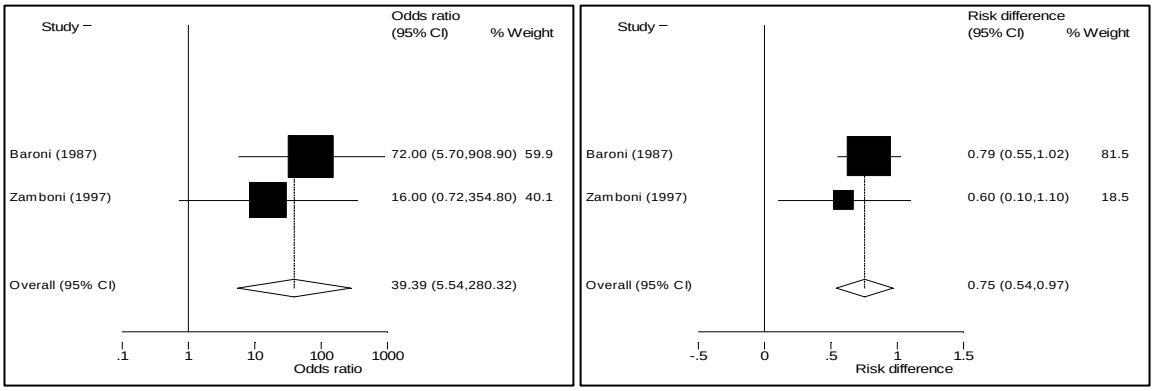


Figure 8. Individual study and pooled results for the relative (left) and absolute (right) risk of wound healing following exposure to HBOT compared to comparison therapy.

Length of hospital stay

The differences in lengths of hospital stays were examined by two studies.[46,49] However, Doctor *et al*[49] presented ranges instead of standard deviations as measures of spread. Both studies reported decreased lengths of stay in the HBOT-treated group compared to those receiving the comparison therapy. Baroni *et al*[46] reported a reduction of 19 days (Mean ± SD: 62.2 ± 30 versus 81.9 ± 94) in the HBOT group compared to the comparison group, while Doctor *et al*[49] reported more modest reductions (Mean: 40.6 versus 47). Neither reached commonly accepted levels of statistical significance.

Summary

The similar characteristics of the collected studies and their statistical homogeneity provided some confidence in the effects of HBOT on specific outcomes. Major amputations were less likely in diabetic patients with chronic ulceronecrotic lesions who were exposed to HBOT compared to those receiving comparison therapies only. For these patients there was some indication that HBOT promoted wound healing and reduced length of hospital stay, but also increased the risk of minor amputations. These last few outcomes represent inferences drawn on a smaller population group, with wide margins of error, and further studies are required. These results, in the light of low uptake rates of the technology for this particular indication, generally indicate there is potential for this technology in the treatment of diabetic wounds.

Non-diabetic wounds

Only one study met entry criteria, Hammarlund and Sundberg's[51] double-blind, randomised controlled trial published in 1994. The study was set in Sweden and recruited 16 patients with a median age of 67 years (Range: 42 – 75 years). Patients were enrolled if they had leg ulcers of more than 1 year's duration and if these lesions did not show progress (by inspection) towards healing during the two months prior to the study, if ankle and first digit blood pressures were within normal ranges, and if they did not smoke or suffer from a concomitant chronic disease condition such as diabetes mellitus. The study did not report losses to follow-up and the randomisation method was inadequately described.

Two balanced groups of 8 subjects were exposed to different concentrations of oxygen in a multiplace chamber at 2.5 ATA for 90 minutes. The frequency of exposure was five times a week for a total of 30 sessions. The intervention group was given 100 percent oxygen while the comparison group received air.

The study looked at the mean changes in wound area over the course of therapy (Table 20). At four and six weeks, there were statistically significant decreases in the wound areas of those receiving 100 percent oxygen compared to those receiving air. The authors also found some indication that improvement continued after hyperbaric therapies were given, although this occurred only for smaller wounds and results were based on a much smaller sample size due to drop outs.

Table 20 Percentage decrease in wound area following six weeks of exposure to 100% oxygen or air in a pressurised chamber (Hammarlund and Sundberg).[51]*

Week of Therapy	Percentage Decrease in Wound Area (Mean ± SD)†		p
	Intervention Group	Comparison Group	
2	6.6 ± 14	2.8 ± 11	0.5557
4	22.0 ± 13	3.7 ± 11	0.0088
6	35.7 ± 17	2.7 ± 11	0.0004

* Abbreviation: SD = standard deviation.

† Compared to baseline (Week 0).

Summary

This trial provided some indication that exposure to 100 percent oxygen in a hyperbaric chamber for lengths up to a month was associated with decreases in the area of chronic, non-diabetic wounds. However, the study included only small numbers of relatively tightly-selected subjects and examined only one outcome measure. More studies in different settings, examining more varied outcomes (eg. absolute wound healing) are required to provide more generalisable evidence of a treatment effect.

Necrotising soft tissue infections

The review identified six studies that met inclusion criteria for this indication.

This section examines studies that focused on necrotising soft tissue infections in general. The two following sections examine the effect of HBOT on two specific diagnoses: necrotising fasciitis and Fournier's gangrene. These diagnoses were evaluated separately.

Studies of necrotising soft tissue infections in general

Two studies that look at necrotising soft tissue infections in general were retrieved from the published literature. A brief description of each study is given in Table 21.

Table 21 Descriptive characteristics of included studies focusing on the use of HBOT in necrotising soft tissue infections.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Brown 1994[52]	III-2	Comparative study	Canada	Jan 1980 to Dec 1991	54	I=51.3 (17.1) C=61.6 (12.6)	I=22:8 C=13:11
Riseman 1990[53]	III-3	Comparative study with historical controls	USA	1980 to '88	29	I=59.7 (14-82)‡ C=68.5 (41-88)	I=11:6 C=7:5

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Figures in parentheses are ranges.

Both studies were performed in North America; neither were RCTs. Most of the study participants were male with mean ages above 50 years.

Study quality

Both studies failed to provide any information about masking procedures. All studies reported complete follow-up of subjects (Table 22).

Table 22 Methodological quality of included studies focusing on the use of HBOT in necrotising soft tissue infections.

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Brown 1994[52]	Comparative study	None	None	No losses
Riseman 1990[53]	Comparative study with historical controls	None	None	No losses

Patient criteria

Patient criteria are shown in Table 23. A variety of diagnoses were included in both studies. In the study by Brown *et al*,[52] patients with necrotising fasciitis or Fournier's gangrene accounted for only 40 percent of the total study population. Riseman *et al*[53] presented no figures.

Table 23 Patient criteria of included studies focusing on the use of HBOT in necrotising soft tissue infections.

First Author and Year of Publication	Patient Criteria
Brown 1994[52]	Patients diagnosed with necrotising faciitis, crepitant anaerobic cellulitis, gangrene, Fournier's gangrene, or nonclostridial/clostridial myonecrosis. Exclusions: complications of radiotherapy, primary peripheral vascular disease with dry gangrene, gangrene as a single diagnosis, joint reconstruction complications, or an infection only involving an extremity.
Riseman 1990[53]	Patients diagnosed with necrotising fasciitis, gas gangrene, or Fournier's gangrene.

Interventions examined

Exposure to hyperbaric oxygen was different in both studies (Table 24). In the study by Brown *et al*,[52] pressures were higher and the frequency of therapy was unstated. Riseman *et al*[53] made use of a treatment regimen that called for frequent exposure to HBOT in the first 24 hours of therapy. Comparison therapies were standard.

Table 24 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in necrotising soft tissue infections.*

First Author and Year of Publication	Intervention Group	Comparison Group
Brown 1994[52]	n=30 Comparison therapy plus treatment in an unstated chamber HBO device at 2.5 to 3.0 ATA for 90 minutes.†	n=24 Debridement, antibiotics, laparotomy.
Riseman 1990[53]	n=17 Comparison therapy plus treatment in a monoplace chamber HBO device. At 2.5 ATA for 90 minutes every 8 hours for the first 24 hours, the twice a day, for a total of 10 treatments.	n=12 Intravenous fluids, debridement, broad spectrum antibiotics (aminoglycoside, clindamycin, and penicillin G or cephalosporin).

* Abbreviations: ATA = atmosphere absolute, n = sample size.

† Duration of therapy not described.

Assessment of heterogeneity

Differences in patient criteria and study designs made it difficult to compare clinical and epidemiological outcomes in the two studies. For this reason, the review undertook no statistical analysis of heterogeneity and made no attempt to arrive at a statistically pooled effect estimate through meta-analysis.

Review of published clinical experience

Both studies looked at the proportion of patients who survived following the diagnosis of necrotising soft tissue infections (Table 25). Both studies showed that HBOT was associated with survival, but only Riseman *et al*[53] reached commonly accepted levels of statistical significance.

Table 25 Survival in patients with necrotising soft tissue infections following exposure to HBOT or comparison therapy.*

First Author and Year of Publication	Survival			p
	Intervention	Comparison	Difference	
Brown 1994[52]	70.0 (53.6, 86.4)	58.3 (38.6, 78.1)	11.7 (-14.0, 37.3)	0.3724
Riseman 1990[53]	76.5 (56.3, 96.6)	33.3 (6.6, 76.6)	43.1 (9.7, 76.6)	0.0202

* Results are in percentages. Figures in parentheses are 95% confidence intervals.

In addition to overall survival, Brown *et al*[52] looked at the mean number of operations and debridements in intervention and comparison groups. In both instances, those receiving HBOT underwent more operations (Mean ± SD: 3.2 ± 1.6 versus 1.7 ± 1.5; $p = 0.0009$) and debridements (Mean ± SD: 2.4 ± 1.5 versus 1.3 ± 1.0; $p = 0.0033$).

Summary

The studies identified looked at different populations of patients and their research designs were dissimilar. Overall, there was some indication that HBOT improved survival in patients with necrotising soft tissue infections. However, one study indicated that the number of operations was increased in the intervention group.

This evidence is insufficient to allow firm, generalisable, conclusions about the effect of HBOT on necrotising infections in general given the methodological issues described above and the unexplained increase in surgical intervention in the intervention group found in one study.

Necrotising fasciitis

For this indication three studies were identified from the published literature that met inclusion criteria. A brief description of each study is given in Table 26.

Table 26 Descriptive characteristics of included studies focusing on the use of HBOT in necrotising fasciitis.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Shupak 1995[54]	III-2	Comparative study	Israel	1984 to 1993	37	I=52.9 (15) C=57.4 (16)	I=14:11 C=9:3
Sawin 1994[55]	III-2	Comparative study	USA	Jan 1982 to Mar 1993	7	9 days (3-15)§	?
Barzilai 1985[56]	III-2	Comparative study	Israel	1979 to 1983	11	I=48.33 (12.5) C=55.88 (9.2)	I=3:0 C=6:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

The studies were published over a period of 10 years. Two were performed in Israel.[54,56] The sample sizes varied from seven to 37. None of the studies were RCTs. Most study participants were males.

The study by Sawin *et al*[55] was distinctly different from the others since the subjects were neonates. In the other two studies the mean age of participants was above 45 years.

Study quality

Most of the studies failed to provide any information about masking procedures, except Sawin *et al*[55] in which no masking was done. All studies reported complete follow-up of subjects (Table 27).

Table 27 Methodological quality of included studies focusing on the use of HBOT in necrotising fasciitis.

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Shupak 1995[54]	Comparative study	None	Unclear	No losses
Sawin 1994[55]	Comparative study	None	None	No losses
Barzilai 1985[56]	Comparative study	None	Unclear	No losses

Patient criteria

Inclusion criteria were defined on the basis of a clinical diagnosis of necrotising fasciitis based on signs and symptoms (Table 28). No attempts at standardisation were made.

Table 28 Patient criteria of included studies focusing on the use of HBOT in necrotising fasciitis.

First Author and Year of Publication	Patient Criteria
Shupak 1995[54]	Patients diagnosed with necrotising fasciitis.
Sawin 1994[55]	Neonates diagnosed with necrotising fasciitis of the abdominal wall.
Barzilai 1985[56]	Patients diagnosed with necrotising fasciitis.

Interventions examined

All comparison therapies consisted of surgical debridement, broad spectrum antibiotics, and dressings (Table 29). Surgical debridement was described as "aggressive," and antibiotic regimens were modified following the results of microbial sensitivity.

In two of the studies,[55,56] HBOT was not described in adequate detail. No description was given of the pressures to which subjects were exposed or the frequency, duration, and total period of therapy.

Table 29 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in necrotising fasciitis.*

First Author and Year of Publication	Intervention Group	Comparison Group
Shupak 1995[54]	n=25 Comparison therapy plus treatment in a monoplace HBO chamber with 100% oxygen at 2.5 ATA for 90 minutes twice a day, then once daily until toxic signs resolve.	n=12 Debridement, broad spectrum antibiotics, dressings.
Sawin 1994[55]	n=4 Comparison therapy plus HBOT.†	n=3 Intravenous antibiotics, surgical debridement in some patients, dressings.
Barzilai 1985[56]	n=3 Comparison therapy plus HBOT.†	n=8 Intravenous fluids and antibiotics (gentamicin, clindamycin, penicillin) modified following sensitivity results, debridement, dressing with nitrofurazone and povidone-iodine.

* Abbreviations: ATA = atmosphere absolute, n = sample size.

† Therapy not described.

Assessment of heterogeneity

The Sawin *et al*[55] study was clearly not comparable with the other two studies on clinical and epidemiological grounds. Even when considering the adult studies alone,[54,56] bias-prone research designs, small sample sizes, and insufficient information about the interventions studied illustrated clinical and epidemiological heterogeneity between the studies. For this reason, the review undertook no statistical analysis of heterogeneity for this indication and made no attempt to arrive at a statistically pooled effect estimate through meta-analysis.

Review of published clinical experience

Sawin *et al*[55] studied two groups of neonates diagnosed with necrotising fasciitis of the abdomen. Hyperbaric oxygen was used as an adjunct to care after 2 deaths from the condition prompted increased vigilance. Two of four neonates receiving HBOT survived, compared to none of three receiving conventional care.

Two studies examined the experience of adults diagnosed with necrotising fasciitis. In the study by Shupak *et al*,[54] survival was seen in 16 of 25 (64%; 95% CI = 43, 82%) patients receiving HBOT compared to 9 of 12 (75%; 95% CI = 43, 95%) receiving the comparison procedure. The study by Barzilai *et al*[56] was performed ten years earlier and examined about one-third the number of patients. Similar results for survival were seen: two of three patients (66%; 95% CI = 9, 99%) receiving HBOT versus five of eight (62%; 95% CI = 24, 91%) receiving the comparison therapy.

Shupak *et al*[54] also examined the number of times the two groups underwent debridement and found that the comparison group underwent a statistically significantly lower mean number of debridements compared to those receiving HBOT (Mean ± SD: 1.5 ± 0.8 versus 3.3 ± 2.0; $p = 0.0004$). No statistically significant differences in length of hospital stay were seen (Mean ± SD: 15.9 ± 6.4 days in the HBOT group versus 20 ± 13.8 days in the comparison group; $p = 0.3657$).

Summary

The studies collected looked at different populations, the sample sizes were small, and information about the HBOT intervention was inadequate. Overall, there is little firm evidence from well-conducted studies to support the use of hyperbaric oxygen therapy for necrotising fasciitis.

Fournier's gangrene

Only the study by Hollabaugh *et al*[57] met entry criteria. The study was a retrospective cohort published in 1998 that retrospectively examined records of patients treated for Fournier's gangrene prior to 1990. The files of 26 patients were reviewed. The mean (± SD) age of the total population was 54.85 ± 15.2 years and all were men. The patients were divided into two groups based on their exposure to HBOT. The authors state explicitly that while HBOT was considered in all cases, institutional availability was the determining factor in a particular subject's receipt of therapy. The authors were not clear about methods used to mask participants. They reported complete follow-up of patients.

Fourteen patients were given HBOT and comparison therapy while 12 received the comparison therapy alone. The latter therapy consisted of debridement, urinary and faecal diversion, and gonadal preservation or orchidectomy. Lesions were dressed with saline, potassium permanganate, or Dakin's solution three times a day until granulation tissue appeared. Broad spectrum antibiotics were given in the first instance, then modified when the results of microbial sensitivity were known.

Patients were exposed to 2.4 ATA for 90 minutes twice a day for seven days, then daily until granulation tissue was evident or until skin grafts had taken.

Patient survival following the diagnosis of Fournier's gangrene was better if HBOT was administered. Of the 14 patients who received HBOT, 13 (92.9%; 95% CI = 79.4, 100%) survived. Of the 12 patients receiving the comparison therapy alone, seven (58.3%; 95% CI = 30.4, 86.2%) survived. The difference of 34.5% (95% CI = 3.5, 65.5%), while based on small samples, was statistically significant at the 5% level ($p = 0.0373$).

Summary

This study provided evidence of a beneficial effect on survival in patients with Fournier's gangrene exposed to HBOT. However, there is some concern about the possibility of systematic differences affecting the outcome. For example, the research design used cannot control for differences in the comparison treatment between locations or over time. More rigorous studies in different settings and examining more varied outcomes are required to provide more generalisable evidence of effect.

General summary of necrotising soft tissue infections

Overall, conflicting results due to inadequacies in the methodological design of studies make it difficult to arrive at a common, quantitative estimate of effect for HBOT. However, any final judgment should be reserved until more conclusive evidence is available.

Osteomyelitis

The study by Esterhai *et al*[58] was a comparative study published in 1987. The study was conducted in the United States and examined 28 consecutive patients (19 males), aged 15 to 74 years (mean = 40), with chronic refractory osteomyelitis uncomplicated by persistent fracture non-union, septic arthritis, total joint arthroplasty or major systemic disease.

The comparison group underwent debridement, and antibiotics were given based on the results of microbial sensitivity. Fourteen subjects were exposed to HBO at 2 ATA for 2 hours daily, six days a week.

Exposure to HBOT did not produce a statistically significant improvement over the comparison therapy in length of hospitalisation, clinical outcome, or recurrence (Table 30).

Table 30 Outcomes in intervention and comparison groups with osteomyelitis (Esterhai *et al*).[58]*

Outcome	Intervention Group (n=14)	Comparison Group (n=14)	p
Mean length of hospitalisation (days)	54 (41-143)†	47 (10-66)†	---
Treatment success (n)	11	13	0.2801
Recurrences‡ (n)	2	1	0.5412

* Abbreviations: n = sample size.

† Figures in parentheses are ranges.

‡ Follow-up ranged from 11 to 77 months (mean = 41.1).

Summary

The regime of HBOT reported in this study does not seem to be beneficial to patients diagnosed with osteomyelitis in terms of their length of hospital stay, the treatment successes, and the risk of recurrence following therapy. However we should note that this regime differs in several respects to HBOT regimes used for other indications, calling into question the extent to which findings may be generalisable.

Osteoradionecrosis

Two aspects of the control of this condition are examined: prevention and treatment.

Prevention

Marx *et al*[59] published a study in 1985 describing the results of a randomised controlled trial conducted in the United States. The trial involved 74 patients (ages and genders not specified) who had an indication for removal of one or more teeth in a segment of the mandible which had received a documented absorbed dose of 6,000 rads or greater, and who agreed to maintain follow-up visits for a minimum of six months. Excluded were patients who received irradiation less than six months or more than 15 years prior to enrolment, had known contraindications to penicillin or exposure to 100% oxygen at 2.4 ATA, showed evidence of persistent tumour or new primary malignant disease, received chemotherapy within six months of enrolment, including steroid drugs, or had concomitant systemic disease which could be expected to affect wound healing.

Patients were randomly assigned to one of two groups. The comparison group (n = 37) received one million units of aqueous penicillin G intravenously prior to surgery and 500 mg phenoxymethylpenicillin four times a day for 10 days after surgery. The intervention group was exposed to HBO in an unstated chamber at 2.4 ATA for 90 minutes. This group underwent 20 sessions before surgery, then 10 sessions after tooth removal, once daily, for five to six days per week. The main outcome of interest was the clinical diagnosis of osteoradionecrosis during follow-up. The diagnosis was made if exposed bone was present six months after therapy.

Two people in the intervention group were diagnosed as having osteoradionecrosis during follow up, compared to 11 people in the comparison group ($p = 0.0060$).

Summary

The study provided evidence that exposure to HBOT is more efficacious than penicillin in the prevention of osteoradionecrosis in this population of patients. The patient sample is representative of the potential target population to which inferences from this report are to be applied.

Treatment

Granstrom *et al*[60] investigated the efficacy of hyperbaric oxygen therapy on the failure rate of osseointegration of implants following irradiation. The comparative study was published in 1999 and enrolled 78 patients over a recruitment period of 16 years. All patients underwent rehabilitation in a Swedish hospital following cancer surgery affecting the head and neck. The study was non-randomised. Masking and losses to follow-up were not described.

