Hyperbaric Oxygen Therapy: a Rapid Assessment

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Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Executive summary

INTRODUCTION

Hyperbaric Oxygen Therapy (HBOT) is the administration of oxygen at pressures greater than normal atmospheric pressure for therapeutic reasons. This treatment is performed in pressure chambers of various sizes, ranging from monoplace chambers for one patient only, to multiplace or multi-compartment treatment chambers in which several patients can sit and where hospital beds or even an entire intensive care setting can be installed and where health workers can attend to the patients.

This therapy has been available for several decades and is used for many indications. Most of these reported indications were, however, based on little or no evidence. As a result, HBOT has been called "a therapy in search of diseases".

HBOT appears to be quite safe and the occasional adverse effects are mainly mild and reversible although they could, potentially, be severe and life threatening. State of the art installation and maintenance and adequate staffing is therefore of tantamount importance. Furthermore, an adequate patient selection to avoid side-effect such as barotraumas is necessary.

it is not entirely clear for which indications HBOT should be supported. The purpose of this report is to gather evidence about clinical effectiveness, to examine the health-economic aspects of HBOT, to describe current practice and organisation in Belgium and to make recommendations for the most appropriate use of this therapy.

CLINICAL EFFECTIVENESS

HBOT has been used for many medical conditions. However, most of the randomised clinical trials have been done in small groups and for many of the indications no proper randomised trials have been performed. We therefore focussed our systematic literature review on meta-analyses and systematic reviews of those indications accepted by either the European or the North American Hyperbaric Medical Societies; the European Committee for Hyperbaric Medicine (ECHM) and the Undersea and Hyperbaric Society' (UHMS). Other indications were only mentioned when summary evidence was available.

We summarized evidence for the following categories: carbon monoxide (CO) intoxication, decompression accidents, gas embolism, anaerobic or mixed anaerobic-aerobic bacterial infections, acute soft tissue ischemia, post radiotherapy tissue damage (soft tissue and bones), delayed wound healing (such as diabetic foot ulcers), chronic refractory osteomyelitis, post-anoxic encephalopathy, thermal burns, hearing disorders, acute ophthalmological ischemia, neuroblastoma stage IV, pneumatosis cystoides intestinalis, exceptional anaemia, and a residual category of miscellaneous indications.

HBOT has become accepted standard therapy in a few life threatening conditions i.e. decompression illness and gas embolism, mainly based on historical empirical evidence. For these indications it is unlikely that evidence from RCTs will become available because such RCTs are considered unethical by many in the field.

There is low quality evidence from small RCTs on the clinical efficacy of HBOT for three indications. In the treatment of diabetic ulcers adjuvant HBOT may help avoid major amputations in the medium term compared to standard therapy without HBOT. For acute deafness presenting early, a slightly better recovery was observed with adjuvant HBOT, although the clinical relevance of this improvement is uncertain. Finally, HBOT may improve healing in selected cases of post radiation therapy tissue damage. In all of these three indications, however, future larger and well conducted RCTs should enhance our evidence base.

Next, there is low quality evidence based on small and heterogeneous trials for the non-efficacy of HBOT on the avoidance of long-term neurological sequels of carbon monoxide intoxication in comparison with normobaric oxygen therapy. For the short-term therapeutic effects on carbon monoxide poisoning, no RCTs have been conducted and current therapy is based on in-vitro and animal models and on theoretical reasoning. Because of the wide consensus on its effectiveness for this indication in the hyperbaric community, future larger and well conducted RCTs should be conducted to reach definitive scientific conclusions for this indication.

Finally, for the other mentioned indications, there is very low quality evidence or no evidence for the efficacy of adjuvant HBOT. Endorsement for these indications by scientific societies and health insurers is mainly consensual and only larger and well conducted RCTs can support or refute the appropriateness of HBOT.

ECONOMIC EVALUATION

A systematic literature review was performed to identify full economic evaluations of HBOT. The objective was to determine whether adjuvant HBOT is a cost-effective option compared with standard care for several indications. Seven full economic evaluations were identified covering four indications, i.e. diabetic foot ulcers, necrotising soft tissue infections, osteoradionecrosis, and non-diabetic wounds.

All studies showed severe limitations for both the incremental cost and for the benefit calculations. Therefore, they can only be seen as an indication that HBOT may be a cost-effective treatment under very specific assumptions of effectiveness and costs. They do not provide good evidence that HBOT is indeed a cost-effective treatment. The suggestion that HBOT could be clinically effective, could improve Quality of Life (QoL), and could reduce health care costs under certain indications urges the need for further large multi-centre randomised trials to find out whether or not this is real. At the same time that effectiveness data would be collected, better quality cost data should also be gathered. As long as adequate effectiveness and cost data are lacking, proper economic evaluations can not be performed.

BELGIAN SITUATION

Belgian Health Insurance provides reimbursement for the first and second day of HBOT. On January 1, 2008, the HBOT tariff level was set at €64.63 and €48.47 for the first and second treatment day, respectively. The reimbursement level is 100%. The nomenclature does not explicitly restrict HBOT to specific indications, but in theory HBOT may only be charged when the patient is in a life-threatening situation. In reality, however, this is subject to a relatively broad interpretation. The expenditures for HBOT by the national health insurance are quite small. In 2006, €83 000 was paid for approximately 1 400 sessions, mainly due to the current restricted reimbursement. We estimated that less than 9% of all HBOT sessions were reimbursed during that year.

There are currently twelve centres in Belgium with hyperbaric facilities, two of them military centres. Most often, HBOT is used for hearing disorders and post-radiotherapy tissue damage, respectively 32% and 30% of all treatment sessions, but indications that are being treated vary widely between centres. Occupancy rates show that there are no apparent capacity problems and the geographic distribution seems adequate.

The largest cost component for HBOT is the personnel cost (~50-75% for multiplace chambers), followed by the investment cost (~15-30%). The cost of oxygen and compression is only marginal. The price per session for the hospital depends, among others, on the number of sessions per day, the occupancy rate, the type of hyperbaric chamber, etc. For example, the average cost of running a monoplace chamber per patient and per session is significantly higher compared to a multiplace chamber. Since personnel costs is the most important cost driver, it is important to work efficiently. Having fewer sessions per day in combination with a higher occupancy rate is more beneficial.

INTERNATIONAL COMPARISON

We made an international comparison of capacity and organisation of HBOT in several western countries. There appears to be no clear international agreement on the use and organisation of HBOT. Reimbursement levels vary and reimbursed indications are mainly consensus based. Compared to surrounding countries, the HBOT capacity is relatively high in Belgium.

CONCLUSION

HBOT has been used for many indications. However, few indications have been subject to properly organised randomized controlled clinical trials. As a result, there is insufficient good-quality data to make a proper assessment of this therapeutic modality. Several reasons have been proposed to explain why so little good research has been performed to provide evidence. Nonetheless, stakeholders and decision makers should be allowed an evidence based approach to find out whether or not it is appropriate to support and reimburse the use of HBOT in specific indications. Recommendations that are mainly consensus based can not be considered good evidence.

Physicians in Belgium provide HBOT for a wide range of indications, but currently the impact of HBOT on the National Health Insurance budget is minimal. This is due to the current restrictive reimbursement rules which only provide a limited reimbursement for the first and second day of treatment.

There is currently insufficient evidence to simply extend reimbursement of this therapy regardless of indication. If, however, decision makers decide to make reimbursement more attractive for specific indications, this should be linked to a proper randomised research setting with the explicit goal to collect effectiveness and cost data.

POLICY RECOMMENDATIONS

1. No expansion of HBOT capacity is recommended since there is obviously no capacity problem and also the geographic distribution appears to be sufficient, even considering the currently "accepted" indications.
2. The use of HBOT in the treatment of decompression accidents and severe gas embolism is supported by historical empirical evidence and by wide consensus. HBOT for the treatment of carbon monoxide poisoning to avoid long-term neurological sequels is not supported by clinical evidence since there is low quality evidence from small RCTs on the clinical non-efficacy of HBOT. For the short-term effectiveness in carbon monoxide poisoning no evidence from RCTs is available.
3. Conditional financing for experimental treatment could be considered and/or research encouraged specifically for those indications were some evidence is already available and that are of sufficient clinical relevance. For diabetic ulcers and selected cases of radiation induced tissue injury, low quality evidence from small RCTs on the clinical efficacy of adjuvant HBOT is available. Also for acute deafness presenting early there is some evidence for a beneficial effect although the clinical relevance of this benefit is questionable.
4. HBOT for other indications is not supported since no or only very low quality evidence is available.
5. For common indications, further research on larger populations could be performed both on a national basis given the number of Belgian centres and locally available expertise, as internationally. For research on rare indications multicentre studies are needed and an initiative at the European level is probably needed to gather evidence for those indications. Specific research financing sources are unclear, although protocols were developed previously with European support.
6. These recommendations should be revised when newer and better data on efficacy of HBOT become available.

Scientific Summary

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ABBREVIATIONS

ACS	Acute Coronary Syndrome
AEC	Annual Equivalent Cost
AGE	Arterial Gas Embolism
AHRQ	Agency for Healthcare Research and Quality (US)
Amb	Ambulatory
AMI	Acute Myocardial Infarction
ASC	Ambulatory Surgical Centre
ATA	Atmospheres Absolute (pressure)
AUD	Australian dollar
CABG	Coronary Artery Bypass Graft
CAD	Canadian dollar
CBA	Cost-Benefit Analysis
CDSR	Cochrane Database of Systematic Reviews
CE	Cost Effectiveness
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CMA	Cost-Minimization Analysis
CNAM	Caisse Nationale de l'Assurance Maladie
CO	Carbon monoxide
COHb	Carboxy Haemoglobin
CRD	Centre for Reviews and Dissemination
CUA	Cost-Utility Analysis
CVZ	College Voor Zorgverzekeringen
DARE	Database of Abstracts of Reviews of Effects
dB	Decibel
DCI	Decompression Illness (summary term for AGE or DCS)
DCS	Decompression Sickness
DDRC	Diving Diseases Research Centre
DRG	Diagnosis Related Group
ECHM	European Committee for Hyperbaric Medicine
EU	European Union
FTE	Full Time Equivalent
GPCI	Geographic Practice Cost Index
Gy	Gray (unit of radiation dose)
HAD scale	Hospital Anxiety and Depression scale

HAS	Haute Authorité de Santé (France)
HBO	Hyperbaric Oxygenation (=HBOT)
HBOT	Hyperbaric Oxygen Therapy (=HBO)
Hosp	Hospitalized
HTA	Health Technology Assessment
ICA	Intracranial Abscess
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICER	Incremental Cost-Effectiveness Ratio
ICR	Index de Complexité Relative
IECS	Instituto de Effectividad Clinica y Sanitaria (Argentina)
INAHTA	International Network of Agencies for Health Technology Assessment
ISSHL	Ideopathic sudden sensorineural hearing loss
LEA	Lower Extremity Amputation
LRTI	Late Radiation Tissue Injury
LYG	Life-Years Gained
MACE	Major Adverse Coronary Event
MAS	Medical Advisory Secreteriat (Canada, Ontario)
MB	Ministerieel Besluit (Ministerial Decree)
MCD	Minimal Clinical Data (see MKG/RCM)
MCO	Médecine, Chirurgie et Obstétrique
MeSH	Medical Subject Headings (NLM)
MFG/RFM	Minimal Financial Data (Minimale Financiële Gegevens – Résumé Fiancier Minimum)
MKG/RCM	Minimal Clinical Data Set (Minimale Klinische Gegevens - Résumé Clinique Minimum)
MSAC	Medical Services Advisory Committee (Australia)
NGAP	Nomenclature Générale des Actes Professionnels
NHS	National Health System (UK)
NHS EED	NHS Economic Evaluation Database
NIH	National Institutes of Health (US)
NIS	National Institute of Statistics
NLM	National Library of Medicine (US)
NNT	Number needed to treat
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NZA	Nederlandse Zorg Authoriteit
NZ$	New Zealand dollar
O2	Oxygen

OPS	Operationen- und Prozedurenschlüssel
PCI	Percutaneous Coronary Intervention
PTA	Pulse Tone Average
PtcO2	Transcutaneous oxygen pressure measurement
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RIZIV / INAMI	Rijksinstituut voor Ziekte en Invaliditeits Verzekering / Institut National d'Assurance Maladie - Invalidité
RNZN	Royal New Zealand Navy
RR	Relative Risk
RVU	Relative Value Unit
SD	Standard Deviation
SE	Standard Error
SF-36	Short-Form General Health Survey
Sv	Sievert (measure of effective radiation dose)
TGR / CTM	Technische Geneeskundige Raad / Conseil Technique Medical
UHMS	Undersea and Hyperbaric Medical Society
UK	United Kingdom (Great Britain)
US	United States of America
VDD	Verband Deutscher Druckkammerzentren
VGE	Venous Gas Embolism
ZBC	Zelfstandige Behandelcentra

1 INTRODUCTION

Hyperbaric Oxygen Therapy (HBOT) is the administration of oxygen at pressures greater than normal atmospheric pressure for therapeutic reasons. It is defined by the Undersea and Hyperbaric Medical Society (UHMS) as 'a treatment in which a patient breathes 100% oxygen while inside a treatment chamber at a pressure higher than sea level pressure, i.e. more than 1 atmosphere absolute (ATA). Hyperbaric oxygenation can also be applied as a diagnostic procedure to decide on the appropriateness of HBOT. The treatment is performed in pressure chambers of various sizes, ranging from monoplace chambers for one patient only, to multiplace or multi-compartment treatment chambers in which several patients can sit and where hospital beds or even an entire intensive care setting can be installed and where health workers can attend to the patients.

Recompression with normal air was initially intended as a treatment for decompression sickness (DCS). In the late 19th century 'caisson disease' became a frequent illness in workers involved in large construction projects (bridges, tunnels) where they had to work in hyperbaric conditions while labouring in 'caissons'. Mortality from this disease, also called bubble disease, was greatly reduced thanks to recompression therapy with normal air. Halfway the 20th century, the use of normal air was replaced by the use of either pure oxygen or specific mixtures of gasses, and HBOT established itself as standard therapy for all types of decompression illness (DCI) caused by diving, aviation or of iatrogenic origin.

Although it was known for a long time that breathing oxygen under increased ambient pressure could lead to an increased amount of oxygen in the blood, the medical use of HBOT for the treatment of conditions other than DCI only started about 50 years ago, when the Dutch cardiac surgeon *Ite Boerema* reported on the use of hyperbaric oxygen during paediatric cardiac surgery. This marked the beginning of a proliferation of hyperbaric chambers in hospitals around the world. During this era numerous new indications were proposed, from CO poisoning to the treatment of senility and the conservation of youthfulness. Many of the reported indications were based on little or no evidence and it was during this period that HBOT gained a reputation of quackery with many in the medical community.

Recently, RCTs were performed for specific indications and evidence on certain indications has appeared. It is the aim of this report to bring together this evidence, to examine the health-economic aspects of HBOT, to describe current practice and organisation in Belgium and to make recommendations for the most appropriate use of this therapeutic technology in this country.

2 HYPERBARIC OXYGENATION THERAPY: HISTORY AND TECHNICAL DESCRIPTION

2.1 BRIEF HISTORY

Hyperbaric therapy refers to therapeutic conditions with ambient pressures higher than normal atmospheric pressure at sea level. This pressure can be expressed in relation to this sea level pressure as Atmosphere pressure absolute (ATA). Hyperbaric conditions thus correspond to pressures higher than 1 ATA and typically occur during underwater diving. At a depth of 10 meters pressure is approximately 2 ATA, and every additional 10 meters of depth corresponds to about one extra ATA.

As early as the 17th century, strong airtight vessels combined with pumps capable of compressing air could be produced and where sporadically even used as treatments for various conditions.[1-3] Serious hyperbaric therapy, however, only began as a treatment of caisson disease, a disease occurring in engineering workers who had to labour in caissons under conditions of compressed air, mainly during the construction of tunnels and bridges in the late 19th century.[2, 4]

The first reports of decompression sickness described this condition as 'the bends', since caisson workers assumed a bent posture to help relieve the pain caused by the nitrogen accrual in their joints. Although the physiology of the disease was only understood much later, recompression therapy at first with normal air, was proposed as early as 1854,[1, 2] and for a long time caisson disease, or decompression sickness (DCS) as it was later called, remained the main therapeutic indication for hyperbaric therapy. As a result of the introduction of a series of improvements of the working environment, including recompression therapy, mortality from this disease that ran as high as 25% originally, was dramatically reduced.[1, 4] Apart from this therapeutic use, however, all kinds of potential beneficial effects were ascribed to modest hyperbaric pressures and hyperbaric chambers were even introduced in health spas. In the nineteen twenties a 5-storey high hyperbaric building was built by O.J. Cunningham, the largest ever.[2, 3] Serious medical interest, however, quickly faded.

With World War II interest in hyperbaric physiology and medicine re-emerged due to the increased demands not only on divers but also increasingly on aviators and later also astronauts who had to work in both hyperbaric and hypobaric conditions. By then also, the use of normal air in hyperbaric chambers had been replaced by that of 100% oxygen or by different mixtures of oxygen, air or helium.

Early experiments in the 19th and 20th century had shown that breathing oxygen while raising the atmospheric pressure could lead to an increased amount of oxygen in the blood and tissues, but mainstream medical interest was only revived when the Dutch cardiac surgeon Ite Boerema reported in 1956 on the use of an operating room with raised atmospheric pressure to allow longer operating time during circulatory arrest in babies and young children with congenital heart defects.[2, 5, 6] His reports marked the beginning of a proliferation of hyperbaric chambers in hospitals around the world, although very soon they would become unnecessary for the original purpose due to the development of new operation methods and of new equipment to perform them. To use and justify the existing hyperbaric chambers new and sometimes bizarre indications were proposed. In 1987, Gabb and Robin published a manuscript entitled *'Hyperbaric oxygen, a therapy in search of diseases'* in which they list over a hundred indications that had, by then, been suggested.[7] Those indications ranged from CO poisoning to senility, the preservation of youthfulness and the treatment of baldness. Many of the reported indications were based on very little or only anecdotic evidence.

In an effort to respond to those shortcomings, medical societies such as the Undersea and Hyperbaric Medical Society (UHMS, www.uhms.org)[8] and the European Committee for Hyperbaric Medicine (ECHM, www.echm.org)[9] were established with the explicit aim to examine the indications for HBOT.

For a long time, however, scientific evidence about HBOT benefits in humans remained scarce and often based on animal studies or small case series,[1] and mainly based on the personal experience of doctors intensively using this therapeutic modality. Recently, some more evidence has appeared and RCTs were performed for specific indications. In recent years several Cochrane reviews were published that carefully examine the available evidence.

2.2 TECHNICAL DESCRIPTION

Oxygen is considered as a drug and it can be administered easily under normobaric conditions, but administering oxygen at pressures higher than 1 ATA requires compression. This is usually done by having the patient breathe pure oxygen or mixtures with other gases while being inside a airtight chamber in which the pressure is greater than 1 ATA. Three primary mechanisms are believed to be involved in the potential beneficial effects: bubble size reduction and elimination in case of decompression sickness and gas embolism (commonly called decompression illnesses or DCI), the achievement of hyperoxia in target organs, and the potential enhancement of immune and healing mechanisms through the correction of pre-existing hypoxia in target organs.[1, 8] HBOT is also considered to act beneficially through the pharmaceutical effect of hyperoxia induced inhibition of beta-integrin dependent white cell adherence to endothelium, as a mechanism to inhibit reperfusion injury.[10]

There are basically two types of hyperbaric chambers, monoplace and multiplace, and the choice of chamber typically depends on the capacity needs and the conditions being treated.

Since oxygen is to be regarded as the active pharmaceutical component, adequate dosing for each of the conditions being treated is necessary. In practice this is done through a combination of dosages, pressures and timing. For DCI, for instance, treatment consists of rapid recompression followed by slow decompression, but for each of the conditions treated by HBOT hyperbaric treatment tables have been devised. In practice, however, the choice of treatment schedules has often been empirical, at least in the past.[1]

A number of publications described a therapy delivering topical oxygen at high flow rates locally to the wound surface, sometimes mistakenly calling this 'hyperbaric oxygen therapy'. However, oxygen delivered with this method is estimated to impact tissues only up to 50 microns deep.[8] This method of delivering oxygen to the tissues will not be discussed in this report as it is neither systemic nor hyperbaric and therefore outside the scope of this assessment.

2.3 ACCEPTED INDICATIONS BY HYPERBARIC MEDICAL SOCIETIES

Several medical societies are active in the world of Hyperbaric Oxygenation Therapy. The largest is the North America based 'Undersea and Hyperbaric Medical Society' (UHMS), formerly the Undersea Medical Society founded in 1967. Originally, the society supported third party reimbursement for 28 indications but in its 2003 report the number of accepted indications had declined to 13 distinct medical conditions.[8] Table 1 lists those 13 conditions.

Table 1. Indications accepted by UHMS (2003)

Condition
Air or gas embolism
Carbon Monoxide poisoning (whether or not complicated by cyanide poisoning)
Clostridial Myositis and Myonecrosis (Gas gangrene)
Crush injuries, compartment syndrome and other acute ischemias
Decompression Sickness
Enhancement of Healing in Selected Problem Wounds
Exceptional anaemia
Intracranial abscess
Necrotising soft tissue infections
Refractory osteomyelitis
Delayed radiation injury including soft tissue and bone necrosis
Skin grafts and flaps
Thermal Burns

Source: UHMS.[8]

In 2004 the European Committee for Hyperbaric Medicine (ECHM) held its 7th European Consensus Conference on Hyperbaric Medicine, where they also agreed on a list of indications (see Table 2).[9] In many aspects this list is similar to the one from UHMS, although it should be understood that definitions used by different societies do not always completely overlap. Moreover, there are also important differences for specific indications and recommendations as will be pointed out in the detailed description of the indications.

Sudden deafness for example, one of the most important indications for HBOT use in Belgium is not on the current UHMS list. The differences and similarities between both lists will be addressed in more detail in the next chapter.

Table 2. Indication accepted by the ECHM (2004)

Condition
Carbon Monoxide (CO) intoxication
Decompression Accident
Gas Embolism
Anaerobic or mixed anaero-aerobic bacterial infections (necrotizing soft tissue infections and selected cases of organ abscesses)
Acute Soft Tissue Ischemia (crush injuries, traumatic amputated limb segments, with recommended transcutaneous oxygen pressure measurement)
Radio-induced Lesions
Delayed wound healing (ischemic lesions or selected non-healing wounds secondary to inflammatory processes)
Chronic refractory osteomyelitis
Post-anoxic encephalopathy
Burns
Sudden Deafness
Ophtalmological Disorders
Neuroblastoma Stage IV
Pneumatosis Cystoides Intestinalis

Source: ECHM.[9]

Apart from these 'accepted' indications there is a multitude of other conditions for which more or less evidence is available, but where treatment is mainly experimental. Those indications for which evidence is available will also be briefly described in the next chapter.

2.4 POTENTIAL HARMS, SAFETY AND PRECAUTIONS

HBOT appears to be relatively safe with few serious adverse effects. Adverse effects are often mild and reversible but could, potentially, be severe and life threatening.[1, 11] As a consequence, strict precautions must be taken while administering HBOT to avoid those complications. In addition, proper installation and maintenance of a HBOT facility and adequate staffing with specifically trained personnel is pivotal. There is always a risk, albeit small, of fire and explosion and it may also be difficult to deal with medical emergencies, especially if a patient is isolated in a chamber. In some countries, such as France, it is reported that the use of monoplace chambers has been completely abandoned and there appears to be growing consensus that the use of monoplace chambers should be avoided.

2.4.1 Barotrauma

Barotrauma is a general term to indicate injury to a tissue through the action of differential pressures and it can occur in body areas where tissue and gas interface, such as the middle ear, the sinuses and the lungs. Middle ear barotrauma is the most commonly reported acute side effect of HBOT, and it was reported to occur in 2% of patients.[1, 8] A prospective study reported that almost one-fifth of all patients experienced some ear pain or discomfort related to problems in middle ear pressure equalization, while visual otological examination confirmed barotraumatic lesions in 3.8% of patients.[12] Barotrauma can be avoided by careful patient selection, excluding patient with contraindications for HBOT such as emphysema, by patient education and by the termination of HBOT when early symptoms occur. Pulmonary barotrauma is a potential problem mainly during the decompression phase of HBOT since the volume of gas in the lungs increases due to the reduced pressure and this extra volume needs to be breathed out. However, the occurrence of this complication has only been reported in sporadic cases.[1, 8]

2.4.2 Oxygen toxicity

Oxygen has to be considered as a drug and it can give rise to the formation of free radicals during high dose oxygen breathing. These free radicals can lead to the oxidation of chemical components of tissue. While in principle any tissue could be affected, it occurs most frequently in the lungs, brain and eyes.[1, 8] Reported forms of ocular toxicity are reversible myopia and cataract development.[1, 13] Cerebral toxicity leading to an acute epileptic seizure has been reported occasionally, although this condition appears to be self-limiting without apparent long-term sequels.[1, 12] Pulmonary toxicity has been described for more than a hundred years and infrequently appears to occur even following low doses of oxygen.[1]

2.4.3 Other hazards

Decompression illness itself is a risk inherent to HBOT for care personnel inside the pressurised chamber not breathing oxygen, but can be avoided by careful usage of compression and decompression schemes. The confinement to a relatively small and closed container can give rise to claustrophobia which in severe cases can make HBOT impossible.[a] Distraction schemes or occasionally light sedation can help overcome these problems. Fire, obviously, is a major hazard since oxygen supports combustion. Therefore, a hyperbaric air-filled chamber where only the patients breathe 100% oxygen through a mask or hood is generally preferred.

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[a] However, claustrophobia has even been described as an indication for HBOT in one case report.[14] It is unclear whether increased atmospheric pressure or the administration of oxygen has an important role in this indication.

In 1997 a review reported 35 incidents resulting in 77 human fatalities over almost 70 years of HBOT use, and also in 1997 a fire in a multiplace hyperbaric chamber in Milan caused the death of 10 patients and a nurse, apparently due to a malfunctioning fire suppression system.[1, 15] Again, prevention strategies are of utmost importance, especially when choosing and maintaining the equipment.

Key points

- **Hyperbaric therapy is a treatment, in which patients breathe pure oxygen (or sometimes other gas mixtures) intermittently while inside a treatment chamber at a pressure higher than sea level pressure.**
- **Hyperbaric therapy originated from the treatment of decompression illness over a hundred years ago.**
- **During the last fifty years, several other indications for hyperbaric therapy have been proposed.**
- **A restricted number of indications have been accepted by the two main scientific hyperbaric societies.**
- **When applied under optimal circumstances, hyperbaric therapy is generally safe.**

3 EVIDENCE FOR CLINICAL EFFECTIVENESS

3.1 INTRODUCTION

Since the late nineteen-fifties HBOT has been increasingly used for indications other than decompression illness (DCI).[1, 2, 7] For most of these indications, serious evidence is at best scarce. Part of this lack of evidence is explained by the hyperbaric community as due to the fact that randomised controlled trials are more difficult to conduct for HBOT indications since these conditions are too complex to allow for easy randomisation, or by the fact that these conditions are sometimes so life threatening that inclusion of the patient in a properly randomised controlled trial (RCT) would be considered unethical.[9] Another problem encountered while designing RCTs is the difficulty of blinding to therapy allocation, which can be achieved by either administering pure oxygen in a hyperbaric chamber without raising the pressure for control patients, as done for example in a CO intoxication trial by Weaver et al.[16] or by placing intervention and control patients in the same hyperbaric chamber, raising the pressure but administering different mixtures of gasses.[17, 18] Finally, since many of those trials are relatively small, there is an important risk for selection bias with negative or inconclusive trials less likely to be reported in peer reviewed publications.

As a result of those difficulties, many of the current recommendations on 'accepted' indications have been obtained by the hyperbaric medical societies through a method of consensus, rather than through evidence based decision making. The evidence considered by those societies is sometimes based on RCTs, but often consists of a combination of in vivo or in vitro studies, animal studies, observational clinical studies and personal experience, while the stated requirement is that the evidence submitted should be *'at least as convincing as that for any other currently accepted treatment modality for that disorder'*.[8]

In 2004 the European Committee for Hyperbaric Medicine (ECHM) organised its 7th European Consensus Conference on Hyperbaric Medicine in Lille (France), to make recommendations on which indication to endorse.[9] The ECHM based this consensus on a mixture of two grading scales, taking into account both the type of recommendation and the evidence supporting this recommendation, as shown in Table 3. It should be noted that for none of the accepted indications level A evidence was available, and many accepted indications were supported on the basis of level C evidence only.

Table 3. Type of recommendation and supporting evidence used in ECHM consensus conference

Type of recommendation	
Type 1	Strongly recommended
Type 2	Recommended
Type 3	Optional
Evidence from human studies supporting recommendation	
Level A	Strong evidence of beneficial action based on at least two concordant, large, double-blind, RCT with no or only weak methodological bias)
Level B	Evidence of beneficial action based on double-blind controlled, randomised studies but with methodological bias, or concerning only small samples, or only a single study
Level C	Weak evidence of beneficial action based only on expert consensus or uncontrolled studies (historic control group, cohort study, etc.)

Source: ECHM.[9]

The structure of this chapter is mainly based on the indications that were accepted by this European consensus conference,[9] but other indications have been added when sufficient evidence is available for an assessment. For each of these indications we will summarise the available evidence.

3.2 LITERATURE SEARCHES ON CLINICAL EFFECTIVENESS

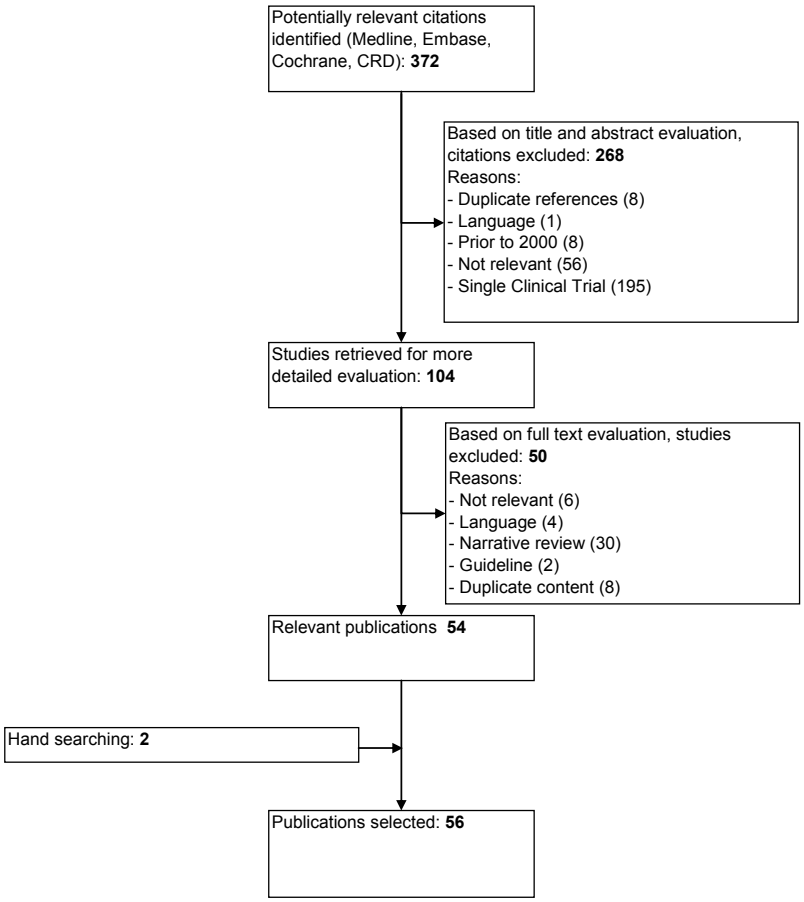
Most of the randomised clinical trials have been done in small groups and for many of the indications no proper randomised trials have been performed. We therefore focussed our search on meta-analyses and systematic reviews.

Relevant literature was sought in Medline, Embase, the Cochrane Database of Systematic Reviews (CDSR), and the DARE, NHS-EED and HTA databases of the Centre for Reviews and Dissemination (CRD). We also searched for ongoing clinical trials in the Cochrane Central Register for Controlled Trials. Details of strategy and search results can be found in the appendix. In addition we searched http://www.hboevidence.com/, a specialized site for EBM information on HBOT for the most recent information.

3.3 DATA SOURCES

From the 372 references of potential systematic reviews and meta-analyses retrieved originally, we selected, based on title and abstract, 104 articles for further consideration. From these we finally selected 54 references (see Figure 1 for details on selection). We also identified an additional article and a thesis through hand searching.[1, 19]

Figure 1. Identification and selection of systematic reviews and Meta-Analyses



The retained references included 17 Cochrane reviews published since 2002 and an Australian doctoral thesis from Michael Bennett who co-authored many of the Cochrane reviews. These 18 key references are listed in Table 4.

Table 4. Cochrane reviews and thesis on various indications for hyperbaric oxygenation

Title	Year
Recompression and adjunctive therapy for decompression illness.[20]	2007
Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus.[21]	2007
Normobaric and hyperbaric oxygen therapy for migraine and cluster headache (Protocol)*.[19, 22]	2007
Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa.[23]	2005
Hyperbaric oxygen for carbon monoxide poisoning.[24]	2005
Hyperbaric oxygen therapy for acute ischemic stroke.[25]	2005
Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union.[26]	2005
Hyperbaric oxygen therapy for late radiation tissue injury.[27]	2005
Hyperbaric oxygen therapy for acute coronary syndrome.[28]	2005
Hyperbaric oxygenation for tumour sensitisation to radiotherapy.[29]	2005
Hyperbaric oxygen therapy for delayed onset muscle soreness and closed soft tissue injury.[30]	2005
Hyperbaric oxygen therapy for thermal burns.[31]	2004
Hyperbaric oxygen therapy for chronic wounds.[32]	2004
Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury.[33]	2004
Hyperbaric oxygen therapy for multiple sclerosis.[34]	2004
Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis.[35]	2002
Interventions for replacing missing teeth: hyperbaric oxygen therapy for irradiated patients who require dental implants.[36]	2002
Thesis: The Evidence Basis of Diving and Hyperbaric Medicine[1]	2006

* The formal Cochrane review is in press but results have been published by Schnabel et al.[19]

Our search also yielded several HTA reports. A few of the recent technology assessments covered the whole domain of HBOT.[14, 37, 38] Other HTA reports focussed on specific indications only, and will be addressed with the specific indications where relevant.

The Cochrane Central Register for Controlled Trials reveals 20 registered RCTs between 2005 and 2007.

Most of these trials investigate miscellaneous indications not-accepted by the two large hyperbaric medical communities, or therapies adjuvant to HBOT. Only two of these deal with CO intoxication (one RCT,[39] and a longitudinal study on affective outcome[40]) one deals with radio induced lesion,[17] and two with diabetic ulcers.[18, 41] The RCT database from the National Institutes of Health (NIH, www.clinicaltrials.gov) lists 31 ongoing or recently completed trials on HBOT. A European Cost B14 program was started in 1998 and after prolongation ended in March 2005.[42] In addition to the development of a database, a common website (www.oxynet.org, a function now largely taken over by www.echm.org) and safety protocols for hyperbaric facilities, this collaboration also developed several research protocols for RCTs that were reportedly started in 2001 and 2002 (http://www.oxynet.org/ProtocolsIndex.htm). The status of these studies remains, however, unclear and it was confirmed that these RCTs were delayed due to lack of funding and are unlikely to provide results within the next 2 or 3 years (personal communication D. Mathieu). Table 5 lists the RCTs currently in the NIH clinical trials database.