The patients were divided into four groups. The three groups directly relevant to this assessment included one group of 32 patients (irradiated group, 18 males, mean age of 67.4 years) with endosseous implants who underwent irradiation prior to surgery. In this group, the mean radiation dose was 57.7 Gray, with a mean observation time of 5.8 years. A second group of 20 patients (HBO group, 11 males, mean age of 61.1 years) were exposed to HBO in a monoplace chamber at about 2.5 ATA for 90 minutes following irradiation (mean dose of 65.4 Gray). Surgery was performed after 20 sessions of HBOT, and patients were exposed to HBO 10 more times following surgery. The effect of HBO on reimplanted devices was examined in a smaller group of 10 patients (reimplant group, 5 males, mean age of 61.1 years) using the same HBOT protocol described above. Results are shown in Table 31.

Table 31 Outcomes in three groups following surgery for osseointegrated implants (Granstrom *et al*).[60]*

Outcome	HBO Group (n=20)	Irradiated Group (n=32)	Reimplant Group (n=10)
Number of implants (n)	99	147	43
Percentage failed (%)	8.1	53.7	79.0
Number of patients with no implant loss (n)	14	4	0
Mortality rate (%)	15.0	21.8	10.0

* Abbreviations: n = sample size.

The HBO group showed a statistically significantly smaller proportion of failed implants ($p = 0.0009$) without a corresponding statistically significant increase in mortality ($p = 0.5546$). An examination of survival functions supported the difference seen in the crude proportions ($p = 0.0010$).

Summary

While the study design was lacking in some respects, the result achieved provides some evidence of the efficacy of HBOT in the treatment of osteoradionecrosis. The generation of evidence from properly randomised clinical trials that focus on other outcomes will provide substantial support or refutation of the importance of the effectiveness of HBOT for this indication.

Skin graft survival

Two studies, dealing with two different procedures – myocutaneous flaps and split skin grafts, were identified. Both were poorly described. While both indicated they were randomised controlled trials, neither described their patient populations well, failing to provide even basic patient descriptions such as age and sex (Table 32).

Table 32 Descriptive characteristics of included studies focusing on the use of HBOT in skin graft survival.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population		
					Size	Age	Sex Ratio
Perrins 1967[61]	II	RCT	UK	?†	48	?	?
Marx 1995[62]	II	RCT	US	?	160	?	?

* Abbreviations: F = female, M = male, RCT = randomised controlled trial

† Unstated, unclear, or unknown.

The earlier study by Perrins[61] used split skin grafts; the Marx[62] study reports the use of HBO following the application of myocutaneous grafts. Each study is examined separately below.

Study quality

Study methodology was inadequately described. The methods used to randomise and mask study participants and outcomes for both studies were unclear (Table 33).

Table 33 Methodological quality of included studies focusing on the use of HBOT in skin graft survival.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Perrins 1967[61]	RCT	Unclear	Single masked	No losses
Marx 1995[62]	RCT	Unclear	Unclear	No losses

* Abbreviation: RCT = randomised controlled trial

Patient criteria

In the study described by Marx,[62] the subjects recruited into the study required a major soft tissue surgery or flap after radiation therapy. Perrins[61] studied patients presenting for skin grafts regardless of the underlying cause of the lesion (Table 34).

Table 34 Patient criteria of included studies focusing on the use of HBOT in skin graft survival.*

First Author and Year of Publication	Patient Criteria
Perrins 1967[61]	Patients presenting for split skin grafting, except infants.
Marx 1995[62]	Patients requiring tissue flaps in tissues radiated to a dose greater than 6,400 cGy.

* Abbreviation: cGy = centiGray

Interventions examined

In both studies, neither the intervention nor the comparison therapies were adequately described (Table 35). Marx[62] gives no details of the frequency and duration of HBOT exposure.

Table 35 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in skin graft survival.*

First Author and Year of Publication	Intervention Group	Comparison Group
Perrins 1967[61]	n=24 Comparison therapy plus treatment in a monoplace HBO chamber at 2 ATA for 2 hours twice a day for 3 days.	n=24 Therapy not described.
Marx 1995[62]	n=80 Comparison therapy plus HBOT for 20 sessions prior to surgery, then 10 sessions after surgery.†	n=80 Therapy not described.

* Abbreviation: n = sample size.

† Therapy not described.

Review of published clinical experience

Perrins[61] noted that 84.2 percent of grafts in the intervention group survived compared to 62.7 percent in the comparison group. The results were highly statistically significant ($p < 0.01$). Simple sensitivity analyses conducted by the author did not change the results.

In the study by Marx,[62] three clinical outcomes were examined – wound infection, dehiscence, and delayed wound healing. For the first two outcomes, minor and major states were differentiated. The results are summarised in Table 36.

Table 36 Outcomes in intervention and comparison groups in Marx.[62]*

Outcome	Intervention Group (n=80)	Comparison Group (n=80)	p
Wound infection (n)			
Minor	3	6	0.3033
Major	2	13	0.0028
Total	5	19	0.0019
Wound dehiscence (n)			
Minor	6	12	0.1333
Major	3	26	0.0000
Total	9	38	0.0000
Delayed wound healing (n)	9	44	0.0000

* Abbreviation: n = sample size.

Summary

These results are difficult to interpret in the light of the failure of both studies to adequately describe their patient populations and comparison interventions, and the limited and poorly described outcomes they measured. Exposure to HBOT may well demonstrate a beneficial effect on the survival of split skin grafts and myocutaneous flaps, but these studies possess serious flaws that strictly limit their generalisability.

Multiple sclerosis

The search of the literature revealed several studies focusing on the use of HBOT on multiple sclerosis.[63-75] Of these, the study by Kleijnen and Knipschild[63] was a systematic review that used broad search strategies, explicit inclusion and exclusion criteria, and performed comprehensive methodological assessments of all studies captured by this report. A search revealed no studies that met the inclusion and exclusion criteria published subsequent to the release of this systematic review. The following discussion is consequently limited to an assessment of the Kleijnen and Knipschild review.

Using explicit search criteria, the review assessed 14 reports of double-blind, randomised or pseudo-randomised clinical trials. After assessing study designs by the use of a 10-point methodological quality score, the authors examined the eight studies with the highest ratings (≥ 7).[66,68-73,75]

In this high-quality subset, patients had chronic progressive or chronic stable multiple sclerosis. Patients were treated in either mono- or multiplace chambers at 1.75 to 2 ATA. The principle outcome was based on changes in the (Expanded) Disability Status Score (EDSS) and the Functional Status Score (FSS) as described by Kurtzke.[76] Both end points showed conflicting results, although the conclusions of a majority of studies showed a lack of statistically significant differences between the groups. Direction of effect was the only means of summarising effect due to the "great differences" in the way the results of individual studies were presented.

Summary

The studies do not consistently demonstrate any beneficial effect of HBOT on clinical outcomes of multiple sclerosis. There is little evidence to support the use of HBOT for this indication at this time.

Cardiovascular disease conditions

The efficacy of HBOT for acute myocardial infarction, cerebrovascular disease, and peripheral obstructive arterial disease is discussed below.

Acute myocardial infarction

Two studies were retrieved from the published literature (Table 37). A difference of 25 years separated the publication of the studies, although both recruited a large number of participants with similar mean ages and sex ratios.

Table 37 Descriptive characteristics of included studies focusing on the use of HBOT in acute myocardial infarction.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age Mean (SD)	Sex Ratio (M:F)
Stavitsky 1998[77]	II	RCT	US, Yugoslavia	Aug 1989 to Dec 1997	112	I=58 (11.1) C= 59 (11.7)	I=49:10 C=48:15
Thurston 1973[78]	II	RCT	UK	Sep 1968 to Jan 1972	208	I=58.1 C=57.2	I=88:15 C=87:18

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial.

† Information is given for total study population values, and intervention and comparison groups.

Study quality

Only the study by Stavitsky *et al*[77] was described in enough detail to determine the adequacy of randomisation. Both studies were unclear about the presence or process of masking. None of the studies reported patients lost to follow-up. Table 38 summarises these findings.

Table 38 Methodological quality of included studies focusing on the use of HBOT in acute myocardial infarction.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Stavitsky 1998[77]	RCT	Adequate	Unclear	No losses
Thurston 1973[78]	RCT	Unclear	Unclear	No losses

* Abbreviation: C = control or comparison group, RCT = randomised controlled trial, T = treatment group

Patient criteria

There is concern about the potential for differences in the criteria on which patient recruitment was based (Table 39). Stavitsky *et al*[77] provided explicit and measurable signs and symptoms. In contrast, Thurston *et al*[78] recruited on the basis of "strong clinical probability" of acute myocardial infarction. An effort to confirm and exclude misdiagnosed participants was done, although these procedures and criteria were not described in detail and may ostensibly be exposed to similar biases.

Table 39 Patient criteria of included studies focusing on the use of HBOT in acute myocardial infarction.

First Author and Year of Publication	Patient Criteria
Stavitsky 1998[77]	Patients aged between 18 and 80 years admitted to the emergency department showing signs (ST elevation ≥ 1 mm in two adjacent electrocardiograph leads) or symptoms (chest pain ≥ 20 minutes but ≤ 6 hours in duration unrelieved by sublingual nitroglycerin) suggestive of an acute myocardial infarction.
Thurston 1973[78]	Patients under 70 years of age with a strong clinical probability of acute myocardial infarction occurring within 24 hours of enrolment, and without contraindications to HBO.

Interventions examined

Both studies made use of "conventional therapy" (Table 40) for the comparison group, but this has changed considerably over the 25 year interval between the identified studies. The use of more effective therapy over time that increased the probability of better

outcomes or that decreased the risk of harmful end-points will tend to make groups more similar to each other when these outcomes are eventually compared.

If the assumption is made that the technology used in the delivery of hyperbaric oxygen was similar in the two studies, then the intervention protocols used by the two research groups differ only in the dose used. However, this difference is by a factor of 16. In the study by Stavitsky *et al*,[77] patients were exposed to HBO at 2 ATA for 2 hours. Thurston *et al*[78] reports exposure to HBO at the same pressure, but prescribed for 16 continuous three-hour cycles (2/3 under pressure).

Table 40 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in acute myocardial infarction.*

First Author and Year of Publication	Intervention Group	Comparison Group
Stavitsky 1998[77]	N=59 Comparison therapy plus treatment in a multiplace HBO chamber with oxygen at 2 ATA for 2 hours.	n=63 Tissue plasminogen activator, streptokinase, aspirin, heparin.
Thurston 1973[78]	N=103 Conventional therapy plus treatment in a multiplace HBO chamber with oxygen at 2 ATA for 2 hours, then 1 hour unpressurised, continuous cycle for 48 hours.	n=105 Conventional therapy plus oxygen by mask at 6 litres per minute.

* Abbreviations: ATA = atmosphere absolute, n = sample size.

Assessment of heterogeneity

The time period between studies and variations in patient criteria and outcomes lead to clinical and epidemiological heterogeneity between the studies. For this reason, the review undertook no statistical analysis of heterogeneity for this indication and made no attempt to arrive at a statistically pooled effect estimate through meta-analysis.

Review of published clinical experience

Thurston *et al*[78] did not find statistically significant differences in in-hospital mortality between the two groups (n=17 (16.5%; 95% CI = 9.3, 23.7%) in the intervention group versus n=24 (22.8%; 95% CI = 14.8, 30.9%) in the comparison group; $p = 0.2496$). However, there were indications that statistical interaction was present between treatment and disease severity on mortality. The authors also report an increase in the incidence of complete heart block in the comparison group (16 versus 4), although denominator data for this end-point and for other forms of arrhythmia are not given.

Stavitsky *et al*[77] looked at the effect of HBOT on several clinical variables. Exposure to HBO did not change the risk of death or the maximum creatine phosphokinase levels. However, the authors report highly statistically significant improvement in the time to pain relief between the two groups. The difference between the groups was 353 ± 69.4 minutes (95% CI = 214.8, 491.2 minutes; $p < 0.0001$)

Summary

At the present time, there is no firm evidence to support the use of HBOT for acute myocardial infarction. The studies that examine this issue either do not find beneficial effects on major end-points or suffer from flaws in design. There is some indication that

HBOT used in conjunction with thrombolytic therapy may be beneficial in pain relief although more studies are needed to arrive at a firm and generalisable conclusion.

Cerebrovascular disease

Two studies of carotid artery stroke were retrieved and assessed (Table 41). Both studies were randomised controlled trials and were published four years apart. The study populations were similar in size, enrolling about 35 to 40 people. One group of participants was older by a mean difference of about 10 years.

Table 41 Descriptive characteristics of included studies focusing on the use of HBOT in cerebrovascular disease.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age Mean (SD)	Sex Ratio (M:F)
Nighoghossian 1995[79]	II	RCT	France	Dec 1988 to Mar 1992	34	I=53 (3) C=54 (3)	I=9:8 C=12:5
Anderson 1991[80]	II	RCT	USA	?‡	39	I=63.7 C=69.1	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for total study population values, and treatment and control groups.

‡ Unstated, unclear, or unknown.

Study quality

The randomisation procedures used by both studies are uncertain; no information was provided to properly assess the methods used (Table 42). Anderson *et al*[80] report the use of double-masked procedures, while Nighoghossian *et al*[79] is unclear. There were a total of 12 losses to follow-up in the study by Anderson *et al*[80] In the comparison group, the five losses were distributed as follows: deaths (n = 2), migration (n = 2), and refusals (n = 1); in the intervention group, there were two deaths, one migration, three refusals, and one stroke. No comparisons of baseline characteristics between those lost to follow-up and those remaining in the study were made.

Table 42 Methodological quality of included studies focusing on the use of HBOT in cerebrovascular disease.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Nighoghossian 1995[79]	RCT	Unclear	Unclear	1
Anderson 1991[80]	RCT	Unclear	Double masked	T=7, C=5

* Abbreviations: C = control or comparison group, RCT = randomised controlled trial, T = treatment group

Patient criteria

The two studies used similar patient inclusion criteria (Table 43). Nighoghossian *et al*[79] enrolled patients between 20 and 75 years of age with neurological deficit highly suggestive of middle cerebral artery occlusion while excluding patients with a history of stroke; those who exhibited substantial improvement or resolution of the deficit within 1 hour; were pregnant; experienced seizures at stroke onset; had metabolic encephalopathy, significant pulmonary disease, congestive heart failure, or uncontrolled hypertension.

Anderson *et al*[80] recruited non-pregnant patients aged 20 to 90 years with onset of neurological deficits due to ischaemic cerebral infarction in the brain region perfused by one carotid artery during the preceding 2 weeks. They excluded patients with minor deficits (<20 on a 100 point scale), or deficits that substantially improved or resolved ≤ 3 hours after onset; and patients with significant pulmonary disease contraindicating HBO exposure, as well as patients with unstable medical conditions.

Table 43 Patient criteria of included studies focusing on the use of HBOT in cerebrovascular disease.

First Author and Year of Publication	Patient Criteria
Nighoghossian 1995[79]	Patients between 20 and 75 years with neurological deficit highly suggestive of middle cerebral artery occlusion. Exclusions: patients with a history of stroke; those that exhibited substantial improvement or resolution of the deficit within 1 hour; were pregnant; experienced seizures at stroke onset; or had metabolic encephalopathy, significant pulmonary disease, congestive heart failure, or uncontrolled hypertension.
Anderson 1991[80]	Non-pregnant patients aged 20 to 90 years with onset of neurological deficits due to ischaemic cerebral infarction in the brain region perfused by one carotid artery during the preceding 2 weeks. Exclusions: patients with minor deficits (less than 20 on a 100 point scale), or deficits that substantially improved or resolved ≤ 3 hours after onset. Patients with significant pulmonary disease contraindicating HBO exposure, as well as patients with unstable medical conditions.

Interventions examined

Both groups in both studies received "standard" therapy (Table 44) with supportive care. Sham HBOT treatments were compared with exposure to HBO in a monoplace chamber at 1.5 ATA. Nighoghossian *et al*[79] exposed the intervention group for 40 minutes over 10 sessions, while Anderson *et al*[80] prescribed hour-long exposures every eight hours for 15 sessions.

Table 44 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in cerebrovascular disease.*

First Author and Year of Publication	Intervention Group	Comparison Group
Nighoghossian 1995[79]	n=17 Low dose heparin. Treatment in a monoplace HBO chamber with oxygen at 1.5 ATA for 40 minutes for 10 sessions.	n=17 Low dose heparin. Treatment in a monoplace HBO chamber with air at 0.2 [*sic*] ATA for 40 minutes for 10 sessions.
Anderson 1991[80]	n=19 Treatment in a monoplace HBO chamber with oxygen at 1.5 ATA for 1 hour every 8 hours for 15 sessions.	n=20 Treatment in a monoplace HBO chamber with air at 1.5 ATA for 1 hour every 8 hours for 15 sessions.

* Abbreviations: ATA = atmosphere absolute.

Assessment of heterogeneity

There is some confusion as to the exact meaning of "standard" therapy in this context. No explicit protocols were mentioned, although Nighoghossian *et al*[79] report the use of low dose heparin in both groups. There was a question of temporal and geographical differences between comparison interventions in these two studies. If these differences occurred in a random manner, they would tend to diminish the common effect from a statistical pooling of results.

Nevertheless, both studies were of sufficient clinical and epidemiological similarity to attempt statistical pooling. Unfortunately, neither study examined the same outcomes in the same way, and individual data points are not given with which to manipulate statistically the effect measures for transformation on a common scale. Therefore, the review did not attempt a pooled estimate of treatment effect. Instead a brief description of results of the two studies follows.

Review of published clinical experience

Nighoghossian *et al*[79] assessed functional outcome at six and 12 months using three scales: the Orgogozo,[81] Rankin disability,[82] and Trouillas scales. The latter was developed specifically for this study. The Orgogozo scale was a 100-point quantitative scale with a score of 100 as normal. It was the only scale used to measure baseline values. In the Rankin and Trouillas scales, a score of zero was considered normal.

The authors found statistically significant differences between the intervention and comparison groups at 1 year based on the Orgogozo and Trouillas scores (Table 45). However, pre- and post-therapeutic differences were not statistically apparent on all scales.

Table 45 Functional neurologic scores in intervention and comparison groups with cerebrovascular disease according to follow-up (Nighoghossian et al).[79]

Scale and Time of Examination	Mean Score		Treatment Difference	
	Intervention Group	Comparison Group	Intervention less Comparison	p
Orgogozo				
Baseline	42.5 (5.1)†	31.5 (5.3)	11.0 (7.4)	0.15
6 months	72.9 (6.6)	54.7 (5.3)	18.2 (10.6)	0.10
12 months	78.2 (6.4)	50.3 (8.7)	27.9 (10.8)	0.02
Trouillas				
6 months	4.6 (0.5)	6.1 (0.7	–1.5 (0.9)	0.19
12 months	4.1 (0.6)	6.3 (0.7)	–2.2 (1.0)	0.03
Rankin				
6 months	2.6 (0.2)	3.2 (0.3)	–0.6 (0.4)	0.13
12 months	2.4 (0.2)	3.0 (0.3)	–0.6 (0.4)	0.11

* Baseline comparisons were made for the Orgogozo scale only.

† Figures in parentheses are standard errors.

Anderson *et al*[80] used a graded neurological examination scale that was sensitive to deficits referable to the region of the brain perfused by branches of the internal carotid artery.[83] A score of 100 was considered normal. Examinations were administered on enrolment, at five days, six weeks, four months (the primary outcome of interest), and one year.

The authors report that comparison therapy patients improved by (Mean ± SEM) 15.9 ± 3.2 points ($p < 0.0003$) while the intervention group experiences an improvement in scores by 12.2 ± 4.8 points ($p < 0.03$). Due to the trend of better improvement in the comparison group compared to the HBO-exposed group, the study was suspended for ethical reasons.

Summary

The collected evidence examines only a small number of clinical outcomes. In these end-points, the effectiveness of exposure to HBO is conflicting. There is evidence of small improvements in functional status, but these are seen a year after therapy is initiated. Whether these changes are scale-independent is questionable. Of potential concern is the evidence that exposure to HBO may be no better than placebo or sham therapy. The review concluded that no firm and generalisable evidence is available to support the use of HBOT for cerebrovascular disease at this time.

Peripheral obstructive arterial disease

The study by Verrazzo *et al*[84] was the only one that met inclusion and exclusion criteria for this indication. Published in 1995, the study was a randomised controlled trial conducted in Italy and enrolled 30 patients suffering from stages II to IV of peripheral obstructive arterial disease. The mean age of participants was 60 years.

The study methodology was inadequately described. Both the methods of randomisation and masking were unclear. The authors reported no losses to follow-up.

The study compared HBOT to oxygen-ozone therapy on such hemorrheologic parameters as haematocrit, erythrocyte filterability, blood viscocity, plasma fibronogen levels, and thrombin time. The comparison therapy consisted of the slow reinfusion of 100 ml of autologous venous blood exposed to an oxygen-ozone mixture. Five treatments were given every other day. Exposure to HBO was in a monoplace chamber with oxygen at 2 ATA for 1 hour, five times a day, every other day.

Treatment with HBO did not show changes in the parameters tested after a comparison with baseline values was performed.

Summary

This small trial provides little evidence of benefit. Methodologically, the use of surrogate endpoints of uncertain relationship to clinical outcome and the uncertain biological activity of the comparison treatment provide cause for concern. The study provided no evidence of the efficacy of HBOT for peripheral obstructive arterial disease.

Soft tissue injuries

The only studies identified as meeting the inclusion and exclusion criteria for this indication were on soft tissue injuries (ankle strain and crush injuries). A brief description of both studies follows.

Acute ankle sprains

The study by Borromeo *et al*[85] compared HBOT with placebo exposure on 32 volunteers with lateral ankle sprains, who were not taking prescription medication, and had not received treatment beyond ice, elevation, compression with an elastic bandage, and crutches. They excluded people with fractures on radiograph, upper respiratory tract infection, active allergies, severe asthma, pulmonary disease, epilepsy, claustrophobia, or

who were pregnant. There were almost twice as many males as females recruited (21 versus 11), and the mean age of the two groups was about 25 years.

The study was a randomised controlled trial conducted in the United States. Randomisation was adequately described, and the study was double masked. There were no losses to follow-up.

All subjects were treated using a two-program protocol involving splinting of the injured appendage, pain relief medication, active range of motion, balance, and isometric exercises, and ice. Those assigned to the intervention group were exposed to HBO in a mono-multiplace hybrid (single person breathing with mask) chamber at 2 ATA for three treatments over seven days. The first session was for 90 minutes; the last two sessions were 60 minutes each. Placebo exposure was similar in the comparison group, except that air was given at 1.1 ATA.

The following end points were examined: ankle pain using a visual analogue scale, ankle oedema using a volumeter, active and passive ankle range of motion, ankle function using a seven-point scoring system, and time to full recovery (defined as attaining a score of seven on the ankle function scale). During the course of therapy to full recovery, no statistically significant differences were apparent between the two groups on all outcomes.

Summary

This study provided no evidence to support the use of HBOT for acute ankle sprains.

Crush injuries

Bouachour *et al*[86] enrolled patients with Gustillo[87] Type II or III acute injury of the lower limb. The patients had surgical management within six hours of injury and they had no history of peripheral occlusive arterial disease. They excluded patients enrolled in another trial, those who were suspected of being pregnant, or those with neurologic, pulmonary, or otorhinolaryngologic disease.

The authors recruited 36 patients into this double-masked randomised controlled trial. All patients underwent debridement, wound irrigation, primary closure, arterial and venous repairs, and fasciotomies. Cloxacillin and ornidazole were given as first line antibiotics with a modification of therapy following the results of microbial sensitivity results. Tedelparin was also given as an antithrombotic agent. Half of the group was exposed to HBO in a multiplace chamber at 2.5 ATA twice a day for six days. The comparison group was exposed to air in the same chamber at a pressure of 1.1 ATA.

The authors examined four major outcomes: wound healing without tissue necrosis requiring surgical excision, new major surgical procedures after entry in the trial, time of healing, and length of hospital stay (Table 46).

Table 46 Major outcomes following treatment for crush injuries in intervention and comparison groups (Bouachour *et al*).[86]

Outcome	Intervention Group (n = 18)	Comparison Group (n = 18)	p
Complete healing without necrosis requiring surgery (n)	17	10	0.0180
Number of patients with new surgical procedures (n)	1	6	0.0880
Healing time (days)	50.2 (21.1)*	55.8 (19.9)	0.4184
Length of hospitalisation (days)	22.4 (12.4)	22.9 (16.3)	0.9181

* Figures in parentheses are standard deviations.

The authors found that a statistically significantly greater proportion of HBOT subjects experienced complete healing of lesions without necrosis compared to those given the placebo therapy.

Summary

This study found that exposure to HBOT benefited patients with crush injuries of the lower limbs, although this benefit was mainly reported in terms of decreasing surgical interventions rather than decreased healing time. Studies examining a broader range of outcomes in larger populations are required to generate firmer and more generalisable conclusions.

Cluster and migraine headaches

The effectiveness of HBOT for migraine and cluster headaches is discussed below.

Cluster headaches

Two studies were identified that met inclusion criteria for this indication (Table 47). Both of these were comparative studies conducted in the same institute in Italy. The study populations were similar in size. There was a preponderance of male participants.

Table 47 Descriptive characteristics of included studies focusing on the use of HBOT in cluster headaches.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age Mean (SD)	Sex Ratio (M:F)
DiSabato 1997[88]	III-2	Comparative study	Italy	?‡	14	I=34.0 (2.2)§ C=41.3 (2.6)	14:0
DiSabato 1996[89]	III-2	Comparative study	Italy	?	14	I=41.8 (3.7)# C=42.3 (5.2)	I=5:2 C=5:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, SD = standard deviation.

† Information is given for total study population values, and intervention and comparison groups.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are standard errors.

\# Figures in parentheses are assumed to be standard deviations. Authors did not provide enough information for a definite conclusion.

Study quality

A description of important methodologic characteristics of the two studies appears in Table 48. Neither study employed randomisation, both were comparative in nature. The

earlier DiSabato *et al*[89] study mentioned masking procedures. Both studies had complete follow-up of subjects.

Table 48 Methodological quality of included studies focusing on the use of HBOT in cluster headaches.

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
DiSabato 1997[88]	Comparative study	None	None	No losses
DiSabato 1996[89]	Comparative study	None	Single masked	No losses

Patient criteria

The two studies enrolled patients with two different types of cluster headaches (table 47). In the 1997 study, DiSabato *et al*[88] enrolled patients with the chronic form of the condition, specifying that participants be afflicted for at least five years before being recruited into the study. A year earlier the authors studied subjects with the episodic type of cluster headaches. Similar exclusion criteria were applied.

Table 49 Patient criteria of included studies focusing on the use of HBOT in cluster headaches.

First Author and Year of Publication	Patient Criteria
DiSabato 1997[88]	Outpatients with chronic cluster headache of at least five years duration diagnosed according to the criteria of the International Headache Society. Exclusions: patients with diseases or forms of head pain other than cluster headaches or patients with organic conditions capable of causing painful syndromes of the head.
DiSabato 1996[89]	Patients with episodic cluster headache diagnosed according to the criteria of the International Headache Society. Exclusions: patients suffering from other diseases or were taking prophylactic headache medication.

Interventions examined

In both studies, patients were managed in a multiplace HBOT chamber for 30 minutes. In the comparison groups, the patients breathed air in an unpressurised chamber. Only the comparison group of the later study was given rescue medication (Table 50).

In their 1997 study, DiSabato *et al*[88] exposed the intervention group to a pressure of 2.5 ATA every two days for 15 sessions. In their earlier study, pressures in the range of 2.0 to 2.5 ATA were used and the number of sessions is not described.

Table 50 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in cluster headaches.*

First Author and Year of Publication	Intervention Group	Comparison Group
DiSabato 1997[88]	n=10 Comparison therapy plus treatment in a multiplace HBO chamber at 2.5 ATA for 30 minutes every 2 days for 15 sessions.	n=4 Indomethacin as rescue medication. Treatment in a multiplace HBO chamber with air for 30 minutes every two days for 15 sessions. No pressurisation was used.
DiSabato 1996[89]	n=7 Treatment in a multiplace HBO chamber at 2.0-2.5 ATA for 30 minutes.	n=7 Treatment in a multiplace HBO chamber with air for 30 minutes. No pressurisation was used.

* Abbreviations: ATA = atmosphere absolute.

Assessment of heterogeneity

The study populations of the two studies are different. Although both groups suffer from cluster headaches and both are diagnosed using explicit criteria, patients differ in the chronicity of the condition. A valid argument may be made that the pathophysiology of these two forms are similar enough to warrant some statement about the global effectiveness of HBOT on the disease. Unfortunately, as will be noted below, neither study examined the same end-points.

Review of published clinical experience

In their 1997 study, DiSabato *et al*[88] rely on graphical methods only to present their clinical data, making derivation of numerical results for further analysis inappropriate. The mean number of attacks was found to decrease in the intervention group compared to the comparison group. There was some indication of a carry-over effect, as the mean number of attacks remained low up to two weeks after treatment was stopped. These results were reflected in the decrease in the mean number of rescue medications taken over the week.

The 1996 study[89] measured a surrogate endpoint, the immunoreactivity of substance P, in patients with episodic cluster headache exposed to either HBOT or normobaric oxygen. The mean density score was found to be decreased in those exposed to HBOT (Mean $\pm$ SD: 8.57 $\pm$ 3.21 versus 15.00 $\pm$ 1.63; $p = 0.0011$). The relationship of this surrogate endpoint to clinical outcome was unclear.

Summary

These studies provided evidence of a beneficial effect on pain relief and physiochemical outcomes in patients with some forms of cluster headache exposed to HBOT. Concerns about the methodology of the studies and their quality strictly limit their usefulness. These concerns included small sample sizes, inadequate masking, and inability to control for Hawthorne effects and temporal or measurement bias. Only one of the studies measured clear, clinically relevant outcomes. More rigorous studies in different settings and examining more varied outcomes in bigger groups of patients are required to provide firmer and more generalisable evidence of effect. At this time, the identified evidence is insufficient to support the use of HBOT in cluster headaches.

Migraine headaches

Two studies met inclusion criteria for this indication (Table 51). Both were randomised controlled trials, the study by Wilson *et al*[90] being a crossover study. Both studies were conducted in the USA and enrolled predominantly female participants. Wilson *et al* studied a population with a mean age of almost 40 years; Myers and Myers[91] provide no age details.

Table 51 Descriptive characteristics of included studies focusing on the use of HBOT in migraine headaches.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	AgeMean (SD)	Sex Ratio (M:F)
Wilson 1998[90]	II	RCT, crossover	USA	?‡	8	38.8 (7.8)§	0:8
Myers 1995[91]	II	RCT	USA	?	20	?	6:14

* Abbreviations: F = female, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for total study population values, and treatment and control groups.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are assumed to be standard deviations. Authors did not provide enough information for a definite conclusion.

Study quality

Table 52 summarises important methodological characteristics of the studies included in this section. Both studies did not provide enough evidence to determine the adequacy of randomisation. The study by Wilson *et al*[90] was double masked; Myers and Myers[91] applied single masking procedures. Both studies reported complete follow-up of patients.

Table 52 Methodological quality of included studies focusing on the use of HBOT in migraine.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Wilson 1998[90]	RCT, crossover	Unclear	Double masked	No losses
Myers 1995[91]	RCT	Unclear	Single masked	No losses

* Abbreviation: RCT = randomised controlled trial

Patient criteria

Wilson *et al*[90] applied explicit criteria for entry and recruitment of participants. The diagnosis of migraine was combined with specific features of the disease (such as duration and regularity) to screen for a particular subset of patients with a severe form of the disease (Table 53). In contrast, Myers and Myers[91] simply require their participants to have been diagnosed previously with the condition.

Table 53 Patient criteria of included studies focusing on the use of HBOT in migraine headaches.

First Author and Year of Publication	Patient Criteria
Wilson 1998[90]	Nonpregnant, otherwise healthy women between 20 and 65 years of age with a diagnosis of migraine with aura confirmed by a neurologist at least 18 months prior to entry into the study. Migraine should have stable episodes occurring regularly without an obvious precipitant and having no significant seasonal component. Exclusions: episodes of migraine headache which routinely last longer than 4 days or result in objective neurologic deficits; episodes whose average occurrence is less than 2 times per month; individuals with migraine headache responsive to standardised preventative or abortive therapy; and individuals with permanent neurologic deficits or any chronic medical disease process which might increase the risk of hyperbaric therapy.
Myers 1995[91]	Adults with a history of migraine headache diagnosed by a physician.

Interventions examined

In both studies, exposure to HBO was tested against normobaric oxygen via a sham procedure (Table 54). Treatment was conducted in a monoplace chamber. Wilson *et al*[90] used a pressure of 1.1 ATA for 60 minutes; Myers and Myers[91] did not pressurise the chamber above ambient pressure, but participants were enclosed in the chamber for 40 minutes. Both intervention protocols used pressures of at least 2 ATA.

Table 54 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in cluster headaches.*

First Author and Year of Publication	Intervention Group	Comparison Group
Wilson 1998[90]	n=8 Treatment in a monoplace HBO chamber with oxygen at 2.4 ATA for 60 minutes	n=8 Treatment in a monoplace HBO chamber with oxygen at 1.1 ATA for 60 minutes.
Myers 1995[91]	n=10 Treatment in a monoplace HBO chamber with oxygen at 2 ATA for 40 minutes.	n=10 Treatment in a monoplace HBO chamber with oxygen at 1 ATA for 40 minutes

* Abbreviations: ATA = atmosphere absolute.

Assessment of heterogeneity

The more stringent criteria employed by Wilson *et al*[90] resulted in a more highly selected group of migraine patients. More importantly, the study population might by systematically different from that studied by Myers and Myers.[91] However, as with cluster headaches, valid arguments to pool the results of these two studies may be made. Again, unfortunately, neither study examined the same end-points. Thus although, arguably, the studies were sufficiently similar on clinical and epidemiological grounds to justify statistical testing for lack of heterogeneity this was not technically possible. Accordingly the review made no attempt to arrive at a statistically pooled effect estimate through meta-analysis.

A brief description of results of the two studies follows.

Review of published clinical experience

Wilson *et al*[90] examined three outcomes. The severity of the headache was assessed subjectively by the use of a visual analogue scale with zero indicating no headache. Pericranial tenderness by manual palpation of 10 tender points and assessed according to

a 4-point rating scale (0 = no pain). Pain tolerance in each of the 10 previously described tender points was assessed using a dolorimeter (a spring-loaded algometer capped with a rubber head) with results being expressed in kilograms per centimetre.

The authors report no differences in the outcomes between the two groups when measured by manual palpation and dolorimetry (Table 55). However, the overall severity of the headache was found to be reduced in a statistically significant fashion in patients exposed to HBO compared to those in the comparison group ($p = 0.03$).

Table 55 Major outcomes following treatment for migraine headaches in intervention and comparison groups (Wilson *et al*).[90]

Outcome	Intervention Group (n = 10)	Comparison Group (n = 10)
Manual palpation		
Pretreatment Mean	19.33 (4.51)*	25.75 (5.03)
Posttreatment Mean	12.33 (5.38)	9.05 (2.02)
p	0.03	0.02
Dolorimetry, kg/cm^2		
Pretreatment Mean	37.88 (6.68)	34.35 (10.92)
Posttreatment Mean	45.07 (6.68)	42.38 (11.47)
p	0.87	0.90
Visual analogue scale		
Pretreatment Mean	7.9 (0.64)	6.5 (0.87)
Posttreatment Mean	3.5 (1.34)	6.3 (1.75)
p	0.03	0.99

* Figures in parentheses are standard errors.

Myers and Myers[91] examined subjective headache pain with the use of a modified visual analogue scale with six descriptors (ranging from "none" to "most severe ever"). Nine of 10 patients exposed to hyperbaric oxygen reported "none" or "mild" response compared to one of 10 subjects in the comparison group ($p = 0.0003$).

Both studies did not use outcome criteria recommended by the International Headache Society.

Summary

Exposure to HBO seems to provide pain relief for migraine headaches. However, more studies in different settings and examining more varied outcomes in larger groups of patients are required to provide conclusive evidence of a firm and generalisable effect.

Facial paralysis

The study by Racic *et al*[92] was the only one that met inclusion and exclusion criteria for this indication. In this double-masked, randomised, placebo-controlled trial, the authors examined the effectiveness of HBOT versus oral prednisone on degenerative changes and recovery in Bell's palsy. The study was conducted in Croatia and recruited volunteers after the diagnosis of Bell's palsy was established by history, physical examination, and testing. The severity of paralysis was graded as mild, moderate, severe, or total according to the systems of House[93] and Pietersen.[94] Only those patients with moderate or worse conditions were studies. The mean age of the study population was above 35 years of age, with males comprising 48 of 79 (61%) subjects.

Thirty-seven subjects (comparison group) were allocated to receive 450 mg of prednisone in 10-mg tablets over 8 days in the following manner: days 1-4, four tablets twice a day; day 5, three tablets three times a day; day 6, two tablets twice a day; day 7, one tablet twice a day; and day 8, one tablet. This group was also exposed to a sham HBOT procedure by placement in a monoplace chamber infused with seven percent oxygen at 2.8 ATA for one hour, twice a day, five days a week for a maximum of 30 sessions.

The remaining 42 subjects (intervention group) were given placebo tablets and were instructed to take them in the manner previously described. This group was exposed to 100% oxygen in the same pressures, duration, and frequency as the comparison group.

The authors report (Table 56) that total recovery from paralysis occurred in 40 of 42 (95.2%; 95% CI = 88.8, 100%) patients from the intervention group compared to 28 of 37 (75.7%; 95% CI = 61.8, 89.5%) patients in the comparison group. The average duration of symptoms was also shorter in the intervention group, as was the proportion found to be positive on the nerve excitability test. These results were statistically significant at the 5 percent level.

Table 56 Major outcomes following treatment for facial paralysis in intervention and comparison groups (Racic *et al*).[92]

Outcome	Intervention Group (n = 42)	Comparison Group (n = 37)	p
Complete recovery (n)	40	28	0.0122
Average duration of symptoms (days)	22	34.4	< 0.001*
Number positive on nerve excitability test (n) During course of treatment At nine months	 5 2	 9 9	 0.1492 0.0122

* This value is reported in the text. No standard deviations were given to allow an independent calculation of this probability.

Summary

This report provided some evidence of the benefit of exposure to HBO for subjects with moderate to severe forms of facial paralysis of less than one week duration. Replication of this study to other settings and an examination of other outcomes are required to come to firm and generalisable conclusions.

Sudden deafness and acoustic trauma

Four studies were identified that meet inclusion criteria for this indication. A brief description of each study is given in Table 57.

Table 57 Descriptive characteristics of included studies focusing on the use of HBOT in sudden deafness and acoustic trauma.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Cavallazi 1996[95]	III-2	Comparative study	Italy	?‡	62	48.2 (29-70)§	32:30
Vavrina 1995[96]	III-2	Comparative study	Switzerland	?	78	I=24.9 (6.3) C=22.7 (7.6)	?
Hoffmann 1993[97] (acute)	II	RCT	Germany	?	20	?	?
Hoffmann 1993[98] (chronic)	II	RCT	Germany	?	44	?	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

The studies were published over a period of three years. All were conducted in Europe. The sample sizes varied from 20 to 78 subjects. Only the study by Vavrina *et al*[96] was not an RCT. None of the studies indicated the dates during which subjects were recruited. The two smallest studies (both conducted by Hoffmann *et al*)[97,98] failed to provide ages and sexes of participants, while the study of Vavrina *et al*[96] did not indicate the distribution of sexes.

Study quality

All the RCTs failed to provide enough detail to assess the adequacy of randomisation (Table 58). Except for one of the studies by Hoffmann *et al*[98] none of the studies provided enough details to assess masking. All of the studies reported complete follow-up of participants.

Table 58 Methodological quality of included studies focusing on the use of HBOT in sudden deafness and acoustic trauma.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Cavallazi 1996[95]	Comparative study	None	Unclear	No losses
Vavrina 1995[96]	Comparative study	None	Unclear	No losses
Hoffmann 1993[97] (acute)	RCT	Unclear	Unclear	No losses
Hoffmann 1993[98] (chronic)	RCT	Unclear	Double-masked	1

* Abbreviation: RCT = Randomised controlled trial

Patient criteria

None of the studies provided objective criteria on which the diagnoses of sudden deafness and acoustic trauma were based. Two of the studies explicitly recruited patients

whose hearing loss was not secondary to other conditions.[95,98] One of the studies conducted by Hoffmann *et al*[98] looked at a study population that experienced hearing loss for a much longer time period than the other three studies.

Laterality of symptoms was described in only one study;[96] the others either gave no details about this characteristic or did not consider it as a criterion for inclusion. Three of the four studies[95-97] required some form of prior contact with the health system (through previous hospitalisation or presentation at a clinic) prior to enrolment.

Table 59 summarises the criteria used by the collected studies.

Table 59 Patient criteria of included studies focusing on the use of HBOT in sudden deafness and acoustic trauma.