Table 5. RCTs in NIH clinical trials database

Name	End date	Sponsor	Enrolment
Pilot Study of the Effect of Hyperbaric Oxygen Treatment on Behavioral and Biomarker Measures in Children With Autism	sep/08	University of California, Davis	Enrolling by invitation
Effects of Hyperbaric Oxygen Therapy in Autistic Children: A Pilot Study	not stated	International Hyperbarics Association	Completed
Hyperbaric Oxygen, Oxidative Stress, NO Bioavailability and Tissue Oxygenation	sep/05	Assaf-Harofeh Medical Center	Completed
Study to Determine if Hyperbaric Oxygen Therapy is Helpful for Treating Radiation Tissue Injuries	aug/10	Baromedical Research Foundation	Recruiting
An Evaluation of Hyperbaric Treatments for Children With Cerebral Palsy	feb/09	Wright State University; Department of Defense; Children's Medical Center of Dayton; Kettering Medical Center Network	Recruiting
Dose Escalation Study of Hyperbaric Oxygen With Radiation and Chemotherapy to Treat Squamous Cell Carcinoma of the Head and Neck	jul/08	Baromedical Research Foundation; Palmetto Health Richland; Mayo Clinic; Dartmouth-Hitchcock Medical Center; Eastern Virginia Medical School	Recruiting
One vs. Three Hyperbaric Oxygen Treatments for Acute Carbon Monoxide Poisoning	may/09	Intermountain Health Care, Inc.; Deseret Foundation	Recruiting
A Controlled Trial of the Clinical Effects of Hyperbaric Therapy in Autistic Children	mar/07	International Hyperbarics Association	Completed
Is it Possible to Treat Cyanide Poisoning With HBO?	nov/06	Rigshospitalet, Denmark	Recruiting
Effects of Hyperbaric Oxygen Therapy on Children With Autism	sep/07	Thoughtful House	Recruiting
Efficacy of Hyperbaric Oxygen Therapy in Laryngectomy Patients	aug/05	National Center for Complementary and Alternative Medicine (NCCAM)	Completed
Hyperbaric Oxygen Therapy and Angiogenesis in Diabetic Patients With Foot Ulcers	not stated	Assaf-Harofeh Medical Center	Recruiting
Hyperbaric Oxygen Treatment in Patients With White Matter Hyperintensities	jul/09	St. Luke's Hospital, Chesterfield, Missouri; Washington University School of Medicine	Recruiting
Effects of Hyperbaric Oxygenation Therapy on Adaptive, Aberrant and Stereotyped Behaviors in Children With Autism	dec/07	The Center for Autism and Related Disorders; The International Child Development Resource Center	Recruiting
Hyperbaric Therapy and Deep Chemical Peeling	jul/07	Assaf-Harofeh Medical Center	Recruiting
Hyperbaric Oxygen in Lower Leg Trauma	jun/10	Bayside Health	Recruiting
Effect of Hyperbaric Therapy on Markers of Oxidative Stress in Children With Autism	feb/06	The International Child Development Resource Center	Recruiting
Hyperbaric Oxygen Therapy Compared With Standard Therapy in Treating Chronic Arm Lymphedema in Patients Who Have Undergone Radiation Therapy for Cancer	not stated	Institute of Cancer Research, United Kingdom	Active, not recruiting
Randomized Controlled Trial of Hyperbaric Oxygen in Patients Who Have Taken Bisphosphonates	dec/10	Duke University	Recruiting
Comparison Between Different Types of Oxygen Treatment Following Traumatic Brain Injury	nov/08	Minneapolis Medical Research Foundation	Recruiting
Hyperbaric Oxygen Therapy in Treating Patients With Radiation Necrosis of the Brain	Jun/05	Barrett Cancer Center; National Cancer Institute (NCI)	Active, not recruiting
Radiation Therapy Plus Hyperbaric Oxygen in Treating Patients With Newly Diagnosed	not stated	Barrett Cancer Center	Active, not recruiting

Glioblastoma Multiforme			
Slowing the Degenerative Process, Long Lasting Effect of Hyperbaric Oxygen Therapy in Retinitis Pigmentosa	not stated	Azienda Policlinico Umberto I	Completed
Effect of Body Mass Index on the Dose of Intrathecal Hyperbaric Bupivacaine for Elective Cesarean Section	dec/07	Samuel Lunenfeld Research Institute, Mount Sinai Hospital	Recruiting
Effect of Repeated Exposures to Compressed Air on Patients With AIDS	not stated	Designed Altobaric Non-Atmospheric Environmental Technology	Suspended
Can Erythopoietin Protect the Cerebral Blood Flow and Oxygenation During Simulated Dive?	jan/07	Rigshospitalet, Denmark	Recruiting
Effects of Mild Hypobaric Hypoxia on Sleep and Post-Sleep Performance	aug/07	Oklahoma State University Center for Health Sciences; The Boeing Company	Active, not recruiting
The Evaluation of OrCel for the Treatment of Venous Ulcers	not stated	Ortec International	Active, not recruiting
The Use of Pentoxifylline and Vitamin E in the Treatment of Late Radiation Related Injuries	not stated	University Health Network, Toronto; Princess Margaret Hospital, Canada	Recruiting
A Study of the Safety and Efficacy of a New Treatment for Diabetic Macular Edema	jun/14	Allergan	Recruiting
Trial to Assess Chelation Therapy (TACT)	jul/09	National Center for Complementary and Alternative Medicine (NCCAM); National Heart, Lung, and Blood Institute (NHLBI)	Recruiting

Source: NIH Clinical Trials database (www.clinicaltrials.gov)

For the evaluation of the effectiveness of HBOT for different indications we have chosen to use the most recent systematic reviews and HTAs available. Where available, we also include results from the more recent RCTs not yet included in those systematic reviews.

3.4 EVIDENCE FOR SPECIFIC INDICATIONS

The specific data sources used are listed in more detail and by indication in the appendix.

3.4.1 Carbon Monoxide (CO) intoxication

3.4.1.1 Short description of the condition

Carbon monoxide (CO) is a gas generated during incomplete combustion of carbon-based (fossil) fuels such as coal. It is a colourless and odourless gas and CO intoxication is an important source of accidental or intentional intoxication worldwide and has a high mortality rate. The affinity of CO to bind to haemoglobin (but also to intra- and extra-cellular haeme-containing proteins), is much greater than that of oxygen, forming carboxy-haemoglobin (COHb) thereby decreasing the ability of the oxygen-carrying capacity of blood in addition to other important pathophysiological mechanisms. Injuries caused by CO have been viewed as mainly due to hypoxic stress mediated through an elevated carboxy-haemoglobin level, but recent investigations have established that systemic oxidative stress can arise from exposure to CO and cause perivascular and neuronal reperfusion injury.[8] The two most vulnerable organs are the brain and the heart.

3.4.1.2 Summary of the evidence

This indication was accepted by the ECHM consensus conference as a type I recommendation supported by level B evidence (see Table 3 for definitions) in case of CO intoxicated patients presenting with unconsciousness at or before admission or with clinical neurological, cardiac, respiratory or psychological symptoms or signs, or in case of pregnancy (level C evidence only).[9] The indication of CO intoxication is also accepted by the UHMS, mainly based on in vitro studies, animal model studies and occasional observational case series.[8] The UHMS recognises, however, that additionally studies are required to clearly define benefits, optimal treatment indication, optimal pressure, timing and number of sessions (one or more).[8]

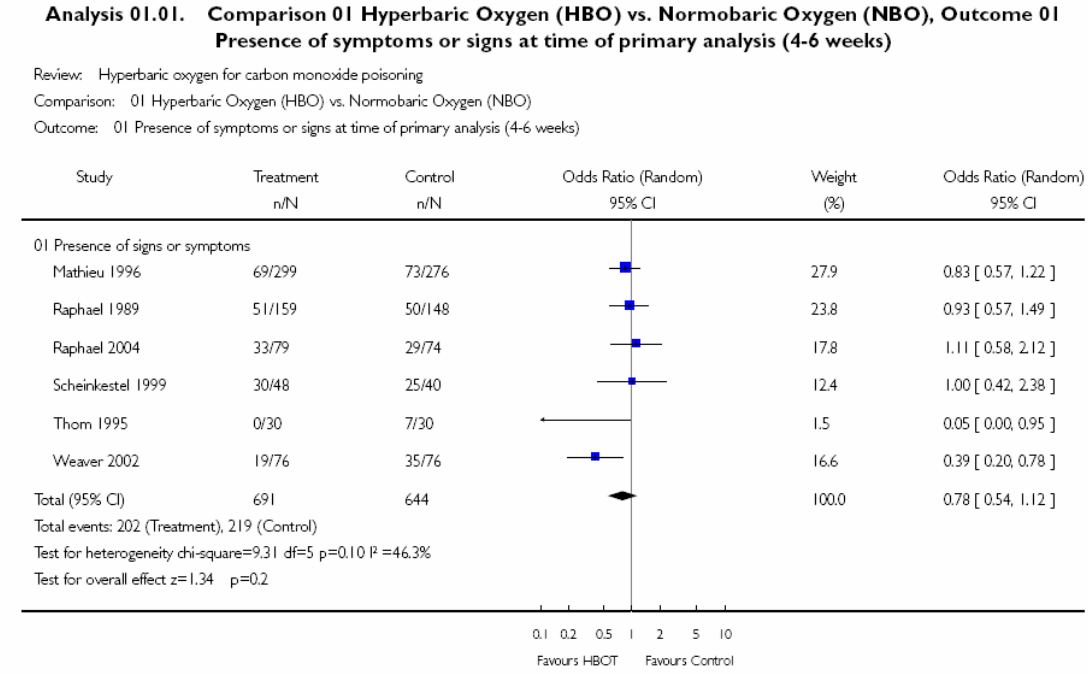
The condition of CO intoxication is sometimes mixed with cyanide poisoning in victims of smoke inhalation, exhibiting a synergistic toxicity. However, it is thought that one must be cautious with HBOT in this setting because the standard antidote for cyanide poisoning involves the formation of met-haemoglobin through the infusion of sodium nitrite. Those met-haemogolobin levels may be lowered by hyperoxia, possibly reducing the efficacy of the antidotal therapy.[8] Pure cyanide poisoning is infrequent but a few isolated reports suggested a potential benefit of HBOT in this condition.[8]

The administration of oxygen, either normobaric or hyperbaric, is considered as the corner stone of CO poisoning treatment, since it is assumed that oxygen will enhance dissociation of CO from haemoglobin and induce enhanced tissue oxygenation. The rationale for hyperbaric oxygenation therapy is that this rate of dissociation of CO from haemoglobin could be expected to be greater that with normobaric oxygenation therapy, and several historical and laboratory studies support this view.[8]

Neither for hyperbaric nor for normobaric oxygen therapy, RCTs evaluating the short-term effects on CO poisoning have been carried out. A few RCTs evaluated the effect of HBOT on long-term neurological sequels but presented conflicting results. A Cochrane review from 2005 by Juurlink et al.[24] summarised the evidence from six RCTs on the long-term neurological sequels of treatment of CO poisoning with HBOT. Four of those studies found no benefit of HBOT on the reduction of neurological sequels while two others did find a benefit (see Figure 2). All studies, however, had major flaws in either design or analysis, and where very heterogeneous both in hyperbaric treatment schemes and regarding comparative treatment. Some of the studies were criticised because treatment pressures were considered too low and therefore it is felt by some in the field that a meta-analysis combining those heterogeneous studies is inappropriate.

The authors of the Cochrane review concluded that existing RCTs did not show that HBOT in patients with carbon monoxide poisoning reduces the incidence of adverse neurological outcomes, but that additional research is needed to better define the role, if any, of HBOT in the treatment. A methodological problem is that there is never a baseline assessment available prior to exposure to CO thus limiting the assessment of symptoms after exposure and therapy. Ideally, randomisation should solve this problem but cannot be relied upon completely in those small studies.

Figure 2. Presence of symptoms or signs at 4-6 weeks, HBO vs. NBO



Source: Juurlink et al.[24]

Bennett's thesis does not deal with this condition explicitly,[1] and neither the AHRQ horizon scan published in 2006 nor an overview of Silver et al. did identify further studies.[14, 43] The IECS study from December 2006 comes to similar conclusions and identifies no more additional studies on this indication.[38] The HAS report published in 2007,[37] repeats these same arguments and concludes that the different opinions are largely caused by the absence of clear evidence and that acceptance of this indication is mainly based on expert opinion and consensus, rather than on direct evidence.

A recent RCT compared different HBOT schedules (different pressure and timing) but was too small (n=28) for definite conclusions and its main conclusion was that it is feasible to randomize CO-poisoned patients.[39]

3.4.2 Decompression accidents

3.4.2.1 Short description of the condition

Decompression sickness (DCS) was the very first indication for HBOT and arises from the generation of bubbles of gas in tissues or in blood during rapid decompression (either ascent from diving, flying or in a hyper- or hypobaric chamber). Those bubbles form when the speed of decompression is too fast for diffusion and perfusion to be able to reduce the partial pressure of the dissolved gas. Clinical manifestation includes pain in the joints, cutaneous eruptions or rashes, neurological dysfunction such as paralysis or loss of consciousness, cardiorespiratory symptoms and pulmonary oedema, shock and death.[8] These symptoms are thought to be caused by a combination of several pathophysiological mechanisms, such as mechanical disruption of the tissue, blood flow impairment, platelet disposition and coagulation activation, endothelial dysfunction etc.[1, 8]

3.4.2.2 Summary of the evidence

Recompression therapy (with air) has been used since 1896, and later on recompression with oxygen as an adjunct (HBOT) has become accepted standard practice although no formal RCTs has ever been conducted. Evidence of effectiveness for this indication is therefore mainly historical. Before it was used during the construction of the Hudson tunnel, the annual mortality from DCS among workers was 25%.

After the introduction of recompression therapy with air, symptoms dramatically improved. In combination with other improvements at the worksite mortality fell to less than 2% annually.[4] More recent studies in workers with caisson disease also show the high effectiveness of recompression therapy.[44]

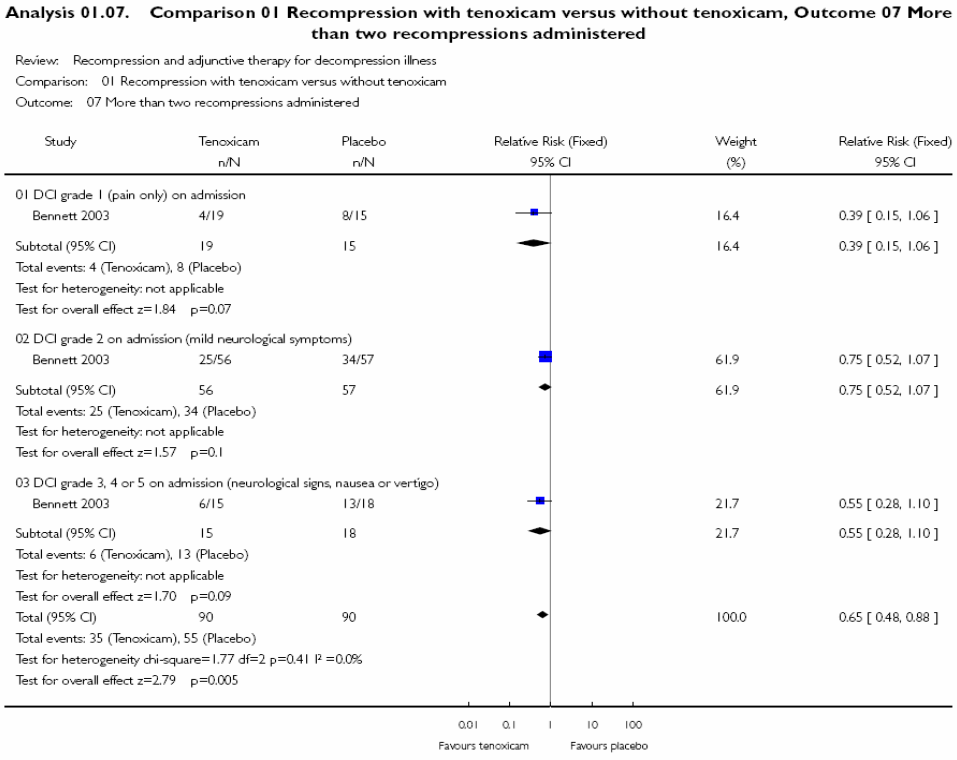
Therefore, most current recommendations and recent RCTs deal mainly with different therapy schedules and adjuvant therapies. Besides, specific guidelines for the prevention of DCS in divers, both professional and recreational, and in professionals working in hyperbaric conductions have been elaborated. Details of these are outside the scope of this report but can be found in the relevant publications.[1, 8, 9]

Several hyperbaric schedules have been described and tested, differing in pressure, time, frequency and number of sessions, and although there are no human RCTs available comparing HBOT to no HBOT it is generally agreed that early hyperbaric treatment is most likely to lead to complete recovery in mild or moderate DCS.[8] Conducting RCTs of HBOT versus a sham alternative is considered by many in the field as unethical, but they agree that there is definitely a need for rigorous RCTs to define optimal treatment schedules, adjuvant therapy and potentially the use of gas mixtures other than 100% oxygen.[45]

A Cochrane review by Bennett et al. from 2007 identified two RCTs.[20] It showed that the addition of an NSAID (Figure 3) may reduce the number or recompressions required due to adequate pain relief.

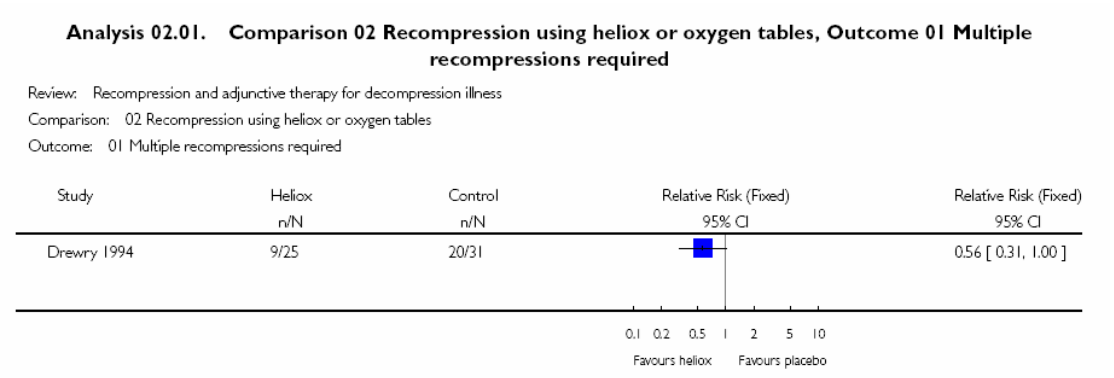
With the use of heliox, a helium/oxygen mixture (Figure 4) the difference was at the limit of statistical significance. Both alternatives did not improve recovery. Neither the HAS nor the IECS assessments added additional information on this indication.[37, 38]

Figure 3. More than two recompressions administered, tenoxicam vs. no tenoxicam



Source: Bennett et al.[20]

Figure 4. Multiple recompression required, heliox vs. oxygen



Source: Bennett et al.[20]

3.4.3 Gas embolism

3.4.3.1 Short description of the condition

Gas Embolism is a rare condition, defined as the presence of gas bubbles in the blood vessels, either arteries (Arterial Gas Embolism, AGE) or veins (Venous Gas Embolism, VGE). AGE has been described during submarine emergency escape training after free ascent after breathing compressed gas resulting from pulmonar barotrauma. It has also been described during normal ascent in divers with predisposing lung pathology or traumatically.[8] VGE occurs commonly after compressed gas diving, but normally the VGE gas bubbles are trapped in the capillaries of the lung without causing symptoms. When the amount of gas bubbles is large it may cause pulmonary symptoms or it may enter the arteries either through the lungs or directly from the right into the left heart in case of septal defects such as patent foramen ovale, a condition occurring in 30 to 40% of individuals.[46, 47] Other than through diving accidents and trauma, there may also be iatrogenic causes for gas embolism, such as accidental air injection, surgical accidents, hemodialysis and many other, more anecdotical conditions have been described. Clinical manifestations are variable and in general much more serious with AGE compared to VGE. In case of diving accidents gas embolism (AGE) is often difficult to distinguish from DCS.[1, 8]

3.4.3.2 Summary of the evidence

Since it often difficult to distinguish between DCS and AGE in diving accidents, the two disease entities are often described together as decompression illness (DCI). The rationale for HBOT in AGE is similar to the one for decompression illness, but again, evidence is mainly historical and anecdotic. For AGE, HBOT is recommended by the UHMS even after initial recovery. It is, however, not recommended for asymptomatic VGE.[8] The ECHM does not formally differentiate between AGE and VGE in their recommendations.[9]

No RCTs have been conducted for this indication comparing HBOT to no HBOT since it has become accepted standard practice based on historical and physiological grounds. However, RCTs might be feasible for those patients with AGE arriving at the hyperbaric unit after a longer delay.[8]

A Cochrane review from 2007, although formally dealing with both decompression sickness and gas embolism, did not give additional information on gas embolism since in the trial on the NSAIDs as adjuvant therapy (see part on decompression accidents) patients with definite AGE were excluded,[48] while the trial on heliox did not report specifically on this condition and it is unclear how many patients with AGE were included.[20] As AGE is a rare disease, this number was probably very limited: the HAS report estimates the yearly number of gas embolism cases in France to less than 90.[37] Neither the HAS nor the IECS assessments added additional information on this indication.[38]

3.4.4 Anaerobic or mixed anaerobic-aerobic bacterial infections

3.4.4.1 Short description of the condition

For the ECHM this indication comprises a mixed group of necrotizing soft tissue infection due to anaerobic or mixed bacterial infections but also selected cases of organ abscesses, including intracranial, pleuro-pulmonary and liver abscess. In the report from the UHMS Therapy Committee three separate indications are covered by this broad indication; Clostridial myositis and myonecrosis, intracranial abscess and necrotizing soft tissue infections.

Clostridial myositis with myonecrosis (gas gangrene) is an acute and quickly evolving emergency situation with an invasive infection of the muscles by the anaerobic, spore-forming Gram-positive rod, Clostridium bacteria, most commonly C. *perfringens*.

Gas gangrene can occur when Clostridial spores are present in tissue with a lowered oxygenation, allowing these anaerobics to grow. These tissues can have reduced oxygenation through important soft tissue damage or through locally failing oxygen supply. The clostridium bacteria produces several exotoxins that can cause extensive damage, both in surrounding healthy tissues causing the infection to spread rapidly,[8] and systemically. The condition can be fatal because the infection spreads so quickly.

The ECHM definition for selected cases of organ abscesses is relatively vague but mainly focuses on those abscesses where conventional therapy failed and where surgical risk is too high and/or the general condition of the patient too compromised. The UHMS specifically describes intracranial abscess (ICA) as an indication, including cerebral abscesses, subdural empyema and epidural empyema, all conditions with a high mortality rate.

A last part of the wide ECHM definition is covered by the UHMS as necrotizing soft tissue infections, resulting form a single or a mixed population of organisms, both aerobic and/or anaerobic, and appearing in various clinical settings especially after trauma, in surgical wounds or around foreign bodies in susceptible hosts.

3.4.4.2 Summary of the evidence

In all of these indications, HBOT is recommended as part of the therapy in addition, obviously, of antibiotics, surgery and supportive therapy.[8, 9] Again, as in most other indications for HBOT, solid results from RCTs are lacking and evidence for therapy is mainly based on belief and pathophysiological reasoning; anaerobic organisms do not like oxygen.

The postulated mechanism of action of HBOT against anaerobic organisms is the formation of free oxygen radicals in the relative absence of free radical degrading enzymes which was shown to have a bacteriostatic effect and in animal models an increased survival was observed.[8] Because of the rapidity of gas gangrene evolution it is recommended to start therapy as soon as the condition is recognised. In humans, clinical observational studies concluded that lowest mortality and morbidity was achieved with initial conservative surgery and rapid initiation of HBOT.[8] Historical studies conducted many decades ago showed that most patients on HBOT who died did so within 24 hours after initiation of therapy, while after 3 HBOT sessions no mortality was registered,[8] hinting to possible confounding by indication.

For ICA there have been several observational case series suggesting a better prognosis with HBOT, but again, confounding by indication is difficult to avoid in these observational settings. Also for other necrotizing soft tissue infections it is assumed that hypoxia is always present and that therefore HBOT could be relevant.

However, and similar as for other indications the carrying out of RCTs for this indication is considered unethical by those closely involved based on available historical but inconsistent data,[49] and on the fact that this has become accepted practice.[8] Therefore, no Cochrane reviews are available to support or refute this practice for those indications. Again, we are dealing here with a condition which was estimated by HAS to affect 250 patients in France annually.[37]

Both the HAS and the IECS assessments conclude that no RCTs are available for this indication and that observational studies are indeed of poor quality.[38]

3.4.5 Acute soft tissue ischemia

3.4.5.1 Short description of the condition

In this grouping of the ECHM several indications are combined, going from major trauma leading to crush injuries with open fractures, reperfusion problems following invasive vascular procedures, compromised skin grafts and myo-cutaneous flaps, or re-implantation of traumatically amputated limb segments.

However, some extend this definition to closed soft tissue injury, even that occurring after unaccustomed exercise,[30] but we limit this assessment to the serious pathology. The UHMS includes in its recommendation the crush injuries, compartment syndrome and other acute tissue ischemia and also the compromised skin grafts and flaps.

The rationale for using HBOT in those conditions is that it is suppose to supplement oxygen availability to hypoxic and threatened tissues during the early post-injury period, and that it is also supposed to increase tissue oxygen tension to levels which make it possible for the host responses to function.[8]

3.4.5.2 Summary of the evidence

The ECHM recommends (type 1, level B) HBOT as adjuvant therapy in post-traumatic crush injuries with open fractures, Gustilo type III B and C (corresponding to high energy wounds greater than 1 cm with extensive soft tissue damage and inadequate soft tissue cover or associated with arterial injury). They also recommend it for compromised skin grafts and myo-cutaneous flaps (type 2, level C), while they consider it optional in case of reperfusion syndromes following invasive vascular procedures or after the re-implantation of traumatically amputated limb segments (both type 3, level C recommendations). Those indications are also present in the UHMS guidelines, including compartment syndromes, but with slightly different recommendations. In practice, however, much liberty is leaved to the individual appreciation of the treating physician. Both organisations recommend the measurement of transcutaneous oxygen pressure as an index to define indications and evolution of treatment (ECHM type 1, level B recommendation).

The evidence for HBOT in these indications is mainly derived from animal studies (especially for the skin grafts and flaps) and human observational case series and was also reported in narrative reviews of those studies.[8]

A small RCT, however, published in 1996 randomised 36 consecutive patients with crush injuries (Gustillo type II or III), able to give informed consent and without contraindications to HBOT, to standard therapy either with or without adjuvant HBOT including the measurement of transcutaneous oxygen pressure.[50] In the HBOT group, 17 out of 18 patients obtained complete healing compared to 10 out of 18 in the placebo group, while new surgical procedures were performed on one patient in the HBO group vs. six in the placebo group. The authors conclude that HBOT is a useful adjunct in the management of crush injuries, and although reaching statistical significance, this trial is obviously too small for far reaching conclusions and the detailed guidelines are evidently very much based on consensus within the expert committees. Also for compromised skin flaps limited and small studies were reported, both small RCTs[51] and small uncontrolled comparative studies,[52] indicating improved healing. Again, the smallness of those RCTs and the high possibility of publication bias towards positive results make it difficult to draw solid evidence based conclusions. But, in the eyes of many hyperbaric physicians *'each flap is unique'*,[8] and randomised trials are therefore unlikely to be performed in the near future.

Both the HAS and the IECS assessments come to similar conclusions as to the availability of evidence.[37, 38]

3.4.6 Post-radiotherapy tissue damage (soft tissue and bones)

3.4.6.1 Short description of the condition

Cancer is a frequently occurring disease and often radiotherapy is part of the treatment. While this has lead to an improved survival, the injuries caused by (therapeutical) ionising irradiation can be severe. They are generally subdivided into acute, sub-acute or delayed reactions.[8, 53] The acute lesions are usually self-limited and should be treated symptomatically. Sub-acute lesions more frequently are located in specific organ systems such as lung, colon, specific bones, larynx, etc., depending on the irradiation site. These, again, usually heal but they can also become chronic. Delayed radiation complications only become apparent after several months, sometimes due to an additional external cause such as surgery.[8] Radiation lesions are typically associated with endarteritis, tissue hypoxia and secondary fibrosis.

3.4.6.2 Summary of the evidence

HBOT has been used as adjuvant therapy to treat chronic radiation-induced lesions since a long time and is approved in varying indications by ECHM and UHMS.[8, 9] Most original publications dealt specifically with radionecrosis of the mandible, but HBOT has subsequently been used and tested at other sites, such as for resistant post-radiotherapy cystitis, and preventive before planned tooth extractions in irradiated tissues (those 3 indications form the type I recommendations from ECHM supported by level B evidence).

Other organ systems mentioned and investigated are post-radiotherapy lesions of the larynx, of the central nervous system, the colon (proctitis/enteritis), post-radiotherapy lesions of soft tissues in head and neck and of other soft tissues, radionecrosis of bones other than the mandible, and preventive before surgery or implants in previously irradiated tissues.

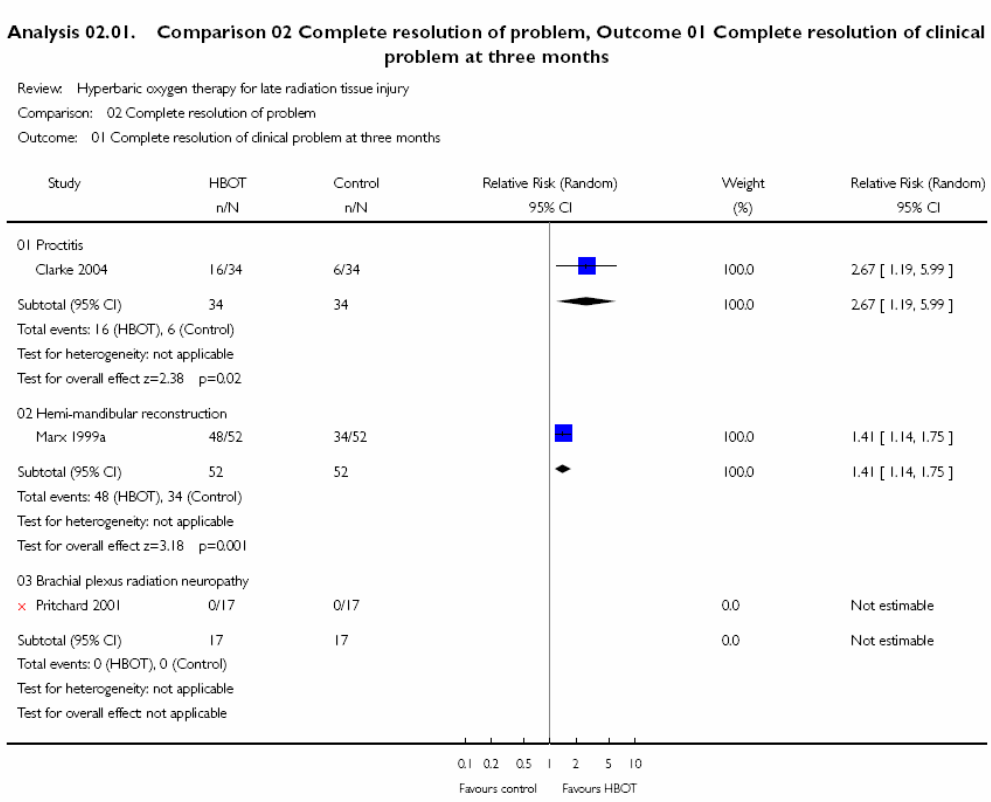
Guidelines differ in their approach of post-radiotherapy tissue damage and again much liberty is given to the treating physician.

Studies in animal models, but also physiological tests in humans through transcutaneous oxygen measurements have shown improvements of vascular density and resultant tissue oxygen content through HBOT.[8] while clinical evidence is often collected by location or organ system.

A series of small RCTs have been conducted and three Cochrane reviews have dealt with this series of indications. The most recent from 2005 described HBOT for late radiation tissue injury in general and included six small RCTs with in total 447 participants.[27] However, therapeutic outcomes where often incomparable between studies and heterogeneity was large. An older review from 2002 dealt with all non-surgical interventions for late radiation proctitis including six studies but none comparing HBOT with alternative treatment.[35] The last one, also from 2002, specifically looked for HBOT in irradiated patients requiring dental implants but found no valid RCTs.[36]

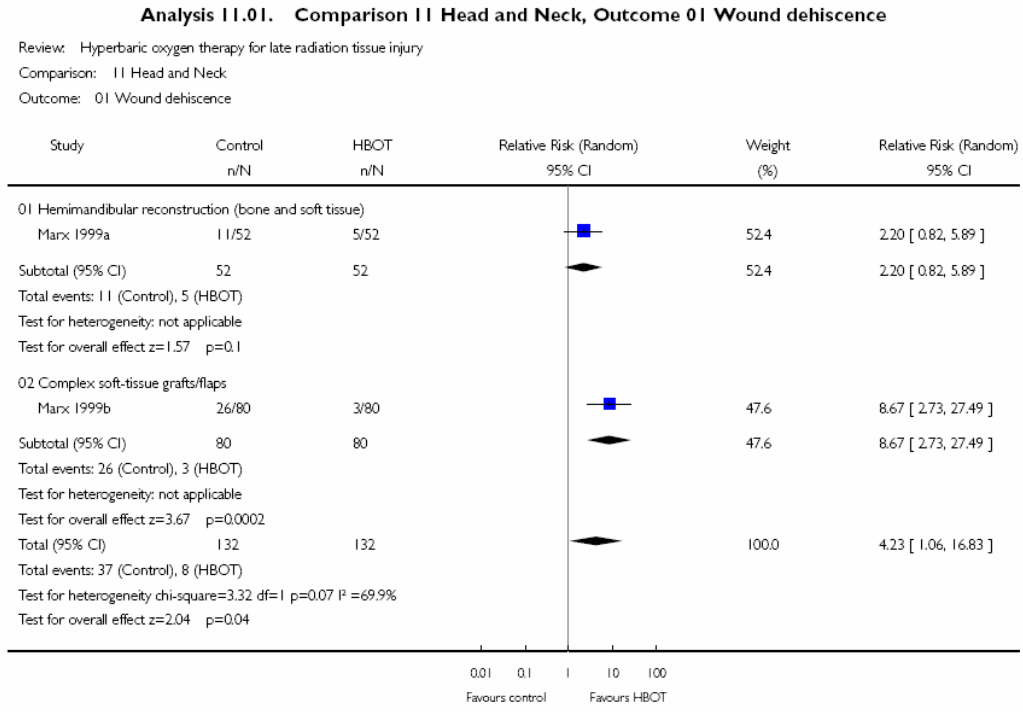
The Cochrane review from 2005,[27] however, suggests that patients with late radiation tissue injury at head, neck, and lower end of the bowel may have improved outcomes with HBOT. Moreover, the authors conclude that HBOT appeared to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field. Evidence did not show important clinical effect on neurological tissues, while for other tissues than those in the locations mentioned above no evidence was found. The main conclusion is that, although HBOT to selected patients and tissues may be justified, further research is required to clearly establish effectiveness. Figure 5 to Figure 9 show some selected forest plots from this review.

Figure 5. Complete resolution of clinical problem at three months



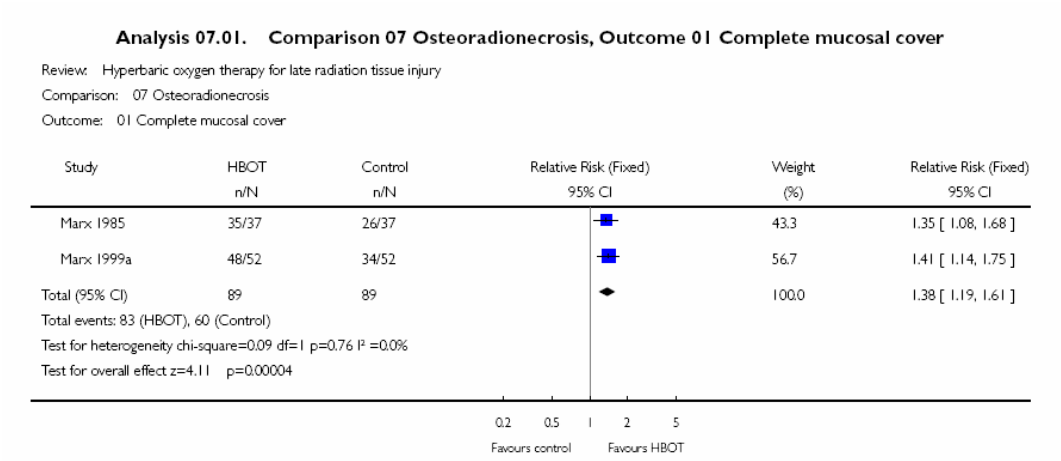
Source: Bennett et al.[27]

Figure 6. Head and Neck: Wound dehiscence



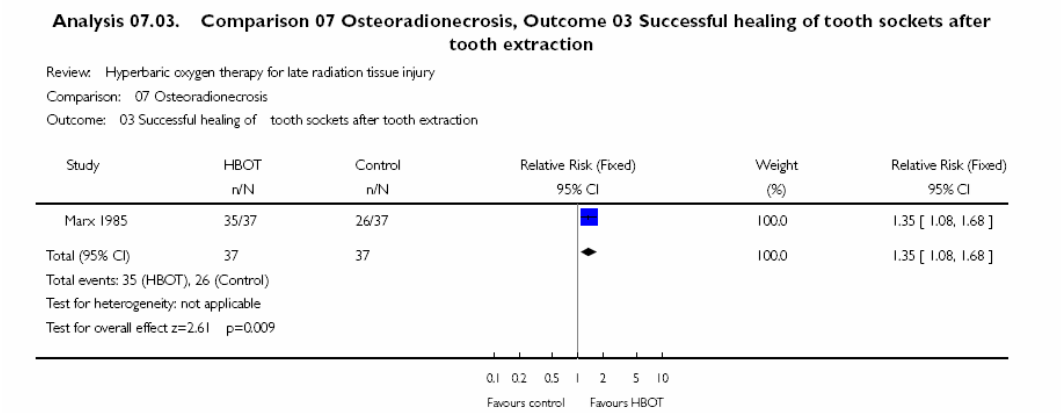
Source: Bennett et al.[27]

Figure 7. Osteoradionecrosis: Complete mucosal cover



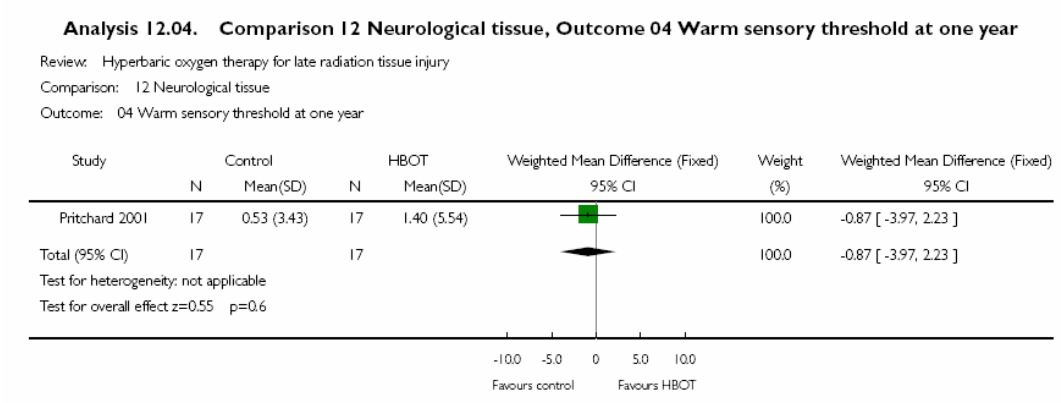
Source: Bennett et al.[27]

Figure 8. Osteoradionecrosis: Successful healing of tooth sockets after tooth extraction



Source: Bennett et al.[27]

Figure 9. Neurological tissue: Warm sensory threshold at one year



Source: Bennett et al.[27]

The HAS and the IECS assessments,[37, 38] and also the MSAC 2003 report come to similar conclusions as to the availability of evidence.[54] In a letter to the editor,[17] it was reported that a final self-assessment questionnaire administered to participants of one of the studies included in the Cochrane review found that also after 6-7 years no treatment effects seem to have been missed.[55]

Within the COST B14 program (see before), a European RCT for adjunctive HBOT in osteo-integration in irradiated patients to prevent implant failures (study co-ordinator: C. Granstrom, Stockholm, Sweden) is reported to have started in October 2001, and another one on the role of HBOT in the treatment of late irradiation sequelae in the pelvic region (study co-ordinator: A. Van der Kleij, Amsterdam, The Netherlands) was reported to be in preparation in 2005.[42] However, no results have been found.