First Author and Year of Publication	Patient Criteria
Cavallazi 1996[95]	Patients presenting with idiopathic sudden sensorineural hearing loss.
Vavrina 1995[96]	Patients with unilateral or bilateral acute acoustic trauma.
Hoffmann 1993[97] (acute)	Patients with sudden deafness, with or without tinnitus, showing no improvement after 14 days of hospitalisation with conservative therapy (ie., infusion with hydroxyethyl starch, pentoxifylline, cortisone) immediately after onset of sudden deafness.
Hoffmann 1993[98] (chronic)	Patients with inner ear hearing loss, with or without tinnitus lasting for at least six months (and without any acute event within the last six months) and without otherwise treatable reasons for their disease.

Interventions examined

The studies used similar intervention protocols (Table 60). In the two studies by Hoffmann *et al*, exposure to HBO was accomplished in a multiplace chamber using a "soft" session – 1.5 ATA for 45 minutes, five days a week. Vavrina *et al*[96] and Cavallazzi *et al*[95] exposed patients for up to 60 minutes. Pressures of 1.4 to 2.2 and 2.5 ATA respectively were used.

Table 60 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in sudden deafness and acoustic trauma.*

First Author and Year of Publication	Intervention Group	Comparison Group
Cavallazi 1996[95]	n=32 Comparison therapy plus treatment in an unstated chamber HBO device at 2.5 ATA for 60 minutes, 15 sessions over 3 weeks.	n=30 Heparin, betamethasone, nicotinic acid, flunarizine, dextran, vitamins, neurotropic, and antiviral drugs.
Vavrina 1995[96]	n=36 Comparison therapy plus treatment in a multiplace HBO chamber at 1.4 - 2.2 ATA for 60 minutes for 5-10 sessions.	n=42 Initially, 150 mg cortisone intravenously followed by ginkgo extracts in saline or dextran. 80 mg oral cortisone after the first day.
Hoffmann 1993[97] (acute)	n=10 Treatment in a multiplace HBO chamber at 1.5 ATA for 45 minutes, five times a week for 10-20 treatments.	n=10 No treatment.
Hoffmann 1993[98] (chronic)	n=22 Treatment in a multiplace HBO chamber with oxygen at 1.5 ATA for 45 minutes, 5 days a week, for 15 treatments	n=22 Treatment in a multiplace HBO chamber with air at 1.5 ATA for 45 minutes, 5 days a week, for 15 treatments

* Abbreviations: ATA = atmosphere absolute, n = sample size

Comparison therapies used were very dissimilar. One of the papers by Hoffmann *et al*,[97] for instance, stated that the comparison group received no therapy for their condition, while another paper[98] by the same authors made use of a sham procedure as a comparison. The two remaining studies studied HBOT as an adjunct to pharmacotherapy. The choice of drugs was interesting given that no particular agent, apart from corticosteroids and fluid therapy, has been shown to be effective in the treatment of the condition. In Vavrina *et al*,[96] cortisone, ginkgo extracts and dextran were used. Cavallazzi *et al*[95] identifies up to nine agents including vitamins and antiviral drugs.

Assessment of heterogeneity

Several difficulties prevented the performance of a statistical pooling of results. Firstly, there were differences in the study designs of the collected studies. The poorly described methodology raised the possibility of systematic differences affecting one group or another. Secondly, one of the studies made use of entry criteria that produced a study population known to have a chronic form of the disorder. Lastly, the comparison therapies used were very dissimilar – ranging from no treatment, to placebo therapy, to the use of multiple pharmacologic agents.

Any combination of pairs of articles exhibited at least one of the difficulties mentioned above. The results of each article are described below.

Review of published clinical experience

Hoffmann *et al* examined changes in objective hearing ability at four frequencies (500, 1000, 2000, and 4000 Hz) and subjective tinnitus between intervention and comparison groups. In their study enrolling patients with acute conditions,[97] the authors reported that 3 of 10 subjects in the intervention group experienced hearing improvements of more than 20 decibels compared to none in those not receiving any therapy. A similar 30 percent more subjects in the intervention group reported improvement in subjective

tinnitus (6 versus 3 subjects). None of the results reached commonly accepted levels of statistical significance.

In patients with chronic disorders, the authors found no significant differences between intervention and comparison groups when examining the proportions who reported improvement in hearing after 15 sessions (33% versus 50%; $p = 0.2525$) or in those who reported improvements in subjective tinnitus (18% versus 41%; $p = 0.0944$).

The main results offered by Cavallazzi *et al*[p5] are puzzling because the text and tables provided different numbers. Not enough data was given to arrive at a definite answer. The intervention was found to promote recovery if therapy was started within 72 hours (intervention group: 95% versus comparison group: 71%) or if the subject's audiogram trended downward (intervention group: 80% versus comparison group: 33%), but no denominator data were provided to judge adequately the variation in these results. Moreover, the *post-hoc* nature of these differences should be recognised.

Vavrina *et al*[p6] was the only study that reported statistically significant improvements in the average absolute gain in hearing. The intervention group improved by (Mean ± SD) 121.3 ± 61.8 decibels compared to the 74.3 ± 57.68 decibel improvement in the comparison group. The difference of 47 decibels (95% CI = 20.03, 73.97 decibels) was highly statistically significant (p = 0.0009). However, the study was also the only one to use a retrospective observational design among the four.

As with the lack of objective definitions for the conditions, none of these studies provided operational definitions for "improvement" or "recovery". The terms were used loosely to describe changes in scores or measures but the magnitude of these changes was unclear.

Summary

The studies provided conflicting evidence of the efficacy of HBOT in the management of sudden deafness and acoustic trauma. Methodological problems were common in the identified studies. Until more rigorous evidence is collected, the use of HBOT in the management of these conditions cannot be supported on the basis of the current inconsistent results.

Cancer

Hyperbaric oxygen therapy as an adjunctive agent is examined for cancers of the head and neck, cervix, and bladder. Other cancers include lymphomas and neoplasms affecting the lungs and nervous system. For most neoplastic indications, the comparator treatments are of historical interest and not relevant to current practice.

Head and neck cancer

Nine studies were retrieved from the published literature. A brief description of each study is given in Table 61.

Table 61 Descriptive characteristics of included studies focusing on the use of HBOT in head and neck cancer.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Whittle 1990[99]	III-2	Comparative study	UK	1963 to 1985	397	?‡	?
Henk 1986[100]	II	RCT	UK	1972 to 1977	107	?	?
Sealy 1986[101]	II	RCT	South Africa	Sep 1980 to Mar 1984	130	I=56 C=55	I=56:8 C=60:6
Berry 1979[102]	II	RCT	UK	Jan 1971 to Dec 1974	24	I=61 (6) C=66 (9)	?
Sause 1979[103]	II	RCT	USA	Nov 1970 to Dec 1976	50	I=57 (38-80)§ C=63 (36-81)	I=8:13 C=15:8
Chang 1973[104]	II	RCT	USA	Jan 1964 to Mar 1971	51	?	2.5:1
Churchill-Davidson 1973[105]	III-3	Comparative study with historical controls	UK	1962 to 1972	171	?	?
Shigamatsu 1973[106]	III-1	Pseudo-randomised controlled trial	Japan	1969 to 1971	42	I=56.6 C=57.7	?
Henk 1970[107]	III-1	Pseudo-randomised controlled trial	UK	Sep 1964 to Jun 1969	213	I=60 C=58	I=76:25 C=71:41

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

The studies were published from 1970 to 1990. Four studies were conducted in the UK, three in the USA and one each in Japan and South Africa. The sample sizes ranged from 24 to 397 patients and the studies were conducted over a period ranging from two to 22 years. Five studies were described as RCTs[100-104] and a further two studies[106, 107] were also reportedly RCTs, but examination of the descriptions of the randomisation methods employed led to the conclusion that they are more accurately described as pseudo-randomised controlled trials.

Study quality

All five studies described as RCTs failed to provide enough detail to assess the adequacy of randomisation (Table 62). Furthermore, as mentioned, two studies that described themselves as RCTs were found to have used inadequate methods of randomisation, namely birth dates (Henk *et al*[107]) and odd and even admission numbers (Shigamatsu *et al*[106]). None of the studies reported masking procedures and as patients in the comparison group were not subjected to a sham HBOT procedure it is reasonable to

assume that all participants knew of their allocation. Four studies reported complete follow-up of participants.[99,104-106]

Table 62 Methodological quality of included studies focusing on the use of HBOT in head and neck cancer.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Whittle 1990[99]	Comparative study	None	None	No losses
Henk 1986[100]	RCT	Unclear	None	One patient
Sealy 1986[101]	RCT	Unclear	None	Six patients
Berry 1979[102]	RCT	Unclear	None	Two patients from HBO group (treated in air)
Sause 1979[103]	RCT	Unclear	None	Six patients
Chang 1973[104]	RCT	Unclear	None	No losses
Churchill-Davidson 1973[105]	Comparative study with historical controls	None	None	No losses
Shigamatsu 1973[106]	Pseudo-randomised controlled trial	Odd and even admission numbers	None	No losses
Henk 1970[107]	Pseudo-randomised controlled trial	Allocation by birth date for first 52 cases, subsequent cases by sealed envelopes	None	Eighteen patients received less than half their treatment in the HBOT group.

* Abbreviation: RCT = randomised controlled trial.

Patient criteria

Table 63 compares the various patient criteria used for enrolment into the identified studies. Although all studies recruited patients with cancer of the head and neck regions, Whittle *et al*[99] included patients with glottic cancer only and Shigamatsu *et al*[106] limited enrolment to patients with maxillary sinus cancer. The remainder of the studies varied in their description of the location of carcinomas in their study populations.

Table 63 Patient criteria of included studies focusing on the use of HBOT in head and neck cancer.

First Author and Year of Publication	Patient Criteria
Whittle 1990[99]	Patients with glottic cancer
Henk 1986[100]	Histologically confirmed cancer of squamous origin in the head and neck. Exclusions: patients with early disease and a good prognosis, e.g. T1 and T2 carcinoma of the larynx and T1N0 carcinoma at other sites.
Sealy 1986[101]	Patients with locally advanced previously untreated squamous carcinoma of the mouth or fixed neck nodes.
Berry 1979[102]	Patients with squamous carcinoma of the maxillary antrum, tongue, oropharynx, mouth, laryngopharynx and larynx.
Sause 1979[103]	Patients with squamous cell carcinomas of the upper air and digestive passages. Exclusions: patients with early lesions of the vocal cord.
Chang 1973[104]	Patients with previously untreated, biopsy proved, squamous cell carcinoma of the oropharynx
Churchill-Davidson 1973[105]	Patients with squamous carcinoma of the head and neck with secondary neck nodes. Exclusions: patients with primary carcinoma of the nasopharynx, proven distant metastases, concurrent medical conditions contraindicated to HBOT (e.g. hypertension, etc.), advanced age.
Shigamatsu 1973[106]	Patients with squamous cell carcinoma of the maxillary sinus. Exclusions: patients older than 70 years, haemoglobin <3g/100ml, T-1 cases and far advanced cases.
Henk 1970[107]	Patients with epithelial tumours of the upper air and food passages. Exclusions: patients with small mouth tumours, carcinoma of the vocal cords, age greater than 75 years, patients who have undergone radiotherapy previously, presence of metastases other than in the cervical nodes.

Interventions examined

HBOT was applied in a monoplace chamber in three studies (Table 64).[99,106,107] The chamber used was not described in the remainder of the studies. Pressures of 3 ATA were used in four studies[99,103,104,107] and 3-4 ATA in one study,[105] while the pressure used was not described in the remainder of the studies. The duration of HBOT was not explicitly stated, but patients remained in the chamber for the duration of their radiotherapy.

The dose and fractionation scheme of radiotherapy varied between studies. Doses used ranged from 250 to 6400 rad in total, and the fractionation schemes ranged from five to 30 fractions.

Table 64 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in head and neck cancer.*

First Author and Year of Publication	Intervention Group	Comparison Group
Whittle 1990[99]	n=157 Placement in a monoplace HBO chamber at 3 ATA up to one hour, plus concurrent radiotherapy at a dose of 32-34 Gy in six fractions over 18 days.	n=240 Conventional radiotherapy in air at a dose of 60-70 Gy, five fractions per week.
Henk 1986[100]	n=54 Placement in a HBOT chamber, pressure and time not stated. Dosage and fractionation scheme for radiotherapy was 3600-4500 rad in 10 fractions in 22 days.	n=53 Conventional radiotherapy in air: 30 fractions over six weeks; dosage received was 6400 rad (proportionally smaller when fields were larger).
Sealy 1986[101]	n=64 Radiotherapy in HBOT. Radiotherapy dose of 36.0 Gy in six fractions over 17 days. Misonidazole (2.0g/m^2 p.o. per fraction) was also prescribed and HBOT at 3 ATA.	n=66 Conventional radiotherapy in air: tumour dose of 63.0 Gy in 30 fractions daily over 38 days.
Berry 1979[102]	n=9 Radiotherapy concurrent with HBOT; dose of radiotherapy was 4000-4500 rad (reduced to 3650-4150 rad in the larynx was involved) in 10 fractions.	n=15 Conventional radiotherapy in air: 4450-5000 rad in 15 fractions or 4850-5500 rad in 20 fractions depending on field size.
Sause 1979[103]	n=21 Radiation therapy: 12 x 400 rad in 32 days during concurrent HBOT at 3 ATA.	n=23 Conventional radiotherapy (250-6250 rad) in air.
Chang 1973[104]	n=26 Radiotherapy at a dose of 600 rad x 6 treatments (two per week for three weeks), concurrently with HBOT at 3 ATA.	n=25 Control group 1: n=12 received radiotherapy in air at a dose of 600 rads per treatment for seven treatments (two per week for 3.5 weeks). Control group 2: n=13 received radiotherapy at 200 rads per treatment for 30 treatments (five per week for six weeks).
Churchill-Davidson 1973[105]	n=102 HBOT at 3-4 ATA with radiotherapy at a maximum dose of 3600 rads in six fractions over 18-19 days.	n=69 Radiotherapy treatment in air.†
Shigamatsu 1973[106]	n=21 Radiotherapy concurrent with HBOT at 3 ATA in a monoplace chamber. Radiotherapy consisted of a total dose of 6000-7000 R in a bi-weekly schedule.	n=21 Radiotherapy in air, 4000-5000 R in 9-10 fractions.
Henk 1970[107]	n=101 Radiotherapy received concurrent to HBOT at 3 ATA in a monoplace chamber. Radiotherapy at a dose of 3500-4500 rads in 10 fractions over three weeks.	n=112 Radiotherapy in air: 3500-4500 rads in 10 equal fractions, over three weeks.

* Abbreviations: ATA = atmosphere absolute, n = sample size

† Therapy not described.

The disparities in intervention protocols were reflected in equally varied comparison protocols. Doses and fractionation schemes varied between the intervention and

comparisons groups in the majority of studies. Furthermore, as previously stated, the comparison groups were not exposed to any sham HBOT procedure, thus it could be argued that the treatment regimes between intervention and comparison groups were quite different.

Assessment of heterogeneity

Taking into consideration the wide differences in study population, study design, patient criteria, and treatment protocols employed by the eight studies that met eligibility criteria, the review undertook no statistical analysis of heterogeneity and made no attempt to arrive at a statistically pooled effect estimate through meta-analysis.

Review of published clinical experience

Overall, the results of the studies were presented poorly and statistical tests used to analyse data were rarely described. Survival rates for varying periods of time and local tumour control were measured in all studies.

Two studies found a significantly better five-year survival rate after HBOT and radiotherapy compared to radiotherapy alone.[100,102] However, five-year survival rates were found not to differ in the studies of Whittle *et al*,[99] Chang *et al*,[104] and Churchill-Davidson *et al*[105] Survival rates measured for shorter time periods were also found not to differ with HBOT therapy in the remainder of the studies.[101,103,106,107] Despite the lack of difference in survival in the studies of Whittle *et al*,[99] Shigamatsu *et al*,[106] and Henk *et al*,[107] local tumour control rates were higher with HBOT treatment in those studies, as they were in the studies of Henk *et al*[100] and Berry *et al*.[102] Sealy *et al*[101] found no statistical difference in local tumour control rates between patient groups. The remaining three studies did not state that statistical analyses were performed, but local tumour control rates do not appear to be different between groups.

Thus, HBOT concurrent with radiotherapy has a limited effect on survival rates for patients with head and neck cancer, while local tumour control was improved in five of nine included studies.

Summary

The identified studies were disparate in their research designs, varied in their populations, discrepant in their therapies, and conflicting in their outcomes and conclusions. Overall, there is a lack of well-conducted studies to support the use of hyperbaric oxygen therapy for head and neck cancer and there is little firm evidence of a beneficial effect..

Cervical cancer

Six published studies were collected (Table 65). The studies were published over seven years and, except for one of the earlier studies, were primarily randomised controlled trials. All studies were conducted in sites located in the United Kingdom or North America. Recruitment of participants occurred over a 15 year period. Study populations were inadequately described.

Table 65 Descriptive characteristics of included studies focusing on the use of HBOT in cervical cancer.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population	
					Size	Age
Brady 1981[108]	II	RCT	USA	Jan 1972 to Oct 1975	65	?†
Watson 1978[109]	II	RCT	UK	1966 to 1973	301	?
Fletcher 1977[110]	II	RCT	USA	Sep 1968 to Mar 1974	233	?
Glassburn 1974[111]	II	RCT	USA	from Nov 1967	40	?
Johnson 1974[112]	III-3	Comparative study with historical controls	Canada and USA	1959 to 1966	64	?
Ward 1974[113]	II	RCT	UK	Dec 1971 to Apr 1973	45	?

* Abbreviation: RCT = randomised controlled trial.

† Unstated, unclear, or unknown.

Study quality

Only two RCTs provided enough information to determine the adequacy of randomisation (Table 66).[109,113] None of the RCTs discussed masking procedures. Brady *et al*[108] report that seven subjects were lost to follow-up after randomisation. All other studies report that all patients were traced.

Table 66 Methodological quality of included studies focusing on the use of HBOT in cervical cancer.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Brady 1981[108]	RCT	Unclear	Unclear	7
Watson 1978[109]	RCT	Adequate	Unclear	No losses
Fletcher 1977[110]	RCT	Unclear	Unclear	No losses
Glassburn 1974[111]	RCT	Unclear	Unclear	No losses
Johnson 1974[112]	Comparative study with historical controls	None	None	No losses
Ward 1974[113]	RCT	Adequate	Unclear	No losses

* Abbreviation: RCT = Randomised controlled trial

Patient criteria

A variety of staging systems were used to enrol patients into the studies (Table 67). These systems were sometimes unmentioned, as was often the case in the earlier studies.[111,112] The inclusion of histologically-proven carcinoma is mentioned in four of the six studies.[108-110,113] All studies originally included patients with advanced disease. In two studies, patients with localised disease (stage I and II) cancers were included.[109,110]

Table 67 Patient criteria of included studies focusing on the use of HBOT in cervical cancer.

First Author and Year of Publication	Patient Criteria
Brady 1981[108]	Patients with squamous cell carcinoma of the cervix (stage IIb, IIIa, IIIb, IVa, International Federation of Gynecology and Obstetrics). Exclusions: pregnancy; previous radiotherapy to the primary site; previous surgery or chemotherapy; prior diagnosis of malignancy other than skin cancer.
Watson 1978[109]	Patients aged 75 years of less with locally advanced carcinoma of the cervix (stages III and IVa, Stockholm) proven histologically; ability to lie flat and be otherwise fit for treatment in a HBO chamber; no previous treatment with radium. Exceptions: 23 patients with stage IIb cancer included in one centre.
Fletcher 1977[110]	Patients with stage IIb (involvement of the lateral half of the parametria without involvement of the pelvic walls or the lower third of the vagina), IIIa (fixation to one pelvic wall), IIIb (fixation to both pelvic walls or involvement of one pelvic wall and the lower third of the vagina), and IVa (biopsy-proven bladder or rectal involvement without distant metastases) carcinoma of the cervix. Exclusion: patients over 70 years of age. Exceptions: 10 patients with stage I-IIa cancer included.
Glassburn 1974[111]	Patients with stage 3a, 3b or 4a carcinoma of the cervix. Exclusions: receipt of prior therapy for cervical carcinoma; second primary tumour other than cancer of the skin; pre-existing medical problems preventing treatment with HBO.
Johnson 1974[112]	Patients with stage III or IV carcinoma of the cervix.
Ward 1974[113]	Patients with clinically (League of Nations) staged 2b or 3 cancers of the uterine cervix; diagnosis histologically confirmed before treatment; not pregnant; no history of major pelvic surgery or pelvic irradiation, salpingitis, or endometriosis; physically and psychologically suitable for treatment in HBO; haemoglobin of at least 80 percent before treatment; no history of malignant disease; 75 years of age or less.

Interventions examined

The HBO protocols used in intervention therapies were not described in three studies (Table 68).[109,110,112] In those reporting use of HBO, inadequate information was given about chambers, duration, or frequencies.

Table 68 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in cervical cancer.*

First Author and Year of Publication	Intervention Group	Comparison Group
Brady 1981[108]	n=29 Stage IIb: 4,000 rad tumour dose in 10 fractions over five weeks. Gynaecological radium dose from 3,000 to 4,500 mg-hrs. No boosters given. Stage IIIa: 4,000 rad tumour dose in 10 fractions over five weeks. Gynaecological radium dose from 3,000 to 4,000 mg-hrs. Booster to site of 400 rad per fraction. Vaginal extensions treated according to investigator. Stage IIIb and IVa: 4,000 rad tumour dose in 10 fractions over 5 weeks. Gynaecological radium dose from 3,000 to 4,500 mg-hrs. Booster to site of 400 rad per fraction. Vaginal extensions treated according to investigator. Treatment in an unstated HBO chamber at 3 ATA for 60 minutes.	n=29 Stage IIb: 5,000 rad tumour dose in 25 fractions over five weeks. Gynaecological radium dose from 3,000 to 4,500 mg-hrs. No boosters given. Stage IIIa: 5,000 rad tumour dose in 25 fractions over five weeks. Gynaecological radium dose from 3,000 to 4,000 mg-hrs. Booster to site of 500 rad per 2 fractions. Vaginal extensions treated according to investigator. Stage IIIb and IVa: 5,000 rad tumour dose in 25 fractions over 5 weeks. Gynaecological radium dose from 3,000 to 4,500 mg-hrs. Booster to site of 500 rad per 2 fractions. Vaginal extensions treated according to investigator.
Watson 1978[109]	n=150 Comparison therapy plus HBOT.†	n=151 Multicentre trial allowing variations in radiotherapy protocols. Maximal dose varied between centres with some prescribing maximum doses of 3,000 rad and others giving a minimum of 5,500 rad. Fractions varied from 6 to 27 doses. Radium applied to some patients.
Fletcher 1977[110]	n=109 Comparison therapy plus treatment in a monoplace HBO chamber with oxygen.†	n=124 Stage IIb: node negative – 4,000 rad tumour dose for four weeks through 15 × 15 cm fields; node positive – 5,500 rad tumour dose in 6.5 weeks at 850 rad per week with appropriate field extension. External beam followed by two radium applications for 48 hours each, two weeks apart, to a maximum of 6,500 mg-hrs. Stage IIIa: node negative – 5,000 rad tumour dose for five weeks through 15 × 15 cm fields; node positive – 5,500 rad tumour dose at 850 rad per week with ipsilateral parametrial boost of 1,000 rad in one week. External beam followed by two radium applications (24 and 48 hours for first and second applications, respectively) to a maximum of 5,000 mg-hrs. Stage IIIb and IVa: 5m000 to 5,500 rad tumour dose with field reduction to 12 × 12 cm for additional 1,000 rad. Single radium application for 60 hours not to exceed 4,000 mg-hrs. External irradiation schedules listed.

Glassburn 1974[111]	n=17 Comparison therapy original protocol. Modified protocol: 4,000 rad tumour dose in 10 fractions over five weeks at a rate of 400 rad per treatment twice weekly. Stage IIIa to IVa: 400 rad booster dose to the lateral pelvic wall. Treatment in a monoplace HBO chamber at 3 ATA for 40 minutes.	n=23 Original protocol: 250 rad per treatment session, four times a week, 1,000 rad per week, for a total of 5,000 rad. Stage IIIa and IIIb: 1,000 rad booster to lateral pelvic structures. Modified protocol: 5,000 rad tumour dose in 10 fractions over five weeks at a rate of 200 rad per treatment five times a week. Stage IIIa to IVa: 500 rad booster dose to the lateral pelvic wall.
Johnson 1974[112]	n=25 Comparison therapy plus HBOT.†	n=39 Three groups with a minimum dose of 6,000 rad in 30 fractions over 6 weeks. Stage IIIa: 500 rad booster dose to the lateral pelvic wall in two treatments with a single radium application of 3,000 to 4,500 mg-hrs and a maximum rectal dose of 8,000 rad. Stage IIIb: 6,000 rad minimum dose with single radium application of 1,500 to 2,000 mg-hrs.
Ward 1974[113]	n=23 Comparison therapy plus treatment in a monoplace HBO chamber at 3 ATA for 30 minutes.	n=22 Two-point tissue doses of 6,000 and 3,950 rad. Rectal dose of 5,000 rad.

* Abbreviations: ATA = atmosphere absolute, n = sample size.

† Therapy not described.

Comparison therapies were not standardised across studies. Most applied overlapping radiotherapy exposures over a variable number of fractions and duration of therapies. The subjects were not placed in HBO chambers.

Assessment of heterogeneity

This review does not attempt to arrive at a common effect estimate through statistical methods due to the inadequacy with which study populations, methodologies, and intervention and comparison protocols were described. Instead, the results of each study are described below.

Review of published clinical experience

In the five-year follow-up published by Brady *et al*,[108] no statistically significant differences between intervention and comparison groups in terms of disease and complication-free survival, median duration, and survival proportions at the end of follow-up (Table 69).

Table 69 Outcomes following treatment for cervical cancer in intervention and comparison groups (Brady *et al*).[108]

Outcome	Intervention Group (n = 29)	Comparison Group (n = 29)	p
Disease and complication free survival (%)			
Overall	48.3	48.3	1.0000
Stage IIb	64.3	42.8	0.2556
Stage IIIb	35.7	53.8	0.3434
Stage IVa	0.0	50.0	
Median duration (years)	4.0	2.5	
Proportion surviving to 5 years (%)	45.0	46.0	0.9390

These contrasted with the conclusions drawn from the multicentre trial by Watson *et al*[109] who found that crude intervention group actuarial survival rates were marginally better yet of borderline statistical significance (unstated statistic, $p = 0.08$). Various stratification techniques uncovered highly statistically significant survival benefits for the intervention protocol in patients with stage III disease after controlling for centre effects ($p = 0.009$). The relevance of these *post-hoc* analyses is unknown but they are unsatisfactory when performed without substantial protection from increasing the probability of detecting a significant difference when none exists (Type I error).

Fletcher *et al*[110] and Glassburn *et al*,[111] failed to detect statistically significant survival advantages between intervention and comparison groups (Table 70). The study by Johnson and Walton[112] selectively report the experience of a subset of participants without divulging the overall comparisons described in their methods section. The experience of 14 subjects assigned to the comparison group are undisclosed. If conservative assumptions are applied (ie, that all missing comparison group subjects died), then the intervention protocol is found to be statistically significantly associated with death over five years ($p = 0.0449$).

Table 70 Outcomes following treatment for cervical cancer in intervention and comparison groups.[110,111]

Outcome	Intervention Group	Comparison Group	p
Fletcher 1977[110]			
Sample size (n)	109	124	
Five-year disease free survival (%)	33.0	41.1	0.2021
Glassburn 1974[111]			
Sample size (n)	17	23	
27-month disease-free survival (%)	41.1	39.1	0.8961
Johnson 1974[112]			
Sample size (n)	25	25	
Five-year disease-free survival (%)	44.0	16.0	0.0308

Summary

The studies failed to provide enough evidence to come to firm conclusions about the effectiveness of exposure to HBO in conjunction with radiotherapy for cervical cancer. Any conclusions reached from these studies would need to take into consideration the disparity in intervention and comparison protocols, poor methodological descriptions, and substantial *post-hoc* comparisons.

Bladder cancer

Four studies were retrieved from the published literature, and judged to meet inclusion and exclusion criteria (Table 71).

Table 71 Descriptive characteristics of included studies focusing on the use of HBOT in bladder cancer.*

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Cade 1978[114]	II	RCT	UK	May 1964 to Dec 1971	236	?†	?
Kirk 1976[115]	II	RCT	UK	1966 to 1970	27	?	?
Dische 1973[116]	II	RCT	UK	from Apr 1966	67	?	?
Plenk 1972[117]	II	RCT	USA	May 1965 to May 1970	40	I=68.8 C=68.2	I=19:0 C=19:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Unstated, unclear, or unknown.

The studies were published over a period of six years. All were randomised controlled trials conducted in the USA or the UK. Patients were recruited in the mid 1960's, although the characteristics of some study populations were unstated.[114-116]

Study quality

The adequacy of randomisation was certain only in two of the studies (Table 72).[114,116] All studies failed to adequately mention masking procedures. Except for the study by Plenk,[117] all studies reported complete follow-up of subjects.

Table 72 Methodological quality of included studies focusing on the use of HBOT in bladder cancer.*

First Author and Year of Publication	Study Design	Randomisation	Masking	Losses to Follow-up
Cade 1978[114]	RCT	Adequate	Unclear	No losses
Kirk 1976[115]	RCT	Unclear	Unclear	Unclear
Dische 1973[116]	RCT	Adequate	Unclear	No losses
Plenk 1972[117]	RCT	Unclear	Unclear	No losses

* Abbreviation: RCT = Randomised controlled trial

Patient criteria

Table 73 lists the inclusion and exclusion criteria used in the four studies. The three most recent studies[114-116] included patients based on very similar criteria that included the confirmation of bladder cancer by histology, suitability to radiotherapy, and extent of tumour spread. The study by Plenk[117] used more relaxed criteria.

Table 73 Patient criteria of included studies focusing on the use of HBOT in bladder cancer.

First Author and Year of Publication	Patient Criteria
Cade 1978[114]	Patients with carcinoma of the bladder of any histological type and who were considered suitable for radiotherapy; the primary tumour has not infiltrated the skin, rectal wall, or other segment of the intestine (vaginal or uterine involvement was allowed if no fistulae were present); and lymph node involvement was confined to the external iliac nodes. Exclusions: impaired renal function (blood urea > 16.7 mmol per litre); inability to enter the hyperbaric oxygen chamber (due to inability to lie flat, or a history of convulsions); unlikely or unable to cooperate in pressurisation; unlikely or unable to complete follow-up; 75 years or alder; total cystectomy or urinary diversion had been performed.
Kirk 1976[115]	Patients under the age of 76 with histologically proven carcinoma of the bladder confined to the pelvis. The patient would have no history of previous radiotherapy or surgery other than cystostomy, transurethral resection, open diathermy, or partial cystectomy. Patients had to be able to lie flat. Blood urea should be less than 16.7 mmol per litre.
Dische 1973[116]	Patients under the age of 76 with bladder cancer proven histologically; with tumours which are potentially curable using radiotherapy; the primary tumour has not infiltrated the skin, rectal wall, or other segment of the intestine (vaginal or uterine involvement was allowed if no fistulae were present); lymph node invasion limited to the true pelvis; Exclusions: inability to lie down in the chamber; diastolic blood pressure persistently greater than 110 mm Hg; history of convulsions; blood urea greater than 16.7 mmol per litre; total cystectomy or urinary diversion had been performed.
Plenk 1972[117]	All patients with bladder cancer who were able to tolerate high pressure oxygen and who did not have distant metastases at the time of initial evaluation.

Interventions examined

Intervention protocols were inadequately described (Table 74). Not all studies mentioned the pressure at which subjects were exposed,[116] few gave the duration of exposure[116,117] and none mentioned the frequency at which the therapy was applied.

Table 74 Therapeutic protocols used in intervention and comparison groups in included studies focusing on the use of HBOT in bladder cancer.*

First Author and Year of Publication	Intervention Group	Comparison Group
Cade 1978[114]	n=118 Comparison therapy plus treatment in an unstated chamber HBO device at 3 ATA.	n=118 Maximum tissue dose from 3,600 to 6,000 rad with minimum tumour dose from 4,250 to 6,000 rad. Radiotherapy was given in divided doses over 18 to 56 days.
Kirk 1976[115]	n=14 Comparison therapy plus treatment in an unstated chamber HBO device at 3 ATA.	n=13 Modal tumour dose of 6,000 rad in 24 fractions given over 5 weeks.
Dische 1973[116]	n=28 Comparison therapy plus treatment in an unstated chamber HBO device for 35 to 40 minutes.	n=39 Therapy 1: minimum dose of 6,000 rad in 30 fractions over 42 days. Therapy 2: minimum dose of 4,725 rad in 15 fractions over 33 days.
Plenk 1972[117]	n=19 Tumour dose of 400 rad in 12 fractions over 29 to 40 days. Treatment in a monoplace HBO chamber with air about 2 ATA for 8-10 minutes.	n=21 Tumour dose of 6,000 rad in 4 to 5 fractions per week for 6 weeks.

* Abbreviations: ATA = atmosphere absolute, n = sample size

The different studies also applied varying doses of radiation to the affected region, ranging from 3,600 to 6,000 rads. Moreover, treatments were spread over differing numbers of days and used dissimilar fractions. In the study by Plenk,[117] patients were exposed to two different radiation doses and dosing schedules based on their exposure to HBO or air.

Assessment of heterogeneity

Due to the inadequacy with which study populations, methodologies, and intervention and comparison protocols were described, this review does not attempt to arrive at a common effect estimate through statistical methods. The results of each study are described below.

Review of published clinical experience

The study by Cade *et al*[114] examined actuarial survival rates (Table 75) and found no statistically significant differences between the survival curves (unstated statistic, $p = 0.72$). Stratification by histological type of tumour failed to uncover differences in survival (transitional tumours, $p = 0.61$; anaplastic tumours, $p = 0.62$; other types, $p = 0.32$).

Table 75 Percentage of population surviving by year since trial entry following treatment for bladder cancer in intervention and comparison groups.[114-117]*

First Author and Year of Publication	Group Assignment	Sample Size	Percentage Survival by Year Since Trial Entry					p†
			1	2	3	4	5	
Cade 1978[114]	Intervention	118	64	42	36	31	28	0.72
	Comparison	118	64	47	37	35	30	
Kirk 1976[115]	Intervention	14	No Data				43	0.52‡
	Comparison	13					31	
Dische 1973[116]	Intervention	28	54	37	27	28	20	NS
	Comparison	39	64	39	37	39	25	
Plenk 1972[117]	Intervention	19	53	37	43	22	No Data	<0.05
	Comparison	21	42	19	8	11		

* Abbreviation: NS = not statistically significant.

† The statistic used to compare survival experiences is not given. These values are as they appear in the publications.

‡ Independent calculation based on exact binomial methods.

Kirk *et al*[115] provide survival proportions only at the fifth year post therapy (Table 75). Exact binomial methods failed to provide evidence of a statistically significant difference between the two groups ($p = 0.52$). The study was halted due to high-dose effects that included post-radiation haematuria of sufficient severity to warrant cystectomies (n = 8) or ureteral transplants (n = 1). Dische[116] failed to find statistically significant differences in the survival experiences of the two groups, even after extensive *post-hoc* stratification according to treatment received or tumour size.

Plenk[117] reported statistically significant survival benefits in those subjects receiving HBO. Median survival times for the intervention and comparison groups were 25.9 and 13.6 months respectively.

Summary

There are conflicting results about the survival benefit afforded by exposure to HBOT in conjunction with radiotherapy for bladder cancer. The lack of methodological rigour, the variations in protocols, and inadequate descriptions of populations make it difficult to arrive at a global assessment of effectiveness.

Lymphomas

The study by Pan *et al*[118] examined the effect of adjunctive HBOT on patients with lymphoma receiving chemotherapy. The study was conducted in China and enrolled 41 patients with clinically diagnosed lymphoma. The authors did not differentiate between Hodgkin's and non-Hodgkin's lymphoma. Using an alternation scheme, patients were assigned to HBOT (20 patients exposed to 2.5 ATA for two hours once a day for 14 days in an unstated chamber) or air (n = 21). All patients received courses of adriamycin, bleomycin, cyclophosphamide, vincristine and dexamethasone. The report did not discuss masking or follow-up procedures.

The authors examined the following end-points: reduction in tumour area (the product of the tumour's largest horizontal and vertical diameters), complete remission time (the length of time from initiation of therapy to disappearance of the tumour), complete remission rate (undefined, but evidently the proportion of tumours that undergo complete remission), complete remission duration (the length of time from complete remission to recurrence or censoring), and survival duration (the length of time from diagnosis of the disease to death or censoring). The authors also looked at decreases in haematologic measures (haemoglobin, white blood cells, platelets) and bone marrow (proliferous degree, division index, megakaryocytes, granulocytes, nucleated erythrocytes). No description of the methods used to determine these outcomes were given.

The authors report statistically significant differences between intervention and comparison groups in terms of reductions in tumour area, complete remission time, rate, and duration, survival duration, and decreases in the haematologic and bone marrow measures except for haemoglobin and megakaryocytes (Table 76).

Table 76 Outcomes following treatment for lymphoma in intervention and comparison groups (Pan *et al.*).[118]

Outcome	Intervention Group (n = 20)	Comparison Group (n = 21)	p
Reduction in tumour area (cm^2)	15.5 (2.8)*	8.8 (2.1)*	<0.0001
Complete remission time (days)	30.0 (7.2)	48.0 (8.4)	<0.0001
Complete remission rate (%)	85.0	47.6	0.0116
Complete remission duration (months)	15.7 (3.1)	8.2 (2.6)	<0.0001
Survival duration (months)	18.9 (3.7)	11.4 (3.3)	<0.0001
Decreases in haematologic measures (%)			
Haemoglobin	80.0	78.2	0.8874
Granulocytes	10.0	90.5	<0.0001
Platelets	20.0	57.1	0.0149
Decreases in bone marrow cells (%)			
Proliferous degree	10.0	71.1	0.0001
Division index	5.0	95.5	<0.0001
Megakaryocytes	50.0	52.4	0.8779
Granulocytes	20.0	66.6	0.0027
Nucleated Erythrocytes	5.0	71.1	<0.0001

* Figures in parentheses are assumed to be standard deviations.

Summary

While methodologically sparse, this study provides some evidence of the efficacy of HBOT in the treatment of lymphomas. The validity of the end-points used is unclear. Properly randomised clinical trials that focus on other outcomes are needed to provide substantial support or refutation of the importance of the effectiveness of HBOT for this indication.

Lung Cancer

Only the study by Sause *et al*[119] is included in this review. The study compared the effect of HBOT versus exposure to air in patients with bronchogenic carcinoma seen at a single centre in the United States between 1970 and 1977. Fifty-six patients were treated at random with 3 ATA of oxygen or air, although the analysis only includes the 47 that completed the prescribed course of therapy. All patients received radiotherapy using a fractionated scheme of 4 Gy over 32 days using ^{60}Co. This scheme was initially developed for use of HBO. The authors admit to eliminating the need for pressurised oxygen in subsequent patients. Descriptions of the population characteristics, type of chamber used, or the HBO protocol followed were not given. The adequacy of randomisation, masking, and extent of follow-up are not discussed. The authors report that there were no statistically significant differences in the rates of survival between the two groups.

Summary

The study provides little evidence of the effect of HBOT in the treatment of lung cancer. More studies in different settings and examining more varied outcomes are required to reach more generalisable evidence of effect.

Neuroblastoma

In 1996, van der Kleij and Voute[120] examined the treatment of recurrent stage IV neuroblastoma using radioactivated ^{131}I-metaiodobenzylguanidine (MIBG) and HBOT. The study was a case series that made comparisons with the survival experience of a

separate and previously-studied series of patients undergoing treatment with ^{131}I-MIBG alone. Patients in this series were recruited from an academic medical centre in the Netherlands. The authors enrolled 51 but present results for the 35 (69%) who completed more than one course of therapy. Overall, patients had a mean age of 6.8 years. There were 19 males and 19 females.

Patients were given ^{131}I-MIBG intravenously. Exposure to HBO was through a multiplace chamber at 3 ATA for 75 minutes, once daily for four days. The primary end point was survival.

Patients lived for a mean duration of 3 years following treatment. Kaplan-Meier plots comparing survival distributions between those receiving HBOT and those treated with ^{131}I-MIBG alone showed better survival in the HBOT group. The results were statistically significant (log rank test, $p = 0.0326$).

Summary

While this study provides some evidence of the effect of HBOT in the treatment of neuroblastoma, until more rigorous evidence is collected, the use of this technology cannot be supported.

Carbon monoxide poisoning

Several studies have been published examining the use of HBOT for acute carbon monoxide poisoning. In 2000, Juurlink *et al*[122] published a systematic review of the literature on this topic, focusing on the efficacy of the procedure on the development of neurologic sequelae one month after treatment. The authors searched for relevant publications from 1966 to 1999 using three electronic databases (Medline, Embase, and the Cochrane Controlled Trials Register) supplemented by examination of reference lists and contact with experts in the field. A search revealed no studies that met the inclusion and exclusion criteria published subsequent to the release of this systematic review. The following discussion is consequently limited to an assessment of the Juurlink *et al* review.