3.4.7 Delayed wound healing

3.4.7.1 Short description of the condition

Problems wounds are a significant problem and are common in an ageing population. The most common are lower extremity ulcers, comprising venous ulcers, pressure ulcers and diabetic ulcers. In the US, foot ulcers in patients with diabetes are reported to contribute to over half of lower extremity amputations in a group at risk representing only 3% of the population.[8] Normal wound healing is normally a sequence of contamination and infection control, the resolution of inflammation and the regeneration of tissue. This normal wound healing process requires oxygen. Delayed wound healing and chronic wounds occur when this normal process is disturbed, and the healing rate of wounds has been shown to be oxygen dependent, by measurement of local oxygen tension in the vicinity of the wound.[8] Although wounds are, by nature, hypoxic the oxygen tensions from surrounding tissue is normally adequate to support normal healing of wounds.

3.4.7.2 Summary of the evidence

Delayed wound healing in selected indications are accepted as indication for HBOT by both ECHM as UHMS. Those indications are mainly in diabetic patients with reduced peripheral perfusion, but also in arteriosclerotic patients in case of chronic critical ischemia (defined as periodical pain persistent at rest and needing regular analgesic treatment for more than two weeks, or ulceration or gangrene of foot and toes with low ankle systolic pressure).[8, 9] Those two indications are for the ECHM type 2, level B recommendations.[9] In addition HBOT is accepted for selected non-healing wounds caused by inflammatory processes (ECHM type 3, level C recommendation).[9] Both organisations stress the importance of transcutaneous oxygen pressure measurements ($PtcO_2$) under hyperbaric conditions, since they provide a direct and quantitative assessment of the availability of oxygen around the wound.[8] Moreover, it can be used to assess the progression of wound healing after a series of HBOT treatments.

There is abundant laboratory, animal study and physiological evidence to support the claims for HBOT to be effective in supporting wound healing. Clinical evidence is also available, mainly for the indication diabetic foot. The pathophysiology of diabetic foot ulceration involves a progressive neuropathy, leading to the deficiency of protective sensation and alterations in blood flow to the skin. In addition, diabetic patients have a greater tendency to develop peripheral artery disease.[8] Added to this the impaired immune response to infection, all these elements lead to ulceration problems that can lead to chronic wounds and eventually amputations.

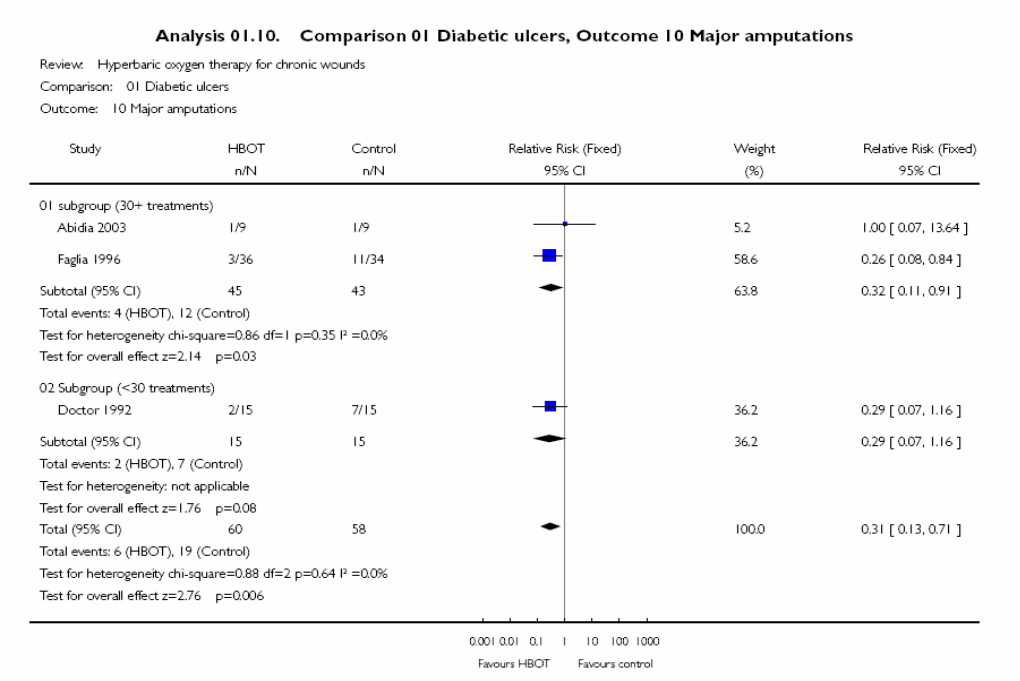
A Cochrane review from 2004 assessed the evidence for HBOT in chronic wounds.[32] This review pooled results from five trials.

Four out of these were devoted to diabetic foot ulcers (with 147 patients in total). The authors calculated that the number needed to treat (NNT) with adjuvant HBOT to prevent one major amputation in the short term would be four. However, two of those trials were not blinded, leaving opportunity for biased decision making in supporting therapeutic decisions and assessments, while only one of the blinded trials report the outcome major amputation. This blinded but very small trial (n=18) showed no effect of adjunctive HBOT on major amputations (see Figure 11).

No direct effect on minor amputations was found (see Figure 12), but it can be anticipated that the avoidance of major amputations results in an increase of minor amputations, indicating treatment success.

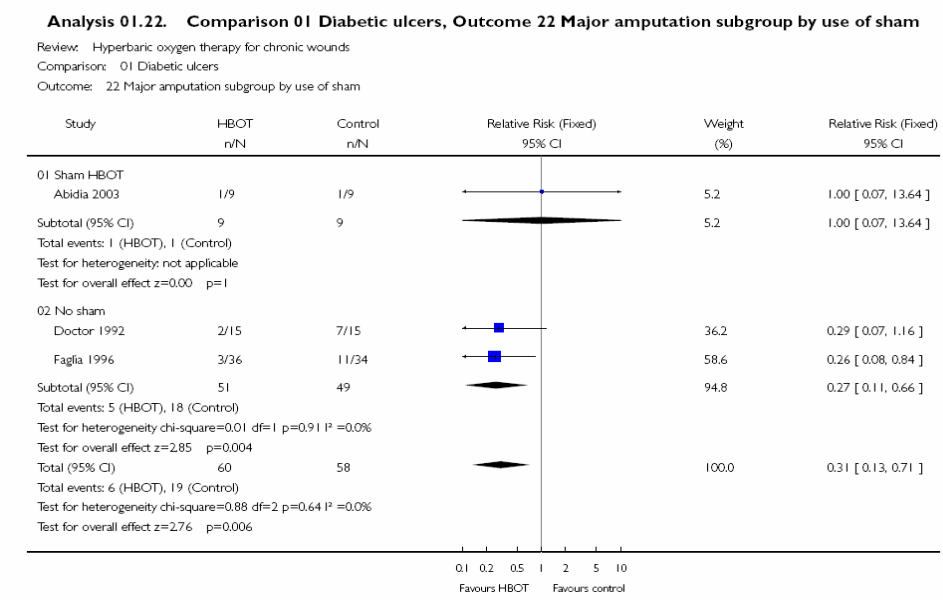
One small trial (n=16) concerned venous ulcers and only suggested a significant benefit of HBOT at six weeks (reduction in ulcer size). For arterial and pressure ulcers not satisfactory trials were identified in this review. The authors, however, express cautious interpretation of these results in view of the small number of patients included in those trials. Forest plots illustrating these findings are shown in Figure 10 to Figure 13.

Figure 10. Diabetic ulcers: Major amputations



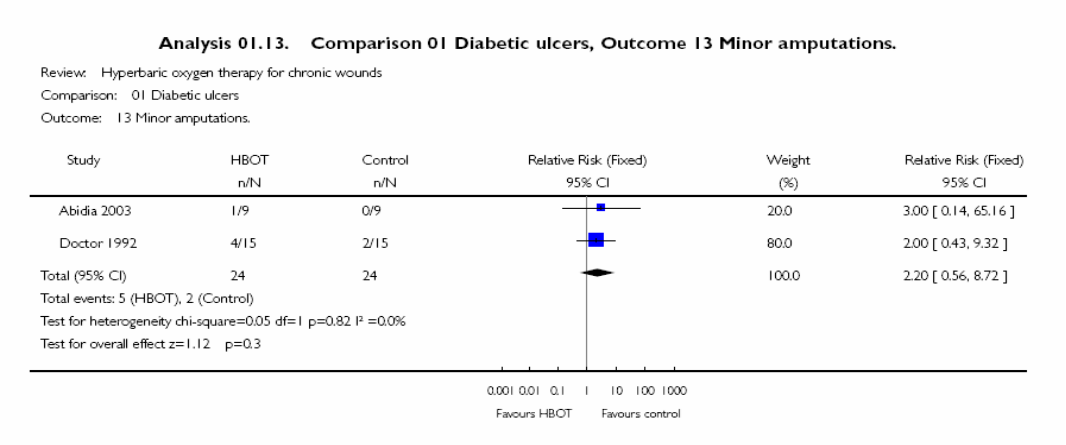
Source: Kranke et al.[32]

Figure 11. Diabetic ulcers: Major amputations subgroups by use of sham



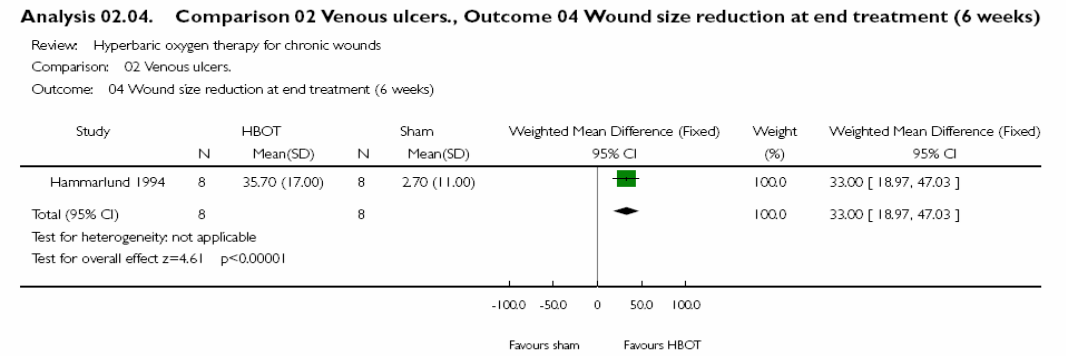
Source: Kranke et al.[32]

Figure 12. Diabetic ulcers: Minor amputations



Source: Kranke et al.[32]

Figure 13. Venous ulcers: Wound size reduction at end treatment (six weeks). Favourable result is indicated by increased relative risk since the outcome is wound size reduction.



Source: Kranke et al.[32] The labeling of the X-axis was adapted by us since a typing error inversed the labels in the original report.

A HTA conducted by the Canadian Medical Advisory Secretariat (Toronto) in 2005 evaluated the same studies and came to similar conclusions, mainly that the studies are too small and that new and well-conducted RCTs are likely to change these estimates.[56, 57] The HAS and the IECS assessments,[37, 38] and also the MSAC 2003 report come to similar conclusions as to the availability of evidence.[54] In 2006, Löndahl et al. described the design of a single centre RCT to investigate efficacy of HBOT in Sweden that will include 100 patients with diabetic foot ulcers.[18] A narrative review from Räkel et al. for the Canadian Diabetes Association about diabetic foot also summarized many of the findings.[58]

Within the COST B14 program (see before), a European RCT for HBOT in the treatment of foot lesions in diabetic patients (study co-ordinator: D. Mathieu, Lille, France) has started in May 2002. In 2005 it was reported that 10 centres were participating and that 56 patients had been included.[42] However, no results have been found.

3.4.8 Chronic refractory osteomyelitis

3.4.8.1 Short description of the condition

Chronic refractory osteomyelitis is a bone infection that does not heal or that recurs after appropriate therapy. Often this occurs in patients with coexisting local or systemic predisposing conditions that compromise their reaction to infection.[8]

3.4.8.2 Summary of the evidence

HBOT as adjuvant therapy (next to antibiotics, nutritional support and surgical intervention) has been advocated since the nineteen sixties. In there guidelines, the ECHM supports this indication as a type 2, level C recommendation.[9] Most evidence, however, comes from in vitro and in vivo animal studies.[8] Clinical studies are limited to a few retrospective and uncontrolled case studies with conflicting results.[8] No Cochrane reviews are available for this indication and neither the HAS nor the IECS report found additional evidence.[37, 38] The evidence for this indication is mainly consensual.

3.4.9 Post-anoxic encephalopathy

3.4.9.1 Short description of the condition

Post-anoxic encephalopathy is an acquired condition where the brain has been damaged through a prolonged period of inadequate oxygen supply. This may be due to various conditions, such as shock, cardiac arrest etc.

3.4.9.2 Summary of the evidence

HBOT is considered optional in the ECHM guidelines (type 3, level C recommendation) and is not mentioned in the UHMS guidelines.[8, 9] Evidence is mainly anecdotic. No Cochrane reviews are available for this indication, but a review of 20 Chinese trials, all of poor quality, did find a significant benefit in the use of HBOT in neonatal hypoxic ischemic encephalopathy with an odds ratio of 0.26 for mortality and 0.41 for neurological sequels.[59] Neither the HAS nor the IECS report found additional evidence.[37, 38] The evidence for this indication is mainly consensual.

3.4.10 Thermal burns

3.4.10.1 Short description of the condition

Severe burns are a very serious condition and cause important physical and psychological injuries and are often life threatening. The burn injury itself, and its healing process involve rather complex processes with local and systemic consequences, including coagulation, haematological changes, inflammatory reactions, and a high risk for infection due to a loss of protective skin barrier, an ideal substrate in the burn wound itself and a compromised immune system.[8]

3.4.10.2 Summary of the evidence

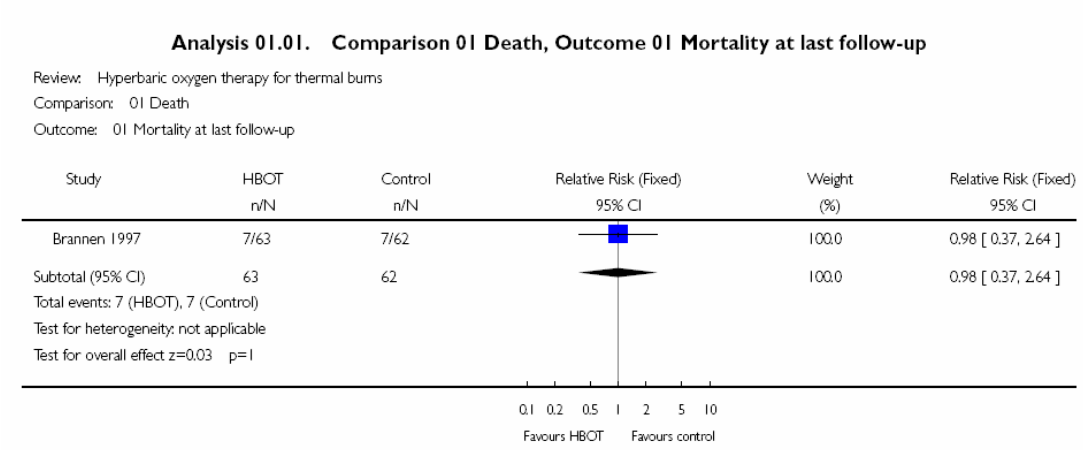
Severe burns (defined as second degree or higher, and over more than 20% of the body surface) are accepted indications for HBOT as adjuvant therapy by both the ECHM (type 3, level C recommendation) and the UHMS, also in the absence of concomitant exposure to CO or smoke. Since the nineteen sixties HBOT has been used and evidence was mainly base on pathophysiological reasoning and laboratory work in vitro and on animal models. Clinical experience mainly originated from uncontrolled case series but also on some early but small RCTs.[8]

A Cochrane review from 2004 identified five RCTs, and two of those fulfilled inclusion criteria.[31] All trials in this review, however, were considered of poor methodological quality and heterogeneous in patients and outcomes.

One trial reported no difference in mortality, need for surgery or length of stay between control and HBOT groups when adjusted for patients' condition.

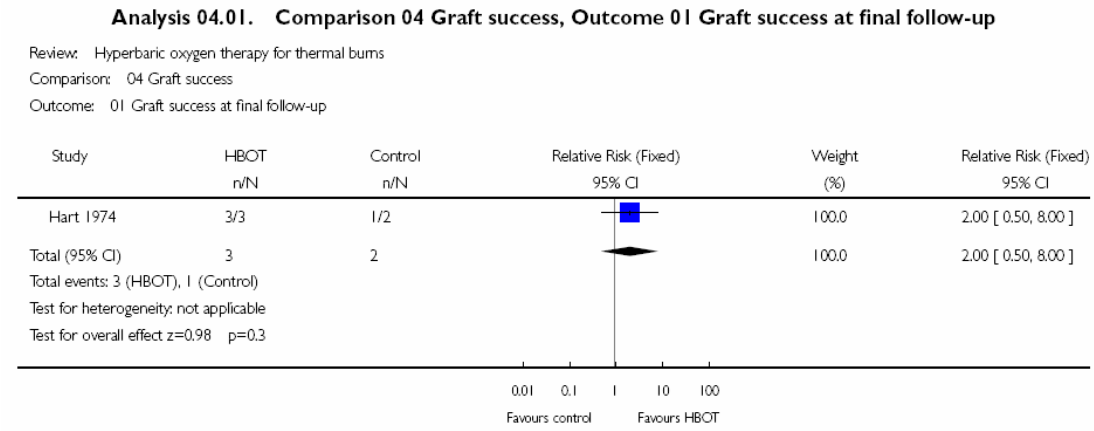
The second trial reported shorter average healing times for patients exposed to HBOT. In general, the authors conclude that little evidence supports the effectiveness of HBOT in the management of thermal burns (see Figure 14 and Figure 15). The HAS and the IECS assessments come to similar conclusions about the absence of evidence,[37, 38] as does the review from Saunders et al.[60] and the horizon scan from AHRQ.[14]

Figure 14. Death at last follow-up



Source: Villanueva et al.[31]

Figure 15. Graft success



Source: Villanueva et al.[31]

3.4.11 Hearing disorders

3.4.11.1 Short description of the condition

Idiopathic sudden sensorineural hearing loss (ISSHL) is rather common and is obviously an important health problem that significantly affects quality of life. It is an acute hearing disorder with an incidence of about 1/10 000 person-years.[21] ISSHL is defined as a hearing loss greater than 30 dB in 3 consecutive audiometric frequencies over 72 hours or less. Aetiology is generally unclear but because of its rapid onset a vascular cause has been suspected, although other pathology can also be involved. Therefore, treatment for ISSHL is generally designed to improve blood circulation and oxygenation of the inner ear. There is, however, a high rate of spontaneous recovery, adding to the complexity of assessing treatment.[21]

3.4.11.2 Summary of the evidence

Sudden deafness is an accepted indication and recommended by EHCM (type 2, level C recommendation) but is not an accepted indication for UHMS. The rationale of HBOT is mainly based on the supposed aetiology of the disease, involving hypoxic events in the cochlear apparatus. HBOT may therefore be able to reverse this hypoxia.[1] It has been used since the nineteen sixties for this indication with conflicting results.

A Cochrane review from 2007 assessed the available evidence from six RCTs.[21] It concluded that for people with early presentation of ISSHL, the application of HBOT significantly improved hearing loss assessed through audiometry at the 25% improvement level (not at the 50% level), as shown in Figure 16 and Figure 17. The average improvement in PTA as proportion of baseline was significantly better in the HBOT group (Figure 18). The clinical significance of the level of improvement remains unclear (Figure 19). There is no evidence of a beneficial effect of HBOT on chronic presentation of ISSHL (Figure 20). However, RCTs currently available are too small, present too many methodological shortcomings and are too poorly reported to draw solid conclusions.

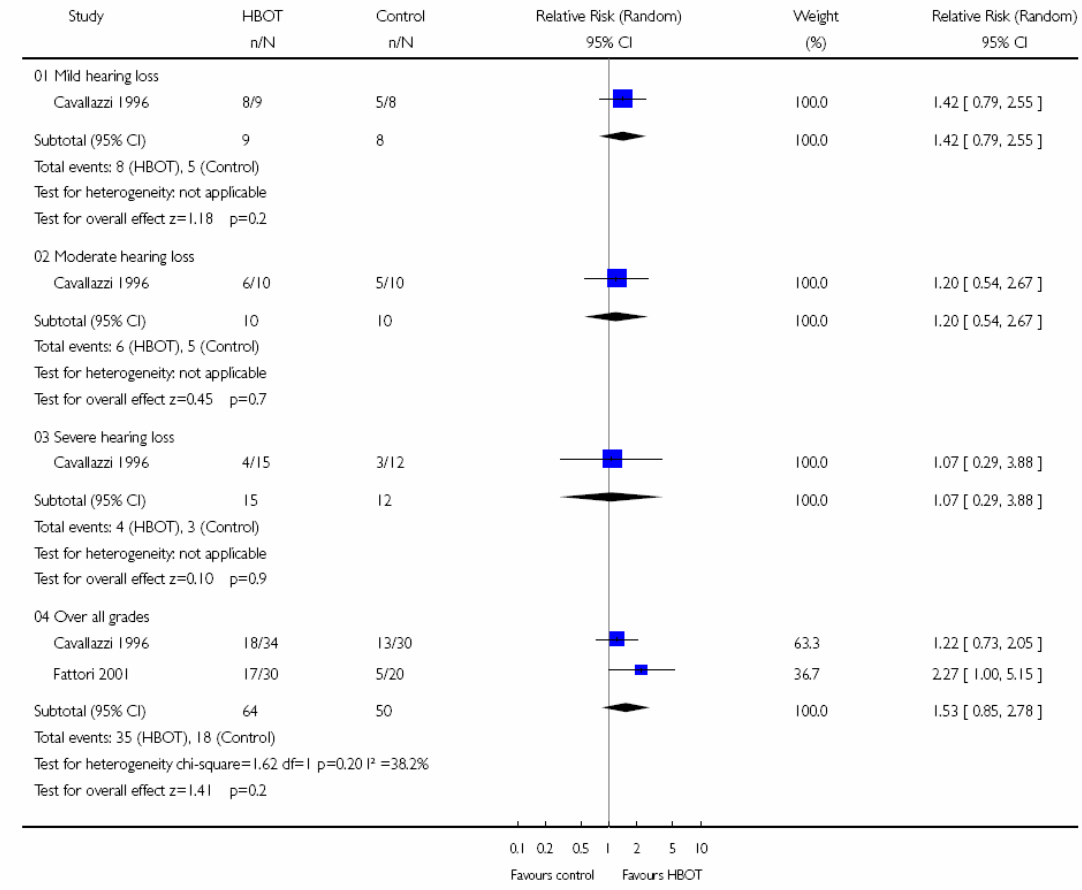
Figure 16. Acute presentation of ISSHL: greater than 50% return of hearing as measured by audiometry

Analysis 01.01. Comparison 01 Acute presentation. Recovery of hearing as measured by audiometry, Outcome 01 Greater than 50% return of hearing

Review: Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus

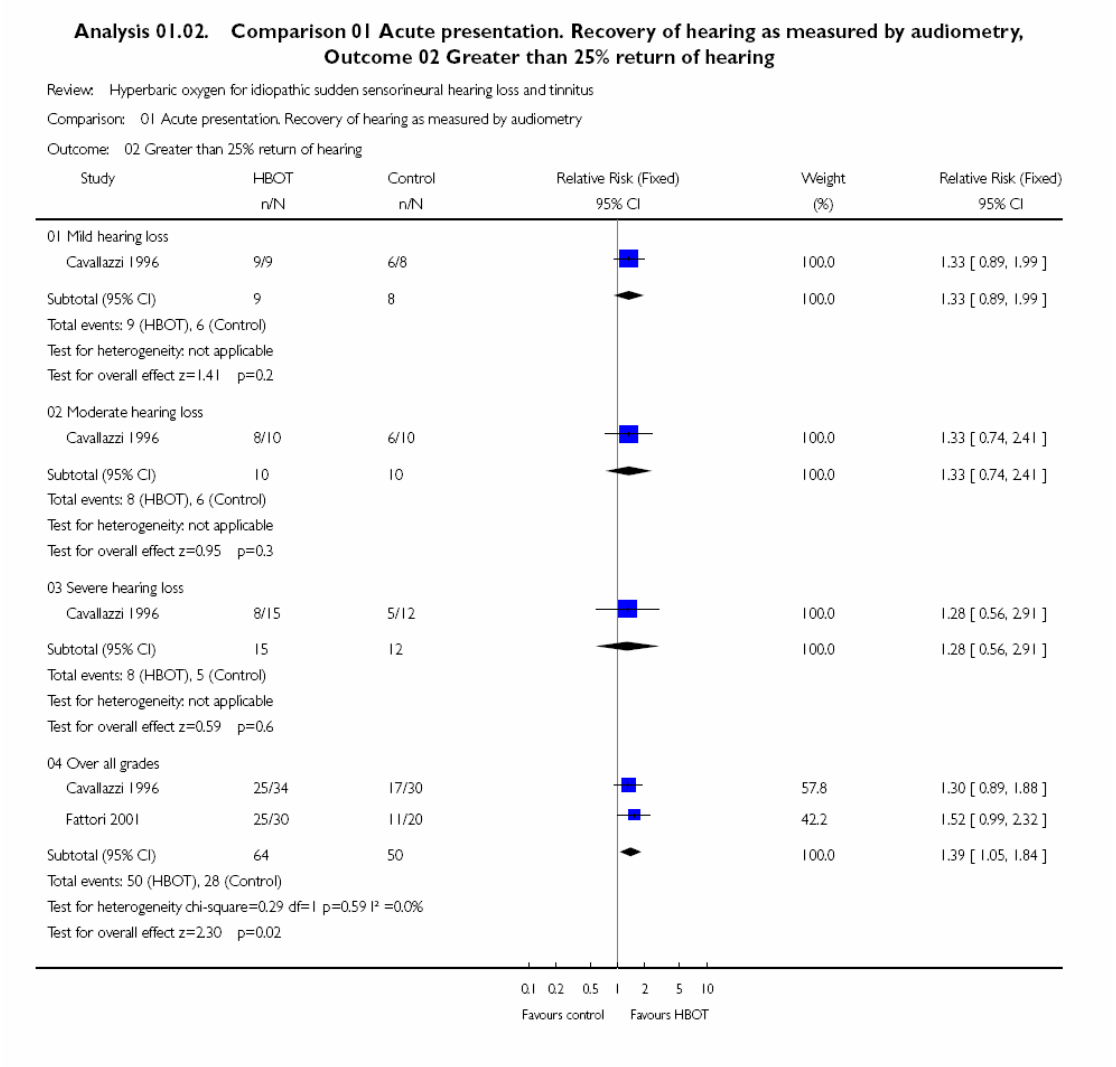
Comparison: 01 Acute presentation. Recovery of hearing as measured by audiometry

Outcome: 01 Greater than 50% return of hearing



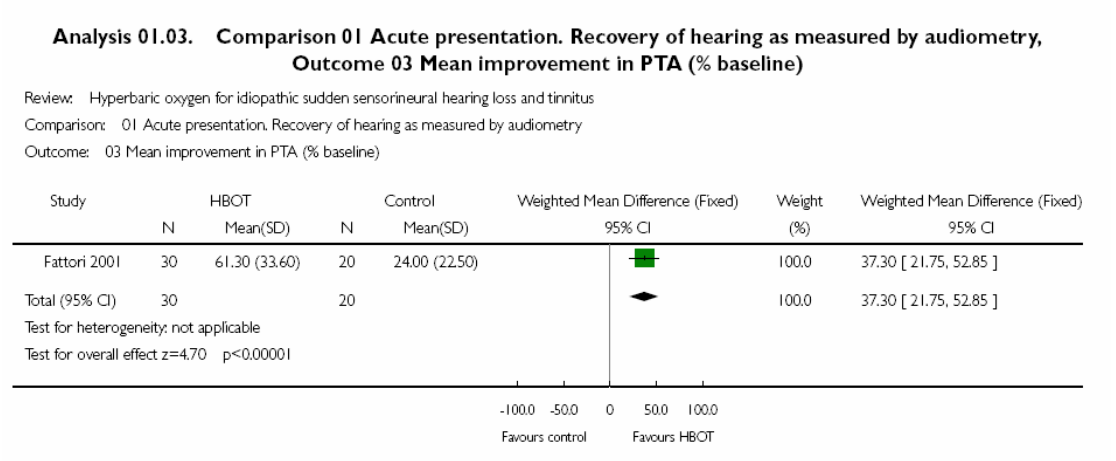
Source: Bennett et al.[21]

Figure 17. Acute presentation of ISSHL: greater than 25% return of hearing as measured by audiometry



Source: Bennett et al.[21]

Figure 18. Acute presentation of ISSHL: mean improvement in PTA as measured by audiometry (% of baseline)



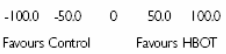
Source: Bennett et al.[21]

Figure 19. Acute presentation of ISSHL: Mean hearing improvement over all frequencies (dB)

Analysis 01.05. Comparison 01 Acute presentation. Recovery of hearing as measured by audiometry, Outcome 05 Mean hearing improvement over all frequencies (dB)

Review: Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus
Comparison: 01 Acute presentation. Recovery of hearing as measured by audiometry
Outcome: 05 Mean hearing improvement over all frequencies (dB)

Study	HBOT N	HBOT Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Mild hearing loss							
Topuz 2004	13	22.53 (12.68)	6	22.33 (9.31)		35.0	0.20 [-9.95, 10.35]
Subtotal (95% CI)	13		6			35.0	0.20 [-9.95, 10.35]
Test for heterogeneity: not applicable							
Test for overall effect z=0.04 p=1							
02 Moderate hearing loss							
Topuz 2004	11	35.45 (22.09)	11	16.18 (9.00)		32.7	19.27 [5.17, 33.37]
Subtotal (95% CI)	11		11			32.7	19.27 [5.17, 33.37]
Test for heterogeneity: not applicable							
Test for overall effect z=2.68 p=0.007							
03 Severe hearing loss							
Topuz 2004	10	50.70 (21.54)	4	13.00 (6.58)		32.3	37.70 [22.87, 52.53]
Subtotal (95% CI)	10		4			32.3	37.70 [22.87, 52.53]
Test for heterogeneity: not applicable							
Test for overall effect z=4.98 p<0.00001							
04 Over all grades							
x Hoffmann 1995b	10	7.50 (0.00)	10	-0.70 (0.00)		0.0	Not estimable
x Schwab 1998	24	15.60 (0.00)	33	10.70 (0.00)		0.0	Not estimable
Subtotal (95% CI)	34		43			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	68		64			100.0	18.55 [-3.50, 40.59]
Test for heterogeneity chi-square=17.46 df=2 p=0.0002 I² =88.5%							
Test for overall effect z=1.65 p=0.1							



Source: Bennett et al.[21]

Figure 20. Chronic presentation of ISSHL: some improvement, all grades as measured by audiometry

Analysis 02.01. Comparison 02 Chronic presentation. Recovery of hearing as measured by audiometry., Outcome 01 Some improvement, all grades

Review: Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus
Comparison: 02 Chronic presentation. Recovery of hearing as measured by audiometry.
Outcome: 01 Some improvement, all grades

Study	HBOT n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Hoffmann 1995	7/22	11/22		100.0	0.64 [0.30, 1.33]
Total (95% CI)	22	22		100.0	0.64 [0.30, 1.33]
Total events: 7 (HBOT), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.20 p=0.2					

Source: Bennett et al.[21]

The HAS,[37] the IECS,[38] and the AHRQ assessments come to similar conclusions.[14] Within the COST B14 program (see before), a European RCT for HBOT in the acute treatment of sudden idiopathic sensorineural hearing loss (study co-ordinator: A. Barthelemy, Marseille, France) is reported to have started in September 2002 with seven centres participating and 56 patients have been included (information from 2005).[42] However, no results have been found.

3.4.12 Acute ophthalmological ischemia

3.4.12.1 Short description of the condition

Central retinal artery occlusion can result in a sudden interruption of the blood supply to the retina, causing unilateral loss of vision. This is a rare disease usually occurring between ages 50 to 80, with sudden, painless, a unilateral visual field defects, sometimes preceded by transient episodes of vision loss (amaurosis fugax).[61] This disease is most often cased by embolism of the retinal artery. Visual prognosis is poor and attempted treatment is based on medical treatment trying to improve perfusion of the retina.

3.4.12.2 Summary of the evidence

The ECHM considers HBOT optional in acute ophtalmological ischemia (type 3, level C recommendation).[9] The indication is not mentioned in the UHMS guidelines.[8] The HAS report takes over the ECHM recommendation,[37] while the IECS report refers to an uncontrolled pilot trial with 21 patients in Germany from Weinberger et al., but without solid conclusions.[38, 62] A STEER report from 2002 found only two retrospective comparisons of case series, one with 16 patients (eight with HBOT but without randomisation) and a second with 35 patients treated with HBOT compared to 37 patients treated in a centre where no HBOT was available. The report concludes that no reliable evidence about the benefits of HOBT could be found in people with acute retinal ischemia. Again, it is concluded that RCTs are feasible and should be carried out.

3.4.13 Neuroblastoma stage IV

3.4.13.1 Short description of the condition

Neuroblastoma is a cancer that arises in immature nerve cells and affects mostly infants and children. Stage 4 is a primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs.[63]

3.4.13.2 Summary of the evidence

According to the ECHM, adjuvant HBOT for this indication should be considered although no RCTs are available to support this.[9] The UHMS does not mention this indication.[8]

The HAS report mainly follows the ECHM recommendation,[37] while neither the AHRQ nor the IECS report do not mention this indication.[14, 38]

3.4.14 Pneumatosis Cystoides Intestinalis

3.4.14.1 Short description of the condition

Pneumatosis Cystoides Intestinalis (PCI) is a rare disease and describes the presence of gas-containing cysts in the bowel wall. It is a radiographic finding and not a diagnosis, as the aetiology varies from benign conditions to fulminant gastrointestinal disease.[64]

3.4.14.2 Summary of the evidence

For the ECHM, HBOT may be used in selected cases of pneumatosis cystoides intestinalis as an alternative to surgery, when there is no sign of acute complications such as perforation, peritonitis and bowel necrosis (type 3, level C recommendation).[9] The UHMS does not mention this indication in its guidelines. The HAS report mainly confirms the indication from ECHM, without additional evidence.[37]

3.4.15 Exceptional anaemia

3.4.15.1 Short description of the condition

Patients with an important loss of red blood cells through haemorrhage, haemolysis or aplasia, may experience suboptimal or even inadequate oxygen carrying capacity by the blood.