The review collected six reports of randomised controlled trials involving non-pregnant adults acutely poisoned with carbon monoxide, regardless of severity. The authors analysed the results of three studies [123,124,125] that scored three or more on the Jadad quality scale.

The authors found that the severity of poisoning varied between trials. Each also employed different doses of HBO. The results for a total of 455 patients were available for analysis. Non-specific neurological symptoms (eg., headache, confusion, difficulty concentrating, and disturbances with sleep) were present in 81 of 237 patients (34.1%) in the intervention group compared to 81 of 218 patients (37.2%) in the comparison group (OR = 0.82; 95% CI = 0.40, 1.66). Sensitivity analysis did not change the results.

Summary

This systematic review failed to demonstrate a significant reduction in neurologic sequelae following HBOT for carbon monoxide poisoning. More methodologically-rigorous studies are required to examine the efficacy of HBOT on other outcomes and in distinct patient subsets.

Necrotising arachnidism

No articles met inclusion and exclusion criteria.

Actinomycosis

No articles met inclusion and exclusion criteria.

Soft tissue radionecrosis

No articles met inclusion and exclusion criteria.

Cerebral palsy

No articles met inclusion and exclusion criteria.

Crohn's disease

No articles met inclusion and exclusion criteria.

Legg-Calve-Perthes disease

No articles met inclusion and exclusion criteria.

Osteoporosis

No articles met inclusion and exclusion criteria.

Limits of the review of safety and effectiveness

Validity refers to the approximate truth from which inferences and conclusions can be drawn. The two types of validity measures that are most relevant to HBOT are internal and external validity. Internal validity assumes that the results of a study are attributable to the intervention and not to other alternative explanations. External validity refers to the generalisability of the results with respect to patients outside the study population. A review of the literature on HBOT identified a wide range of methodological problems. In this review, approximately 50% of the studies adopted quasi-experimental or non-randomised designs as part of their methodology. This is problematic when trying to reach credible conclusions regarding the effectiveness of HBOT for specific indications.

Internal validity

Of the studies evaluating HBOT a number of threats to internal validity were identified.

History

This threat applies when an observed effect might be due to an external event occurring in conjunction with the intervention. In order to control for this bias, researchers would

need to insulate patients from outside influences or choose outcomes which cannot plausibly be affected by external factors. This is most evident when therapies span several years as in those for thermal burns and acute myocardial infarction.

Regression to the mean

Regression to the mean occurs in studies that have asymmetrically sampled from the population A result of this sampling effect is regression of the sample mean toward the population mean from pre- to post-test. For example, patients who exhibit a randomly high score at the beginning of a trial will show a lower value post intervention and patients with extremely low scores will present with higher scores at the end of the trial. A selection regression threat can also occur when the intervention and control groups are not comparable. For example, if the HBOT group had a disproportionate number of subjects with extremely high values compared to controls we would expect the HBOT group to regress a greater distance towards the overall population mean. The HBOT group would therefore appear to have better outcomes than controls. Under these circumstances it would be wrong to attribute such differential change to HBOT since it may be a result of statistical regression. Comparative studies in cluster headaches and sudden deafness might be predisposed to this threat.

Placebo effect

The placebo effect arises from the tendency of individuals to report a favourable response regardless of the physiological efficacy of treatment. For studies that do not use a placebo control group it is impossible to determine whether subjective outcomes are due to the treatment effect or to other factors such as differential treatment of the study group or the patients' belief that the treatment is beneficial. Blinding is also necessary to negate the placebo effect. Participants in a trial may change their behaviour (change of lifestyle or withdraw from the study) in a systematic way if they are aware of which group they have been allocated. This also applies to researchers who may change their treatment practices for patients in the group that is presumed to produce a more or less favourable result depending on their hypothesis. Therefore the use of a placebo group with blinding will ensure that all aspects of the intervention offered to patients are identical except for the actual experimental treatment.

Maturation

The effect of maturation can arise from differential rates of normal growth between pre- and post-test. Thus the changes that would occur as a result of the ongoing developmental process (such as healing and mortality) may be confused with the impact of treatment. In the event that intervention and control groups are maturing at different rates, with respect to outcome, it cannot be assumed that post-test differences are a result of treatment.

Testing effects

A testing effect can be the result of familiarity from repeated testing. Patients can modify their responses or behaviour in order to achieve more favourable test results. The extent to which this validity threat applies to HBOT is small since the majority of outcomes were objective measures.

Mortality

A selection mortality threat arises when there is a differential non-random dropout of participants in one of the study arms. This effect may be due to systematic difference between experimental groups. Therefore it is important for studies to specify their losses, per treatment arm and to use intention to treat analysis in order to ensure that the experimental groups are equivalent at the end of the study.

Instrumentation

Instrumentation effects are usually the result of changes in instrument measurement from pre- to post-test. This effect usually arises when observers become more experienced with the instruments and the process at the end of the study. Other effects of instrumentation are the shift in measurement at different points for example if measurement intervals are narrower at the ends of a scale in comparison of to the mid-points a ceiling or basement effect can arise. Comparative studies in thermal burns, non-diabetic wounds, and migraine headaches might be prone to this threat.

External validity

External validity assumes that the results of a study can be generalised to another context (ie., a different study sample, setting or time). To ensure that the HBOT results are generalisable, we need to be confident the study samples are representative of the populations to which the treatment is directed.

Sampling bias

One of the major threats to the external validity of HBOT is sampling bias. Sampling bias can arise when the study sample is systematically different from those outside the study population. Since all of HBOT studies were undertaken in a medical setting the patients participating in these studies may over-represent the more serious end of the disease spectrum. One of the major questions that needs to be asked is whether the results form these studies can be generalised to those with less severe conditions.

Repeatability

External validity can also be assumed if studies can be repeated in different settings (such as different communities) and at different times. For the indication cardiovascular disease two RCTs were retrieved, one from the UK and the other from Yugoslavia. Both of these studies recruited a large number of participants with similar age groups and sex ratios. Although a difference of 25 years separated the publications of these studies, they both observed similar results. It would be safe to say that these studies have good external validity.

Biased reporting

Biased reporting can also effect external validity. Many of the studies used in this assessment only reported results for patients who accepted HBOT or were compliant with treatment. Therefore our estimates of effectiveness for HBOT can only generalised to those patients who are similarly compliant. Can we assume the same effect for those patients who find HBOT unacceptable or fail to comply? Under these circumstances the effect of HBOT will be biased, since the estimates of effectiveness are only reflective of HBOT users.

Reactive effects

A reactive effect can occur when patients are aware that they are participating in an experimental trial and they react to the context rather than the treatment. Since all HBOT studies were conducted under standard clinical conditions, the potential for this type of bias would appear to be small.

What are the economic considerations?

Introduction

The purpose of this economic appraisal is to give some indication of the likely value for money of monoplace hyperbaric oxygen therapy (HBOT) in Australia. Multiplace chambers were not included in the appraisal as the majority of multiplace treatments are provided through the public hospital system. The cost per patient treated in the current public multiplace units are likely to be higher than in a monoplace unit given the wider role of multiplace units including the provision of 24 hour emergency care. We assessed value for money by calculating the likely extra cost per additional unit of improved health outcome for a range of indications for HBOT. The ratio of additional cost to additional benefit is termed the 'incremental cost effectiveness ratio'.

The overall cost effectiveness of hyperbaric monoplace hyperbaric oxygen therapy (HBOT) will depend on (a) the cost per course of treatment, (b) the effectiveness of treatment in each indication treated, and (c) the mix of indications treated. Given the high fixed cost of treatment the average cost per course of treatment will be dependent on throughput and the degree of capacity utilisation. The effectiveness of treatment is likely to vary across indications. The overall extra cost per unit of additional outcome or incremental cost effectiveness ratio will be a weighted average of the cost-effectiveness in the indications for which HBOT is used, where the weights are the share of capacity used. Given that the indications do not have homogeneous outcomes, it was not possible to calculate a single cost effectiveness ratio.

No published cost-effectiveness studies or cost studies of HBOT in Australia were found. A series of indicative cost-effectiveness ratios were calculated for a number of indications for HBOT which have shown some clinical evidence of effectiveness. The indicative cost-effectiveness analysis in this appraisal uses costs of HBOT treatment based on expert opinion combined with the results from the effectiveness assessment in this report. It does not represent a full economic analysis of the value of HBOT. It is limited by data on effectiveness from the clinical trials reviewed. Resource use associated with monoplace hyperbaric oxygen therapy has been estimated using a combination of data from clinical trials and expert opinion. Some very limited modelling was done to generalise resource use associated with disease treatment pathways. The estimated direct cost of HBOT in a monoplace unit has not been based on a prospective study of treatment in practice. Nor have the implications for disease management been fully assessed. The appraisal represents only an indication of the potential cost effectiveness of monoplace HBOT, rather than a complete and detailed estimate of the cost effectiveness analysis of the technology.

Cost of HBOT

The cost of HBOT is composed of capital and operating costs. Operating costs include staff, maintenance and overhead costs. The cost per session and per treatment depends on the duration and number of sessions per annum. Two studies on the use of HBOT in

diabetic wounds, Faglia *et al*[47] and Baroni *et al*,[46] reported that subjects were exposed to about 35 HBOT sessions on average. Zamboni *et al*[50] reported 30 sessions per patient. The cost of HBOT treatment in the set of primary cost-effectiveness analyses here is based on 30 sessions per patient. It is noted that the number of sessions per patient may vary across indications. Chronic wounds may take 15-20 treatments, and soft-tissue radionecrosis 30-40 treatments, but the clinical studies for diabetic wounds and necrotising soft tissue infections report sessions per patient outside these ranges. Hence, with uncertainty about the number of sessions per patient for different indications, the incremental cost-effectiveness ratios are estimated using estimates of 15 and 40 HBOT sessions per patient in sensitivity analysis. There is also some uncertainty surrounding the staffing of an HBOT unit which may have one or more chambers. Smaller facilities with one chamber may not have the same staff to patient ratio or the same staff mix as facilities with more than one monoplace chamber, and may not be able to spread the cost of labour and overheads. The result may be considerable variation in the average cost per session and the cost per treatment.

The average cost of HBOT treatment per course of treatment is estimated to be $6,941. Full details of the assumptions and calculations are given in Appendix E. Sensitivity analysis suggests that the cost per course of treatment is not robust but is sensitive to the assumed cost of the physician, the number of staff, the number of machines per staff, and the number of sessions per day and the number of treatments per patient. In the sensitivity analysis, the cost of a hyperbaric physician is limited to one Medicare specialist assessment fee prior to a course of treatment. This estimates the cost of HBOT with a doctor who may not be present during treatment. In fact it is expected that a doctor will always be available, but may be engaged in other duties. It is also possible that some units could run with more than one machine but only one specialist doctor. In the absence of a detailed study of the cost of monoplace therapy in Australia, it has not been possible to calculate a robust estimate of the average cost per session or per course of treatment for monoplace HBOT. There remains considerable uncertainty about the context in which a monoplace unit would operate. It is unclear whether the current draft guidelines for staffing would be observed in practice and what the typical configuration of machines would be. In the primary cost effectiveness analyses an average cost per course of treatment of $6,941 was used. This is in the upper third of the estimated potential range of $2,466 with four chambers in operation to $9,255 with 40 sessions per patient.

Diabetic wounds

Major amputation

The risk for major amputations was assessed in five studies of HBOT in diabetic wounds (Table 16). Four of the five studies reported absolute reductions in risk for major amputation associated with HBOT, with Faglia *et al*[47, 48] and Doctor *et al*[49] reaching statistical significance (Figure 4). The pooled risk difference indicates that a reduction of 20% (95% CI: 11%, 30%; p<0.0001) in the number of major amputations is experienced by subjects following exposure to HBOT.

Total costs of HBOT treatment and the predicted cost offsets from avoiding major amputations, can be used to estimate an incremental net cost per major amputation avoided.

Cost of major amputation

The hospitalisation cost of AN-DRG 411 Amputation (21.5 days average length of stay) is $14,805.[121] In the absence of more precise data for a variety of causes, this DRG cost is used to approximate the cost of a major amputation. This cost is an average cost for all types of amputation and may not be an accurate cost for major amputations specifically associated with diabetes. More precise Australian patient level cost data could be used. However even these data may be an overestimate of the resources saved by reducing the number of amputations overall. In some of the studies of HBOT, patients were recruited from in-patients. In those studies there was some evidence of a reduced length of stay with HBOT but this was not significant. Attributing the full cost of a hospital stay involving an amputation (21.5 days in the national casemix data) as a saving with HBOT may be an overestimate for patients already admitted for a diabetic wound. No information on the change in resource use associated with a major amputation for patients admitted as a result of a diabetic wound is available. Such data could only come from a prospective randomised trial of HBOT in which resource use data were collected.

Major amputations are also expected to incur rehabilitation costs, and these are expected to increase the costs associated with major amputations. The hospitalisation cost of AN-DRG 941 Rehabilitation (20 days average length of stay) is $8,758.[121] This may not be an accurate cost for rehabilitation associated with amputations given the extra cost of prostheses. However, in the absence of more precise data, this DRG cost is used to approximate the acute hospitalisation cost of rehabilitation for major amputations. The costs of rehabilitation after being discharged from hospital have not been included in the analysis in Tables 77and 78.

An incremental cost-effectiveness analysis with and without cost offsets from amputations avoided is shown in Table 77.

Table 77 Estimation of incremental cost per major amputation avoided – 100 patients

100 patients	Intervention Group (HBOT)	Comparison Group (no HBOT)	Incremental
Incremental treatment costs of HBOT	$694,105	-	$694,105
Major Amputations			20 avoided
Incremental HBOT cost per amputation avoided			$34,705
Difference in cost of major amputation (cost savings)	20 major amputations prevented		($296,100)
Difference in cost of rehabilitation (cost savings)			($175,160)
Net Cost			$222,845
Incremental cost per major amputation avoided			$11,142

There is an argument to limit the analysis to major amputations, on the grounds that only these were statistically significant in the pooled analysis. As shown in Table 77 if no cost offsets are considered, the incremental cost per major amputation avoided is estimated as $34,705. When the cost offsets of major amputations are considered, the incremental cost per major amputation avoided is $11,142. The analysis in Table 77 only uses the acute hospitalisation cost of major amputations and rehabilitation. If outpatient

rehabilitation costs are included, HBOT treatment of diabetic wounds could be potentially cost saving in terms of major amputations.

Minor amputation

Two studies of HBOT in diabetic wounds (Doctor *et al*[49] and Faglia *et al*[47]) reported increases in the risk of minor amputations following HBOT compared to comparison therapies, although none reached statistical significance. The pooled absolute risk difference indicates an increase of 9 percent (95% CI: -8%, 25%) in the number of minor amputations experienced by subjects following exposure to HBOT (Figure 7).

If it is assumed there are no cost offsets from reduced amputations then HBOT, with a cost per patient of $6,941 and a risk reduction in total amputations of 11%, has a cost per amputation avoided of $63,100 and the cost per major amputation avoided is $34,705.

Although the increased risk of minor amputations is not statistically significant, it might be reasonable to offset the cost savings from major amputations with the cost of a possible increase in minor amputations.

The cost of a minor amputation of the toe or forefoot is approximated by the cost of AN-DRG 428 – Foot Procedures of $2,194 with an average length of stay of 2.7 days.[121] This DRG cost may not be an accurate cost of amputations of the toe or forefoot associated with diabetes, but is used here to approximate the cost of a minor amputation, in the absence of more precise data.

The incremental cost-effectiveness analysis of HBOT per amputation avoided is shown in Table 78.

Table 78 Estimation of incremental cost per amputation avoided – 100 patients

100 patients	Intervention Group (HBOT)	Comparison Group (no HBOT)	Incremental
Incremental treatment costs of HBOT	$694,105	-	$694,105
Difference in cost of major amputation (cost savings)	20 major amputations prevented		($296,100)
Difference in cost of rehabilitation (cost savings)			($175,160)
Difference in cost of minor amputation	9 minor amputations		$19,746
Net Costs			$ 242,591
Major Amputations			20 avoided
Minor Amputations			9
Total Amputations			11 avoided
Incremental cost per amputation avoided			$22,054

Including both major and minor amputation risks, the incremental cost per amputation avoided by HBOT in the treatment of diabetic wounds is estimated to be $22,054.

Sensitivity analysis

Table 79 shows the results of the sensitivity analysis using the 95% CI of effectiveness from the pooled analysis of treatment effect (pages 23 to 25) varying the costs of a doctor in attendance during treatment, the number of HBOT sessions per patient and the number of chambers in the facility.

Table 79 Sensitivity analysis – amputations in diabetic wounds

Sensitivity Analysis	Increased Cost per amputation avoided (major and minor)
	$22,054 – primary case
Risk difference of 11% (reduced risk for HBOT) for major amputation and risk difference of 25% (increased risk for HBOT) for minor amputation (worst case scenario using limits of 95% CI)	Comparison therapy dominant (more effective – less amputations – combined major and minor)
Risk difference of 30% (reduced risk for HBOT) for major amputation and risk difference of 8% (reduced risk for HBOT) for minor amputation (best case scenario using limits of 95% CI)	Cost saving
Cost of doctor/specialist covered by cost of patient assessment prior to a course of HBOT treatment	Cost saving
15 HBOT sessions per patient	Cost saving
40 HBOT sessions per patient	$43,087
Operating costs shared between 2 HBOT units	Cost saving
Operating costs shared between 4 HBOT units	Cost saving

Table 79 shows that HBOT treatment costs less than the comparison treatment (including costs of amputation), if the staff requirements of a hyperbaric nurse, technician and physician are shared among two or four HBOT chambers in a hyperbaric facility, if a patient only requires 15 HBOT sessions, or if the cost of a hyperbaric physician is limited to one Medicare specialist assessment fee per patient prior to a course of treatment. In the worst case scenario using the limits of the 95% CI, the comparison therapy is dominant over HBOT as the comparison therapy costs less, and the total combined number of computations is 14 less with the comparison therapy (11 less major amputations with HBOT, 25 more minor amputations with HBOT).

Summary

If the clinical evidence of effectiveness is reliable in suggesting an average risk difference of at least 11% in amputations then the cost per amputation avoided with HBOT is not likely to exceed $63,100. If rehabilitation costs are included there may be a cost saving. However if diabetic wounds was the only indication with proven effectiveness treated with HBOT, and other indications are used most of the time, then HBOT might have a cost-effectiveness ratio of many times those calculated above. The percentage of cases treated which are likely to be diabetic wounds is unknown.

Wound healing

Two of the five studies of HBOT in the effectiveness assessment of diabetic wounds examined wound healing as an outcome of interest, although none offered an objective definition of the phenomenon. The small number of patients (only 38 subjects) translates to wide confidence intervals in estimates of individual and pooled treatment effects.

Subjects exposed to HBOT are about 40 times more likely to experience healing of their lesions compared to those receiving comparison therapies (Figure 8).

The sample sizes in the studies which included wound healing as an outcome are too small to safely infer effectiveness. Therefore, an incremental cost per wound healed can not reasonably be estimated.

Non-diabetic wounds

Hammarlund and Sundberg[51] exposed two groups of 8 subjects with leg ulcers of more than one-year's duration, to different concentrations of oxygen (intervention group 100 percent oxygen while the comparison group received air) in a multiplace chamber. The frequency of exposure was five times a week for a total of 30 sessions.

The study looked at the mean changes in wound area over the course of therapy (Table 20). At 4 and 6 weeks, there were statistically significant decreases in the wound areas of the HBOT group compared to the comparison group. The intervention group had a 35.7% decrease in wound area from baseline, compared to 2.7% decrease in wound area for the comparison group, at 6 weeks.

This suggests that HBOT treatment of chronic leg ulcers might result in an expected one third reduction in wound area for a treatment cost of $6,941 per patient. The clinical significance of this outcome or its significance to patient welfare in the longer term is not sufficiently clear to assess whether this is an acceptable figure.

Necrotising soft tissue infections

The effectiveness assessment (Table 21) reports on two studies from the published literature that looked at necrotising soft tissue infections in general. Both studies showed that HBOT was associated with survival, but only Riseman *et al*[53] reached statistical significance. 76.5% of patients in the intervention group survived compared to 33.3% in the comparison group, a difference of 43.1% (95% CI: 9.7%, 76.6%, p=0.0202).

An incremental HBOT treatment cost per death avoided can be estimated, based on the results from Riseman *et al*[53] The incremental cost-effectiveness analysis is shown in Table 80. The incremental HBOT treatment cost per death avoided is estimated to be $16,105, in patients with necrotising soft tissue infections. The analysis above is based on an average of 30 HBOT sessions per patient (for all indications) (Table 24). Riseman *et al*[53] reported a total of 10 treatments per patient. Using an estimate of 10 sessions per patient results in a total monoplace chamber cost (operating and capital costs based on full capacity) per treatment of $231.37 and a total cost per patient of $2,314, which then lowers the incremental cost per death avoided. However the duration of survival in each group is unknown. An estimated cost per survivor is less meaningful than a cost per survival time. While a cost per death avoided of $16,105 might appear to be a very acceptable cost, it may be that the survival curves of the treated patients and the comparator group converge quickly and the life years gained may be very small. In addition a significant positive result was only reported in one study.

Table 80 Estimation of incremental cost per death avoided – 100 patients

100 patients	Intervention Group (HBOT)	Comparison Group (no HBOT)	Incremental
Incremental treatment costs of HBOT	$694,105	-	$694,105
Survivals	76.5	33.3	43.1
Incremental cost per death avoided			$16,105

Sensitivity analysis

Table 81 shows the results of the sensitivity analysis using the 95% CI of effectiveness, and the sensitivity analysis varying the costs of a doctor in attendance during treatment, varying the number of HBOT sessions per patient and the number of chambers in the facility.

Table 81 Sensitivity analysis – survival in necrotising soft tissue infections

Sensitivity Analysis	Incremental cost per death avoided at trial completion
	$16,105 – primary case
Difference of 9.7% (lower limit of 95% CI)	$71,557
Difference of 76.6% (upper limit of 95% CI)	$9,061
Cost of doctor/specialist covered by cost of patient assessment prior to a course of HBOT treatment	$10,437
10 HBOT sessions per patient	$5,368
15 HBOT sessions per patient	$8,052
40 HBOT sessions per patient	$21,473
Operating costs shared between 2 HBOT units	$9,182
Operating costs shared between 4 HBOT units	$5,721

Table 81 shows that if each patient has only 10 HBOT sessions, the incremental cost per death avoided is $5,368. In the worst case scenario using the lower limit of the 95% CI of the difference in effectiveness, the incremental cost per death avoided is $71,557.

Summary

The incremental HBOT treatment cost per death avoided is estimated to be $10,860, in patients with necrotising soft tissue infections. The data suggests a 95% confidence that the cost per life saved is less than $71,557. However it is unclear what the duration of the effect is and whether the apparent survival gain from HBOT in this indication represents a significant improvement in longevity. It should be noted that necrotising soft tissue infections are relatively uncommon and therefore likely to represent a small part of the throughput of an HBO unit. MSAC therefore needs to consider the potential cost effectiveness of HBOT in this indication in the context of the wider use of HBOT.

Crush injuries

Bouachour *et al*[86] examined four major outcomes: wound healing without tissue necrosis requiring surgical excision, new major surgical procedures after entry in the trial, time of healing, and length of hospital stay (Table 46), in patients with Gustillo Type II or III acute injury of the lower limb. Complete wound healing without tissue necrosis requiring

surgical excision was obtained for 17 patients in the HBOT group versus 10 patients in the comparison group (p=0.018). New major surgical procedures were performed on one patient in the HBOT group versus 6 patients in the comparison group (p=0.088). No significant differences were found in the length of hospital stay and number of wound dressings between groups.

The healing time is likely to be similar between groups (ie. the healing time is around 50 days for both groups). HBOT therefore may be of similar efficacy to conventional treatment, but could result in cost savings from a reduction in surgical procedures. It has not been possible to estimate the cost of these procedures. The costs of wound dressings between groups are also likely to be similar between groups. Hence, although there may be potential cost savings in terms of a reduction in wound debridement and other surgery, these have not been costed in an incremental cost-effectiveness analysis.

Osteoradionecrosis

Marx *et al*[59] randomised into two groups patients who had an indication for removal of one or more teeth in a segment of the mandible that had received a documented absorbed dose of 6,000 rads or greater and who had agreed to maintain follow-up visits for a minimum of six months. The comparison group received aqueous penicillin G intravenously prior to surgery and phenoxymethylpenicillin after surgery. The intervention group was exposed to HBOT. The main outcome of interest was the clinical diagnosis of osteoradionecrosis during follow-up. Two out of 37 patients (5.41%) in the intervention group were diagnosed as having osteoradionecrosis during follow up, compared to 11 out of 37 patients (29.73%) in the comparison group (p=0.0060).

An incremental cost per case of osteoradionecrosis avoided has been estimated based on the results from Marx *et al*[59] The relatively low costs for the comparison group of aqueous penicillin G and phenoxymethylpenicillin are included. Benzylpenicillin (BenPen) 1.2g is recommended to be given intravenously half to one hour before dental procedures (MIMS Australia, 1999); Marx *et al*[59] reported giving one million units prior to surgery. For costing purposes the dosage from MIMS was used. One pack of BenPen (injection 3g (10's) cost $47.95 on the PBS (item no. 3399X, PBS Schedule, Feb. 2000). 500 mg of phenoxymethylpenicillin (Abbocillin-VK) was also given to patients in the comparison group four times a day for 10 days after surgery. One pack of Abbocillin-VK (500 mg tablets, 50's) cost $14.57 on the PBS (item no. 3361X, PBS Schedule, Feb. 2000).

The incremental cost-effectiveness analysis is shown in Table 82. The incremental cost per case of osteoradionecrosis avoided is estimated to be $28,480.

Table 82 Estimation of incremental cost per case of osteoradionecrosis avoided based on Marx (1985) – 100 patients

100 patients	Intervention Group (HBOT)	Comparison Group (penicillin G and phenoxymethylpenicillin)	Incremental
Treatment costs	$694,105	$1,357	$692,748
Cases of osteoradionecrosis	5.41	29.73	24.32
Incremental cost per case of osteoradionecrosis avoided			$28,480

Sensitivity analysis

Table 83 shows the results of the sensitivity analysis varying the efficacy of the comparator group using the 95% CI, costs of a doctor in attendance during treatment, varying the number of HBOT sessions per patient and the number of chambers in the facility.

Table 83 Sensitivity analysis – osteoradionecrosis

Sensitivity Analysis	Incremental cost per case of osteoradionecrosis avoided
	$28,480 – primary case
15.87% of patients in the comparator group with osteoradionecrosis (lower 95% CI)	$66,187
46.98% of patients in the comparator group with osteoradionecrosis (upper 95% CI)	$16,663
Cost of doctor/specialist covered by cost of patient assessment prior to a course of HBOT treatment	$18,438
15 HBOT sessions per patient	$14,212
40 HBOT sessions per patient	$37,991
Operating costs shared between 2 HBOT units	$16,214
Operating costs shared between 4 HBOT units	$10,081

Table 83 shows that if the staff requirements of a hyperbaric nurse, technician and physician are shared among four HBOT chambers in a hyperbaric facility, the incremental cost per case of osteoradionecrosis avoided is $10,081. The incremental cost per case of osteoradionecrosis avoided is $66,187, using the lower limit of the 95% CI for the efficacy of the comparator group, keeping the efficacy of the HBOT group fixed.

Summary

The incremental treatment cost per case of osteoradionecrosis avoided is estimated to be $28,480, in patients who had an indication for removal of one or more teeth in a segment of the mandible. Sensitivity analysis suggests a range of $10,081-$66,187 per case of osteoradionecrosis avoided.

Conclusions

The indicative cost-effective ratios estimated for a small number of indications i.e. HBOT in diabetic wounds, necrotising soft tissue infections, and osteoradionecrosis, are summarised in Table 84.

Table 84 Summary of indicative cost-effectiveness ratios in four indications

Diabetic Wounds - Incremental Cost per Amputation Avoided	$22,054 (cost saving to $63,100)
Non-Diabetic Wounds - Reduction in Wound Area	Treatment cost of $6,941 per patient for a one third reduction in wound area
Incremental Cost per Death Avoided - Necrotising Soft Tissue Infections	$16,105 ($5,368-$71,557)
Incremental Cost per Case of Osteoradionecrosis Avoided	$28,480 ($10,081-$66,187)

In addition:

- the indicative cost-effectiveness ratios are based on the clinical evidence presented in the effectiveness assessment of this report. There remains considerable uncertainty surrounding the clinical evidence of the effectiveness in these indications.

  - in particular, the two studies of HBOT in necrotising soft tissue infections looked at different populations of patients and study designs were disparate. Hence, no firm conclusions can be made on the effectiveness of HBOT in necrotising soft tissue infections.

  - the assumed risk of minor amputations and wound healing in diabetic wounds is based on inferences drawn on a small population group.

- the estimates of the cost of HBOT treatment are not precise estimates based on actual studies, but are based on estimates of staffing and capital costs of a hyperbaric monoplace unit, from expert opinion. Hence, the cost-effectiveness ratios presented here are only indicative estimates which may be sensitive to more precise estimates of the costs of HBOT treatment.

- cost offsets have been estimated from published cost data and inferences from trial data. These inferences are tentative given that the underlying studies, even where well-conducted, were not designed to capture resource-use data.

- the results are sensitive not only to the estimated effectiveness of HBOT but also to the cost of treatment. In particular, the charge for doctor time is a critical element in the costing. While it is clear that a consultant physician is usually responsible for an HBOT service it remains uncertain how much of their time and cost should be attributed to each case treated. Attributing a once-off Medicare fee results in a cost per patient treated with 30 sessions of $4,499, while attributing a consultation fee for each session results in a cost per patient treated of $6,941. In order to be conservative, the cost of $6,941 per patient treated was adopted.

- overall, the indicative cost-effectiveness ratios in Table 84 suggest that HBOT could be cost-effective in diabetic wounds, and necrotising soft tissue infections. It could save resources in the treatment of diabetic wounds and necrotising soft tissue infections. This conclusion is dependent upon the level of confidence in the trial evidence on HBOT in these indications. The cost of $28,480 per case of osteoradionecrosis avoided does not take into account the cost offsets associated with prevention of osteoradionecrosis (eg avoidance of a mandibular resection).

Conclusions

Safety

Potential risks for patients undergoing therapy with hyperbaric oxygen are myopia, barotrauma, claustrophobia or oxygen toxicity. Estimates of incidence are uncertain, although most adverse events are self-limiting and resolve after termination of therapy. Serious, life-threatening events are rare, but real, causes of major concern.

Published guidelines seek to provide industry-wide acceptance of recommendations and requirements for the safe operation of hyperbaric facilities. Staffing levels, training, and qualifications are explicitly provided by these documents.

Effectiveness

The evaluation found evidence of HBOT effectiveness in diabetic wounds and limited evidence of effectiveness in the prevention of osteoradionecrosis, crush injuries, cluster and migraine headaches and facial paralysis. Insufficient evidence or conflicting evidence for HBOT use was found in the following conditions: thermal burns, non-diabetic wounds, necrotising soft tissue infections, treatment of osteoradionecrosis, skin graft survival, cerebrovascular disease, peripheral obstructive arterial disease, sudden deafness, cancer of the head and neck, cervix and bladder, lymphoma and neuroblastoma, carbon monoxide poisoning, necrotising arachnidism, actinomycosis, soft tissue radionecrosis, cerebral palsy, Crohn's disease, Legg-Calve-Perthes disease and osteoporosis.

There is evidence of a lack of any beneficial effect in multiple sclerosis and limited evidence of a lack of effectiveness in osteomyelitis, acute myocardial infarction, acute ankle sprains and cancer of the lung.

The following indications were not formally evaluated as the Supporting Committee agreed that they have little clinical acceptance and/or have been minimally reported in the literature: cyanide poisoning, head trauma, cerebral oedema, acquired brain injury, cognitive impairment, senile dementia, glaucoma, keratoendotheliosis, HIV infection, anaemia from exceptional blood loss, insulin dependent diabetes mellitus, facial neuritis, arthritis, spinal injuries and non-union of fractures.

Cost-effectiveness

The estimated cost of monoplace HBOT treatment in this report is not a precise estimate based on actual studies, but is based on estimates of staffing and capital costs of a hyperbaric monoplace unit from expert opinion. Moreover the evidence of effectiveness used is subject to considerable uncertainty as detailed in the clinical effectiveness sections of the report. This means that the cost-effectiveness ratios presented here are only indicative estimates, which may be sensitive to more precise estimates of the costs and effectiveness of HBOT treatment. Based on this evidence it seems that HBOT could be cost-effective in the treatment of diabetic wounds, and necrotising soft tissue infections. It could save resources in those treatments. The cost of $28,480 per case of

osteoradionecrosis avoided does take into account the cost offsets associated with prevention of osteoradionecrosis (eg avoidance of a mandibular resection).

Recommendations

MSAC recommended that public funding should be supported for hyperbaric oxygen therapy (HBOT) administered in either a multiplace or monoplace chamber, as appropriate, for the following indications:

- decompression illness, gas gangrene, air or gas embolism. HBOT is widely accepted as standard clinical care in the management of these life-threatening conditions for which there are limited alternative treatment options;

- diabetic wounds including diabetic gangrene and diabetic foot ulcers. There is evidence that HBOT 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; and,

- necrotising soft tissue infections including necrotising fasciitis and Fournier's gangrene and the prevention and treatment of osteoradionecrosis. These are serious conditions in which HBOT provides a non-invasive treatment option which may have a beneficial effect and offer cost-savings. Further studies are required to provide more conclusive evidence of an effect but are difficult to undertake due to the ethical and practical constraints of conducting trials in these conditions. Public funding should be continued for HBOT use in these conditions until conclusive evidence becomes available that indicates it is not effective or that other treatments are preferable and more cost-effective.

Since there is currently insufficient evidence pertaining to HBOT use in the following indications, MSAC recommended that public funding should not be supported for HBOT administered in either a multiplace or monoplace chamber, for:

- thermal burns, non-diabetic wounds and decubitus (or pressure) ulcers, necrotising arachnidism, actinomycosis, soft tissue radionecrosis, osteomyelitis, 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, carbon monoxide poisoning, cyanide poisoning, head trauma, cerebral oedema, acquired brain injury, cognitive impairment, senile dementia, glaucoma, keratoendotheliosis, HIV infection, anaemia from exceptional blood loss, insulin-dependent diabetes mellitus, facial neuritis, arthritis, spinal injuries and non-union of fractures.

MSAC has not considered safety standards for HBOT services administered in either multiplace or monoplace chambers, in detail, but endorses a standard for facilities, staffing and training which meets that in development by Standards Australia.

- The Minister for Health and Aged Care accepted this recommendation on 9 February 2001 -

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to advise the Commonwealth Minister for Health and Aged Care on:

- the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- references related either to new and/or existing medical technologies and procedures; and,
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning.

Member	Expertise
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care
Dr Richard King	gastroenterology
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	paediatrics
Dr David Robinson	plastic surgery
Associate Professor John Simes	clinical epidemiology and clinical trials
Professor Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council

Appendix B Supporting committee

Supporting committee for MSAC application 1018-1020
Hyperbaric oxygen therapy for adjunctive care

Professor Peter Phelan (Chair) BSc, MBBS, MRACP, MD, FRACP Emeritus Professor of Paediatrics University of Melbourne	MSAC member
Dr Michael Bennet MBBS, DA (Eng), FFARCSI, FANZCA, MM (Clin Epi) Medical Director, Department of Diving and Hyperbaric Medicine, Staff Specialist Anaesthetist, Prince of Wales Hospital, Sydney	nominated by the Australian and New Zealand Hyperbaric MedicineGroup
Dr Paul McCrory MBBS, FRACP, FACSP, FACSM, FASMF, FRSM Director, Olympic Park Sports Medicine Centre, Melbourne Consultant Neurologist, Box Hill Hospital, Melbourne Research Fellow, University of Melbourne, Austin & Repatriation Medical Centre	nominated by the Australian College of Sports Physicians
Dr John Primrose MBBS (Hons), FRACR Senior Medical Adviser Health Access and Financing Division Department of Health and Aged Care	advisor to MSAC
Dr David Robinson MBBS, FRACS, FRCS President of Senior Medical Staff Association, Princess Alexandra Hospital, Brisbane	MSAC member
Dr Ross Taylor MBBS, FRACGP, DDU, GDTh General Practitioner, Brisbane	nominated by the Royal Australian College of General Practitioners
Mrs Robin Toohey Chair, Illawarra Consumer Health Council National Council of Women, Australia Co-ordinator, Status of Women Adviser, Rural and Urban Women	nominated by the Consumers Health Forum

Dr David Wilkinson BMBS, Dip RACOG, DA (UK), FANZCA Director, Hyperbaric Medicine Unit Dept of Anaesthesia & Intensive Care, Royal Adelaide Hospital Staff Specialist Anaesthetist, Womens & Childrens Hospital, SA	co-opted member
Dr Robert Wong B Sc. MBBS, FFARACS, DipDHM, FANZCA, Director of Hyperbaric Medicine, Fremantle Hospital, WA Anaesthetist, Royal Perth Hospital, WA	nominated by the Australian and New Zealand College of Anaesthetists

Appendix C Studies included in this review

Thermal burns

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Brannen 1997[38]	II	RCT	USA	?‡	125	?	I=50:12 C=44:19
Niezgoda 1997[39]	II	RCT	USA	?	12	?	7:5
Hammarlund 1991[40]	III-2	Comparative study	Sweden	?	9	26 (24-29)§	9:0
Cianci 1990[41]	III-2	Comparative study	USA	Jan 1982 to Jul 1987	21	I=28 (9) C=29 (8.3)	?
Gorman 1988[42]	III-3	Comparative study with historical controls	Australia	T=Jul 1986 to Jun 1988 C=Jan 1983 to Jun 1986	180	I=34.2 (14.9) C=38.6 (17.2)	?
Niu 1987[43]	III-2	Comparative study	Taiwan	After 1981	875	I=27 (2-82)§ C=26 (7/12-80)	?
Waisbren 1982[44]	III-2	Comparative study	USA	?	72	I=35.2 (15.0)# C=35.6 (14.8)	?
Hart 1974[45]	II	RCT	USA	Nov 1972 to Jan 1974	16	I=21.62 C=21.31	14:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Median of total population. Figures in parentheses are ranges.

Figures in parentheses are assumed to be standard deviations. Authors did not provide enough information for a definite conclusion.

Diabetic wounds

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Faglia 1998[48]	III-2	Comparative study	Italy	1990 to 1993	115	63.4 (9.9)	84:31
Zamboni 1997[50]	III-2	Comparative study	USA	?‡	10	I=63.6 (8.9) C=53.8 (7.8)	I=4:1 C=4:1
Faglia 1996[47]	II	RCT	Italy	Aug 1993 to Aug '95	68	I=61.7 (10.4) C=65.6 (9.1)	I=27:8 C=21:12
Doctor 1992[49]	II	RCT	India	2 years. No specific dates.	30	I=56.2 (45-70)§ C=59.8 (48-70)	I=3:1 C=2:1
Baroni 1987[46]	III-2	Comparative study	Italy	Jan 1982 to Dec 1984	28	I=57.7 (7.4) C=59.4 (7.6)	I=11:7 C=6:4

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

Non-diabetic wounds

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Hammarlund 1994[51]	II	RCT	Sweden	?‡	16	67 (42-75)	9:7

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Necrotising soft tissue infections: general

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Brown 1994[52]	III-2	Comparative study	Canada	Jan 1980 to Dec 1991	54	I=51.3 (17.1) C=61.6 (12.6)	I=22:8 C=13:11
Riseman 1990[53]	III-3	Comparative study with historical controls	USA	1980 to 1988	29	I=59.7 (14-82)‡ C=68.5 (41-88)	I=11:6 C=7:5

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Figures in parentheses are ranges.

Necrotising soft tissue infections: necrotising fasciitis

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Shupak 1995[54]	III-2	Comparative study	Israel	1984 to 1993	37	I=52.9 (15) C=57.4 (16)	I=14:11 C=9:3
Sawin 1994[55]	III-2	Comparative study	USA	Jan 1982 to Mar 1993	7	9 days (3-15)§	?
Barzilai 1985[56]	III-2	Comparative study	Israel	1979 to 1983	11	I=48.33 (12.5) C=55.88 (9.2)	I=3:0 C=6:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

Necrotising soft tissue infections: Fournier's gangrene

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Hollabaugh 1998[57]	III-2	Comparative study	USA	?‡	26	54.85 (15.2)	26:0

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Osteomyelitis

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Esterhai 1987[58]	III-2	Comparative study	USA	?‡	28	40 (15-74)	19:9

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Osteoradionecrosis: prevention

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Marx 1985[59]	II	RCT	USA	?‡	74	?	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Osteoradionecrosis: treatment

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Granstrom 1999[60]	III-2	Comparative study	Sweden	Dec 1981 to Oct 1997	78	64.9 (23-94)	47:31

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Skin graft survival

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population		
					Size	Age	Sex Ratio
Perrins 1967[61]	II	RCT	UK	?†	48	?	?
Marx 1995[62]	II	RCT	US	?	160	?	?