3.4.15.2 Summary of the evidence

Where safely available as in Western Europe, the transfusion of red blood cells is the most obvious answer to this problem. However, some people might refuse blood transfusions upon religious grounds, although this problem occurs less in Europe than for example in the US. Trust in the safety of locally obtained donor blood also might play an important role in the acceptance or refusal of patients to receive transfusions, but again this should be no problem in most European countries.

Not surprisingly, the indication of exceptional anaemia is only accepted by UHMS in exceptional cases where the patient cannot receive or refuses to accept a transfusion,[8] but this indication is not withheld by ECHM.[9] The evidence for this indication is mainly based on animal models and on small human case series and case reports.[8] A review of this observational evidence found generally positive results.[65]

3.4.16 Miscellaneous indications (not accepted by ECHM nor by UHMS)

Apart from the above mentioned accepted indications by ECHM, UHMS or both, there are numerous other indications, often based on little or no evidence.

In Table 6 those indications that were covered by existing technology assessments or meta-analyses are shown and we indicate the most relevant references and a short summary of the main conclusions.

Table 6. Miscellaneous indications for HBOT (only when treated in existing technology assessment or meta-analyses)

Acute Coronary Syndrome	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 13[1]
	Cochrane review: Hyperbaric oxygen therapy for acute coronary syndrome.[28]
	Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Short summary of the evidence: very low quality evidence from very small trials for a lower risk of major adverse cardiac events and for a more rapid relieve from pain. No significant effect on mortality.	
Acute Ischemic Stroke	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 15[1]
	Cochrane review 2005: Hyperbaric oxygen therapy for acute ischaemic stroke.[25]
	Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
	Carson et al.[66]
Short summary of the evidence: no evidence for improved clinical outcomes when applied during the acute presentation of ischemic stroke. Evidence from three RCTs is insufficient but clinical benefit does not seem likely.	
Acute Traumatic Brain Injury	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 17[1]
	Cochrane review 2004: Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury.[33]
	Oxigenoterapia Hiperbárica: Utilidad Diagnósticae Indicaciones (IECS 2006)[38]
	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]

Short summary of the evidence: very low quality evidence from small trials for a reduced risk of death, without evidence for improved outcomes in terms of quality of life.	
Autism	AETMIS 2007: Place de l'oxygénothérapie hyperbare dans la prise en charge de l'autisme. Review[67]
Short summary of the evidence: very low quality evidence from a few anecdotic case series and one very small RCT (10 cases) seems to indicate some reduction in autism symptoms but validity cannot be demonstrated. Several small RCTs are currently being conducted with different pressure and oxygen parameters.	
Cerebral Palsy	AETMIS 2007: Place of hyperbaric oxygen therapy in the management of cerebral palsy[68]
Short summary of the evidence: no evidence for the efficacy of HBOT for the treatment of cerebral palsy. Some small RCTs are currently being conducted for this indication.	
Delayed onset muscle soreness and closed soft tissue injury	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 14[1]
	Cochrane review 2005: Hyperbaric oxygen therapy for delayed onset muscle soreness and closed soft tissue injury.[30]
Short summary of the evidence: no evidence that HBOT helped people with muscle injury following unaccustomed exercise and low quality evidence that people given HBOT had slightly more pain. Further research on this indication is not considered a high priority.	
Facial Palsy	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
	MSAC 2000[69]
Short summary of the evidence: very low quality evidence from a single small RCT (n=79) for a better complete recovery and a shorter duration of symptoms using HBOT compared to prednisone therapy.	
Fracture healing	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 18[1]
	Cochrane review 2005: Hyperbaric oxygen therapy for promoting fracture healing and treating fracture non-union.[26]
	Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Short summary of the evidence: no evidence available for the efficacy of HBOT on fracture healing.	
Malignant otitis externa	Cochrane review 2005: Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa.[23]
Short summary of the evidence: no evidence available for the efficacy of HBOT when compared to treatment with antibiotics and/or surgery.	
Migraine and cluster headache	Cochrane review (protocol 2005 and pre-publication 2007): Normobaric and hyperbaric oxygen therapy for migraine and cluster headache (Protocol)*.[19, 22]
	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Short summary of the evidence: very low quality evidence from nine small RCTs (n=201) for the effectiveness of HBOT for the termination of acute migraine, and for cluster headache when compared to sham but no evidence of effectiveness when compared to ergotamine therapy.	
Multiple sclerosis	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 16[1]
	Cochrane review 2004: Hyperbaric oxygen therapy for multiple sclerosis.[34]
	Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Short summary of the evidence: very low quality evidence from nine small RCTs (n=219) for no beneficial effect of HBOT.	
Tinnitus	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 11[1]
	Cochrane review 2007: Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus.[21]
	Bennett et al.[70]

Short summary of the evidence: low quality evidence from one small RCT for no beneficial effect of HBOT.	
Tumour sensitisation to radiotherapy	Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 19[1]
	Cochrane review 2005: Hyperbaric oxygenation for tumour sensitisation to radiotherapy.[29]
	Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
	Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Short summary of the evidence: very low quality evidence from nineteen trials (n=2286) with major methodological flaws for an improved local tumour control and mortality for cancers of the head and neck, and local tumour recurrence of cancers of head, neck and uterine cervix. Little evidence is available for other anatomical sites.	

3.5 GENERAL CONCLUSIONS

Over the years HBOT has been proposed for a myriad of indications but only a limited number of those have been endorsed by the two major scientific hyperbaric societies. In this chapter we focussed on the evidence for those 'accepted' indications.

For various reasons the quality of evidence for the efficacy of HBOT is low to very low for most of the indications. It has become accepted standard therapy in a few life threatening conditions i.e. decompression illness and gas embolism, mainly based on historical empirical evidence. For these indications it is unlikely that evidence from RCTs will become available because such RCTs are considered unethical. For other indications, the use of HBOT is mainly based on theoretical reasoning and animal models, while clinical evidence is often only based on case series comparing outcomes in centres with and without hyperbaric facilities or with historical controls. These analyses are, obviously, hugely prone to bias.

For these indications, where RCTs are in theory feasible, there appears to be a general reluctance to conduct or to fund them, as illustrated for example with the trials that originated from the COST B14 collaboration on HBOT, that were designed and started but still not reported. Moreover, these trials especially when involving sham therapy to maintain double-blinding, are complex and technically not feasible in every hyperbaric facility. As a result, RCTs are few and the available RCTs are small, possibly leading to a publication bias towards positive results. It is unlikely that better evidence will become available in the near future for many of the indications.

Given the paucity of evidence there is a large level of uncertainty about the role and need of HBOT in daily medical practice in Belgium and abroad, and we have graded the available evidence according to GRADE taskforce principles.[71]

With available evidence we conclude that:

1. There is empirical evidence for the effectiveness of recompression therapy with or without adjuvant oxygen, and there is wide consensus, but no major RCTs are available or being conducted, for the clinical efficacy of HBOT in the treatment of:
    - decompression accidents (DCS) (evidence level: high)
    - severe gas embolism (evidence level: low)
2. There is low quality evidence from small RCTs on the clinical efficacy of HBOT, but future larger and well conducted RCTs could enhance our knowledge base for:
    - adjuvant HBOT in patients with diabetic ulcers may help avoid major amputations in the medium term compared to standard therapy without HBOT
    - in acute deafness presenting early a slightly better recovery was observed with adjuvant HBOT but the clinical relevance is uncertain
    - improved healing in selected cases of radiation induced tissue injury

3. There is very low quality evidence for the non-efficacy of HBOT and because of the wide consensus on its effectiveness and long-standing traditions in the hyperbaric community, future larger and well conducted RCTs should be conducted to reach definitive scientific conclusions:
    - long-term neurological sequels of carbon monoxide intoxication (HBOT compared to normobaric oxygenation)
4. There is very low quality or no evidence for the efficacy of adjuvant HBOT, endorsement is mainly consensual and future larger and well conducted RCTs should first enlarge our knowledge base for:
    - short-term effects of carbon monoxide intoxication
    - delayed wound healing other than that associated with diabetes
    - anaerobic or mixed anaerobic-aerobic bacterial infections
    - acute soft tissue ischemia
    - post-anoxic encephalopathy
    - chronic refractory osteomyelitis
    - acute ophtalmological ischemia
    - thermal burns
    - neuroblastoma stage IV
    - pneumatosis cystoides intestinalis
    - exceptional anaemia (but considered largely irrelevant in Europe)
    - miscellaneous indications such as autism, tumour sensitisation to radiotherapy, migraine, tinnitus etc. (see Table 6)

Key points

- **Although HBOT is an old technique, evidence from well conducted RCTs is poor, due to small trials, lack of blinding and randomization problems. Possible causes for this paucity of data are the technical difficulties to conduct these trials, the small number of patients in individual centres, and the absence of a driving financial interest to perform those trials.**
- **There is empirical evidence and wide consensus, on the efficacy of HBOT in the treatment of decompression accidents and severe gas embolism.**
- **There is low quality evidence from small RCTs on the clinical efficacy of adjuvant HBOT in patients with diabetic ulcers, acute deafness presenting early and selected cases of post-radiotherapy tissue damage.**
- **There is very low quality evidence from small and heterogeneous RCTs on the clinical non-efficacy of HBOT on long-term neurological sequels in carbon monoxide intoxication (compared to normobaric oxygenation).**
- **There is very low quality or no evidence for the efficacy of adjuvant HBOT in other indications and endorsement by scientific societies is mainly consensual.**
- **Data on the efficacy of HBOT in a series of new indications is beginning to appear and trials are ongoing. Therefore, new and validated indications could become apparent in the future.**

4 REVIEW OF ECONOMIC STUDIES

4.1 INTRODUCTION

In this chapter we provide a systematic literature review and a detailed and critical appraisal of results. The objective is to determine if adjuvant HBOT is a cost-effective option compared with standard care for several indications.

4.2 METHODS

4.2.1 Literature search strategy

A comprehensive review of the literature was undertaken to identify all literature that may provide evidence with regard to the cost effectiveness of HBOT. Websites of HTA institutes and electronic databases were searched.

4.2.1.1 HTA institute reports

As a starting point, websites of HTA institutes were consulted. The search of INAHTA's (International Network of Agencies for Health Technology Assessment) HTA database helped to identify assessment reports issued by national or regional HTA agencies on HBOT. This consultation was completed by a manual search for reports regarding HBOT on the websites of HTA institutes mentioned on the INAHTA website. This search was performed independently by two researchers (CO and MN). The final search was performed on January 3, 2008.

4.2.1.2 Electronic databases

In January 2008, databases were searched to identify all relevant HTA reports, systematic reviews and full economic evaluations measuring the cost-effectiveness of HBOT. The following electronic databases were consulted: Medline, Embase, Centre for Reviews and Dissemination (CRD) databases (Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and Health Technology Assessments (HTA)), Cochrane Database of Systematic Reviews (CDSR), and Econlit. No restrictions on the time period and language were imposed. An overview of the search strategy and results are provided in appendix.

4.2.2 Selection criteria

All returned references were assessed based on title, abstract and keywords. When no abstract was available or the reference was unclear or ambiguous, consideration of the reference was made on the basis of full-text assessment. Reference lists of retrieved papers were checked for additional relevant references. This whole literature search and selection procedure was repeated by a second reviewer to assess the quality of this process.

Papers fulfilling several selection criteria were included in the economic review. Full economic evaluations that compare two or more alternatives and consider both costs and consequences, including cost-effectiveness, cost-utility and cost-benefit analysis, were eligible. The outcomes should be expressed as costs per life-years gained (LYG), costs per quality-adjusted life years (QALYs) gained, or any other appropriate disease-specific health outcome. The latter refers to e.g. the cost per amputation avoided.

Other types of studies, such as cost descriptions or cost comparisons were not seen as full economic evaluations (Figure 21).

Figure 21. Classification of economic studies

		Are both costs (inputs) and consequences (outputs) of the alternatives examined?		
		No		Yes
		Examines consequences only	Examines costs only	
Is there a comparison of at least two alternatives?	No	*Partial evaluation*		*Partial evaluation*
		Outcome description	Cost description	Cost-outcome description
	Yes	*Partial evaluation*		*Full economic evaluation*
		Efficacy or effectiveness evaluation	Cost comparison	Cost-utility analysis (CUA) Cost-benefit analysis (CBA) Cost-effectiveness analysis (CEA) Cost-minimisation analysis (CMA)

Adapted from Drummond et al.[72]

The populations described in the study are patients eligible for receiving HBOT, which can be interpreted very broadly as shown previously. The intervention being evaluated logically had to be HBOT. All full economic evaluation fulfilling the selection criteria were summarized in an in-house data extraction form (see appendix Table 61).

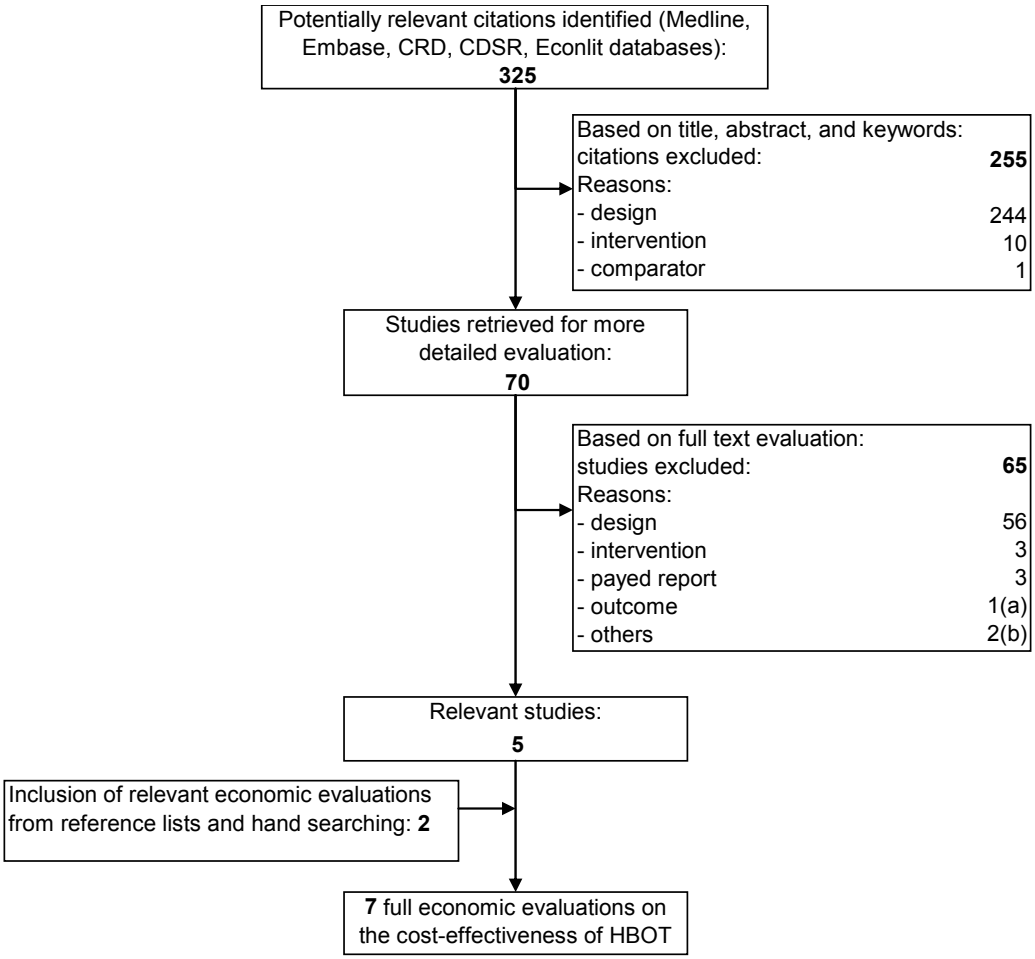
4.3 RESULTS

Searching the HTA websites, 16 HTA reports were extracted. Information regarding the cost-effectiveness was very limited. Most of the reports focussed on efficacy or effectiveness of HBOT treatment.[14, 37, 38, 56, 57, 67, 68, 73-,78] Only three reports covered the issue of cost-effectiveness and performed a cost-effectiveness analysis themselves.[54, 69, 79] References of all 16 reports, however, were searched for original cost-effectiveness analyses.

325 articles were found searching the electronic databases (see appendix). From the 325 articles, 255 were excluded based on title, abstract and keywords (Figure 22). The majority of studies were no full economic evaluations. The remaining 70 studies were retrieved in full text. Five studies fulfilled our selection criteria.[54, 69, 79-81] Reference lists of the initial 70 studies were hand searched for further references. Two additional references matched our inclusion criteria.[82, 83] The seven selected studies are the following:

1) Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: A double-blind randomized-controlled trial. European Journal of Vascular and Endovascular Surgery. 2003;25(6):513-8.
2) Dempsey J, Hynes N, Smith T, Sproat J. A cost effectiveness analysis of hyperbaric therapy in osteoradionectosis. The Canadian Journal of Plastic Surgery. 1997;5(4):221-9.
3) Guo S, Counte MA, Gillespie KN, Schmitz H. Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. International Journal of Technology Assessment in Health Care. 2003;19(4):731-7.
4) Hailey D, Jacobs P, Perry D, Chuck A, Morrison A, Boudreau R. Adjunctive hyperbaric oxygen therapy for diabetic foot ulcer: an economic analysis. Systematic review. Canadian Agency for Drugs and Technologies in Health (CADTH); 2007. Technology Report No 75
5) Medical Services Advisory Committee. Hyperbaric oxygen therapy (#1018-1020). Report. Medical Services Advisory Committee (MSAC); 2000.
6) Medical Services Advisory Committee. Hyperbaric oxygen therapy (#1054). Report. Medical Services Advisory Committee (MSAC); 2003.
7) Wheen L. The effectiveness and cost of oxygen therapy for diabetic foot wounds. Spums Journal. 1994;24(4):182-90.

Figure 22. Identification and selection of studies



CRD: Centre for Reviews and Dissemination; CDSR: Cochrane Database of Systematic Reviews; HBOT: hyperbaric oxygen therapy

a: the study of Cianci and Hunt[84] looked at the recurrence of wounds after being treated with HBOT

b: the study of Boykin et al.[85] was a case report in which the case of a soft-tissue radiation necrosis ulceration of the leg successfully treated with adjunctive HBOT was presented. The study of Dolezal[86] could not be retrieved.

Not all selected economic evaluations expressed results in costs per LYG, costs per QALY gained, or cost for a disease specific outcome. If HBOT would be more effective than its comparator and costs less, this results in a dominant strategy. As such, even though the studies look as cost analyses, they could be seen as full economic evaluations (looking at both costs and consequences of two alternative treatments) and were included in our overview.

Several references referred to book chapters.[87-91] The analyses of Marroni were obtained.[88, 89] The quality of the input data on mortality, morbidity and hospitalization was assessed as not being of high enough quality since no sources were provided for the rough estimates. Therefore, the studies were not retained. The reference to the German study of Rychlik was not found. Another study by Rychlik, however, which included the cost-effectiveness analysis of HBOT as an example, was retrieved.[92] The quality of this study was also assessed to be of low quality since sources for the input variables were not always mentioned, sensitivity analysis was reportedly performed but no results were given, and no conclusion or discussion with respect to the cost-effectiveness of HBOT was presented.

The original publication,[93] which was mentioned in the references of this article as being submitted to a German journal, was not found in any database. Another document of Rychlik could be obtained.[94] The input values of this non-peer reviewed document contained contradictions. For example, the control group consisted of 33 patients, of which 22, 12 and 11 patients had no, minor or major amputations, respectively. Another document[95] using data from Rychlik was also excluded. It was assessed as not being a good economic evaluation with reliable input parameters. Finally, the book chapter of Persels[90] was not an economic evaluation comparing both costs and effectiveness of HBOT and alternative treatment.

The study of Mulla et al.[96] applying a regression method to determine the predictors of length of stay and total patient charges for necrotizing fasciitis was not taken into account. In this analysis HBOT was not associated with increased costs, nor with an improvement in survival. As acknowledged by the authors, however, these results were difficult to interpret due to the small number of patients who received HBOT (n = 19) and the small number of deaths overall.

The economic evaluations included in our overview are arranged according to indication. In this part, we provide a short description of the study, results and conclusions of the authors. Details are provided as far as the raw data are mentioned in the studies. As a result, more or less detailed data will be provided for each study. In a following part, we will discuss the economic analyses.

4.3.1 Diabetic foot ulcers

4.3.1.1 Abidia et al.[80]

The UK study of Abidia et al. (2003) described a double-blind RCT including a limited cost comparison for HBOT versus no HBOT in the treatment of diabetic patients with ischemic, non-healing lower extremity ulcers. Eighteen diabetic patients were recruited of which two patients withdrew during the course of the study (one in the control group required urgent vascular intervention and one in the treatment group dropped out for personal reasons). All patients, their carers and medical assessors were blinded to the treatment.

Patients were randomly assigned either to receive 100% oxygen (treatment group) or air (control group), at 2.4 ATA for 90 minutes daily for a total of 30 treatments. Wound care was standardised for all patients (including offloading, aggressive debridement and dressing, and antibiotic therapy if there were clinical signs of infection).

The mean total cost of visits for ulcer dressing (£58 per outpatient hospital visit) per patient in the control group was compared with the respective cost in the treatment group in addition to the cost of HBOT (£100 for each session) per patient and the cost of dealing with any complications arising from the treatment.

Patients were assessed at baseline, after 15 and after 30 treatments, and 6 weeks later. Two more follow-up visits were performed at 6 months and 1 year. Quality of life (QoL) was measured using the generic form SF-36 and Hospital Anxiety and Depression scale (HAD scale). The follow-up was discontinued after 1 year because the authors felt that any difference observed between the two groups beyond one year could not be confidently attributed to HBOT and was more likely to be due to natural progression of peripheral arterial disease.[80]

Outcomes of this study are shown in Table 7. At 1 year follow up, complete healing was achieved in five out of eight ulcers in the treatment group compared with none out of eight ulcers in the control group (p=0.026). Furthermore, the median decrease of the wound areas was 100% in the treatment group at six weeks follow up compared with 52% in the control group (p=0.027). However, values at 6-month follow-up were 100 and 95% respectively. This study did not show any significant differences in major or minor amputation rates between the two groups.

Table 7. Ulcers description and outcome

group	treatment	control	p value
Ulcer size (mm^2)*	106 (12-823)	78 (18-866)	NS
Ulcer depth (mm)*	2.3 (0.5-4)	1.6 (0.5-4)	NS
Wagner Grade I	0	1	NS
Wagner Grade II	8	7	NS
Signs of infection	3/8	2/8	NS
Ulcer duration (months)	6 (2-18)	9 (3-60)	NS
Ulcers healed:			
At 6 weeks	5/8	1/8	NS
At 6 months	5/8	2/8	NS
At one year	5/8	0/8	p=0.026
Reduction in ulcer size			
At 6 weeks	100% (34-100)	52% ((-29)-100)	p=0.027
At 6 months	100% ((-206)-100)	95% (0-100)	NS
Major amputation	1	1	NS
Minor amputation	1	0	NS

* Results as median and (range).
Adapted from Abidia et al.[80]

With respect to QoL, patients in both the treatment and control groups showed a significant improvement in the depression score in the HAD scale (p=0.011 and 0.023 respectively) while only the control group had a significant reduction in their anxiety score (p=0.042). In summary, hyperbaric oxygen did not produce any significant improvements in QoL measures greater than those seen in patients in the control group as measured by the SF-36 and HAD scale. The authors suggest this was because the physical functioning of patients was not mainly limited by the ulcers, but also by other co-morbid conditions, e.g. intermittent claudication, arthritis, and cardiac problems. They also mention that a disease-specific QoL measure instead of a generic one would have been more appropriate in detecting benefit achieved with ulcer healing.

With respect to costs, the mean number of visits for dressing of the study ulcer was 33.75 (±62) and 136.5 (±126) per year per patient in respectively the treatment and the control group. The mean total cost per patient per year for ulcer dressing visits was £1 972 and £7 946, respectively. Since the cost of the entire hyperbaric oxygen treatment course per patient was £3 000 there was a significant potential cost saving by using adjunctive hyperbaric oxygen amounting to an average of £2 960 for each patient treated.

In conclusion, HBOT may have the potential to enhance healing of ischemic diabetic lower-extremity ulcers and the cost-effectiveness analysis showed that despite the extra cost involved in using hyperbaric oxygen, there was a potential saving in the total cost of treatment for each patient during the study.

4.3.1.2 Guo et al.[81]

The US study of Guo et al. (2003) described a decision tree model constructed to estimate the cost-effectiveness of HBOT in the treatment of diabetic ulcers. The hypothetical cohort of 1000 patients sixty years of age with severe diabetic foot ulcers could receive conventional wound care with or without adjunctive use of HBOT. Results were expressed as costs per QALY. QALYs for each patient were derived from assigning EuroQol weights[97] to four different treatment outcomes: primarily healed: 0.6; healed with minor lower extremity amputations (LEA): 0.6; healed with major LEA: 0.31; and death: 0. Table 8 describes some other input parameters from this study.

Table 8. Base case model parameters[81]

	healing	minor LEAs	major LEAs
HBOT treatment	55%[a]	35%[a]	10%[a]
No HBOT treatment	33%[a]	26%[a]	41%[a]
Mortality[b]	2.8%[c]	2.8%	16.3%[d]

LEA: lower extremity amputations

a: based on the average of four prospective, controlled clinical studies: Faglia et al.,[98] Doctor et al.,[99] Baroni et al.,[100] and Zamboni et al.[101]; b: the mortality rate was assumed to be constant over the 12-year period; c: Bild et al.[102]; d: Baddeley et al.[103]

The time window of the analysis was 1, 5 and 12 years. The 5-year interval was chosen to represent the private payers' perspective, because 5 years later the patients automatically become Medicare beneficiaries.

The 12-year interval was selected to represent the societal perspective, because the life expectancy for people at age 60 was approximately 20 years,[104] and the life expectancy for people with diabetes would be approximately 8 years shorter than that of people without diabetes.[105] A discount rate of 3% was applied to adjust QALYs gained in future years.

Cost items included were costs for HBOT ($407 per treatment, inclusive technical and physician fees), and costs for a minor or major LEA ($40 673 and $39 404 respectively, inclusive surgery, inpatient care, rehabilitation, first-year outpatient visits, and physician fees). An average of 29 HBOT sessions per case was taken into account. Costs were inflated to 2001 dollars. Finally, scenario analysis was conducted to measure the range of CE ratios between the least and most efficacious input parameters of the four prospective, controlled studies.

Due to HBOT, 155 cases of major LEAs were averted (205 versus 50 LEAs in the control and HBOT group, respectively) and approximately 50.2, 265.3, and 608.7 QALYs were gained at years 1, 5, and 12, respectively, in the hypothetical cohort. There was also an increase of 45 cases of minor LEAs (130 versus 175 LEAs in the control and HBOT group, respectively). The incremental cost-effectiveness ratio (ICER) was estimated to be $27 310, $5 166, and $2 255 per QALY, at years 1, 5, and 12, respectively. In the scenario analyses, the ICERs varied substantially. Results were very sensitive to the efficaciousness probabilities. For example, the CE ratio at year 1 was $142 923, $27 310 per QALY, and cost saving ($-72 799) in the worst, base, and best case scenarios, respectively. Results were also sensitive to the quality weights, especially for major LEA, the number of HBOT sessions per case, the HBOT cost per treatment, and the treatment costs of major and minor LEA per case.

The authors concluded that HBOT in the treatment of diabetic ulcers was cost effective, especially in the long term. They also acknowledged that results were limited by the clinical studies that provide the basis of the estimates.

4.3.1.3 Hailey et al.[79]

The Canadian study of Hailey et al. (2007) used a decision model to estimate the cost-effectiveness of adjunctive HBOT in comparison with standard care alone. The model used a 65-year-old patient cohort with diabetic foot ulcers. The model was very similar to that of Guo et al.[81] with the addition of one extra health state, i.e. unhealed. Results were expressed in costs per QALY. The related utilities for the health states were 0.6 for a primarily healed wound, 0.61 for healed with a minor LEA, 0.31 for healed with a major LEA, 0.44 if unhealed with no related surgery, and 0 for death.[97, 106] Table 9 presents outcome probabilities in the first year and mortality parameters.

Table 9. Base case model parameters[79]

	healing	minor LEAs	major LEAs	unhealed
HBOT treatment	56%[a]	27%[a]	11%[a]	6%[a]
No HBOT treatment	24%[a]	16%[a]	33%[a]	28%a
Number of deaths annually	0.083[b]	0.083	0.133[c] - 0.083	0.083

LEA: lower extremity amputations
a: based on the average of seven controlled clinical studies: Baroni et al.,[100] Doctor er al.,[99] Faglia et al.,[98] Zamboni et al.,[101] Faglia et al.,[107] Kalani et al,[108] and Abidia et al.[80] b: 1/12=0.083, as a result, the mortality rate (i.e., deaths divided by survivors) will increase with each passing year.[105] c: There is a 5% addition to the mortality rate in the first year for persons who have a major LEA.[109]

The time horizon was 12 years. This was equal to the life expectancy of 18 years for a person in Alberta,[110] adjusted with a ratio for the expected lifetime of a person with diabetes, which was 0.67.[105] No discount rate was mentioned. The perspective was that of a ministry of health.

The total cost for 30 HBOT treatments was 3 652 Canadian dollars (CAD) (30 x CAD110 per dive + CAD352 physician fees for first day, minor consult, and additional time). The annual cost per patient is summarized in Table 10. The costs for minor and major LEA include the operation costs. All costs were adjusted to 2004 values using the Consumer Price Index. Two sensitivity analyses, changing the outcome probabilities (16% major LEA instead of 6%) and the cost of HBOT, were conducted to assess the stability of the model.

Table 10. Annual costs (in CAD, 2004 values)[79]

	healing	minor LEAs	major LEAs	unhealed
First year	4 228	10 823	19 195	9 386
Subsequent year	3 890	10 484	11 712	9 428

The life expectancy was 5.96 and 5.84 life years or 3.64 and 3.01 QALYs in the HBOT and control arm, respectively. This was associated with a 12-year cost for a patient receiving HBOT of CAD40 695 compared to CAD49 786 for standard care alone. Because outcomes were assumed better and costs were less in the HBOT arm, adjunctive HBOT used with standard care dominated standard care alone. This remained the case in the sensitivity analyses.

In conclusion, adjunctive HBOT used with standard care was a dominant strategy. It would be necessary for health authorities to ensure that there was sufficient HBOT capacity to cope with diabetic foot ulcers and that patients had reasonable access to HBOT facilities.

4.3.1.4 Medical Services Advisory Committee[69]

In this Australian report (2000) the cost-effectiveness of monoplace HBOT was calculated in comparison with procedures not using HBOT. Multiplace chambers, which are most of the times provided through the public hospital system, were not included in the appraisal. The cost per patient treated in public multiplace units would likely be higher than in a monoplace unit given the wider role of multiplace units including the provision of 24 hour emergency care. No explicit information on the time window or perspective was provided. Results were expressed as cost per amputation avoided, which included only major or both major and minor amputations.

The risk for major amputations was based on five studies reporting absolute risk reductions associated with HBOT.[98-101, 107] The pooled risk difference indicated a reduction of 20% (95% CI: 11-30%). The risk for minor amputations was based on two studies which reported a non-significant increase in the risk of minor amputations.[98, 99] The pooled risk difference indicated an increase of 9% (95% CI: -8-25%) following HBOT.

The cost of HBOT, including both capital and operating costs of a hyperbaric monoplace unit, was based on 30 sessions per patient. Sensitivity analysis was performed, in which e.g. the number of dives was changed to 15 and 40 due to the uncertainty about the number of sessions per patient for different indications. DRG costs were used to approximate the costs of a major amputation and rehabilitation. The average cost for all types of amputation was 14 805 Australian dollars (AUD). For rehabilitation this was AUD8 758. The DRG for foot procedures was used to approximate the costs of a minor amputation, which was AUD2 194.

In the base case, the cost per course of treatment was AUD6 941. In this cost, a consultation fee for each session was included. Only attributing a once-off Medicare fee would results in a cost of AUD4 499 for 30 sessions. The cost per major amputation avoided by HBOT in the treatment of diabetic wounds was estimated to be AUD11 142. The cost per amputation avoided (both major and minor) was AUD22 054. Sensitivity analysis suggested that this result was not robust. With 40 HBOT sessions per treatment, the cost per amputation avoided was AUD43 087. HBOT treatment could cost less than the comparison treatment under several conditions, such as, sharing operating costs among more than one unit, giving 15 HBOT sessions per patient, and a risk reduction of 30% and 8% for major and minor amputations respectively. In contrast, with a risk reduction of 11% for major amputations and a risk increase of 25% for minor amputations (worst case scenario using the limits of the 95% CI), the comparison therapy became dominant.

In conclusion, monoplace HBOT could be cost-effective in the treatment of diabetic wounds and could save resources in this treatment. The authors recognised however that the true cost of monoplace HBOT may be considerably different depending on how the facility was staffed and operated, and that there was considerable uncertainty surrounding the true effectiveness of HBOT and associated health cost offsets in this indication.

4.3.1.5 Wheen et al.[83]

The New Zealand analysis of Wheen et al. (1994) performed an economic analysis of HBOT in the management of diabetic foot wounds.

The cost items included were hospitalization costs (NZ$120/day in the Royal New Zealand Navy (RNZN) Hospital and NZ$450 in a public hospital), costs of the amputation (NZ$493), prosthesis supply and training (NZ$1 300), occupational therapy (NZ$113) and physiotherapy input (NZ$64), costs for a walking frame (NZ$100) and crutches (NZ$89).

The outcomes were based on the study of Baroni et al.[100] since this was the only prospective and controlled (not randomised) trial at the moment of the study. The treatment group of 18 patients showed a significantly increased healing rate (89% versus 10%) and a decreased amputation rate (11% versus 40%) compared with the control group of 10 patients. The mean hospitalisation period was also 20 days shorter (62 versus 82 days) for those patients receiving HBOT.

The average cost per patient was significantly less for the group treated with HBOT at the RNZN Hospital (NZ$10 565) than for the control group (NZ$38 359). This was mainly due to the difference in bed stay cost per day (NZ$120 versus NZ$450). Applying the same hospital stay cost of NZ$450 to the HBOT treatment group resulted in an average cost per patient of 31 026, which was still lower than the average cost of the control group.

Despite the additional cost of HBOT, the combination of a shorter length of stay, amputation and rehabilitation costs resulted in lower total average cost for the treatment group compared with the control group.

4.3.1.6 Comments

The first study of Abidia et al.[80] showed there was an improvement in ulcers healed at one year and a potential cost saving with the use of HBOT. On the other hand, there was no improvement in QoL or amputation rates. The authors acknowledged that one of the limitations of their study was that only the cost of dressing changes and HBOT were included. Furthermore, the authors also state that the results must be viewed with caution and viewed as preliminary because of the small sample size.

Guo et al[81] also mentioned some limitations of their study. One of the assumptions was that foot ulcers would not recur once they were healed. If foot ulcers would recur, this would increase cost-effectiveness ratios. In contrast, taking into account the improved speed of wound healing and reduction of the level of wound care utilization would decrease the ICER. With respect to costs, the costs of treating side effects were excluded because they were assumed to occur rarely. Finally, the authors mentioned the cost-effectiveness estimation was based on studies that had methodological weaknesses.[111] The probabilities of treatment outcomes were based on four prospective, controlled, clinical studies in which different number of treatments and treatment schemes of HBOT was given. Furthermore, two of these studies[98, 99] were randomized but not blinded and the other two[100, 101] were both not randomized.

Similar as in the previous study, Hailey et al[79] also assumed that LEAs occur in the first year. If patients were healed in the first year, they would not have a subsequent LEA. Patients who were unhealed in the first year would remain so for the remainder of their lifetime and would receive wound care intermittently. We are aware that no more detailed data were available; however, this remains a very strong assumption. Hailey et al. also admit that both cost and effectiveness estimates are not of high quality. With respect to effectiveness, they point at the fact that there are few comparative studies of HBOT, and all of them have limitations. Costs, which were based on data from a few centres without standardized reporting, were assessed of not being of high quality.

Even though the result was dominant, and sensitivity analyses showed results to be robust, Hailey and colleagues admit there was uncertainty regarding the cost-effectiveness of using HBOT versus standard care.