* Abbreviations: F = female, M = male, RCT = randomised controlled trial

† Unstated, unclear, or unknown.

Cardiovascular disease conditions: acute myocardial infarction

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age Mean (SD)	Sex Ratio (M:F)
Stavitsky 1998[77]	II	RCT	US, Yugoslavia	Aug 1989 to Dec 1997	112	I=58 (11.1) C= 59 (11.7)	I=49:10 C=48:15
Thurston 1973[78]	II	RCT	UK	Sep 1968 to Jan 1972	208	I=58.1 C=57.2	I=88:15 C=87:18

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial.

† Information is given for total study population values, and intervention and comparison groups.

Cardiovascular disease conditions: cerebrovascular disease

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age Mean (SD)	Sex Ratio (M:F)
Nighoghossian 1995[79]	II	RCT	France	Dec 1988 to Mar 1992	34	I=53 (3) C=54 (3)	I=9:8 C=12:5
Anderson 1991[80]	II	RCT	USA	?‡	39	I=63.7 C=69.1	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for total study population values, and treatment and control groups.

‡ Unstated, unclear, or unknown.

Cardiovascular disease conditions: peripheral obstructive arterial disease

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Verrazzo 1995[84]	II	RCT	Italy	?‡	30	60	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Soft tissue injuries: acute ankle sprains

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Borromeo 1997[85]	II	RCT	USA	?‡	32	25	21:11

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Soft tissue injuries: crush injuries

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Bouachour 1996[86]	II	RCT	USA	?‡	36	?	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Cluster headaches

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age Mean (SD)	Sex Ratio (M:F)
DiSabato 1997[88]	III-2	Comparative study	Italy	?‡	14	I=34.0 (2.2)§ C=41.3 (2.6)	14:0
DiSabato 1996[89]	III-2	Comparative study	Italy	?	14	I=41.8 (3.7)# C=42.3 (5.2)	I=5:2 C=5:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, SD = standard deviation.

† Information is given for total study population values, and intervention and comparison groups.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are standard errors.

Figures in parentheses are assumed to be standard deviations. Authors did not provide enough information for a definite conclusion.

Migraine headaches

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age Mean (SD)	Sex Ratio (M:F)
Wilson 1998[90]	II	RCT, crossover	USA	?‡	8	38.8 (7.8)§	0:8
Myers 1995[91]	II	RCT	USA	?	20	?	6:14

* Abbreviations: F = female, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for total study population values, and treatment and control groups.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are assumed to be standard deviations. Authors did not provide enough information for a definite conclusion.

Facial paralysis

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Racic 1997[92]	II	RCT	Croatia	?‡	79	35	48:79

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Sudden deafness and acoustic trauma

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Cavallazi 1996[95]	III-2	Comparative study	Italy	?‡	62	48.2 (29-70)§	32:30
Vavrina 1995[96]	III-2	Comparative study	Switzerland	?	78	I=24.9 (6.3) C=22.7 (7.6)	?
Hoffmann 1993[97] (acute)	II	RCT	Germany	?	20	?	?
Hoffmann 1993[98] (chronic)	II	RCT	Germany	?	44	?	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

Cancer: head and neck

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Whittle 1990[99]	III-2	Comparative study	UK	1963 to 1985	397	?‡	?
Henk 1986[100]	II	RCT	UK	1972 to 1977	107	?	?
Sealy 1986[101]	II	RCT	South Africa	Sep 1980 to Mar 1984	130	I=56 C=55	I=56:8 C=60:6
Berry 1979[102]	II	RCT	UK	Jan 1971 to Dec 1974	24	I=61 (6) C=66 (9)	?
Sause 1979[103]	II	RCT	USA	Nov 1970 to Dec 1976	50	I=57 (38-80)§ C=63 (36-81)	I=8:13 C=15:8
Chang 1973[104]	II	RCT	USA	Jan 1964 to Mar 1971	51	?	2.5:1
Churchill-Davidson 1973[105]	III-3	Comparative study with historical controls	UK	1962 to 1972	171	?	?
Shigamatsu 1973[106]	III-1	Pseudo-randomised controlled trial	Japan	1969 to 1971	42	I=56.6 C=57.7	?
Henk 1970[107]	III-1	Pseudo-randomised controlled trial	UK	Sep 1964 to Jun 1969	213	I=60 C=58	I=76:25 C=71:41

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for intervention and comparison groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

§ Figures in parentheses are ranges.

Cancer: cervix

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population	
					Size	Age
Brady 1981[108]	II	RCT	USA	Jan 1972 to Oct 1975	65	?†
Watson 1978[109]	II	RCT	UK	1966 to 1973	301	?
Fletcher 1977[110]	II	RCT	USA	Sep 1968 to Mar 1974	233	?
Glassburn 1974[111]	II	RCT	USA	from Nov 1967	40	?
Johnson 1974[112]	III-3	Comparative study with historical controls	Canada and USA	1959 to 1966	64	?
Ward 1974[113]	II	RCT	UK	Dec 1971 to Apr 1973	45	?

* Abbreviation: RCT = randomised controlled trial.

† Unstated, unclear, or unknown.

Cancer: bladder

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Cade 1978[114]	II	RCT	UK	May 1964 to Dec 1971	236	?†	?
Kirk 1976[115]	II	RCT	UK	1966 to 1970	27	?	?
Dische 1973[116]	II	RCT	UK	from Apr 1966	67	?	?
Plenk 1972[117]	II	RCT	USA	May 1965 to May 1970	40	I=68.8 C=68.2	I=19:0 C=19:2

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Unstated, unclear, or unknown.

Cancer: lymphomas

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Pan 1993[118]	III-1	Comparative study	China	?‡	41	?	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Cancer: lung

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
Sause 1981[119]	II	RCT	USA	1970 to 1977	56	?‡	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Cancer: neuroblastoma

First Author and Year of Publication	NHMRC Level	Study Design	Location	Dates of Enrolment	Characteristics of Study Population†		
					Size	Age (years) Mean (SD)	Sex Ratio (M:F)
van der Kleij 1996[120]	III-3	Single-arm comparison study	The Netherlands	?‡	51	6.8	?

* Abbreviations: C = comparison group, F = female, I = intervention group, M = male, RCT = randomised controlled trial, SD = standard deviation.

† Information is given for treatment and control groups, if available. Otherwise, total study population values are stated.

‡ Unstated, unclear, or unknown.

Appendix D Studies excluded in this review

Thermal burns

1. Lee HC, Niu KC, Chen SH, Chang LP, Lee AJ. Hyperbaric oxygen therapy in clinical application: a report of 12 year's experience. Chung Hua I Hsueh Tsa Chih 1989;43:307-16. [Lack of a control group.]

Diabetic wounds

1. Lee SS, Chen CY, Chan YS, Yen CY, Chao EK, Ueng SWN. Hyperbaric oxygen in the treatment of diabetic foot infection. Chang Gung Medical journal 1997;20:17-22. [Lack of a non-HBOT group.]

2. Leslie CA, Sapico FL, Ginunas VJ, Adkins RH. Randomised controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. Diabetes Care 1988;11:111-15. [Lack of an HBO chamber used.]

Non-diabetic wounds

1. Pressure Ulcer Treatment Guideline Panel. Quick reference guide for clinicians: pressure ulcer treatment. Journal of the American Academy of Nurse Practitioners 1995;7:389-406. [Lack of primary data.]

Necrotising soft tissue infections

1. Benizri E, Fabiani P, Migliori G, Chevallier D, Peyrottes A, Raucoules M, Amiel J, Mouiel J, Toubol J. Gangrene of the perineum. Urology 1996;47:935-9. [Lack of a non-HBOT group.]

2. Capelli-Schellpfeffer M, Gerber GS. The use of hyperbaric oxygen in urology. Journal of Urology 1999;162:647-54. [Narrative review.]

3. Elliot DC, Kufera JA, Myers RA. Necrotizing soft tissue infections: risk factors for mortality and strategies for management. Annals of Surgery 1996;224:672-83. [Lack of a non-HBOT group.]

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Appendix E Calculation of monoplace unit costs

The total cost per year, comprising both capital costs and costs of operating a hyperbaric monoplace unit, has been estimated. The number of sessions (treatments) and courses of treatments (patients) per year have also been estimated to compute costs per session and costs per course of treatment., number of sessions and courses of treatment per year

An average of 90 minutes per treatment is required per session,[2] but this is expected not to allow for patient assessment and patient preparation. The duration of time required to turn around a chamber is estimated to be 2 to 2.5 hours. The number of sessions per day for a monoplace unit is estimated to be 4, the estimated maximum feasible number of sessions in an 8-hour day. The number of sessions per day is varied to 3 in sensitivity analysis. The number of sessions per year with 4 sessions per day is then calculated to be 960, using a 5-day working week and 48 weeks per year (estimated 48-50 weeks in operation per year).

Each course of treatment is expected to comprise 20-30 sessions (from the assessment report). An estimate of 30 sessions per course of treatment was used in the analysis. The estimated 960 sessions per year is then estimated to be equivalent to 32 courses of treatment per year.

Capital costs

The cost of a hyperbaric monoplace unit has been estimated to range from A$100,000 to A$233,000. An acrylic chamber could cost US$90,000-US$120,000(A$137,000-A$183,000) with about A$50,000 on top for a fit out of the suite of rooms including oxygen supply. A steel chamber costs $100,000 to $150,000 (indicated by a manufacturer in Melbourne). A monoplace unit costs A$120,000 to A$230,000 (personal communication from applicant). A capital and installation cost of A$300,000 was also given. Discussions with experts in the field suggested an estimate of A$200,000. This is used in all the primary analyses. It is within the range of costs for an acrylic chamber. A sensitivity analysis on the cost of a unit from A$100,000 to A$300,000 was also conducted.

The cost of capital is assumed to be 9% per annum. The commercial rates for the cost of borrowing (personal communication from applicant) are 8-10%. The sensitivity analysis used a 5% cost of capital per annum.

The estimated effective life of the monoplace unit is 10 years (personal communication from applicant). A sensitivity analysis was conducted using an effective life of 30 years (estimated life of steel and acrylic monochambers).

The capital cost per annum is calculated as the constant payment required per year, with the expected cost of capital, effective life and present value of the capital equipment. In the primary case, the capital cost per annum is estimated to be $31,164.

The capital cost per session is $32.46. The capital cost per course of treatment is $974.

Operating costs

Staffing costs

Draft guidelines suggest that staffing of a hyperbaric facility ought to be a full time equivalent hyperbaric physician, a full-time hyperbaric nurse, and a hyperbaric technician. It may be that a hyperbaric facility will have a number of monoplace chambers and the operating cost will be split between them. In the primary analysis, one monoplace chamber per hyperbaric facility was assumed. The cost per treatment was modelled on the basis of two and four chambers per facility.

The costs of a hyperbaric nurse per annum is estimated to be $43,638, the base salary of a full-time specialist clinical nurse. The average cost of a medical technician is estimated as $38,467 per annum (salary of technical officer level I lower end of range of $577.30 per week and technical officer level II upper end of range of $902.20 per week). In the sensitivity analysis the impact on the cost per session and course of treatment of not having a full-time technician per unit was examined. In discussion with experts it was the view of some that units may operate with only a nurse trained to operate a chamber. It is unlikely that a hyperbaric facility with only one monoplace chamber will employ two full time staff assisting a full time physician.

The cost of a hyperbaric specialist physician is more difficult to estimate since there is no reliable data on the time spent by a physician in the care of patients in a monoplace hyperbaric unit. One approach is to assume that the doctor is paid a fee per session. The current Medicare fee for a hyperbaric treatment is $190. However it is not clear that this fee represents the true opportunity cost of a specialist's time. It may include a payment for the amortisation of capital and other overhead costs. Another approach is to use the typical specialist consultation fee under Medicare. This is arguably a more accurate estimate of the opportunity cost of time. A third possibility is to use the salary of hyperbaric physician in a public hospital. This would allow for the time spent by the director of a unit in addition to direct patient care. In the primary analysis it is assumed that the average cost per patient of a hyperbaric specialist is the fee for an initial specialist visit multiplied by the number of sessions. The cost of an initial specialist visit is $65.80.[9]

The total staffing cost is estimated to be $145,273 p.a.

In sensitivity analysis, the scenario used was one where a hyperbaric nurse, doctor and technician, is required per hyperbaric facility with 2 and 4 HBOT monoplace chambers. The cost is modelled using a salary of $100,000, which is in the mid-range of salaries paid to a specialist hyperbaric physician in Australia.

Overhead and maintenance costs

The overhead cost is expected to be 28% of operating (staffing) costs, based on the mean indirect cost for non-admitted patient services (1997-98 outpatient services for 8 hospitals). It is assumed that the facility has spare capacity and the cost of space for the monoplace unit is included in overhead costs. The maintenance cost per year is assumed to be $5,000 (personal communication from applicant).

The total overhead costs of operating a monoplace unit is estimated to be $40,676 per annum.

Hence, the total operating costs of a single monoplace chamber are $190,949 p.a. The total operating cost per session is estimated to be $198.91, and the total operating cost per course of treatment $5,967.

The total capital and operating costs are $222,113 p.a. The total cost (capital and operating costs) per session is $231.37, and the total cost per course of treatment is $6,941.

Sensitivity analysis

The results of the sensitivity analysis are summarised in table E1

Table 85 Sensitivity analysis of the cost of monoplace hyperbaric oxygen therapy

Scenario	Total cost p.a.	Total cost per session	Total cost per patient (course of treatment)
Primary Case 4 sessions per day, 120 minutes per session	$222,113	$231	$6,941
No. of sessions per day is 3, 150 minutes per session	$201,900	$280	$8,412
15 sessions per patient	$222,113	$231	$3,471
40 sessions per patient	$222,113	$231	$9,255
Capital costs $100,000	$206,531	$215	$6,454
Capital costs $300,000	$237,695	$248	$7,428
Cost of capital is 5%	$216,850	$226	$6,777
Effective life is 30 years	$210,417	$219	$6,576
Staff not required (FT technician)	$172,876	$180	$5,402
Cost of public salaried doctor	$258,945	$270	$8,092
Cost of one specialist visit only per course of treatment	$143,954	$150	$4,499
Operating cost shared between 2 units	$126,639	$132	$3,957
Operating cost shared between 4 units	$78,901	$82	$2,466
Salaried doctor with 2 units	$145,055	151	$4,532
Salaried doctor with 4 units	$88,109	92	$2,753

The total costs per year ranges from $78,901 when the staffing cost is shared by four HBOT units per facility (assuming the HBOT nurse, technician and doctor attend to four HBOT chambers), to $258,945 with the full public hospital salary of a hyperbaric oxygen specialist attributed to a single chamber. The total cost per session ranges from $82 (with chambers in operation) to $280 per session (when the average number of sessions per day is three). The total cost per course of treatment ranges from $2,466 with four chambers in operation to $9,255 (with 40 sessions per patient).

Appendix F Member organisations of the International Network of Agencies for Health Technology Assessment

AETS	Agencia de Evaluacion de Tecnologias Sanitarias	Spain
AETSA	Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia	Spain
AHFMR	Alberta Heritage Foundation for Medical Research	Canada
AHRQ	Agency for Healthcare Research and Quality	USA
ANAES	L'Agence Nationale d'Accreditation et d'Evaluation en Sante	France
ASERNIP/S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical	Australia
CAHTA	Catalan Agency for Health Technology Assessment	Spain
CCOHTA	Canadian Coordinating Office for Health Technology Assessment	Canada
CEDIT	Comite d´evaluation et de Diffusion des Innovations Technologiques	France
CETS	Conseil d'Evaluation des technologies de la sante	Canada
CVZ	College voor Zorgverzekeringen	Netherlands
DIHTA	Danish Institute for Health Technology Assessment	Denmark
DIMDI	German Institute for Medical Documentation and Information	Germany
DSI	Danish Institute for Health Services Research and Development	Denmark
ETESA	Unidad De Technologias de Salud	Chile
FINOHTA	Finnish Office for Health Care Technology Assessment	Finland
GR	Gezondheidsraad	Netherlands
UKHSC	UK Horizon Scanning Center	UK
ICTAHC	Israel Center for Technology Assessment in Health Care	Israel
INHEM	Instituto Higiene y Epidemiologia	Cuba
ITA	HTA-unit of the Institute of Technology Assessment	Austria
MSAC	Medical Services Advisory Committee	Australia
NCCHTA	UK NHS National Coordinating Centre for Health Technology Assessment	UK
NHSCRD	NHS Centre for Reviews and Dissemination	UK
NZHTA	New Zealand Health Technology Assessment	New Zealand
OSTEBA	Basque Office for Health Technology Assessment Health Department	Spain
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
MTS of SFOSS	Medical Technology Section, Swiss Federal Office of Social Security	Switzerland
SMM	Norwegian Centre for Health Technology Assessment	Norway
SSC/TA	Swiss Science Council/Technology Assessment	Switzerland
TNO	TNO Prevention and Health	Netherlands
VATAP	Veterans Affairs Technology Assessment Program	USA

Appendix G Reviews received from other health technology assessment organisations

1. British Columbia Office Of Health Technology Assessment. Hyperbaric oxygen for osteomyelitis and osteoradionecrosis. Vancouver, Canada: BCOHTA, 1992.

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Appendix H Internet sites

All sites accessed in November 1999

Site Name	Uniform Resource Locator
Beverly Hills Center for Hyperbaric Medicine	http://www.hyperbaricrx.com/ home.html
Duke Center For Hyperbaric Medicine and Environmental Physiology	http://hyperbaric.mc.duke.edu/
Environmental Tectonics Corporation	http://www.etcusa.com/ hbo_intr. htm/
HBOT Online	http://www.hbot.com/
Hyperbaric Chamber Systems and Oxygen Chambers for HBOT Therapy	http://www.american-hyperbaric. com/
Hyperbaric Chamber Systems for HBOT Oxygen Therapy	http://www.hyperbaric-therapy. com/
Hyperbaric Chambers Systems & Management	http://www.hyperbaric.com/
Hyperbaric Oxygen Chamber	http://www.hypertec-o2.com/
Hyperbaric Oxygen Chamber Manufacturer	http://www.hyperbaric-chamber. com/
Hyperbaric Oxygen Chambers	http://www.hyperbar.com/
Hyperbaric Oxygen Therapy - Hyperbaric Services, Inc.	http://www.hyperbaric-services. com/
Hyperbaric Oxygen Therapy 4 Cerebral Palsy	http://www.hot4rcpkidsfoundation. on.ca/
Hyperbaric Oxygen Therapy Chambers Tampa Hyperbaric Enterprise, Inc.	http://www.oxytank.com/
Hyperbaric Oxygen Therapy of Arizona - Oxygen for Life	http://www.hbotofaz.org/aboutus/ index.html
Hyperbaric Oxygen, Inc.	http://www.hyperbarico2.com/
Hyperbaric Physiology	http://www.oxytank.com/quanda. htm/
Hyperbaric Services of America, Inc.	http://www.hyperbaricservices. com/
Hyperbaric Treatment Centre - Hyperbaric Oxygen Therapy	http://www.hyperbarictreatment. on.ca/index.htm/
Medical College of Wisconsin	http://www.mcw.edu/whelan/
Monterey HyperBaric Oxygen Therapy	http://www.mhbot.com/
National Baromedical Services	http://www.baromedical.com/
Ocean Hyperbaric Center	http://hyperbaric-oxygen.com/
Oxygen and Ozone Therapies	http://www.oxytherapy.com/
San Antonio Wound Care & Hyperbaric Medicine Center	http://www.hyperbaricmedicine. com/
Sands Hyperbaric Systems LLC	http://www.hyperbarics.net/

Sechrist Industries -- Hyperbaric Oxygen Chambers	http://www.sechristind.com/
Total Wound Specialists	http://www.totalwoundspecialists.com/
Undersea & Hyperbaric Medicine Society	http://www.uhms.org/
Wound Care Consultants – Hyperbaric Oxygen Therapy	http://www.wound.com/hbo2.html

Abbreviations

AMI	Acute myocardial infarction
ATA	Atmosphere absolute
CABG	Coronary artery bypass grafting
CI	Confidence interval
CVD	Cerebrovascular disease
d	day, daily
Gy	Gray
h	hour
HBO	Hyperbaric oxygen
HBOT	Hyperbaric oxygen therapy
kPa	kiloPascal
m	month
min	minute
MeSH	Medical subject heading
N or n	Population or sample size
OR	Odds ratio
POAD	Peripheral occlusive arterial disease
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomised controlled trial
SD	Standard deviation
SE or SEM	Standard error of the mean
y	year

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