In the Australian study,[69] the same caveats are mentioned. Costs are rough estimates. The estimates of HBOT treatment costs are not precise estimates based on actual studies, but are based on estimates of staffing and capital costs of a hyperbaric monoplace unit obtained from expert opinion. The cost for major amputations was the average cost for all types of amputations. First of all, this may not be an appropriate estimate for patients with diabetes. Secondly, the authors also remark that no information on the incremental resource use is available. Calculating the full costs for amputation as a saving due to HBOT may overestimate cost savings since costs may already have been incurred for diabetic wounds. Costs for rehabilitation and minor amputation may also not be accurate but were used in the absence of more precise data. There also remained considerable uncertainty surrounding the clinical evidence of the effectiveness, especially the assumed risk of minor amputations and wound healing being based on small populations. The authors stated that their appraisal represents only an indication of the potential cost effectiveness of monoplace HBOT, rather than a complete and detailed estimate of the cost effectiveness of the technology.

Finally, the study of Wheen et al. [83] contains similar weaknesses as the other studies. On the one hand, more cost items are included in this study, such as prosthesis supply and training, occupational therapy and physiotherapy input, and costs for a walking frame and crutches. On the other hand, the main cost difference between HBOT and standard therapy was caused by differential pricing for hospital stay for HBOT (NZ$120) versus standard therapy (NZ$450). The latter results in misleading base case results. For effectiveness, the input parameters were based on one of the most optimistic studies.

In conclusion, all the economic evaluations have their weaknesses, both on cost and effectiveness side. This is in the first place due to a lack of qualitative input data.

Therefore, the studies only indicate the potential cost effectiveness of HBOT versus standard therapy. Further research is necessary to estimate the real-world cost-effectiveness of HBOT.

4.3.2 Necrotising soft tissue infections

4.3.2.1 Medical Services Advisory Committee[69]

The Australian HTA report (2000) also included an analysis for the indication of necrotising soft tissue infections. In this report, two studies were found that looked at this indication.[112, 113] They looked at the proportion of patients who survived following the diagnosis of necrotising soft tissue infections. Both showed that HBOT was associated with improved survival, only one being statistical significant.[113] In this study, 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). With a HBOT treatment cost of AUD6 941 (30 sessions), this resulted in an incremental cost per death avoided of AUD16 105.

Sensitivity analysis using the upper and lower bound of the 95% CI suggested this cost to be AUD9 061 and AUD71 557, respectively. Results were also very sensitive to the number of sessions and sharing of operating costs between units.

Similar as for diabetic wounds, the authors concluded monoplace HBOT could potentially be cost-effective in the treatment of necrotising soft tissue infections and could save resources. They recognised, however, that the true cost of monoplace HBOT may be considerably different and that there was considerable uncertainty surrounding the true effectiveness of HBOT and associated health cost offsets in this indication.

4.3.2.2 Comments

Again, great uncertainty regarding costs and effects are present in the economic evaluation. The authors remark that no firm conclusions could be reached on the effectiveness of HBOT in necrotising soft tissue infections since the two studies of HBOT in this indication looked at different populations and had different study designs.[69] Only one of the studies also reported a statistically significant positive result on survival. This endpoint used in the economic evaluation is difficult to interpret: "*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.*"[69]

In conclusion, HBOT could potentially be cost effective in the treatment of necrotising soft tissue infections. However, there is great uncertainty surrounding the true effectiveness of HBOT versus standard therapy and cost offsets are not very clear.

4.3.3 Osteoradionecrosis

4.3.3.1 Dempsey et al.[82]

In this retrospective Canadian study (1997), a cost effectiveness analysis of hyperbaric therapy in osteoradionectosis of the mandible was performed from a societal perspective. Twenty-one patients who underwent HBOT at the Hamilton Civic Hospitals (Ontario) were included. A hypothetical control group was created and matched to the study group. Costs were given in 1995 CAD and discounted at 5%.

The researchers looked at how many patients healed. Outcomes for the hypothetical group undergoing conservative therapy were taken from the literature. From these expected values, 65% of patients would heal before reconstructive surgery, 23% would heal after reconstructive surgery and 12% would not have their disease resolved. Due to large variations in values reported in literature, the percentage of patients healing before reconstructive surgery was varied over a wide range (8-75%) in a sensitivity analysis.

Costs for the hypothetical conservative therapy group, including costs of medications, sequestrectomies, dental extractions, out-patient visits, in-patient days and reconstructive surgery, were also calculated based on expected outcomes obtained from the literature.

The cost for one dive in the chamber was CAD350.59, including the capital and operational cost, the fees charged to the Ontario Health Insurance and the patient cost per dive. Cost per day, average number of in-patient days and cost of reconstructive surgery were changed in sensitivity analyses.

The total cost to treat the 21 hypothetical patients was found to be CAD1 327 444, or an average of CAD63 211 per patient. In contrast, this was CAD211 362 for the 21 patients treated with HBOT or an average cost of CAD10 064 per patient. The number of days in the hospital was an important cost driver. The osteoradionecrosis of the 21 patients in the treatment group healed, whereas, based on expected outcomes from the literature, three cases would not be resolved under conservative therapy in the hypothetical patient group.

According to the authors of this study, HBOT was both less expensive and more effective than conservative therapy and, thus, demonstrated dominance.

4.3.3.2 Medical Services Advisory Committee[69]

A third indication included in the Australian HTA report (2000) was osteoradionecrosis. The study of Marx et al.[114] randomised two groups of patients who had an indication for removal of one or more teeth in a segment of the mandible. 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 (5.4%) in the intervention group were diagnosed as having osteoradionecrosis during follow up, compared to 11 out of 37 patients (29.7%) in the comparison group, a difference of 24.3% (95% CI: 15.9%, 47.0%, p=0.0060).[69]

The treatment cost in the comparison group was on average AUD13.6 compared to AUD6 941 in the intervention group (30 HBOT sessions). This resulted in an incremental cost of AUD28 480 per case of osteoradionecrosis avoided. Sensitivity analysis using the upper and lower bound of the 95% CI suggested this cost to be AUD16 663 and AUD66 187, respectively. Results were again sensitive to the number of sessions and sharing of operating costs between units.

4.3.3.3 Comments

The main weakness of the study of Dempsey et al.[82] is that it compares an HBOT group with a hypothetical group. The assumptions on the outcomes for the latter group undergoing conservative therapy were taken from literature. Mitton et al. remark that the non-HBOT outcome assumptions were based on weak evidence, and no reference was provided for the non-HBOT length of stay, leading to uncertainty in reported cost savings.[115] This indirect comparison resulted in very uncertain health gains and cost differences and can not be regarded as reliable. Results should therefore be interpreted with caution. A more precise measure of the true effectiveness of HBOT in this indication is needed to calculate reliable cost-effectiveness ratios.

The Australian report was based on one study on the effectiveness of HBOT in osteoradionecrosis.

This resulted in an incremental cost of AUD28 480 per case of osteoradionecrosis avoided. As mentioned by the authors, this did not take into account the cost offsets associated with prevention of osteoradionecrosis. Nonetheless, this cost per osteoradionecrosis avoided is very difficult to interpret by decision makers.

In conclusion, and similar as for other indications, due to the absence of good effectiveness and cost data, the cost-effectiveness of HBOT in this indication is unknown.

4.3.4 Non-diabetic chronic wounds

4.3.4.1 Medical Services Advisory Committee[54, 69]

Finally, the Australian HTA report (2000 & 2003) also looked at HBOT for non-diabetic wounds. The double-blind, randomised controlled trial of Hammarlund and Sundberg[116] looked at the percentage decrease in the wound area of non-diabetic patients following six weeks of exposure to 100% oxygen or air in a pressurised chamber, for a total of 30 sessions. Two groups of eight patients with leg ulcers of more than one year's duration participated. The mean reduction was 35.7% (SD=17) and 2.7% (SD=11) after six weeks in the intervention and comparison group, respectively. This suggested that the treatment cost for a one third reduction in the wound area was AUD6 941 per patient (30 sessions).[54, 69]

The study of Hammarlund and Sundberg[116] also reported an increase in healing at week 18 of 25%, which was translated in an extra AUD27 764 per additional person cured of a chronic leg ulcer. However, given the non significant p-value of 0.4667 for the risk difference in the study, the authors could not be confident that this was a reasonable estimate of the cost-effectiveness of HBOT for this indication.[54]

4.3.4.2 Comments

The study on which the effectiveness measure was based upon only recruited 16 patients. As mentioned by the authors of the Australian report, these were relatively tightly-selected subjects and the study examined only one outcome measure, i.e. reduction in wound area. The clinical significance of this outcome or its significance to patient welfare in the longer term was not sufficiently clear.[69] Larger and well conducted studies are necessary to provide evidence of a treatment effect of HBOT in this indication. A translation of treatment effects in (quality-adjusted) life-years gained and cost differences, including all relevant cost items, is necessary to calculate the cost-effectiveness ratio of HBOT versus standard care in the treatment of non-diabetic wounds.

4.4 DISCUSSION

We chose not to develop a specific cost-effectiveness model for HBOT treatment in Belgium. In the first place, very limited data were available on the effectiveness of HBOT in only some of the indications. These data were primarily based on small trials with important methodological flaws. Furthermore, good cost data are not available. There are weaknesses both with respect to which cost items should be included and on the valuation of these variables.

4.4.1 Effectiveness

The limitations on effectiveness estimates are discussed in the previous chapter. These estimates are mostly based on small sample sizes, sometimes observational and non-randomised or un-blinded studies. This results in great uncertainty about the treatment effect and provides only limited evidence.

Not all important and relevant end points were taken into account. For example, the studies on HBOT for the treatment of diabetic foot ulcers did not consider recurrence of foot ulcers once they were healed. Cianci and Hunt[84] suggested that wounds healed with adjunctive HBOT have excellent durability. Initial limb salvage was accomplished in 35 of the 41 patients (85%).[84] In other words, limb salvage rates may be high, but assuming no recurrence is no reflection of reality. Furthermore, no direct comparison towards patients not being treated with HBOT was available, while the incremental effects determine the denominator of the ICER. Both the short- and long-term treatment effects should be taken into account to reflect the real incremental benefits of HBOT.

Correct survival data should be gathered to estimate life-years gained, if any. For example, diabetic patients with foot ulcers have a different long-term survival pattern than those without foot ulcers.

Survival at 3 years was 72% for the foot ulcer patients versus 87% for a group of age- and sex-matched diabetic patients without foot ulcers ($p < 0.001$).[117] The mortality associated with amputation is also high. As mentioned by Wheen et al.,[83] in-hospital mortality was between 11 and 13% in the US[118, 119] and 18% in Denmark.[120] These mortality rates should be taken into account when gained life years are calculated.

Furthermore, a correct estimation of QoL is necessary to estimate QALYs. According to Ragnarson-Tennvall et al.,[97] QoL significantly reduces in patients with ulcers or after major amputations. These patients may not be able to take the stairs, drive a car, etc. Overall, living independently may become very difficult. The consequences of losing a lower limb and being transferred to a new environment can also be psychologically devastating.[121] It is, however, not clear for how many patients and how much QoL improves. As mentioned above, for diabetic foot ulcers, Abidia et al.[80] also measured QoL including the generic SF-36 and Hospital Anxiety and Depression scale (HAD scale) and did not find significant improvements in QoL measures with HBOT greater than those seen in patients in the control group. With respect to HBOT in osteoradionecrosis, Dempsey et al.[82] suggested that hyperbaric oxygen treated patients required fewer analgesics after their 10th treatment and anecdotally also experienced longer periods of undisturbed sleep. In contrast, conservative treatment patients would not experience significant reductions in pain and often become dependent on narcotics. This study, however, did not directly compare HBOT with conservative treatment. Finally, Pritchard et al.[55] included a measure of QoL (SF-36 health status) following treatment with HBOT versus air in patients with radiation-induced brachial plexopathy. They reported the results following 30 sessions. QoL at one week and 52 weeks appeared to have deteriorated in both groups and any differences between the groups were not consistently in favour of HBOT.[69] In summary, currently, the extent of both LYG and QoL gains, and thus QALYs gained, is hard to estimate.

4.4.2 Costs

The additional expenses associated with HBOT need to be correctly measured against health outcomes and cost consequences. The investment costs for the hyperbaric chamber are high and differ according to the type of chamber (see part on cost calculation). The monoplace chamber is the less costly option for initial setup and operation but provides less opportunity for patient interaction while in the chamber.[73] Additional costs for renovations or construction to house the chamber could also be substantial.[74] Next to these installation costs, the maintenance costs, cost for consumables and durables, and operational costs of the multidisciplinary team capable of treating all the recognized indications for HBOT should be taken into account. Other short- and long-term incremental costs differ according to indication. In the following paragraphs, we provide an overview of variables which should be taken into account for an economic evaluation of HBOT and the treatment of diabetic foot ulcers. For other indications, other variables may be important.

HBOT treatment is suggested to decrease amputation rates. Initially, this will influence the extra cost of prostheses. Cost differences also exist between infected ulcers being healed and not requiring amputation versus lower-extremity amputations. In a US study, this cost was about $17 500 and more than $30 000, respectively.[106] Apelqvist et al.[122] (1995) analyzed the three year follow-up costs for 274 patients with diabetic foot ulcer from the time of healing. Total costs for patients who achieved primary healing and did not have critical ischemia were $16 100 per patient compared to $43 100 and $63 100 per patient for patients who had required a minor or major amputation, respectively.

Hospitalisation stay costs may also differ. In the study of Baroni et al.[100] the mean length of stay for the control group was 81.9 days versus 62.2 days in the HBOT group. Smaller reductions in hospital stays were noticed in two other studies. The HBOT group had an average decrease in length of stay of 6.4 days (40.6 versus 47 days) in the study of Doctor et al.[99] and 7.6 days (43.2 versus 50.8 days) according to Faglia et al.[98] There is, however, a very large variation in length of stay between countries. As mentioned by Wheen et al.,[83] the mean hospital stay for amputations was 29.6 days in the US.[123] In contrast, in Denmark, this was 81 days for below knee amputations.[120]

It is not clear what the difference in hospital stay would be due to HBOT in a Belgian setting.

Furthermore, cost may be induced for increased home care and social services. Mitton et al.[74] point at the possibility that if patients left hospital more quickly, home care costs might actually increase. They could, however, not identify any study that addressed this issue. On the other hand, there could be a decrease in use of home care as a consequence of an improved wound healing.

Rehabilitation costs should also be considered. If HBOT decreases amputations rates for patients with diabetic foot ulcers, then less rehabilitation costs would follow from this.

Six to nine months may be necessary to maximize walking ability.[119] This could have an influence on both QoL and costs. Rehabilitation costs were mentioned to add an additional $40 000 to $50 000.[124]

Furthermore, longer term consequences should be taken into account. Recurrent ulcers, stump modifications and new amputations may lead to extra incremental costs. As mentioned above, limb salvage rates may be high but are not 100%. A below knee amputation may require subsequent re-intervention to an above knee amputation. Readmissions for the opposite leg are also possible. The incidence of subsequent amputation of the opposite leg varied from between 25 and 33% in Sweden,[125, 126] to 45% in the US.[127] Consequences of recurring ulceration and treatment are currently lacking in all economic evaluations. First of all, more detailed information on the probabilities and costs of these aspects are necessary to perform good economic evaluations.

Other indirect non-medical incremental costs, such as accommodation adaptation, loss of earnings, transportation costs, etc. could also be considerable.

All these short- and long-term consequences together will determine whether or not HBOT has the potential to become a cost effective treatment.

4.4.3 Other aspects

As mentioned in the previous chapter, HBOT can not be regarded as an entirely benign intervention. HBOT is associated with some risk of *adverse events*. Although serious adverse events are rare, estimates of incidence are rather uncertain. In a small population, Ciaravino mentioned that 34 of his patients (63%) developed complications, most commonly barotrauma to the ears, which occurred in 23 patients (43%).[128] Most adverse events seem to be self-limiting and resolve after termination of therapy and serious, life-threatening events are rare.[69] Even though these events are rare, they should be taken into account.

It is also important to take the correct *comparator* when performing further research. For example, for the treatment of ulcers, as mentioned by Hailey et al.,[79] newer types of dressings and other technologies are becoming available so that the comparative advantage of adjunctive HBOT may change. Choosing the appropriate comparator is essential in the search for the added value of HBOT.

HBOT has been used inappropriately for many conditions in the past.[129] Evidence of benefit is weak for many indications, and there might be additional incremental costs due to increased use of conditions for which HBOT is not effective.[115] A proper *selection of indications* for which HBOT can be used is essential and would increase its overall cost effectiveness. Furthermore, within each indication, the cost effectiveness of HBOT could be enhanced when patients who are unlikely to respond to it are excluded. No good data on *patient selection* are currently available.

The cost effectiveness could also be improved by optimizing the *number of sessions*. If there is no evidence of improvement, continuing treatment diminishes its cost effectiveness. In this regard, the objective of treatment is also important.

As mentioned by Fife et al.,[130] for the treatment of lower-extremity lesions, rather than complete healing of a lesion, the objective today is more often a partial healing by granulation to the point that epithelization can continue without further hyperbaric therapy. As a consequence, achieving the complete healing category might not be the best objective for cost-effective treatment of patients with HBOT.[130]

4.5 CONCLUSION

HBOT may provide several benefits such as reducing length of hospital stay, reduction in amputations, improvement in patients QoL, reduction in outpatient care, etc. According to several authors, this could result both in increasing benefits and decreasing costs, resulting in a cost saving treatment. For example, it seems that HBOT could be cost-effective in the treatment of diabetic wounds. All studies, however, show limitations for both incremental cost and benefit calculations. Therefore, they can only be seen as an indication that HBOT may be a cost-effective treatment. They do not provide good evidence that HBOT is a cost-effective treatment. The suggestion that HBOT could be clinically effective, could improve QoL, and could reduce health care costs in certain indications highlights the need for further large multi-centre trials to find out whether or not this is the case. While evidence data would be collected, good cost data should also be gathered. Incremental costs and benefits which are part of both the short- and long-term treatment pathway should be taken into account. As long as good qualitative evidence and cost data are lacking, good qualitative economic evaluations can not be performed.

Key points

- **Being an adjunct to standard therapy, HBOT is associated with increased (initial) treatment costs.**
- **Even though potential harms caused by HBOT appear to be small, it is a waste of valuable resources to use HBOT for conditions for which it is not effective.**
- **Economic evaluations currently are based on insufficient data and therefore have important limitations for both the incremental cost and benefit calculations.**
- **It is not possible to estimate cost-effectiveness of HBOT without good data on effectiveness, costs and quality of life.**
- **HBOT might be effective, improve QoL, and reduce costs in certain indications. Therefore, it deserves further attention and there is need for large multi-centre trials to gather both short- and long-term evidence and cost data.**

5 THE BELGIAN SITUATION

5.1 HISTORICAL CONTEXT

Up to the beginning of the nineteen sixties there was no organized emergency care in Belgium. With the Law of July 8, 1964 on urgent medical assistance, the government aimed to start up the "Dienst/Service 900". Under this law, the Ministry of Health donated a large number of standard and reanimation ambulances to the hospitals during the subsequent years. Ten hospitals (mostly teaching hospitals) also received a hyperbaric monoplace chamber. At that time, the predominant indications were acute, i.e. CO intoxication and decompression illness, for which one or a few sessions were sufficient. Therefore, the ministry, which already had financed the hyperbaric equipment itself, introduced in 1972 a relatively low fee for a maximum of two sessions.[131]

5.2 CURRENT RIZIV/INAMI NOMENCLATURE AND REGULATION

5.2.1 RIZIV/INAMI fee-for-service system in general

Under the RIZIV/INAMI fee-for-service system, hospitals register all specific medical acts and procedures in order to receive direct reimbursement from the national health insurance for that part of the cost that is refundable by social security. This system also determines what the patient will need to pay out of pocket. The whole set of rules for this registration and those payments is laid down in a so-called 'RIVIZ/INAMI nomenclature' that is in constant evolution.

5.2.2 RIZIV/INAMI nomenclature for hyperbaric oxygen therapy

5.2.2.1 Overview of codes

In the RIZIV/INAMI nomenclature, reimbursement is provided for the first and second day through the following reanimation billing codes for 'installation and supervision' of HBOT. There is no financing for the following days (See Table 11).

Table 11. Fee-for-service codes RIZIV/INAMI

Code	Amb/Hos	Definition
212516 212520	Amb Hosp	Installation of and supervision on oxygen therapy in hyperbaric chamber (regardless the number of sessions): The first day
212531 212542	Amb Hosp	Installation of and supervision on oxygen therapy in hyperbaric chamber (regardless the number of sessions): The second day

Amb: ambulatory; Hosp: hospitalized
Source: https://www.riziv.fgov.be/webapp/nomen/ (accessed on 29 November 2007)

5.2.2.2 Regulation on the application

In theory, HBOT can only be charged when the patient is in a life-threatening situation (source: RIZIV/INAMI). There are specific conditions attached to this reimbursement, and hyperbaric oxygen can, for example, not be cumulated with a number of other procedures, such as neurodiagnostic, polygraphic and polysomnographic investigations, surveillance on hypothermy, etc. A copy of the detailed regulation can be found in appendix (in Dutch).

5.2.2.3 Invoicing practices in hospitals

The nomenclature code does not explicitly restrict HBOT to specific indications. As a result, it allows for broad interpretation. In daily practice, HBOT centres apply the codes in various ways. Some centres only charge the RIZIV/INAMI for hospitalized patients, because the invoicing is only allowed in life-threatening situations, which is often not the case for ambulatory patients.

For diving accidents, some centres do not charge the RIZIV/INAMI but send the bill to the patient who then reclaims the money from the sports insurer.

5.2.2.4 Nomenclature for the military hospital

The Military hospital Queen Astrid is not under the jurisdiction of the Hospital law. As a result, even though this military centre also provides services to citizens, the above mentioned nomenclature does not apply to it. For their ambulatory patients, i.e. the majority of their patients, there is no invoicing to RIZIV/INAMI. For hospitalized patients, however, a Ministerial Decree of February 4th 1999[b] provides an invoicing code covering the hospitalization, treatment and care, pharmaceutical products, other supplies and the medical-technical acts for patients treated with hyperbaric oxygen (see Table 12). This invoicing code does not cover the installation of and supervision on oxygen therapy in the hyperbaric chamber. For this specific act, and similarly for ambulatory patients, there is no invoicing to the national insurer.

Table 12. Fee-for-service code for the military hospital

Code	Amb/Hos	Definition
760642	Hosp	Hospitalization at the military hospital, patient day price for hospitalization required for treatment with oxygen therapy in hyperbaric chamber

Amb: ambulatory; Hosp: hospitalized
Source: https://www.riziv.fgov.be/webapp/nomen/ (accessed on 29 November 2007)

5.3 CURRENT RIZIV TARIFF

5.3.1 RIZIV/INAMI tariff level

On January 1, 2008, the HBOT tariff level for both hospitalized and ambulatory patients was set at €64.63 (N96) and €48.47 (N72) for the first and second treatment day, respectively. As mentioned previously, there is no fee for consecutive treatments.

5.3.2 RIZIV/INAMI reimbursement level

The reimbursement level is 100% of the tariff for both the first and second day of HBOT treatment, for this procedure there is no invoicing to the patient.

5.3.3 RIZIV/INAMI military hospital fee

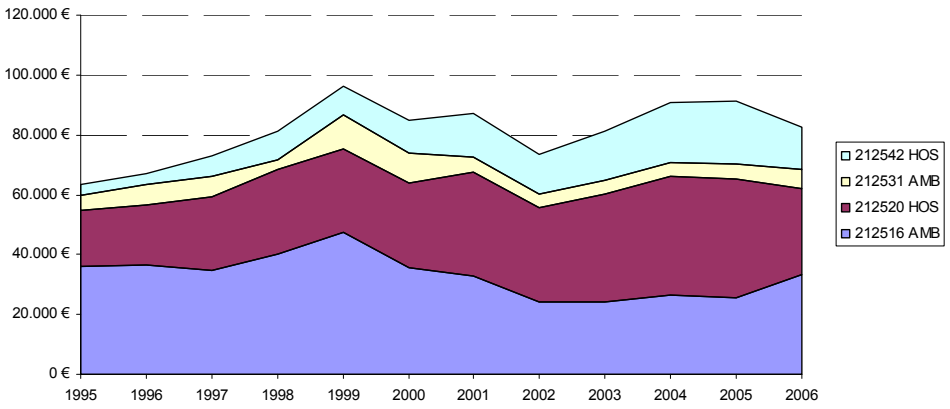
For the military hospital, the per diem fee for a patient receiving HBOT is €712.54 (January 1, 2008).

5.4 RIZIV/INAMI EXPENDITURES FOR HBOT IN BELGIUM

The expenditures for HBOT by the national health insurance are relatively small. In 2006, about €83 000 was paid (Figure 23), for approximately 1 400 sessions (Figure 24), less than 9% of more than 16 400 sessions given during that year (see section 5.7.1).

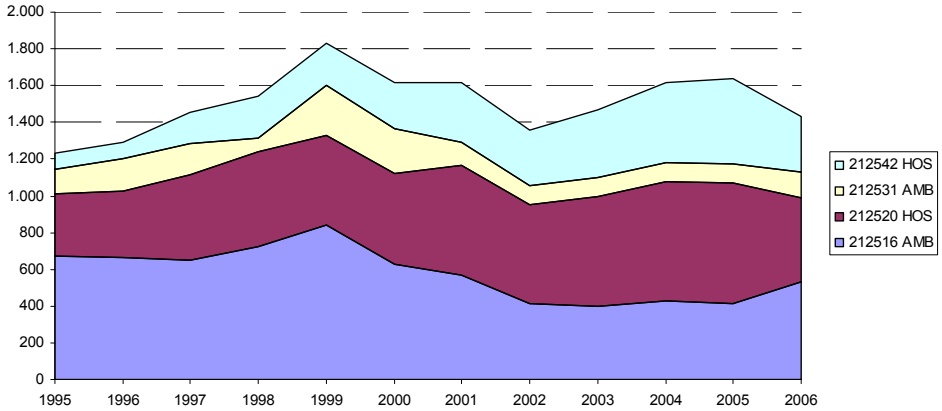
[b] MB (Ministerieel besluit) van 4 februari 1999 tot vaststelling van de tegemoetkoming van de verplichte verzekering voor geneeskundige verzorging en uitkeringen in de verpleegdagprijs van een opneming in de dienst van het Militair Hospitaal te Brussel die speciaal is uitgerust voor de behandeling met zuurstoftherapie in hyperbare drukkamer.
AM (Arrêté Ministériel) 4-2-1999 - intervention dans le prix de la journée d'entretien d'une admission dans le service de l'Hôpital Militaire à Bruxelles spécialement équipé pour le traitement par oxygénothérapie en caisson hyperbare.

Figure 23. Evolution of RIZIV/INAMI expenditures for HBOT



Amb: ambulatory; Hosp: hospitalized; Source: RIZIV/INAMI

Figure 24. Evolution of RIZIV/INAMI reimbursed cases for HBOT



Amb: ambulatory; Hosp: hospitalized; Source: RIZIV/INAMI

5.5 PREVIOUS PROPOSAL FOR AN ADAPTED NOMENCLATURE

A proposal for a new Royal Decree, regarding the reimbursement rules and conditions of HBOT was prepared, and has been presented and discussed at the TGR/CTM (Technische Geneeskundige Raad/Conseil Technique Medical, session of 25 May 2004). This previous proposal was largely based on the European Consensus as defined by the ECHM committee in 2004,[9] but was only marginally based on evidence on effectiveness. An obvious strength of the current reimbursement rules is that they are very effective in restricting overutilisation of HBOT thereby containing the budget.

In this proposal, the existing nomenclature numbers 212516-212520 / 212531-212542 were reserved for HBOT in a monoplace chamber. New nomenclature numbers with a higher fee level were proposed for multiplace chambers (N corresponds to €0.673 on January 1, 2008).

Indication	N° of sessions	Fee level
Serious CO intoxication	max three times	Monoplace chamber: First day: N96 Second and following day: N72 Multiplace chamber: First day: N192 Second and following day: N168
Decompression disease	max seven times	
Arterial gas embolism	max seven times	
Anaerobic myonecrosis	max seven times	

A new nomenclature number was proposed for diagnostic HBOT in a multiplace hyperbaric chamber (K corresponds to €1.077 on January 1, 2008).

Service	N° of sessions	Fee level
Transcutaneous oxygen measurement under hyperbaric oxygen inhalation Only in consideration of starting therapeutic HBOT for chronic critical ischemia in case of diabetes or arteriosclerosis	Only once per two years	K156

Additionally, new nomenclature numbers were proposed for the following indications in a multiplace hyperbaric chamber.

Indications	N° of sessions	Fee level
Chronic critical ischemia: ▪ in case of diabetes o when transcutaneous oxygen measurement >100 mmHg when inhaling 100% O2 at 2.5 ATA ▪ in case of arteriosclerosis o when transcutaneous oxygen measurement > 50 mmHg when inhaling 100% O2 at 2.5 ATA	Max 40 times in two years	K45
Radionecrosis: ▪ Treatment of osteoradionecrosis of head and neck or ▪ Soft tissue radionecrosis (except for radiation-enteritis)	Max 40 times	
Osteomyelitis: ▪ Chronic osteomyelitis, refractory after more than six weeks antibiotics therapy and after at least one surgical intervention; or ▪ Osteomyelitis of skull base or sternum	Max 30 times during two years	
Sudden deafness, refractory for classical drug therapy	Max 15 times during five years	
Crush trauma or compartment-syndrome of the limbs, post-traumatic reperfusion syndromes or compromised skin grafts or myocutaneous flaps	Max 10 times	

5.6 PROVIDERS OF HBOT

Ten civil and two military centres currently have a hyperbaric chamber (see Figure 25 and Table 13). As mentioned above, ten hospitals originally received a monoplace chamber in the period 1967-1972.[131]

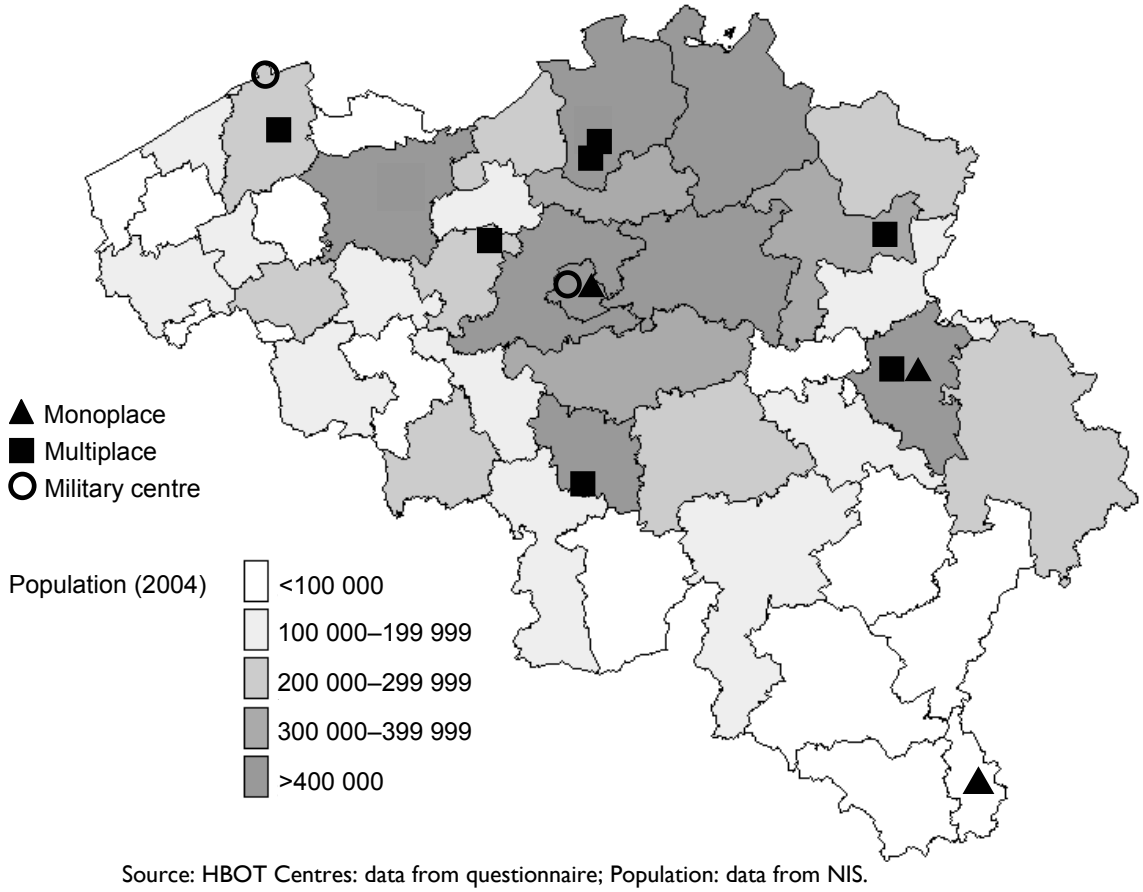
Of these ten, ZNA Stuivenberg Antwerpen, AZ St-Jan Brugge and CHR La Citadelle Liège replaced their old monoplace chambers by a multiplace. Hôpital Civil Charleroi initially replaced its chamber by another monoplace chamber but currently also has a multiplace chamber at their disposal. The University Hospital St Pierre and CHU Sart Tilman Liège replaced their old chamber by a new monoplace chamber. UZ Gent also replaced its chamber by a new monoplace chamber but, in the meanwhile, has stopped its hyperbaric activities.

Two university hospitals never replaced their monoplace chamber: UZ VUB Jette closed its chamber in May 2007 and UZ Leuven closed its chamber about a decade ago.

A few hospitals that initially did not receive a monoplace chamber from the ministry purchased a chamber themselves: OLV Aalst, UZ Antwerpen and ZOL St-Jan Genk purchased a multiplace chamber while Cliniques du sud du Luxembourg Arlon installed a monoplace.

Finally, there are two military centres for hyperbaric therapy: the military hospital at Neder-over-Heembeek and the marine basis of Zeebrugge. The latter is the only hyperbaric centre outside a hospital. Initially, this centre only treated military people with diving accidents. Today, citizens with various pathologies also receive HBOT in this facility.

Figure 25. Overview of Belgian centres with (a) hyperbaric chamber(s)



Source: HBOT Centres: data from questionnaire; Population: data from NIS.

Table 13. Overview of Belgian centres with (a) hyperbaric chamber(s)

Hospital	Chamber type	Number of patients
OLV Ziekenhuis – Aalst [1]	Multiplace	10 sitting or 2 lying
ZNA Stuivenberg Antwerpen [1]	Multiplace	5 sitting or 1 lying
UZ Antwerpen – Edegem [1]	Multiplace	12 sitting or 2 lying
Cliniques du Sud Luxembourg Arlon	Monoplace	1 lying
AZ Sint Jan – Brugge [1]	Multiplace	7 sitting or 2 lying
Hôpital Universitaire St.Pierre Bruxelles	Monoplace	1 lying
CHU de Charleroi Hôpital Vésale, Montigny-le-Tilleul	Multiplace	12 sitting or 2 lying
Ziekenhuis Oost Limburg (ZOL) Genk [1]	Multiplace	12 sitting or 4 lying
CHR La Citadelle – Liege [1]	Multiplace	6 sitting or 2 lying
CHU Sart Tilman – Liege	Monoplace	1 lying
Military Hospital Brussels	2 x Multiplace	20 sitting or 5 lying
Marine basis Zeebrugge	2 x Multiplace	18 sitting or 2 lying

[1] These six hospitals have a recognized diabetic foot clinic.

According to RIZIV/INAMI data from 1989 to 2005, 65[c] Belgian hospitals have invoiced HBOT codes. Since the majority of these hospitals do not have a hyperbaric chamber, they transfer their patients to a nearby hospital for provision of this therapy. Currently, there is no apparent capacity problem and geographic distribution seems sufficient.

5.7 CURRENT PRACTICE BY INDICATION

5.7.1 Results from questionnaire to hyperbaric centres

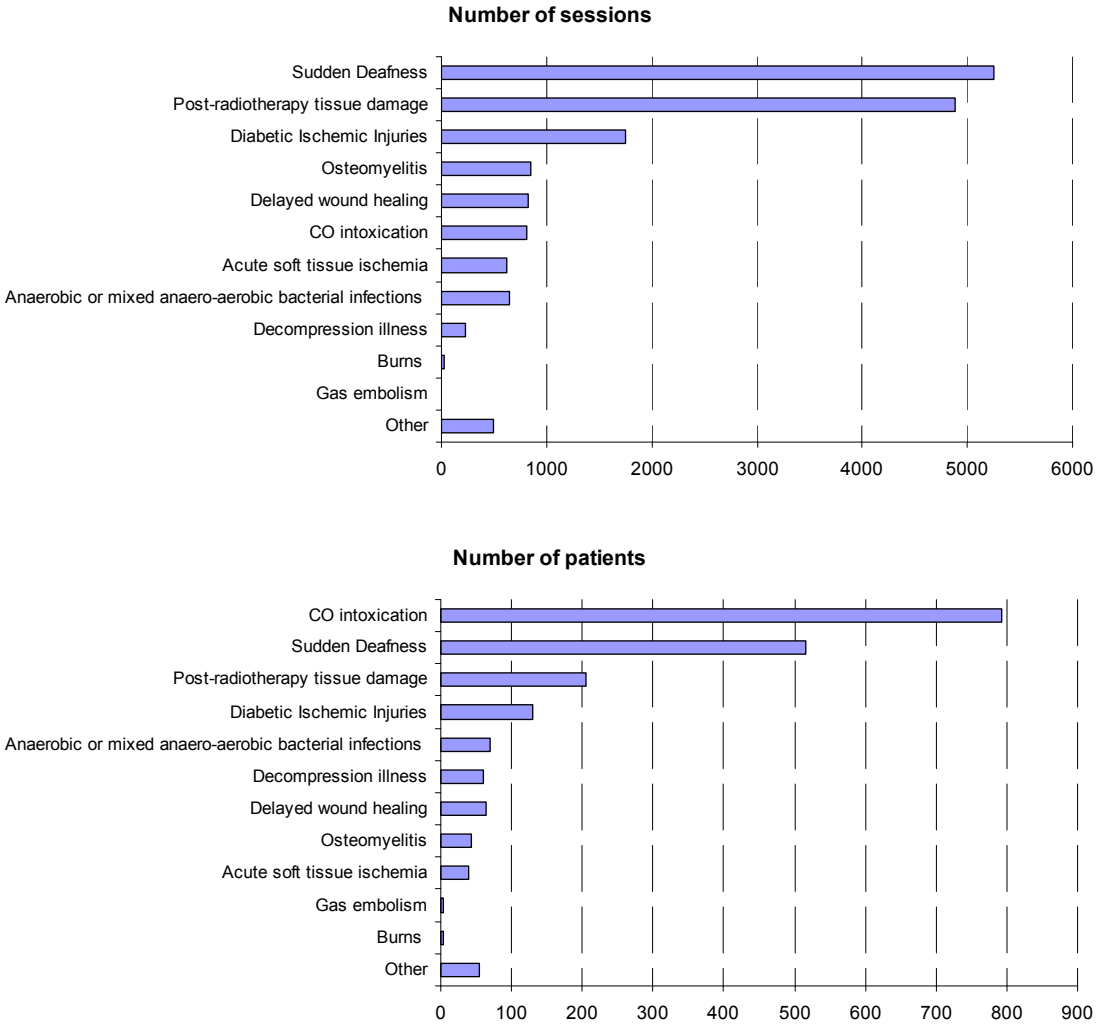
We asked the 12 centres in Belgium to voluntarily report their activities using a questionnaire. An example of this questionnaire is included in appendix. For each of the centres, the person responsible for the hyperbaric chamber was contacted by phone and a questionnaire was then distributed by e-mail. Non-responders received a reminder three weeks after the first mailing by phone and e-mail. Eventually, 11 centres responded leading to a slight underestimation of numbers. The results of this survey are presented in this chapter.

Overview by indication

Based on the data received form those eleven HBOT centres, a total of 1 980 patients were treated in 2006, which accounted for 16 402 sessions. The hyperbaric chamber is most often used for the following two indications: hearing disorders (32% of all reported treatment sessions, 26% of all reported patients), and post-radiotherapy tissue damage (30% of sessions, 10% of patients). However, CO-intoxication provided the largest amount of patients for a single indication (40% of patients) (see Figure 26).

[c] Hospitals that have merged during this period were only counted once.

Figure 26. National use of HBOT in 2006: overview by indication (in number of patients and sessions)



Source: data from questionnaire.
For one hospital, only the total number of sessions for the full year was available. For our estimates, we combined these aggregated data with the average number of sessions by indication from the other hospitals.

Patient mix variations between the centres

The data from the questionnaire reveal a large variation in chamber utilization from centre to centre. Three of the centres use their chamber predominantly for post-radiotherapy tissue damage, i.e. for 66%, 48%, and 40% of their sessions, whereas at three other centres this indication accounts for only 0%, 8% and 9% of the total sessions respectively. One centre uses its chamber mostly for CO intoxication patients (50%). At the other centres, this treatment accounts for only 1 to 18% of all sessions. At three centres the chamber is frequently used for sudden deafness (66%, 39% and 33%), whereas at four other centres this patient group accounts for only 0%, 0%, 2% and 6% of the sessions. All treatments for decompression illness occurred in five centres.

The following three figures show that there is a difference in indications being treated according to type of chamber and to whether or not there is a diabetic foot clinic. In hospitals with a multiplace chamber, sudden deafness is treated more often in comparison to hospitals with monoplace chambers (Figure 27 versus Figure 28 and

Figure 29). Treatment of diabetic ischemic injuries happens, not surprisingly, more often in multiplace hyperbaric facilities with a diabetic foot clinic (Figure 28 versus Figure 29).

Figure 27. Monoplace facilities: 280 patient sessions in 2006

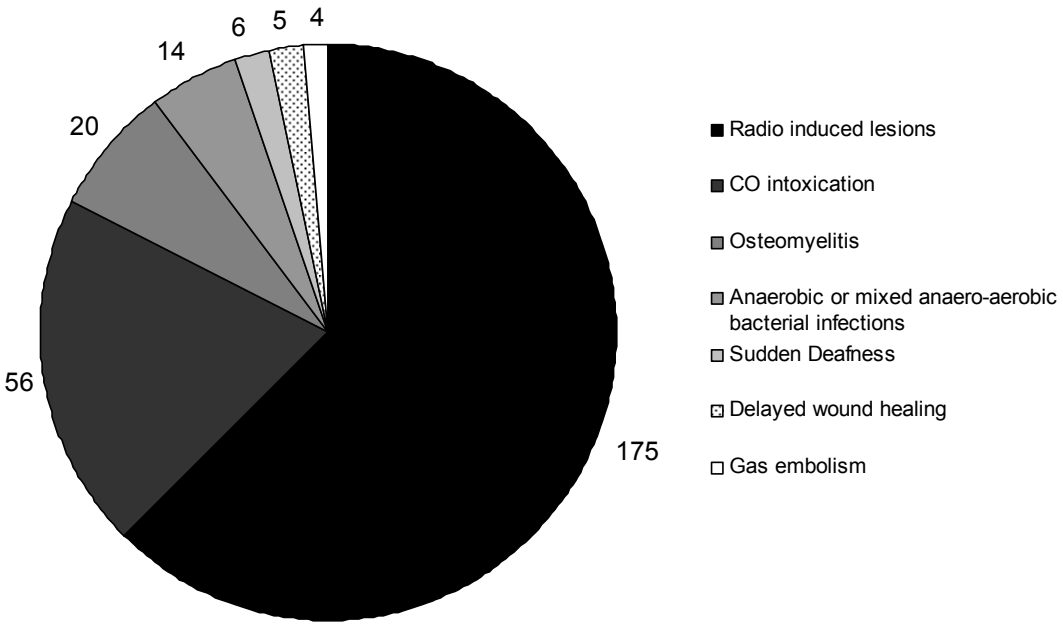


Figure 28. Multiplace facilities with diabetic foot clinic: 10 751 patient sessions in 2006

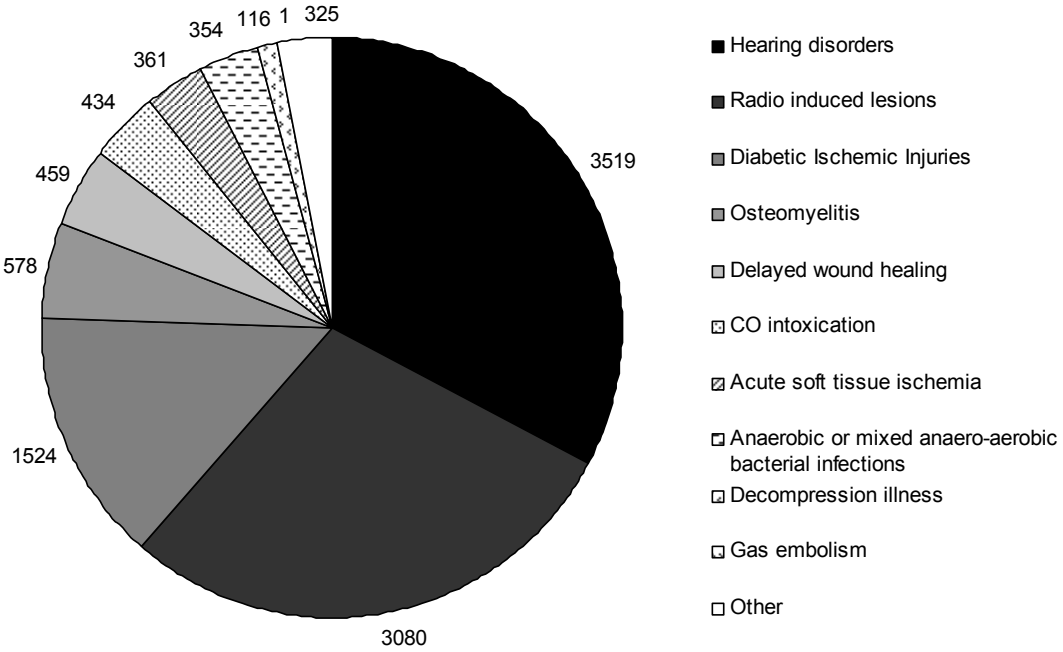
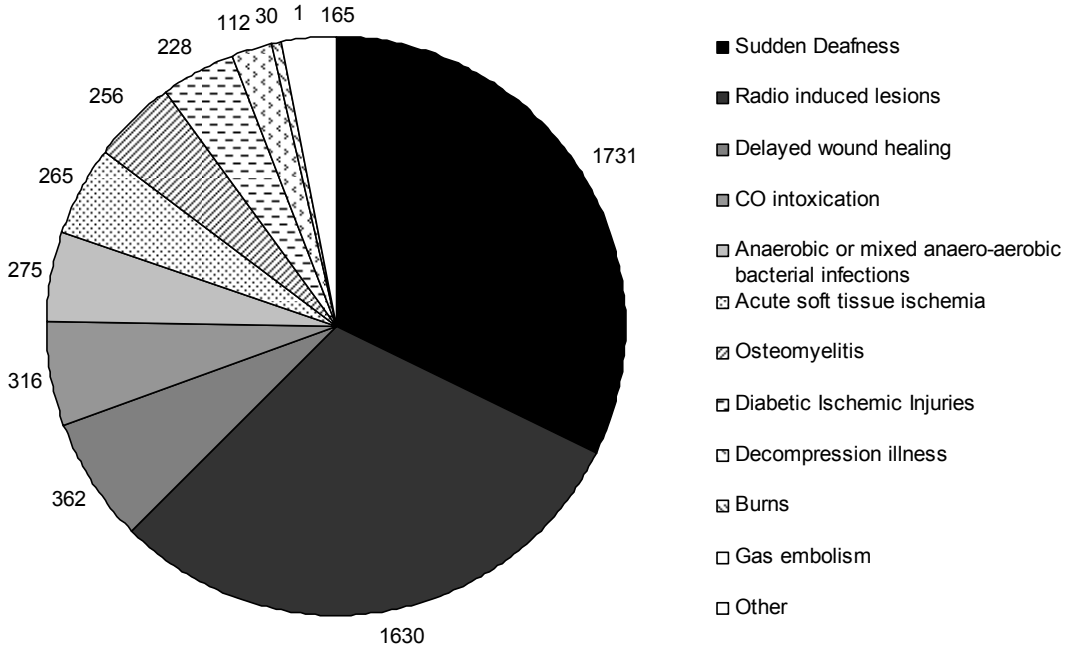


Figure 29. Multiplace facilities without diabetic foot clinic: 5 371 patient sessions in 2006



Capacity utilization of chambers

The capacity utilization of the chambers depends on the number of treatment sessions per day and the average occupancy rate of the chamber during the sessions.

Number of treatment sessions per day

A treatment session takes about 150 minutes, i.e. a dive of 90 minutes and approximately half an hour work before and after the treatment. As a result, a hyperbaric chamber could effectively be used for up to four treatment sessions per day. However, at the Belgian centres, the chambers are used either ad hoc for emergency cases (mainly for the monoplace chambers), or at a fixed scheme of one or two sessions per day (for multiplace chambers).

Number of patient treatment sessions per year

Based on the data we received, the monoplace chambers are used from about 15 to 270 sessions per year. The multiplace chambers are used from 870 "treatment sessions" per year (meaning 870 times that a patient receives a 90 min session) up to 2 700 at two hospitals and about 3 200 at the Military Hospital.

Occupancy rate of the chambers during a session

Based on the two above mentioned inputs and combined with the size of the chamber, the average occupancy rate of the chambers was calculated. Not taking into account whether a patient is sitting or lying, the estimated occupancy rate for the multiplace chambers varies from 30% to over 90%.

5.7.2 Results from financial and clinical registration data

The primary objective of this combined Minimal Clinical Data (MCD) and Minimal Financial Data (MFD) analysis is to complement the data provided through questionnaire by the HBOT centres concerning utilisation of HBOT. It is important to note that ambulatory patients are not included in this analysis.

5.7.2.1 Description of the Minimal Clinical Data set

The minimal clinical data (in Belgium: Résumé Clinique Minimal/Minimale Klinische Gegevens, RCM/MKG) is a compulsory registration of information concerning each hospital stay, whether in classical hospitalization or in one-day clinic. All information is transferred to the Ministry of Health, where the information is compiled by registration year. The data are validated internally and compared with reference lists (on the hospital level and by the Ministry) but the clinical coherency of recorded diagnoses and procedures are not specifically validated. The KCE report on Clinical Quality Indicators[132] provides more details about biases and flaws linked to MCD analysis.

5.7.2.2 Minimal Clinical Data set and Minimal Financial Data (MFD): methodology for this study

Relevant ICD-9-CM procedure codes

The following clinical ICD-9-CM procedure codes were selected (ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification):

- ICD-9-CM 93.95: "Hyperbaric oxygenation"
- ICD-9-CM 93.97: "Decompression chamber"

Relevant billing codes

The following billing codes from the nomenclature apply:

- 212520: "Installatie van en toezicht op zuurstoftherapie in hyperbare drukkamer (ongeacht het aantal zittingen): De eerste dag" / "Installation et surveillance d'une oxygénothérapie en caisson hyperbare (quel que soit le nombre de séances): Le premier jour"
- 212542: "Installatie van en toezicht op zuurstoftherapie in hyperbare drukkamer (ongeacht het aantal zittingen): De tweede dag" / Installation et surveillance d'une oxygénothérapie en caisson hyperbare (quel que soit le nombre de séances): Le second jour

The codes 212516 and 212531 do no apply for MCD/MFD analysis since these are ambulatory codes. The code 760642 does not apply since the military hospital is not registered in the MCD/MFD.

Data selection

The following data were analyzed for the years 2000-2004:

- All coupled stays MCD-MFD
  - having ICD-9-CM 93.95 or 93.97 in field <iccode> in dataset <procicd9> or
  - having 212520 or 212542 in field <nomenclatuurcode> in dataset <prestaties> from MFD
- All non-coupled stays from MCD and day stays having ICD-9-CM 93.95 or 93.97 in field <iccode> in dataset <procicd9>
- The non-coupled stays from MFD having 212520 or 212542 in field <nomenclatuurcode> in dataset <prestaties> from MFD, were not analysed, since for the non-coupled MFD data, there is no diagnosis available. Neither the Anonymous Day Hospitalization data (available for 2004-2005) were analyzed for the same reason.

Overview of retrieved MCD-MFD data

In total 3 959 stays were retrieved, of which 3 179 correctly coupled stays, 60 incorrectly coupled stays, 323 non-coupled MCD stays and 397 non-coupled MFD stays. A full overview of the retrieved data set is provided in appendix.

Diagnosis selection

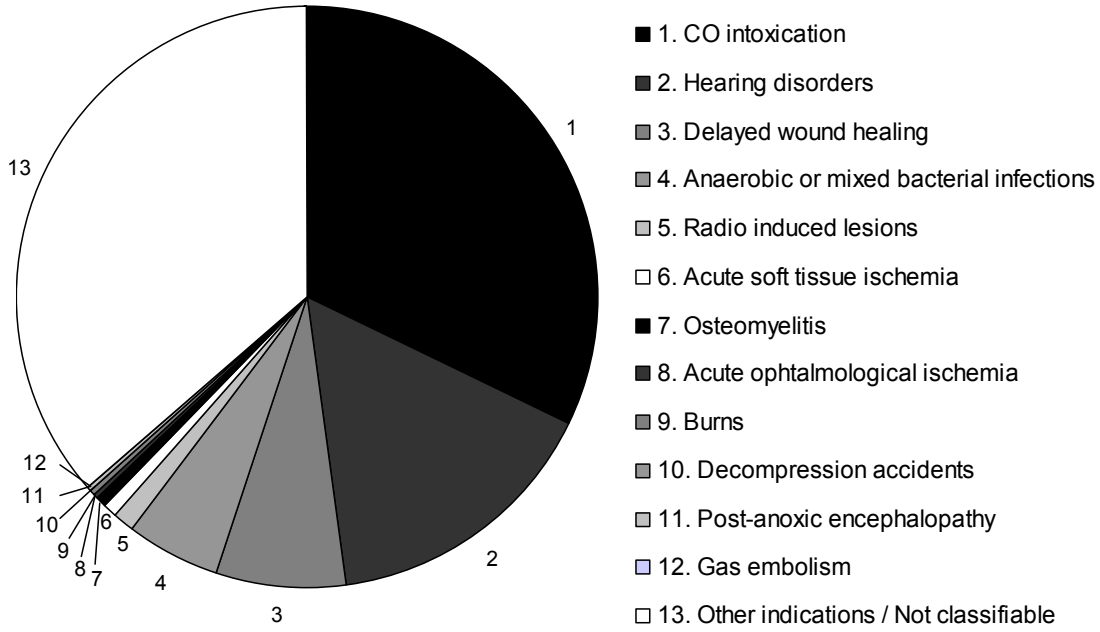
First of all, for MCD with a relevant procedure code, the diagnosis related to the procedure code was selected. If this related diagnosis was a dummy or a diagnosis 'urgent care', the primary diagnosis of the "deelverblijf" (with the same specialization number) was taken. If the resulting diagnosis still was a dummy or an 'urgent care' diagnosis, the primary diagnosis of the full stay was selected. After performing these steps, the diagnosis remained 'urgent care' in 13 cases.

For the coupled MFD with a relevant billing code but no relevant procedure code, the primary diagnosis of the full stay (with the lowest specialization number, being 1) was taken. If the resulting diagnosis was a dummy or a diagnosis 'urgent care', the first-mentioned diagnosis from the full stay, not being a dummy or an 'urgent care' diagnosis, was taken.

5.7.2.3 Results: diagnoses in MCD-MFD data

A total of 3 534 stays between 2000 and 2004 were analyzed for diagnosis. For 2 263 stays, a diagnosis directly linked to the procedure code was available and for 1 271 stays a diagnosis was available through the linkage MCD-MFD (See Table 63 in appendix). After determining a relevant diagnosis code for each stay (see diagnosis selection), we obtained 726 different diagnoses. These diagnoses were grouped into 13 larger categories (Figure 30).

Figure 30. Overview of HBOT in MCD-MFD by diagnosis (based on 3 238 hospital stays in 2000-2004)



Note: From the 3 534 analyzed stays, 296 stays had a diagnosis which occurred only once in the list and were omitted from the analysis

In the category 'other indications', we find, amongst others, the following related diagnoses: anaemia, depression, epilepsy, delivery (breech presentation or "foetal need"), cardiac arrest, headache, etc.

5.8 COST ANALYSIS FROM A PATIENT'S POINT OF VIEW

In this cost analysis, the following costs for the patient are considered: treatment and physician consultation, hospitalization, and transport costs.

5.8.1 Treatment and consultation cost

For the first and second day of HBOT treatment, the fee is determined by RIZIV/INAMI and is 100% reimbursed. From the third day onwards, the centres can freely set their fee. Based on the questionnaire, some centres offer the treatment for free and the hospital bears the full cost of treatment, others ask a fee of around €20-30 per 90-minutes session (covering costs of the treatment, the material needed and the consultation), or a fixed fee of €200 if more than five sessions are needed. One hospital has an agreement with a local sickness fund to reimburse €45 per session. Extra fees could be charged for treatment during the night, weekends and legal holidays. For transcutaneous oxygen measurement, some hospitals ask an extra fee of about €50, while others provide this for free. For monitoring with strip an extra fee is sometimes charged.

HBOT treatment at the military hospital or the marine basis at Zeebrugge is free of charge for the patient. The only exception is for diving accidents when the sports insurer intervenes. For diving accidents, a longer treatment (e.g. US Navy TT6 treatment) may be given, which comes at a considerably higher cost.

A physician consultation fee often has to be paid on top of the HBOT fee. The general fees apply, which imply an out-of-pocket payment of €7.24 for a normally insured patient and €2.47 for a preferentially insured patient.

5.8.2 Hospitalization cost

The daily patient out-of-pocket fees for the hospital stay are shown in Table 14. This price depends on the length of stay and the patient's insurance status. Since transport costs are not reimbursed and because there is no difference in reimbursement of ambulatory versus hospitalized treatment, there is limited, if any, financial incentive for the patient to choose for the ambulatory treatment.

Table 14. Hospitalization costs (2008)

	1st day	2nd to 90th day	From 91th day
Normally insured	€40.86	€13.59	€13.59
With children	€32.10	€4.83	€4.83
Preferential insured	€4.83	€4.83	€4.83

The patient also pays a marginal fixed fee of €0.62 per day for reimbursed drugs, even when the patient has not consumed any drugs.

5.8.3 Transportation cost

As a general rule, outpatient transportation costs are to be paid by the patient. As an exception, for radionecrosis patients having HBOT as part of their follow-up after chemo- and radiotherapy, transportation costs may be reimbursed under public regulations, following a Ministerial Decree of July 6, 1989, and modified by a ministerial decree of May 25, 2007.[d]

Transportation costs (two-way) are then reimbursed according to public transports travel expenses or at a rate of €0.25 per kilometre.

5.9 COST ANALYSIS FROM A HOSPITAL'S POINT OF VIEW

The aim of this analysis is to evaluate the cost of a hyperbaric oxygen session. The costs included are both capital costs (the hyperbaric chamber investment) and operational costs (personnel costs, maintenance costs, oxygen and compressed air, patient consumables, and other overhead costs). Costs not included in this analysis are the pre-treatment consultation costs of the physician, hospitalization costs, and transportation costs. Other costs for e.g. intensive care patients are also disregarded. We would like to stress that this cost analysis is a theoretical calculation of costs. Further research to gather more detailed real-world cost data is desirable.

5.9.1 Investment costs and expected lifetime of equipment

The investment price for multiplace chambers was obtained from Hytech, a supplier from the Netherlands, which only sells multiplace chambers but no monoplace chambers. We also received price information from ETC, an international supplier (headquartered in the US), however, given the higher shipping costs, we preferred to use the price information from the Dutch company. For monoplace chambers, we used price information from ETC and an indicative market price from Hytech. Table 15 shows the average cost and ranges which were used in our cost analysis. To check these numbers, the obtained multiplace chamber price data was compared with figures we received from two Belgian hospitals. Their investment cost, adjusted for inflation, showed comparable figures. For monoplace chambers, Treweek et al.[133] (2006) calculated a price of £102 000 (or about €144 000) for the chamber and the oxygen recirculation system. This cost falls within our price range.

Table 15. Investment cost

	Investment cost (VAT incl.)*		
	Range (€)	**Average (€)**	**Lifetime**
Multiplace chamber 12 persons	750 000 – 850 000	800 000	25 ys +
Multiplace chamber 6 persons	660 000 – 760 000	710 000	25 ys +
Monoplace chamber	115 000 – 165 000	140 000	10 ys +

VAT: value-added tax

* Including shipping and installation costs

According to the vendors of hyperbaric chambers, the expected lifetime of a multiplace chamber is 25 to 30 years or even more. Today, there are examples of multiplace chambers that were built more than 30 years ago and that are still in use. According to the manufacturers, multiplace chambers would have a more extended lifetime than monoplace chambers.

[d] MB tot wijziging van het MB van 6 juli 1989 tot vaststelling van de tegemoetkoming van de verplichte ziekte- en invaliditeitsverzekering en van de toekenningsvoorwaarden voor die tegemoetkoming in de reiskosten van ambulant behandelde patiënten aangetast door ziekten die hetzij een chemotherapeutische behandeling bij middel van geneesmiddelen behorend tot de categorie A, hetzij een behandeling met stralingen vergen.
AM du 6 juillet 1989 fixant l'intervention de l'assurance obligatoire contre la maladie et l'invalidité et les conditions d'octroi de cette intervention dans les frais de voyage des patients traités ambulatoirement atteints de pathologies nécessitant soit un traitement chimiothérapique au moyen d'une médication de la catégorie A, soit un traitement par radiations.

A monoplace chamber must be inspected at ten years and if satisfactory can be used for another ten years. In line with the MSAC (2000) report[69] and analysis of Treweek et al.[133], an average lifetime of ten years is assumed for monoplace chambers.

An annual equivalent cost (AEC) was calculated over a period of 25 and ten years for a multi- and monoplace, respectively. According to the KCE guidelines,[134] a discount rate of 3% was applied using the following formula:[72]

$$K = AEC + AEC/(1 + r) + AEC/(1 + r)^2 + \ldots AEC/(1 + r)^{n-1}$$

$$\rightarrow AEC = K / (A_{n-1,r} + 1)$$

- AEC = annual equivalent cost
- n = useful life of equipment
- r = discount rate (3%)
- A(n,r) = the annuity factor (n years at interest rate r)
- K = purchase price

5.9.2 Operational costs

In this cost analysis, the operational costs contain the following items: personnel, equipment maintenance, oxygen and compressed air, patient consumables, general maintenance, and overhead.

5.9.2.1 Personnel requirements

According to ECHM recommendations, a minimum work force is necessary to ensure safety. For a multiplace chamber, a physician, a care-attendant (nurse) and an operator should be present. For a monoplace chamber, only a physician and an operator are required. We assumed that the physician is still able to perform other tasks at e.g. the emergency unit. A 50% presence for HBOT was assumed. Additionally, a person for emergency assistance should be available. Furthermore, there are also personnel costs for the management and administration of the hyperbaric chamber.

In most centres, a session takes 90 minutes. In some centres, however, a number of breaks are given, increasing the required time to 99, 110 or 120 minutes. We took into account the shortest treatment session of 90 minutes. On top of this, another 30 to 60 minutes per session is required for patient assessment, treatment preparation and quality assurance.[69] An overview of our assumptions is provided in Table 16, Table 17 and Table 18. In order to calculate the total number of sessions that can be given per year, it is assumed that the chamber is operated 5 days per week and 48 weeks per year.

Table 16. Required time and personnel during a treatment session

	Required time	Required personnel
For multiplace scenarios		
Patient assessment, treatment preparation and finalization and quality assurance	60 min	1 physician (50%) 1 nurse
Patient treatment	90 min	1 physician (50%) 1 attendant (nurse) 1 operator (nurse)
For monoplace scenarios		
Patient assessment, treatment preparation and finalization and quality assurance	60 min	1 physician (50%) 1 nurse
Patient treatment	90 min	1 physician (50%) 1 operator (nurse)

Table 17. Required time for management and administration

	Required time	Required personnel
For multiplace scenarios		
Administration	30 min. fixed administration per session + 6 min. per patient	1 nurse
For monoplace scenarios		
Administration	30 min. per session	1 nurse

Table 18. Weekly/Yearly work schedule

Treatment days/week	5 days/week
Treatment weeks/year	48 weeks/year

For the cost of the hyperbaric physician, the average cost of an emergency care specialist or an anaesthesiologist with an average seniority of 20 years at two university hospitals is used. For the cost of a nurse, the average cost of an A1 and A2 nurse with an average seniority of 20 years at two university hospitals is used (Table 19). The assumptions to calculate the cost per hour for each of the staff members are shown in Table 20.

Table 19. Average cost per FTE

Employee	Average Yearly Cost per FTE*	Average Gross wage per FTE
Physician	151 000	101 000
Nurse (average A1, A2)	58 500	37 500
Nurse A1	62 000	40 000
Nurse A2	55 000	35 000

FTE: full time equivalent

* including gross wage, employer's contributions (35% on gross wage), holiday pay (legally at 92% of gross month wage), end of year pay (~30 % of gross month wage + 35% employer's contributions). Including also an indirect personnel cost of 4 000€ per FTE for HR services, HR administration, office equipment, IT, telecom and other administrative costs (source: UZA).

Table 20. Personnel parameters

Working hours / week per FTE	38	
Working weeks / year per FTE	45	Taking into account holidays
% productive hrs / total working hrs	90%	Taking into account sick time and other service-related duties (general meetings, training, …)

5.9.2.2 Equipment maintenance

For a 6-person multiplace chamber, we received an estimate for equipment maintenance cost from AZ Sint Jan Brugge. For a 12-person multiplace chamber, we received an estimate from UZ Antwerpen. This maintenance cost includes preventive and corrective maintenance, replacement of components and a maintenance contract with the supplier. As a percentage of the above mentioned investment price, the maintenance cost varied from 1.4% to 1.5%. Therefore, we assume a mean maintenance cost of 1.5% (with a range of 1 to 2%) (Table 21).

Table 21. Equipment maintenance cost data

	Mean equipment maintenance cost (€)	% of investment price
Multiplace chamber 6 persons	10 650	1.5 % (range: 1% – 2 %)
Multiplace chamber 12 persons	12 000	1.5 % (range: 1% – 2 %)
Monoplace chamber	2 100	1.5 % (range: 1% – 2 %)

5.9.2.3 Oxygen and compressed air cost

The assumptions on oxygen and compressed air costs are presented in Table 22.

Table 22. Oxygen and compressed air cost calculation

Oxygen	Cost/Consumption	Source
Unit cost of oxygen	€0.5 / m3 (€0.5 / 1000 liter)	(Estimate St Jan Brugge)
Oxygen consumption	50 liter / min * 90 min	(Estimate St Jan Brugge)
	➔ €2.25 per patient per session	
Compressed air		
Cost of compressed air	€1 per session	(Estimate St Jan Brugge)

5.9.2.4 Patient consumables

Patient consumables are estimated at €7 per patient (source: UZ Antwerpen) for materials such as masks and filters. Since the number of sessions varies both between and within indications, we preferred to calculate the cost per session.

To calculate the total cost per patient, the number of sessions should be multiplied with the cost per session and the consumable cost per patient should be added.

5.9.2.5 Overhead: property, maintenance, heating and general costs

It is important to note that the general overhead costs (such as property, maintenance, heating and other general costs) are already covered by the hospital financing (part A1 and B1). However, in order to make the cost overview complete, these cost factors are also included in this cost study.

Overhead costs are calculated based on data obtained from UZ Antwerpen, AZ St Jan Brugge and UCL. Property costs cover the depreciation of the building. General overhead covers the following items: internal patient transport, internal and external transport of consumables, taxes, insurance costs, religious service and mortuary. Maintenance costs cover the following costs: cleaning personnel, cleaning products, general technical maintenance, security and utilities (water, gas, electricity). Heating costs cover both the fuel and heating engineer costs. See Table 23 for an overview of these cost items.

Table 23. Property and general overhead costs (€ per m2)

	Average of 3 hospitals
Depreciation of building	42.02
General overhead	42.38
Maintenance	73.16
Heating	15.91
Total	173.47

The following floor space assumptions are made in order to determine these overhead costs (Table 24):

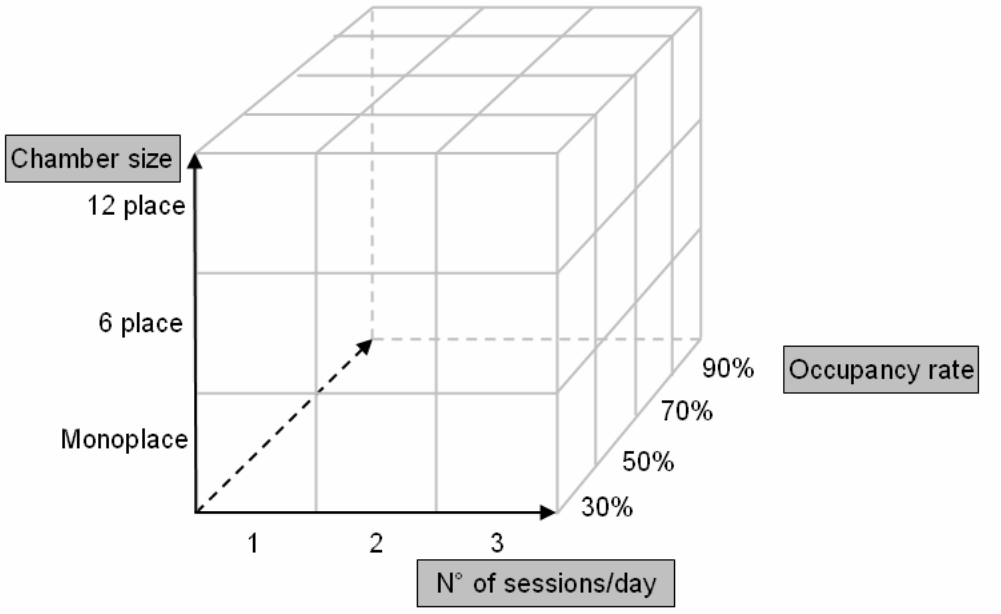
Table 24. Floor space assumptions for overhead costs

	Floor space assumptions	Source
Monoplace	13.5 m^2	Treweek et al.[133] ("3m x 4.5m x 3m")
6-persons chamber	65 m^2	AZ St Jan Brugge
12-persons chamber	88 m^2	UZ Antwerpen

5.9.3 Overview of analyzed scenarios

Different scenarios were simulated according to chamber size, average number of sessions per day, and average occupancy rate of the chamber. Concerning chamber size, three scenarios are analyzed: a monoplace chamber, a six- and a 12-place chamber. Most of the Belgian centres can be put into one of these three categories (see section 5.6). Furthermore, there are three scenarios on the average number of sessions per day, i.e. one, two or three. Theoretically, up to four sessions could be given per day. Currently, however, only up to two sessions are given at the Belgian centres. Therefore, we restrict our analysis to the three proposed scenarios. Finally, four scenarios on the occupancy rate are analyzed: 30%, 50%, 70% and 90%. These are the approximate occupancy rates that were actually observed at Belgian hospitals (see section 5.7.1). By combining all these scenarios, 36 outcomes are obtained (Figure 31). However, not all of these scenarios are realistic, e.g. a chamber with 3 sessions per day with occupancy rate of only 30%, since it would reasonable to assume that instead one or two sessions per day would be given with a higher occupancy rate. However, for the completeness of the exercise, no scenarios were omitted.

Figure 31. Overview of scenarios



5.9.4 Variables with probability distribution functions

Many of the input variables in this cost analysis are estimates of costs that in reality can be quite variable and uncertain. For some of these uncertain values we therefore determined probability distribution functions. The following distribution functions were applied (see Table 25).

Table 25. Distribution functions for input variables

Variable	Base Case value	Lower Bound	Upper Bound	Distribution
Investment 12-multiplace	800 000	750 000	850 000	Uniform
Investment 6-multiplace	710 000	660 000	760 000	Uniform
Investment monoplace	140 000	115 000	165 000	Uniform
Maintenance cost as % of inv. Price	1.5%	1%	2%	Beta

For investment price a uniform distribution is applied. For the proportion variable maintenance cost (as % of investment price), a beta distribution is applied. The impact of lifetime of the equipment is afterwards analyzed through one-way sensitivity analysis (see section 5.9.6).

5.9.5 Results: cost per patient per session

By applying probabilistic modelling and running 1000 Monte Carlo simulations, the uncertainty of the input variables is translated into uncertainty on the result. In the following figure (Figure 32), the mean cost per patient per session is shown for each of the 36 scenarios. Table 26 also provides the credibility interval, total number of patients being treated and use of personnel.

Figure 32. Average cost per session: 3-way scenario analysis

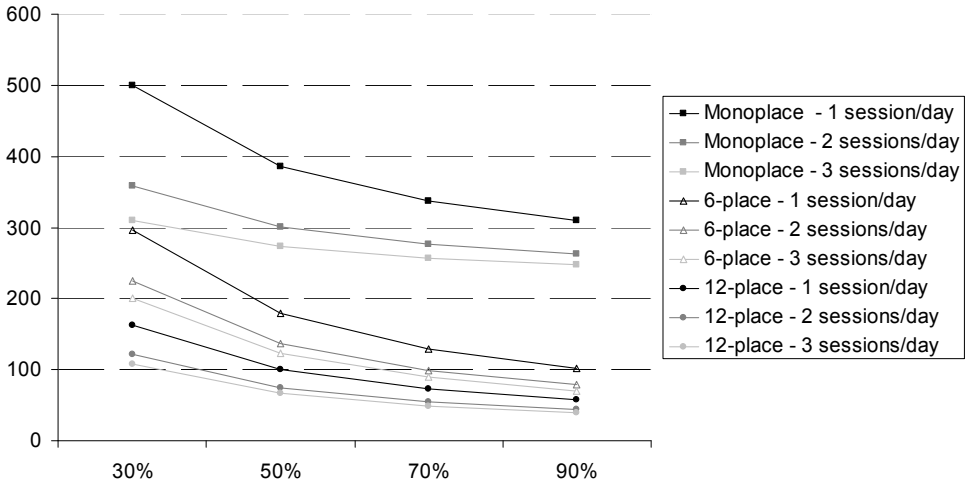


Table 26. Summary of results

	Average cost per session	95% Credibility Interval	Total number of patient sessions yearly	FTE's physician	FTE's nurse
Monoplace					
1 session/day – 30%	499	456 - 544	72	0.06	0.14
1 session/day – 50%	386	360 - 413	120	0.10	0.23
1 session/day - 70%	338	319 - 357	168	0.14	0.33
1 session/day - 90%	311	296 - 326	216	0.18	0.42
2 sessions/day – 30%	358	336 - 380	144	0.12	0.28
2 sessions/day – 50%	301	288 - 315	240	0.19	0.47
2 sessions/day - 70%	277	268 - 287	336	0.27	0.65
2 sessions/day - 90%	263	256 - 271	432	0.35	0.84
3 sessions/day – 30%	311	296 - 326	216	0.18	0.42
3 sessions/day – 50%	273	264 - 282	360	0.29	0.70
3 sessions/day - 70%	257	250 - 263	504	0.41	0.98
3 sessions/day - 90%	248	243 - 253	648	0.53	1.26
6-place chamber					
1 session/day – 30%	295	284 - 307	432	0.19	0.73
1 session/day – 50%	180	173 - 186	720	0.19	0.75
1 session/day - 70%	130	125 - 135	1008	0.19	0.77
1 session/day - 90%	102	99 - 106	1296	0.19	0.79
2 sessions/day – 30%	224	219 - 230	864	0.39	1.46
2 sessions/day – 50%	137	133 - 140	1440	0.39	1.50
2 sessions/day - 70%	99	97 - 102	2016	0.39	1.53
2 sessions/day - 90%	79	77 - 80	2592	0.39	1.57
3 sessions/day – 30%	201	197 - 204	1296	0.58	2.19
3 sessions/day – 50%	123	120 - 125	2160	0.58	2.25
3 sessions/day - 70%	89	88 - 91	3024	0.58	2.30
3 sessions/day - 90%	71	69 - 72	3888	0.58	2.36
12-place chamber					
1 session/day – 30%	163	157 - 169	864	0.19	0.76
1 session/day – 50%	100	96 - 104	1440	0.19	0.80
1 session/day - 70%	73	70 - 76	2016	0.19	0.83
1 session/day - 90%	58	56 - 60	2592	0.19	0.87
2 sessions/day – 30%	121	118 - 124	1728	0.39	1.52
2 sessions/day – 50%	75	73 - 77	2880	0.39	1.59
2 sessions/day - 70%	55	54 - 56	4032	0.39	1.67
2 sessions/day - 90%	44	43 - 45	5184	0.39	1.74
3 sessions/day – 30%	107	105 - 109	2592	0.58	2.27
3 sessions/day – 50%	67	65 - 68	4320	0.58	2.39
3 sessions/day - 70%	49	48 - 50	6048	0.58	2.50
3 sessions/day - 90%	39	39 - 40	7776	0.58	2.61

Figure 33 to Figure 35 show the weight of different cost components in the total average cost per session for three different scenarios. These rather realistic scenarios, i.e. with one or two sessions per day and a high occupancy rate, show that the main cost driver is personnel costs.

Figure 33. Cost per session subdivided by cost component (6-place chamber, one session per day, and 90% occupancy rate)

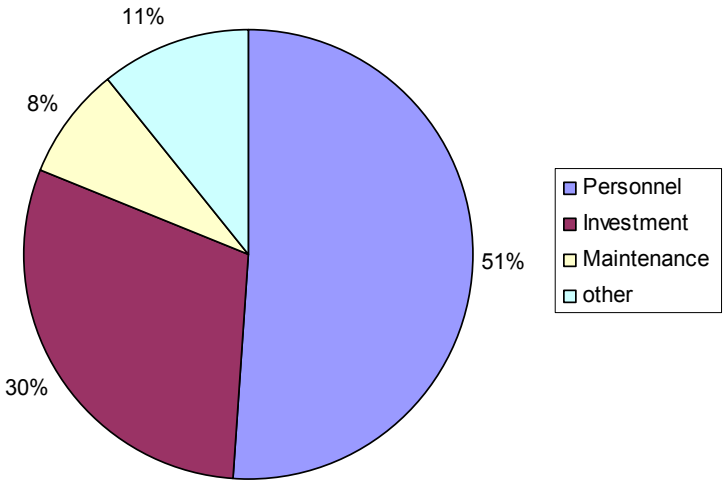


Figure 34. Cost per session subdivided by cost component (6-place chamber, two sessions per day, and 90% occupancy rate)

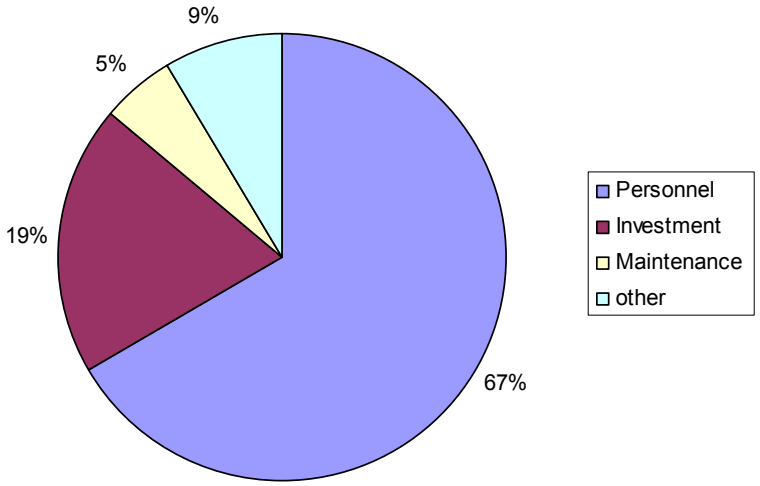
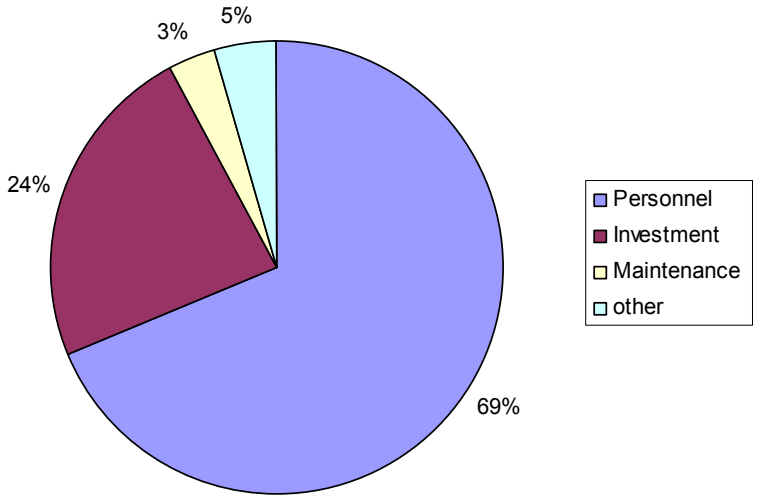


Figure 35. Cost per session subdivided by cost component (monoplace chamber, one session per day, and 90% occupancy rate)



5.9.6 Impact of lifetime of the equipment

In order to calculate the impact of a shorter or longer lifetime of the hyperbaric chamber, a one-way sensitivity analysis was performed. Figure 36 and Figure 37 show that the impact of the lifetime of the equipment is rather limited.

This is in line with our expectations, as personnel costs are the most important cost factor of this therapy.

Figure 36. One-way sensitivity analysis: impact of equipment lifetime on cost per session (monoplace chamber, two sessions per day, and 90% occupancy rate)

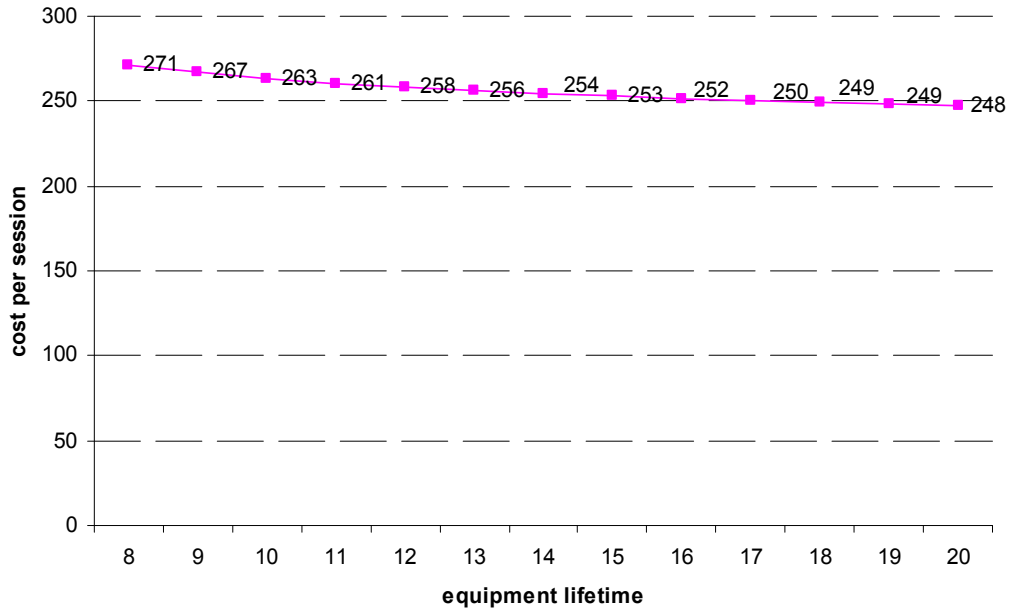
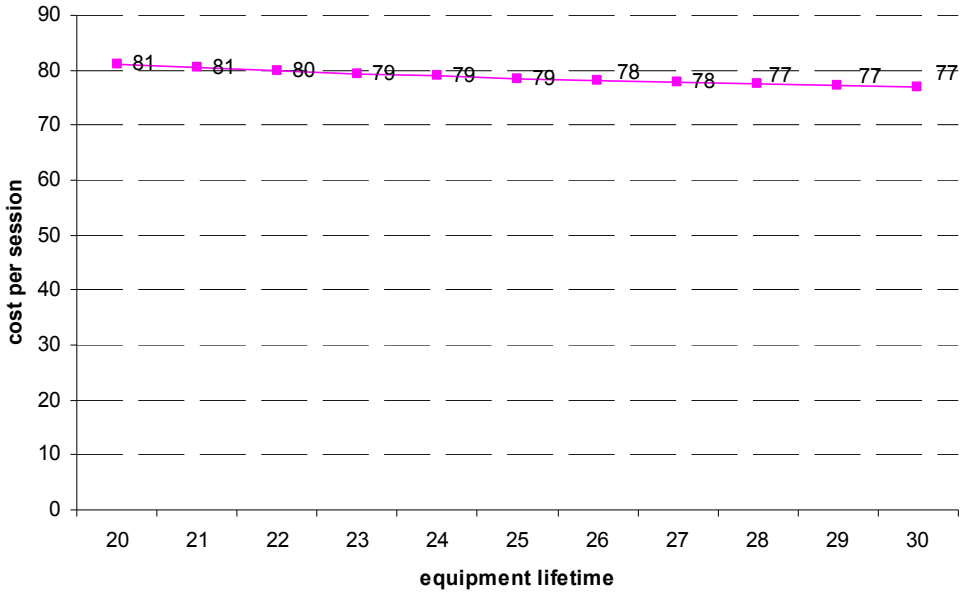


Figure 37. One-way sensitivity analysis: impact of equipment lifetime on cost per session (6-place chamber, two sessions per day, and 90% occupancy rate)



5.9.7 Discussion

The largest cost component of the hyperbaric therapy is the personnel cost (48-77% varying from scenario for multiplace chambers), followed by the investment cost of the hyperbaric chamber (15-32%). The cost of oxygen and pressurized air is only marginal (1-6%).

The cost of running a monoplace chamber is significantly higher than that of a multiplace chamber. If a monoplace chamber is used one session a day with an occupancy rate of 90%, the cost per session is on average €311, compared to the cost of a 6- and 12-place of €102 and €58, respectively, taking into account the same number of sessions per day (one session) and occupancy rate (90%). The significantly larger cost for the monoplace chamber is driven by the higher average personnel cost per patient and the relatively larger investment cost per patient (in absolute numbers).

Furthermore, and not surprisingly, we observe that a higher occupancy rate and more sessions per day result in a lower average cost per session. Moreover, we also notice that in order to control the personnel costs, it is more cost-efficient to work fewer sessions per day with a higher occupancy rate, than vice versa. For example, in a 12-place chamber, one session per day with a 90% occupancy rate results in an average cost per session of €58. In contrast, three sessions per day with a 30% occupancy rate, offering the same amount of patient sessions, results in an average cost of €107.

Currently, HBOT centres offer one or two sessions per day. With two sessions per day and an occupancy rate of 90%, a monoplace chamber offers 432 treatment sessions per year. This is nearly 2 600 and 5 200 patient sessions per year for a 6-place and 12-place chamber, respectively. Currently, there is no shortage of capacity since several centres have a lower occupancy rate and because more treatment sessions per day could be offered.

Key points

- **In Belgium, there are ten civil and two military centres with a hyperbaric chamber.**
- **According to data from these centres, more than 2 000 patients were treated in 2006 and more than 16 000 sessions were given.**
- **For less than 9% of all sessions, there was a partial reimbursement from health insurance.**
- **The Belgian HBOT chambers are predominantly used for two indications: hearing disorders (32% of all treatment sessions) and radio induced lesions (30% of all sessions).**
- **There is a large variation in patient mix from centre to centre.**
- **The current fee-for-service codes leave room for a relatively broad interpretation. In daily practice, HBOT centres apply the codes in various ways.**
- **On the condition that the hyperbaric chamber is efficiently run, HBOT can cost less than €100 per patient per session.**
- **The major cost driver is the personnel cost. It is therefore more efficient to work fewer sessions per day with a higher occupancy rate than vice versa.**
- **A 6-place and 12-place chamber can offer respectively 2 600 and 5 200 patient treatment sessions per year (two sessions per day and 90% occupancy rate).**
- **There is no capacity problem and geographic distribution seems sufficient.**

6 INTERNATIONAL COMPARISON

6.1 THE NETHERLANDS

6.1.1 Hyperbaric centres

The Netherlands had 16.32 million inhabitants in 2005 and an area size of 41 000 km^2.[e] In the Netherlands there are 11 hyperbaric centres. They are listed in Table 27.

Table 27. Hyperbaric centres in the Netherlands

Place	Location	Max. n° of persons	Pressure (bar)
Amsterdam	AMC	20	2
Bergen op Zoom	Hyperbaar Centrum Oosterschelde	4	10
Den Helder	Duikmedisch Centrum	8	10
Empel	Genie Fort Landmacht	3	5
Hoogeveen	Inst. Hyperbare Geneeskunde	12	
Maarsseveen	Duikcentrum MP	4	6
IJmuiden	Wijsmuller	6	6
Rotterdam	SmitTak (mobiele tank)	2	6
Rotterdam	Inst. Hyperbare Geneeskunde	unknown	unknown
Vlissingen	Van den Akker	3	10
Zwijndrecht (NL)	Hyperbaar Zuurstof Centrum Rijnmond	unknown	unknown

Source: http://www.b-artcreatives.nl/dive4life/reco.htm (12 December 2007); http://www.ivhg.nl/

6.1.2 Covered indications

According to the CVZ (College Voor Zorgverzekeringen),[135] there is sufficient scientific data and a broad acceptation within the professional group for several indications. For these indications, HBOT is therefore covered by the national insurance package under the specific conditions:

- Decompression illness and gas embolism
- CO intoxication, in case of decreased consciousness at moment of hospitalization, clinical neurologic, cardiac, pulmonary or psychic symptoms, pregnancy
- Soft tissue infections (anaerobic or mixed) as additional treatment to maximum chirurgical therapy: gas gangrene, necrotising fasciitis, anaerobic cellulitis
- Crush injuries, compartment syndromes, and other acute traumatic ischemia
- Osteoradionecrosis of the mandible, as well as treatment as prevention with implants
- Hemorrhagic cystitis after irradiation when conventional therapy is not effective
- Radiation proctitis and enteritis
- Compromised skin grafts and myocutaneous flaps
- Diabetic ulcers in case of insufficiënt result from maximum conventional treatment
- Chronic refractory osteomyelitis
- Larynx radionecrosis
- Re-implantation of fingers/extremities

According to the CVZ, there is a lower level of evidence for other indications for which there is only casuistic literature, small series or it concerning rare/serious diseases.

[e] Source : OECD demographic data 2007

As for these rare diseases a high level of evidence cannot be expected, the CVZ applies an adjusted evaluation procedure. For these diseases, the CVZ has based its evaluation on the state of research and practice within the international professional group. The CVZ has not evaluated the necessity and effectiveness of the treatment. This needs to be evaluated case by case by the insurer. It concerns the following indications for which the effectiveness of the therapy needs to be evaluated at individual level by the insurer:

- Relapse neuroblastoma grade IV
- Osteoradionecrosis at other places than the mandible
- Radionecrosis soft tissue other than head/neck/pelvic
- Surgery and implants of irradiated tissues other than the head/neck area
- Pneumatosis intestinalis.

6.1.3 Non-covered indications

HBOT is not part of the insured care for the following indications, as there is neither sufficient scientific proof nor a broad acceptation within the professional group:

- Acute deafness
- Tinnitus
- Non-diabetic ulcers, such as decubitus, arteriosclerotic and venous ulcers
- Cerebral hypoxia, traumatic or after a stroke
- Burns
- Ischemic ocular disorders/abnormalities
- Radionecrosis of the central nervous system
- Multiple sclerosis (based on Cochrane review 2004)
- Acute coronary syndrome (based on Cochrane review 2005)
- Malign otitis externa (based on Cochrane review 2005)
- Acute traumatic brain damage (based on Cochrane review 2004)
- Anoxic encephalopathy

6.1.4 Reimbursement level

The NZA (Nederlandse Zorg Authoriteit) published the following reimbursement price for treatment with hyperbaric oxygen (declaration code 39995) per session per patient (independent from whether alone or in group)[f]:

- Hospital costs: €160.00
- Fee for specialists: €0.00

For hospitals, this amount is fixed and compulsory. For ZBCs (Zelfstandige Behandelcentra), clinics and independent specialists this is a maximum amount and in practice many insurers only pay about 75% of this maximum (based on expert communication).

6.2 FRANCE

6.2.1 Hyperbaric centres

France had a population of 60.87 million people in 2005 on an area of 549 000 km^2.[g] There are 23 civil and 4 military centres offering HBOT (Table 28).

[f] Source: http://ctg.bit-ic.nl/Nzatarieven/top.do

[g] Source : OECD demographic data 2007

Table 28. Hyperbaric chambers in France

Caissons civils
Le Havre - Hôpital Jacques Monod
Bordeaux - Centre Hospitalier Pellegrin-Tripode
Brest - C.H.U. de la Cavale Blanche
Aix En Provence - Clinique Axium
Ajaccio - Centre Hospitalier de la Miséricorde
Marseille - CHU Sainte-Marguerite
Marseille - Polyclinique Clairval
Marseille – Clinique Cardiovasculaire Valmante
Marseille – Clinique La Résidence du Parc
Nice - Hôpital Pasteur
Perpignan - Clinique Saint Pierre
Toulon - Hôpital Font-Pré
Paris - Centre Médico-Chirurgical de la Porte de PANTIN
Paris - Hôpital Raymond Poincaré
Angers - Centre Hospitalier Régional d'Angers
Avignon - Polyclinique Urbain V
Besancon - C.H.R.U Jean Minjoz (caisson biplace)
Lille - Hopital Albert Calmette
Lyon - Hopital Edouard Herriot
Nancy - Hopital Central
Reims - Hôpital Maison Blanche
Strasbourg - Hôpital de Hautepierre
Toulouse - CHU Purpan
Caissons militaires
Brest - Caisson hyperbare de la Base protégée
Toulon - Hôpital d'Instruction des Armées SAINTE-ANNE
Paris - Hôpital d'Instruction des Armées du VAL DE GRACE
Metz - Hopital d'Instruction des Armées LEGOUEST

Source : http://www.medsubhyp.com/ ("Société de Physiologie et de Médecine Subaquatiques et Hyperbares de langue française")

6.2.2 Covered indications

There is no restrictive list for HBOT reimbursement in France.

6.2.3 Reimbursement level[h]

Before 2004

Before 2004, the tarification of public and private hospitals was different. The public hospitals were paid per DRG by a global budget. For these hospitals, there was no specific tariff per HBOT session independently from the patient's pathology. For the private practice (clinics or independent practitioners) the reimbursement was based on the NGAP (nomenclature générale des actes professionnels) with a system of characters and coefficients. As such, a session YYYY144 was invoiced at the level of K15, a session YYYY169 at K50 and YYYY196 at K100 (see Table 30).

Transition towards T2A system ("Tarification à l'Activité")

Since 2004, France has changed towards the T2A system of which one of the objectives is to have a convergence of public and private hospitals for the reimbursement. There has been an elaboration of a new catalogue with "acts" based on three parameters, amongst which l'ICR (index de complexité relative) which aims at objectifying the remuneration per "act" in function of the financial investment, operational costs, time and intellectual investment of the physician. In this system, two "acts" for HBOT are currently recognized (Table 29):

[h] According to personal communication with Prof. Dr. D. Mathieu (CHRU Lille) December 2007

Table 29. Two acts for HBOT currently recognized in the T2A system

Session for a patient "MCO" (Médecine, Chirurgie et Obstétrique) (emergency or non emergency)	€137
Intensive Care unit patient	€640 added, including all ICU treatments

The CNAM (Caisse Nationale de l'Assurance Maladie) that pilots this reform of nomenclature currently discusses with the medical hyperbarists how to enrich the nomenclature in order to better reflect the real costs.

For the public sector, the transition to the T2A is progressively made. In 2008, the tariff should be fully implemented. For the transition of the liberal sector, provisional "acts" have been created in the nomenclature, which are equal to the old "acts" of the NGAP (Table 30).

Table 30. Provisory acts for the liberal sector (in transition to the T2A 100%)

Code	Description	Tarif acte en €
YYYY144	Séance d'oxygénothérapie hyperbare, en série, avec séance quotidienne d'une heure, comprenant toute modalité de surveillance, à une pression de deux à trois bars absolus (ATA)	€28.8 par séance quotidienne d'une heure par séance et par patient
YYYY169	Traitement hyperbare avec médecin en dehors du caisson. Avec ou sans enrichissement en oxygène. Traitement hyperbare des états de détresse cardiorespiratoire et des accidents de plongée, comprenant l'ensemble des actes de réanimation nécessaires	€96 par vacation de 6 heures
YYYY196	Traitement hyperbare avec médecin à l'intérieur du caisson. Traitement hyperbare des états de détresse cardiorespiratoire et des accidents de plongée, comprenant l'ensemble des actes de réanimation nécessaires	€192.00 par vacation de 6 heures

Source: http://www.codage.ext.cnamts.fr/ November 2007

6.3 UNITED KINGDOM

6.3.1 Hyperbaric centres

The UK had 59.99 million inhabitants in 2005 on an area of 245 000 km^2.[i] There are 18 centres member of the British Hyperbaric Association.
In the UK, a distinction is made between four categories of hyperbaric centres, providing different categories of services:

Table 31. Four categories of hyperbaric centres in the UK

Category	Description
Category 1	Facilities should be capable of receiving patients in any diagnostic category who may require Advanced Life Support either immediately or during hyperbaric treatment.
Category 2	Facilities should be capable of receiving patients in any diagnostic category who are judged by the referring medical officer not to be likely to require Advanced Life Support during hyperbaric treatment.
Category 3	Facilities should be capable of receiving emergency referrals of divers and compressed air tunnel workers. These facilities should also be capable of providing elective treatment of residual symptoms of decompression illness. Patients may be accepted, in the name of the Medical Director (whose role is defined in para 24 of the Cox Report), even when no Hyperbaric Duty Doctor is available at the time of referral provided, in the view of the referring clinician, the patient's condition demands immediate action. This does not obviate the need for discussion with the Hyperbaric Duty Doctor who should attend the patient as soon as is practicable.
Category 4	Facilities should be capable of receiving elective and emergency referrals of patients in any diagnostic category who are judged by the referring medical officer, on the advice of the Hyperbaric Duty Doctor, not to be likely to require access during hyperbaric treatment. Normally monoplace chambers are not suitable for the immediate treatment of acute decompression illness.

Source: http://www.hyperbaric.org.uk/chamberCategories.htm

[i] Source: OECD demographic data 2007

The majority of units providing services to the NHS are registered with the British Hyperbaric Association which is not regulatory, but aims to provide standards for benchmarking purposes and to facilitate research.[i] There are 18 centres member of the British Hyperbaric Association (Table 32).

Table 32. Hyperbaric chambers in the UK

Location	Chamber category
Aberdeen	1
Gosport / Cosham	1
Great Yarmouth	1
Guernsey	1
Hull	1
Isle of Cumbrae	3
Isle of Man	2
Jersey	3
London (Whipp's Cross)	1
London (Highgate)	1
Manchester	4
Oban	2
Orkney	2
Peterborough	4
Plymouth (DDRC)	1
Poole	1
TWI Technology Centre	unknown
Wirral	1

Source: http://www.hyperbaric.org.uk/memberChambers.htm

6.3.2 Covered indications

Unlike those countries in which the range of health care benefits covered under social or private health insurance plans is defined explicitly, the NHS does not specify an explicit list of services to be provided.[136] District health authorities are free to contract service agreements with hospitals and other providers, specifying what services are to be provided and the terms on which they are to be supplied. For HBOT, district health authorities tend to use the UHMS guidelines,[8] but more and more of them are only paying for HBOT when there is RCT evidence to back its use. Some health authorities only fund the treatment of decompression illness.

6.3.3 Fees for HBOT

Fees are determined under the service agreements contracted between the different district health authorities and providers. As no national fixed fees are set, these may vary widely from district to district. Based on personal communication with Plymouth Hyperbaric Medical Centre, the cost range per hyperbaric session is as follows at DDRC (Diving Diseases Research Centre UK):

- Standard session of 90 minutes: £96 - £240 (for non-emergency cases)
- Emergency < 5hrs: £5 736.42 / 2 hrs + £1 032.55 /h
- Emergency 6 – 17 hrs: £9 695.53 + £860.47 /h
- Emergency >18 hrs: £19 274.35 + £114.72 /h
- USNTT6: at the same rate of emergency treatments

Emergency cases are for CO intoxication and diving accidents, necrotising fasciitis or gas gangrene. It is, however, difficult to compare the incidence and prevalence of indications between countries because of possible differences in definitions. CO intoxication, for example, appears to occur less frequently in the UK: only 36 fatalities and 128 casualties were recorded in 2006 for the whole of the UK,[137] compared to

[i] Source: www.dh.gov.uk/en/PolicyAndGuidance/HealthAndSocialCareTopics/SpecialisedServicesDefinition/DH_4001709

approximately 700 patients treated yearly for this indication in Belgian HBOT centres (see chapter 5).

6.4 UNITED STATES

The US had 296.41 million inhabitants in 2005 on an area of 9.38 million km^2.[k] There are 603 US centres listed on the UHMS website that have one or more hyperbaric chambers. Most of them are located in Florida (78) and Texas (75).

6.4.1 Medicare covered indications[l]

Program reimbursement for HBOT therapy is limited to that which is administered in a chamber (including the one man unit) and is limited to the following conditions:

- Acute carbon monoxide intoxication,
- Decompression illness,
- Gas embolism,
- Gas gangrene,
- Acute traumatic peripheral ischemia: HBO therapy is a valuable adjunctive treatment to be used in combination with accepted standard therapeutic measures when loss of function, limb, or life is threatened.
- Crush injuries and suturing of severed limbs. As in the previous conditions, HBOT would be an adjunctive treatment when loss of function, limb, or life is threatened.
- Progressive necrotizing infections (necrotizing fasciitis),
- Acute peripheral arterial insufficiency,
- Preparation and preservation of compromised skin grafts (not for primary management of wounds),
- Chronic refractory osteomyelitis, unresponsive to conventional medical and surgical management,
- Osteoradionecrosis as an adjunct to conventional treatment,
- Soft tissue radionecrosis as an adjunct to conventional treatment,
- Cyanide poisoning,
- Actinomycosis, only as an adjunct to conventional therapy when the disease process is refractory to antibiotics and surgical treatment,
- Diabetic wounds of the lower extremities in patients who meet the following three criteria:
    - Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
    - Patient has a wound classified as Wagner grade III or higher; and
    - Patient has failed an adequate course of standard wound therapy.

The use of HBO therapy is covered as adjunctive therapy only after there are no measurable signs of healing for at least 30 days of treatment with standard wound therapy and must be used in addition to standard wound care. Standard wound care in patients with diabetic wounds includes:

- Assessment of a patient's vascular status and correction of any vascular problems in the affected limb if possible,

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k Source: OECD demographic data 2007

l Source: Medicare National Coverage Determinations Manual, chapter 1, Part 1 (Rev. 77, 09-12-07) (Section .29 Hyperbaric Oxygen Therapy) (Rev. 48, Issued: 03-17-06; *-/*/Effective/Implementation Dates: 06-19-06)

- Optimization of nutritional status,
- Optimization of glucose control,
- Debridement by any means to remove devitalized tissue,
- Maintenance of a clean, moist bed of granulation tissue with appropriate moist dressings,
- Appropriate off-loading,
- Necessary treatment to resolve any infection that might be present.

Failure to respond to standard wound care occurs when there are no measurable signs of healing for at least 30 consecutive days. Wounds must be evaluated at least every 30 days during administration of HBO therapy. Continued treatment with HBO therapy is not covered if measurable signs of healing have not been demonstrated within any 30-day period of treatment.

6.4.2 Non covered indications

All other indications are not covered under the Medicare program. These include:

- Cutaneous, decubitus, and stasis ulcers
- Chronic peripheral vascular insufficiency
- Anaerobic septicemia and infection other than clostridial
- Skin burns (thermal)
- Senility
- Myocardial infarction
- Cardiogenic shock
- Sickle cell anaemia
- Acute thermal and chemical pulmonary damage, i.e., smoke inhalation with pulmonary
- Acute or chronic cerebral vascular insufficiency
- Hepatic necrosis
- Aerobic septicaemia
- Nonvascular causes of chronic brain syndrome (Pick's disease, Alzheimer's disease, Korsakoff's disease)
- Tetanus
- Systemic aerobic infection
- Organ transplantation
- Organ storage
- Pulmonary emphysema
- Exceptional blood loss anaemia
- Multiple Sclerosis
- Arthritic Diseases
- Acute cerebral oedema

6.4.3 Medicare charges for HBOT

6.4.3.1 Medicare Charges for physical supervision: Professional charge

Procedure code 99183 is billed for "physician attendance and supervision of HBOT, per session". The range of Medicare prices and limiting charges for code 99183 per session in different geographical areas is as follows (Table 33):[m]

Table 33. Medicare prices and limiting charges for physical supervision

	Non-Facility Price	Facility Price	Non-Facility Limiting Charge	Facility Limiting Charge
Min	162.73	99.42	177.79	108.62
Max	269.90	130.15	294.87	142.19
Avg	204.45	112.64	223.36	123.05

The Medicare physician fee schedule amounts are reflecting the variation in practice costs from area to area. A geographic practice cost index (GPCI) has been established for every Medicare payment locality for each of the three components of a procedure's relative value unit (i.e. the RVUs for work, practice expense, and malpractice).

Medicare law places limitations on how much non-participating physicians / suppliers can charge as fees for their services / supplies. Medicare refers to these limits as "limiting charges". For participating physicians / suppliers a price is fixed depending from area to area.

A supplier is considered a "Facility" when it performs services under the following circumstances:[n]

- Inpatient or outpatient hospital settings
- Emergency rooms
- Skilled nursing facilities
- Ambulatory surgical centres (ASCs)
- Inpatient psych facilities
- Comp inpatient rehabilitation facilities
- Community mental health centres
- Military treatment facilities
- Ambulance (land)
- Ambulance (air or water)
- Psychiatric facility partial hospital
- Psychiatric resort treatment centres

All other settings are considered as a "non-facility". In these settings a "non-facility price" should be charged. Most small physician practices fall under this category.

6.4.3.2 Medicare Facility charges: Technical charge

According to personal communication with K. McIntyre from Wound Care and Hyperbaric Medicine at Norfolk, the Medicare technical charge is around $600.00 per treatment.

[m] Source: http://www.cms.hhs.gov/pfslookup/02_pfssearch.asp. Accessed in December 2007

[n] Source: http://www.providerpro.net/public/dka-g-medicare-110405.php Accessed in February 2008

6.5 GERMANY

6.5.1 Hyperbaric centres

Germany had 82.47 million inhabitants in 2005 on an area of 357 000 km^2.[o] According to one source there are approximately 80 multi-person hyperbaric oxygen chambers in Germany[p]. On the VDD ("Verband Deutscher Druckkammerzentren") website, 24 member hyperbaric centres are listed (Table 34).

Table 34. Members of Verband Deutscher Druckkammerzentren

Druckkammerzentrum, Hamburg
HBO-Druckkammer-zentrum, Soltau
Institut für Hyperbar- u. Tauchmedizin, Berlin
Inselklinik Heringsdorf GmbH&Co.KG, Seebad Heringsdorf
Druckkammerzentrum, Hannover
HBO-Druckkammer-Kassel
HBO-Zentrum Mittelhessen GmbH, Wetzlar
Institut für HBO u. Tauchmedizin im Fachklinikum, Brandis
Sauerstoff-Therapiezentrum ORL-Vitamed GmbH&Co.KG, Düsseldorf
Praxis für Hyperbarmedizin Münster
Klinik a. Kurpark GmbH Bad Rothenfelde
HBO-Zentrum Euregio Aachen
DKZ Düren Druckkammer-Medizin KG - Paulusklinik Düren
Zentrum für Sauerstoffüberdruck- und Tauch- und Höhenmedizin Frankfurt
Druckkammerzentrum Offenbach
Druckkammerzentrum Wiesbaden am Rotkreuzkrankenhaus Wiesbaden
HBO-Zentrum Rhein-Main, Hofheim
OXYMED Privat-Institut Ramstein-Miesenbach
Druckkammerzentrum, Heidelberg
DCS1 Stuttgart
Druckkammerzentrum Freiburg GmbH Freiburg
Hyperbares Sauerstoff-Zentrum GmbH München
Druckkammer- zentrum, Traunstein
Institut f. Überdruck-Medizin Regensburg

Source : www.vddhbo.de

6.5.2 Covered indications

In Germany, there is an invoicing code for HBOT in the OPS ("Operationen- und Prozedurenschlüssel") (see Table 35). However, no value has yet been attributed to this code (according to personal communication from the Aachen University Clinic (U. Siekmann, January 2008) and the HBO-Zentrum Euregio Aachen). Therefore, currently, no single indication is nationally reimbursed by the legal insurance. Some hospitals, however, may have local contracts with insurers to reimburse a number of indications at an agreed fee.

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[o] Source : OECD demographic data 2007

[p] Source: http://www.tinnitusformula.com/infocenter/articles/treatments/hyperbaric.aspx

Table 35. HBOT code in OPS Germany

8-721		Hyperbare Oxygenation [HBO]
8-721.0		Behandlungsdauer bis 145 Minuten ohne Intensivüberwachung
8-721.1		Behandlungsdauer bis 145 Minuten mit Intensivüberwachung
8-721.2		Behandlungsdauer von 145-280 Minuten mit Intensivüberwachung
8-721.3		Behandlungsdauer über 280 Minuten mit Intensivüberwachung
8-721.4		Behandlungsdauer von 145-280 Minuten ohne Intensivüberwachung
8-721.x		Sonstige
8-721.y		N.n.bez.

Source: http://www.dimdi.de/static/de/klassi/prozeduren/ops301/opshtml2008/fr-ops.htm

6.5.3 Fees for HBOT

As mentioned above, there is currently no national fee attributed to the invoicing code for HBOT in the OPS. At the German Diving and Hyperbaric Medical Society, the following fees are charged:

- Standard HBO: €180 – 250
- Emergency HBO: < €1 100
- USNTT6: €1 460

6.6 AUSTRALIA

6.6.1 Hyperbaric centres

Australia had a population of 20.34 million people in 2005 on an area of 7.69 million km^2.[q] In Australia and New Zealand, there are only 12 comprehensive hyperbaric facilities located within hospitals and a number of small free standing facilities. These facilities tend to concentrate on a narrow spectrum of diseases.[1]

6.6.2 Covered indications and fees for HBOT

Table 36 presents an overview of covered indications and the fee-for-service by Medicare in Australia.

[q] Source: OECD demographic data 2007

Table 36. Overview of covered indications and fee-for-service

Item	Description	Fee/Benefit
13015	HBOT, for treatment of ▪ soft tissue radionecrosis or ▪ chronic or recurring wounds where hypoxia can be demonstrated, for a period in the hyperbaric chamber of between 1 hour 30 minutes and 3 hours This item is funded on an interim basis and will cease on 31 October 2010.	Fee: $230.05 Benefit: 75%/85%
13020	HBOT, for treatment of ▪ decompression illness, ▪ gas gangrene, ▪ air or gas embolism; ▪ diabetic wounds including diabetic gangrene and diabetic foot ulcers; ▪ necrotising soft tissue infections including necrotising fasciitis or Fournier's gangrene; or ▪ for the prevention and treatment of osteoradionecrosis, for a period in the hyperbaric chamber of between 1 hour 30 minutes and 3 hours	Fee: $233.70 Benefit: 75%/85%
13025	HBOT for treatment of ▪ decompression illness, ▪ air or gas embolism, for a period in the hyperbaric chamber greater than 3 hours - per hour (or part of an hour)	Fee: $104.50 Benefit: 75%/85%
13030	HBOT performed in a comprehensive hyperbaric medicine facility where the medical practitioner is pressurised in the hyperbaric chamber for the purpose of providing continuous life saving emergency treatment, including any associated attendance - per hour (or part of an hour)	Fee: $147.60 Benefit: 75%/85%

Source: Medicare Benefits Schedule : http://www9.health.gov.au/mbs/search.cfm

6.7 INTERNATIONAL COMPARISON: CONCLUSION

There is no clear agreement on the use of HBOT when comparing the use of this therapy across countries. The acceptance of HBOT is mainly based on consensus for several indications. In proportion to the number of inhabitants and area, Belgium has a relatively large capacity of HBOT centres. With an area of about 30 500 km², Belgium has on average one HBOT centre per ~2 500 km². This is on average one centre per 3 700, 13 600, 15 500, 20 300 and 640 800 km² for the Netherlands, UK, US, France, and Australia respectively. In proportion to the number of inhabitants, only the US has a higher proportion of HBOT centres which are mainly monoplace chambers. This corresponds to about one centre per 875 000 inhabitants in Belgium. In contrast, there is on average one HBOT centre per 1.5, 1.7, 2.3, and 3.3 million inhabitants for the Netherlands, Australia, France, and the UK respectively.

Key points

- **Internationally, reimbursement levels vary and reimbursed indications are mainly consensus based**
- **Compared to surrounding countries, HBOT capacity is relatively high in Belgium**

7 CONCLUSIONS

In this report we attempt to describe the history of hyperbaric oxygenation therapy (HBOT), the evidence for its use, the economic value of its application and cost for patients, hospitals and society, and also the current application of this technology in Belgium and in other countries.

Despite the fact that HBOT has been in use for several decades, evidence on its effectiveness is remarkably poor. Although its use appears to be, under strict precautions, relatively save, it is important to evaluate this therapy carefully for several indications, to avoid overutilisation in indications where no benefit is likely, and to avoid underutilisation when potential benefits might be foregone because of lack of knowledge.

Several indications have been accepted by medical scientific societies, but due to the paucity of properly randomised clinical study results, those acceptances are mainly based on a consensual decision making process rather than on an evidence based medicine approach. For a limited number of indications (mainly decompression illness) HBOT is likely to be important. For some indications there is limited evidence for benefits, for a few other indications HBOT is unlikely to be beneficial, and for several other indications HBOT might be beneficial but we just do not know. Therefore it is important to organise randomised clinical studies to sort out those uncertainties.

In Table 37 we present an overview of the key results of this report.

Table 37. Overview of indications for HBOT, the evidence on effectiveness, acceptance by scientific bodies, current Belgian practice and propose maximum number of sessions

Indication	Evidence	ECHM accepted indication*[9]	UHMS accepted indication[8]	Current Belgian practice**	Proposed maximum number of sessions***
CO Intoxication	No evidence on short term outcomes and low quality evidence for non-efficacy on neurologic sequels	Yes	Yes	Sessions: 724 (5%) Patients: 710 (40.5%)	3
Decompression Accidents	Empirical evidence (evidence level high), but no RCTs	Yes	Yes	Sessions: 228 (1.6%) Patients: 60 (3.4%)	7
Gas Embolism	Empirical evidence (evidence level low), but no RCTs	Yes	Yes	Sessions: 6 (0.04%) Patients: 4 (0.2%)	7
Anaerobic or mixed Anaerobic-Aerobic Bacterial Infections	Very low quality or no evidence	Yes	Yes	Sessions: 545 (3.8%) Patients: 62 (3.5%)	7
Acute Soft Tissue Ischemia	Very low quality or no evidence	Yes	Yes	Sessions: 626 (4.4%) Patients: 39 (2.2%)	10
Post-radiotherapy tissue damage	Low quality evidence from small RCTs on the clinical efficacy of HBOT in selected cases of post-radiotherapy tissue damage	Yes	Yes	Sessions: 4357 (30.3%) Patients: 181 (10.3%)	40
Delayed Wound Healing	Low quality evidence from small RCTs on the clinical efficacy of adjuvant HBOT in patients with diabetic ulcers with effect on major amputations in the medium term Very low quality or no evidence for the efficacy of adjuvant HBOT for delayed wound healing other than that associated with diabetes	Yes	Yes	Delayed wound healing Sessions: 772 (5.4%) Patients: 58 (3.3%) Diabetic ischemic injuries Sessions: 1122 (7.8%) Patients: 85 (4.8%)	40 in two years
Osteomyelitis	Very low quality or no evidence for the efficacy of adjuvant HBOT for chronic refractory osteomyelitis	Yes	Yes	Sessions: 823 (5.7%) Patients: 41 (2.3%)	30 in two years
Post-anoxic Encephalopathy	Very low quality or no evidence for the efficacy of adjuvant HBOT	Yes	No		
Thermal Burns	Very low quality or no evidence for the efficacy of adjuvant HBOT	Yes	Yes	Sessions: 30 (0.2%) Patients: 3 (0.2%)	
Hearing Disorders	Low quality evidence from small RCTs on the clinical efficacy of HBOT in acute deafness presenting early. A slightly better recovery was observed with adjuvant HBOT but the clinical relevance is uncertain	Yes	No	Sessions: 4736 (32.9%) Patients: 463 (26.4%)	15 in five years
Ophtalmological Disorders	Very low quality or no evidence for the efficacy of adjuvant HBOT for acute ophtalmological ischemia	Yes	No		
Neuroblastoma Stage IV	Very low quality or no evidence for the efficacy of adjuvant HBOT	Yes	No		
Pneumatosis Cystoides Intestinalis	Very low quality or no evidence for the efficacy of adjuvant HBOT	Yes	No		
Exceptional Anaemia	Very low quality or no evidence for the efficacy of adjuvant HBOT	No	Yes		

* For levels of evidence, see appendix

** Data from Belgian questionnaire see chapter 5.7

*** Proposal approved in 2004 by the Technische Geneeskundige Raad/Conseil Technique Medical; see chapter 5.5

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9 APPENDICES

APPENDIX FOR THE CHAPTER ON CLINICAL EFFECTIVENESS (CHAPTER 3)

SEARCH STRATEGY

As explained in the chapter on clinical effectiveness, most of the individual RCTs have been performed in small groups. Therefore, we have focussed our search on meta-analyses and systematic reviews. Exploratory searches learned that the MeSH term *'hyperbaric oxygenation'* covered very well the subject but we additionally also used these words as keyword in our Medline and Embase searches.

All searches were performed in early December 2007 and details about the searches in Medline/Pubmed and Embase are shown in Table 38. We additionally searched the CRD databases (DARE, NHS/EED and HTA) with the MeSH term 'Hyperbaric oxygenation', providing 48 hits, and the several Cochrane databases with the same MeSH term leading to 271 documents. Overall 472 references were obtained through this procedure, in many cases, however, either duplicates of what was detected in the previous searches or individual clinical trials. After electronic elimination of duplicates we retained 372 references. The final selection and exclusion process of manuscripts is represented in the flow chart in Figure 1 in the chapter on clinical effectiveness.

Table 38. Search strategy and results for Medline/Pubmed and Embase

Medline (Pubmed)		
#1	Search hyperbaric oxygenation[Mesh]	8459
#2	Search systematic[sb]	99648
#3	Search #1 AND #2	86
#4	Search hyperbaric	11439
#5	Search oxygenation	41576
#6	Search #4 and #5	8597
#7	Search #1 or #6	8597
#8	Search #7 and #2	87
#9	# 8 and Publication Date from 2000/01/01	82
Embase		
#1	('hyperbaric oxygenation'/exp OR 'hyperbaric oxygenation') AND [2000-2007]/py	3013
#2	('systematic review'/exp OR 'systematic review') AND [2000-2007]/py	27830
#3	#1 AND #2	71

DATA SOURCES FOR THE VARIOUS INDICATIONS

The data sources used for the various indications are listed in Table 39 to Table 54.

Table 39. Data sources for CO intoxication

Reviews and HTAs
ECHM accepted indication: Yes, type 1 recommendation, supported by level B evidence for specific patients[9]
UHMS accepted indication: Yes (CO poisoning and CO poisoning complicated by cyanide poisoning #2)[8]
Cochrane review 2005: Hyperbaric oxygen for carbon monoxide poisoning[24]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Saunders et al.[60]
Recently published RCTs
Hampson et al.[39]

Table 40. Data sources for Decompression Accidents

Reviews and HTAs
ECHM accepted indication: Yes, type 1 recommendation, supported by level C evidence[9]
UHMS accepted indication: Yes (Decompression sickness #5)[8]
Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 20[1]
Cochrane review 2007: Recompression and adjunctive therapy for decompression illness.[20]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Recently published RCTs
None identified

Table 41. Data sources for Gas Embolism

Reviews and HTAs
ECHM accepted indication: Yes, type 1 recommendation, supported by level C evidence[9]
UHMS accepted indication: Yes (air or gas embolism #1)[8]
Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 20[1]
Cochrane review 2007: Recompression and adjunctive therapy for decompression illness.[20]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Recently published RCTs
None identified

Table 42. Data sources for Anaerobic or mixed Anaerobic-Aerobic Bacterial Infections

Reviews and HTAs
ECHM accepted indication: Yes, type 1 recommendation, supported by level C evidence[9]
UHMS accepted indication: Yes (clostridial myositis and myonecrosis #3, intracranial abscess #8, necrotizing soft tissue infections #9)[8]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Jallali et al.[49]
Recently published RCTs
None identified

Table 43. Data sources for Acute Soft Tissue Ischemia

Reviews and HTAs
ECHM accepted indication: Yes, type 1, 2 or 3 recommendation, supported by level B or C evidence depending on specific indication[9]
UHMS accepted indication: Yes (crush injury, compartment syndrome and other acute ischemias #4, skin grafts and flaps #12)[8]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Saunders et al.[60]
Recently published RCTs
None identified

Table 44. Data sources for post-radiotherapy tissue damage

Reviews and HTAs
ECHM accepted indication: Yes, type 1, 2 or 3 recommendation, supported by level B or C evidence depending on specific indication[9]
UHMS accepted indication: Yes (delayed radiation injury #11)[8]
Cochrane review 2005: Hyperbaric oxygen therapy for late radiation tissue injury.[27]
Cochrane review 2002: Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis.[35]
Cochrane review 2002: Interventions for replacing missing teeth: hyperbaric oxygen therapy for irradiated patients who require dental implants.[36]
Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 9[1]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
MSAC 2003: Hyperbaric oxygen therapy for the treatment of non-healing refractory wounds in non-diabetic patients and refractory soft tissue radiation injuries[54]
Saunders et al.[60]
Feldmeier et al.[138]
Recently published RCTs
Follow up on study by Pritchard et al.[17]

Table 45. Data sources for Delayed Wound Healing

Reviews and HTAs
ECHM accepted indication: Yes, type 2 or 3 recommendation, supported by level B or C evidence depending on specific indication[9]
UHMS accepted indication: Yes (enhancement of healing in selected problem wounds #6)[8]
Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 10[1]
Cochrane review 2004: Hyperbaric oxygen therapy for chronic wounds.[32]
CADTH 2007: Overview of adjunctive hyperbaric oxygen therapy for diabetic foot ulcer. Review[57]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
MAS 2005: Hyperbaric oxygen therapy for non-healing ulcers in diabetes mellitus[56]
MSAC 2003: Hyperbaric oxygen therapy for the treatment of non-healing refractory wounds in non-diabetic patients and refractory soft tissue radiation injusries[54]
Roeckl-Wiedmann et al.[139]
Recently published RCT design
Löndahl et al.[18]

Table 46. Data sources for Osteomyelitis

Reviews and HTAs
ECHM accepted indication: Yes, type 2 recommendation, supported by level C evidence[9]
UHMS accepted indication: Yes (refractory osteomyelitis #10)[8]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Recently published RCTs
None identified

Table 47. Data sources for Post-anoxic Encephalopathy

Reviews and HTAs
ECHM accepted indication: Yes, type 3 recommendation, supported by level C evidence[9]
UHMS accepted indication: No[8]
Liu et al.[59]
Recently published RCTs
None identified

Table 48. Data sources for Thermal Burns

Reviews and HTAs
ECHM accepted indication: Yes, type 3 recommendation supported by level C evidence[9]
UHMS accepted indication: Yes (thermal burns #13)[8]
Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 12[1]
Cochrane review 2004: Hyperbaric oxygen therapy for thermal burns.[31]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Saunders et al.[60]
Recently published RCTs
None identified

Table 49. Data sources for Hearing Disorders

Reviews and HTAs
ECHM accepted indication: Yes, type 2 recommendation, supported by level C evidence[9]
UHMS accepted indication: No[8]
Thesis: The Evidence Basis of Diving and Hyperbaric Medicine, chapter 11[1]
Cochrane review 2007: Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus.[21]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
Uses of Hyperbaric Oxygen Therapy (AHRQ 2006)[14]
Bennett et al.[70]
Recently published RCTs
None identified

Table 50. Data sources for Ophtalmological Disorders

Reviews and HTAs
ECHM accepted indication: Yes, type 3 recommendation, supported by level C evidence[9]
UHMS accepted indication: No[8]
Oxigenoterapia Hiperbárica: Utilidad Diagnóstica e Indicaciones (IECS 2006)[38]
STEER 2002: Hyperbaric oxygen therapy for central retinal artery occlusion[61]
Weinberger et al.{Weinberger, 2002 #743}
Recently published RCTs
None identified

Table 51. Data sources for Neuroblastoma Stage IV

Reviews and HTAs
ECHM accepted indication: Yes, type 2 recommendation, supported by level C evidence[9]
UHMS accepted indication: No[8]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Recently published RCTs
None identified

Table 52. Data sources for Pneumatosis Cystoides Intestinalis

Reviews and HTAs
ECHM accepted indication: Yes, type 3 recommendation, supported by level C evidence[9]
UHMS accepted indication: No[8]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Recently published RCTs
None identified

Table 53. Data sources for Exceptional Anaemia

Reviews and HTAs
ECHM accepted indication: No[9]
UHMS accepted indication: Yes (exceptional anaemia #7)[8]
Oxygénothérapie Hyperbare (HAS 2007)[37]
Van Meter et al.[65]
Recently published RCTs
None identified

APPENDIX FOR THE CHAPTER ON ECONOMIC EVALUATION (CHAPTER 4)

SEARCH FOR COST-EFFECTIVENESS STUDIES

In January 2008, the websites of HTA institutes (Table 54) and following databases were searched: Medline, Embase, Centre for Reviews and Dissemination (CRD) databases (Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and Health Technology Assessments (HTA)), Cochrane Database of Systematic Reviews (CDSR), and Econlit. In the CDSR database, only the results of the categories Technology Assessments, Economic Evaluations, and Other Reviews were retained for this economic search. The following six tables (Table 55 to Table 60) provide an overview of the search strategy.

Table 54. List of INAHTA member websites searched for HTA reports

Agency	Country
AETMIS - Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS - Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA - Andalusian Agency for Health Technology Assessment	Spain
AHRQ - Agency for Healthcare Research and Quality	USA
AHTA - Adelaide Health Technology Assessment	Australia
AHTAPol - Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S - Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
AVALIA-T - Galician Agency for Health Technology Assessment	Spain
CADTH - Canadian Agency for Drugs and Technologies in Health	Canada
CAHTA - Catalan Agency for Health Technology Assessment and Research	Spain
CEDIT - Comité dÉvaluation et de Diffusion des Innovations Technologiques	France
CENETEC - Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CMT - Center for Medical Technology Assessment	Sweden
CRD - Centre for Reviews and Dissemination	United Kingdom
CVZ - College voor Zorgverzekeringen	The Netherlands
DACEHTA - Danish Centre for Evaluation and Health Technology Assessment	Denmark
DAHTA @DIMDI - German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS - Secretaria de Ciëncia, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DSI - Danish Institute for Health Services Research	Denmark
FinOHTA - Finnish Office for Health Care Technology Assessment	Finland
GR – Gezondheidsraad	The Netherlands
HAS - Haute Autorité de Santé	France
HunHTA - Unit of Health Economics and Health Technology Assessment	Hungary
IAHS - Institute of Applied Health Sciences	United Kingdom
ICTAHC - Israel Center for Technology Assessment in Health Care	Israel
IECS - Institute for Clinical Effectiveness and Health Policy	Argentina
IHE - Institute of Health Economics	Canada
IMSS - Mexican Institute of Social Security	Mexico
IQWiG - Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE - Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA - Ludwig Boltzmann Institut für Health Technonoly Assessment	Austria
MAS - Medical Advisory Secretariat	Canada
MSAC - Medicare Services Advisory Committee	Australia

MTU-SFOPH - Medical Technology Unit – Swiss Federal Office of Public Health	Switzerland
NCCHTA - National Coordinating Centre for Health Technology Assessment	United Kingdom
NHS QIS - Quality Improvement Scotland	United Kingdom
NHSC - National Horizon Scanning Centre	United Kingdom
NOKC - Norwegian Knowledge Centre for Health Services	Norway
NZHTA - New Zealand Health Technology Assessment	New Zealand
OSTEBA - Basque Office for Health Technology Assessment	Spain
SBU - Swedish Council on Technology Assessment in Health Care	Sweden
UETS - Unidad de evaluacíon Technologias Santarias	Spain
VATAP - VA Technology Assessment Program	USA
VSMTVA - Health Statistics and Medical Technologies State Agency	Latvia
ZonMw - The Medical and Health Research Council of The Netherlands	The Netherlands

Table 55. Search strategy and results for MEDLINE using the OVID interface (1996 to November Week 2 2007) (performed on 4 January 2008)

1	economics/	4410
2	exp "Costs and Cost Analysis"/	72066
3	"Value of Life"/ec [Economics]	158
4	Economics, Dental/	102
5	exp Economics, Hospital/	6550
6	Economics, Medical/	560
7	Economics, Nursing/	388
8	Economics, Pharmaceutical/	1475
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	79265
10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	173728
11	(expenditure$ not energy).tw.	6412
12	(value adj1 money).tw.	4
13	budget$.tw.	6217
14	10 or 11 or 12 or 13	179877
15	9 or 14	212721
16	letter.pt.	297361
17	editorial.pt.	130027
18	historical article.pt.	73621
19	16 or 17 or 18	495053
20	15 not 19	201355
21	Animals/	1586043
22	human/	4259975
23	21 not (21 and 22)	1062640
24	20 not 23	185646
25	(metabolic adj cost).ti,ab,sh.	270
26	((energy or oxygen) adj cost).ti,ab,sh.	903
27	24 not (25 or 26)	184769
28	hyperbaric.mp.	3667
29	27 and 28	**105**

Table 56. Search strategy and results for MEDLINE using the OVID interface (In-Process & Other Non-Indexed Citations) (performed on 4 January 2008)

1	cost$.mp. [mp=title, original title, abstract, name of substance word]	10690
2	economic$.mp. [mp=title, original title, abstract, name of substance word]	4533
3	budget$.mp. [mp=title, original title, abstract, name of substance word]	557
4	expenditure$.mp. [mp=title, original title, abstract, name of substance word]	1079
5	1 or 2 or 3 or 4	15171
6	hyperbaric.mp. [mp=title, original title, abstract, name of substance word]	203
7	5 and 6	**4**

Table 57. Search strategy and results for EMBASE (performed on 4 January 2008)

1	'socioeconomics'/exp	103303
2	'cost benefit analysis'/exp	46084
3	'cost effectiveness analysis'/exp	53003
4	'cost of illness'/exp	8191
5	'cost control'/exp	31905
6	'economic aspect'/exp	737921
7	'financial management'/exp	183472
8	'health care cost'/exp	125339
9	'health care financing'/exp	8996
10	'health economics'/exp	401677
11	'hospital cost'/exp	17245
12	'finance'/exp	7941
13	'funding'/exp	2417
14	fiscal	4436
15	financial	110172
16	#12 OR #13 OR #14 OR #15	121877
17	'cost minimization analysis'/exp	1282
18	estimate*:ti,ab,de,cl	343220
19	cost*:ti,ab,de,cl	386135
20	variable*:ti,ab,de,cl	340102
21	unit:ti,ab,de,cl	1318413
22	'#19 *4 #18' OR '#18 *4 #19'	174829
23	'#19 *4 #20' OR '#20 *4 #19'	173186
24	'#19 *4 #21' OR '#21 *4 #19'	78058
25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #16 OR #17 OR #22 OR #23 OR #24	1146787
26	'hyperbaric oxygen'	11228
27	#25 AND #26	416
28	#27 AND [humans]/lim AND [embase]/lim AND [2000-2007]/py	**201**

Table 58. Search strategy and results for CRD: DARE, NHS EED and HTA (performed on 4 January 2008)

MeSH Hyperbaric Oxygenation	
DARE	**9**
NHS EED	**12**
HTA	**28**

Table 59. Search strategy and results for CDSR (performed on 4 January 2008)

MeSH descriptor Hyperbaric Oxygenation, this term only	
Cochrane Reviews	(16)
Other Reviews	**7**
Clinical Trials	(196)
Technology Assessments	**27**
Economic Evaluations	**12**

Table 60. Search strategy and results for Econlit using the OVID interface (1969 to December 2007) (performed on 4 January, 2008)

hyperbaric.mp. [mp=heading words, abstract, title, country as subject]	**0**

RESULTS OF SEARCH STRATEGY

A total of 405 papers were identified: 109 with Medline, 201 with Embase, 49 with the NHS EED, DARE, and HTA databases, and 46 from the Cochrane Database of Systematic Reviews (the following categories were included: Technology Assessments, Economic Evaluations, and Other Reviews) (Table 61). After removing 80 duplicates, 325 articles were left.

Table 61. search for cost-effectiveness studies: summary

Database	Years	References
MEDLINE	1996-2nd week	105
MEDLINE In-Process &	4 January 2008	4
EMBASE	2000-2007	201
CRD	4 January 2008	
DARE		9
NHS EED		12
HTA		28
CDSR	4 January 2008	
Other reviews		7
Technology Assessments		27
Economic Evaluations		12
Econlit	4 January 2008	0
Total references identified		405
Duplicates		80
Total		**325**

CRD: Centre for Reviews and Dissemination; DARE: Database of Abstracts of Reviews of Effects; NHS EED: NHS Economic Evaluation Database; CDSR: Cochrane Database of Systematic Reviews

OTHERS

Table 62. An example of the data extraction form

Author	
Country	
Design	
Perspective	
Time window	
Interventions	
Population	
Assumptions	
Data source	
Cost items	
Data source	
Discounting	
Costs	
Outcomes	
Cost-	
Sensitivity	
Conclusions	
Remarks	

APPENDIX FOR THE CHAPTER ON THE BELGIAN SITUATION (CHAPTER 5)

APPLICATION RULES OF FEE-FOR-SERVICE LIST

Hoofdstuk V (Speciale technische geneeskundige verstrekkingen)

Afdeling 3: Anesthesiologie

Art. 13§1. Worden beschouwd als verstrekkingen waarvoor de bekwaming is vereist van geneesheer, specialist voor inwendige geneeskunde, voor cardiologie, voor pneumologie, voor gastro-enterologie, voor reumatologie, voor pediatrie, voor anesthesiologie, voor heelkunde, voor neurochirurgie, voor orthopedie, voor plastische heelkunde, voor urologie of voor neurologie

… Installatie van en toezicht op zuurstoftherapie in hyperbare drukkamer (ongeacht het aantal zittingen): de eerste dag (212516 en 212520) en de tweede dag (212531 en 212542)…

Deze verstrekkingen mogen niet worden gecumuleerd met 474530 tot 474563.

Art. 12 §3

1° De honoraria voor anesthesie mogen niet worden gecumuleerd met de honoraria voor raadpleging in de spreekkamer van de geneesheer of voor bezoek bij de zieke thuis.

2° De honoraria voor anesthesieverstrekkingen omvatten:

d) Het postoperatief toezicht op de gevolgen van die anesthesie. Niettemin mogen de verstrekkingen …, 212516-212520, … worden aangerekend bij een patiënt bij wie een heelkundige ingreep is verricht waarvan de betrekkelijke waarde gelijk is aan of hoger is dan K 500 of N 700 of I 700.

Afdeling 4: Reanimatie

Art. 13 §2.

2° Het honorarium voor de verstrekkingen 211013 tot 212041 en 212516 tot 214126 mag niet worden samengevoegd met het honorarium voor toezicht op de in een ziekenhuis opgenomen rechthebbenden, met uitzondering van honoraria voor de verstrekkingen van invasieve reanimatie of positieve ventilatie bij kinderen jonger dan 7 jaar.

6° De verstrekkingen 211013 tot en met 212041, 212516 tot en met 214045 en … mogen alleen worden aangerekend wanneer het gaat om zieken die lijden aan een zo ernstige tijdelijke depressie van een vitale functie dat de dood kan worden gevreesd.

7° Het aantal dagen dat is opgegeven in de omschrijving van de verstrekkingen 211013 tot 212041 en 212516 tot 214045, is het maximum aantal dagen dat voor éénzelfde opnemingstijdvak mag worden aangerekend.

De verstrekkingen 212015-212026 of 212030-212041 mogen niet worden aangerekend indien tijdens éénzelfde opnemingstijdvak drie of meer dan drie verstrekkingen 211013 tot 211142 of 212516 tot 214045 worden aangerekend.

Afdeling 8: inwendige geneeskunde

Art. 20 §1 f)

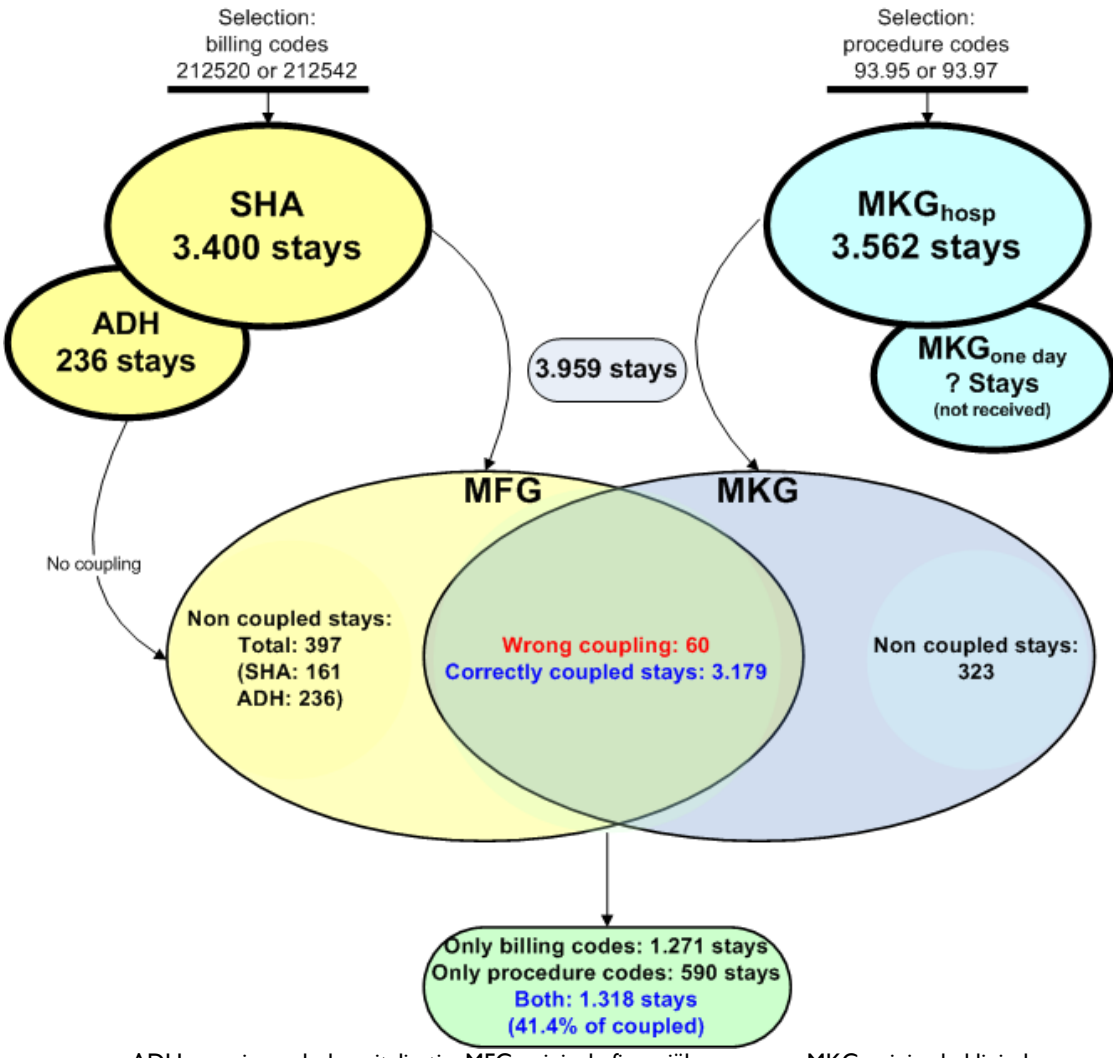
477374 tot 477385. Deze verstrekking mag niet worden gecumuleerd met … en 212516 tot 214126

Art. 26 §4. Voor de verstrekkingen 211013 tot 212041 en 212516 tot 214045 mag alleen voor de verstrekkingen 211013-211014, 211116-211120, 212015-212026, 212516-212520, 213010-213021 of 214012-214023 bijkomende honorarium voor 's nachts, tijdens het weekeind of op een feestdag verrichte dringende technische

verstrekkingen worden betaald, voor zover de installatie is verricht tijdens de vermelde uren en dagen.

OVERVIEW OF MCD-MFD DATA

Figure 38. Overview of retrieved MCD-MFD data



ADH: anonieme daghospitalisatie; MFG: mininale financiële gegevens; MKG: minimale klinische gegevens; SHA: séjours hospitaliers anonyms

Table 63. Number of stays with billing code 212 520 and/or 212 542 in MFG and/or procedure code 9395/97 in MKG

Correct coupling	MKG	MFG	Billing code	ICD-P codes	# Stays	
Yes	Yes	Yes	Yes	Yes	1.318	For 2 263 stays, a diagnosis directly linked to the procedure code is available
Yes	Yes	Yes	No	Yes	590	
No	Yes	Yes	Yes	Yes	30	
No	Yes	Yes	No	Yes	2	
No	Yes	No	No	Yes	323	
Yes	Yes	Yes	Yes	No	1.271	For 1 271 stays a diagnosis is available through the linkage MKG-MFG
No	Yes	Yes	Yes	No	28	For 425 non-coupled stays, no correctly linked diagnosis is available
No	No	Yes	Yes	No	161	
No	No	Yes	No	No	236	

KCE ENQUÊTE 'OXYGÉNOTHÉRAPIE HYPERBARE'

Capacité disponible

Votre centre dispose actuellement de quel type de chambres hyperbares?	Chambre 1: ☐ monoplace ☐ duoplace ☐ multiplace : |__|__| n° de patients assis |__|__| n° de patients couchés Année d'achat: |__|__|__|__| Chambre 2: ☐ monoplace ☐ duoplace ☐ multiplace : |__|__| n° de patients assis |__|__| n° de patients couchés Année d'achat: |__|__|__|__| Si votre centre dispose de plus de 2 chambres, merci d'inclure l'information là-dessus en annexe.
Votre centre, envisage-t-il l'achat d'une nouvelle chambre hyperbare? Si oui, laquelle?	☐ Oui ☐ Non ☐ monoplace ☐ duoplace ☐ multiplace : |__|__| n° de patients assis |__|__| n° de patients couchés Année d'achat prévue: |__|__|__|__|

Indications pour lesquelles l'oxygénothérapie hyperbare est utilisés dans votre centre et nombre moyen de sessions par indication

Remarque: Si vous enregistrez vos traitements hyperbare dans une base de données, vous pouvez nous l'envoyez également de manière anonymisée. Nous vous assurons un traitement discrèt et anonyme des données, qui ne seront utilisées que pour cette étude.

Pour quelles indications, votre centre, utilise-t-il l'oxygénothérapie hyperbare (aussi bien en ambulatoire qu'en hospitalisé) **Vous pouvez utiliser la classification ci-dessous (1 jusqu'à 16), mais vous pouvez également utiliser votre propre classification (la plus détaillée possible), si vous préférez.**	
1. Intoxication au monoxyde de carbone	Nombre de patients l'année passée*: ⌊___⌋⌊___⌋ *Veuillez introduire le nombre de patients de 2006, ou d'une année précédente, si 2006 n'est pas disponible: 20 ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
2. Accident de décompression en traitement initial	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
3. Ulcères ou gangrène ischémiques chez des patients diabétiques	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
4. Ulcères ou gangrène ischémiques chez des patients non diabétiques	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
5. Embolie gazeuse	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
6. Infection nécrosante des tissus mous	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
7. Abcès intracrânien, pleuro-pulmonaire, hépatique	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
8. Ecrasement de membre	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
9. Osteomyélite chronique réfractaire	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋
10. Brûlures du second degré et supérieures à 20%	Nombre de patients: ⌊___⌋⌊___⌋ Nombre moyen de sessions par patient ⌊___⌋⌊___⌋

11. Lésions radio-induites	Nombre de patients: ⌊__⌋⌊__⌋ Nombre moyen de sessions par patient ⌊__⌋⌊__⌋
12. Neuroblastome de stade IV	Nombre de patients: ⌊__⌋⌊__⌋ Nombre moyen de sessions par patient ⌊__⌋⌊__⌋
13. Surdité Brusque	Nombre de patients: ⌊__⌋⌊__⌋ Nombre moyen de sessions par patient ⌊__⌋⌊__⌋
14. Pneumatose kystique de l'intestin	Nombre de patients: ⌊__⌋⌊__⌋ Nombre moyen de sessions par patient ⌊__⌋⌊__⌋
15. Pathologies ophtalmologiques	Nombre de patients: ⌊__⌋⌊__⌋ Nombre moyen de sessions par patient ⌊__⌋⌊__⌋
16. Autres indications	☐ Oui ☐ Non Si oui, pour quelles indications: Nombre de patients: ⌊__⌋⌊__⌋

Nombre total des patients traités par an

Nombre total de patients par an traités avec cette thérapie dans votre centre	⌊__⌋⌊__⌋⌊__⌋ patients / an
Durée moyenne par session	⌊__⌋⌊__⌋ minutes

Prix pour le patient

Remarque: ces données de prix seront anonymisée dans notre étude. Nous calculerons la moyenne, le minimum et maximum pour la Belgique en nous ne publierons ces données que sous une form agrégée.

Combien le patient paye-t-il par session?	1er jour: – Session 1 ⌊__⌋⌊__⌋⌊__⌋ € – Session 2 ⌊__⌋⌊__⌋⌊__⌋ € 2ième jour: – Session 1 ⌊__⌋⌊__⌋⌊__⌋ € – Session 2 ⌊__⌋⌊__⌋⌊__⌋ € 3ième et jours suivants: ⌊__⌋⌊__⌋⌊__⌋ € / session

Merci pour votre collaboration

KCE VRAGENLIJST VOOR HET PROJECT 'HYPERBARE ZUURSTOFTHERAPIE'

Beschikbare capaciteit

Over welke hyperbare zuurstoftherapiekamers beschikt uw centrum momenteel	Kamer 1: ☐ monoplace ☐ duoplace ☐ multiplace : |__|__| aantal patienten zittend |__|__| aantal patienten liggend gewoon bed |__|__| aantal patienten liggend intensief bed Jaar van aankoop: |__|__|__|__| Kamer 2: ☐ monoplace ☐ duoplace ☐ multiplace : |__|__| aantal patiënten zittend |__|__| aantal patienten liggend gewoon bed |__|__| aantal patienten liggend intensief bed Jaar van aankoop: |__|__|__|__| Indien meer kamers dan 2, gelieve de informatie over deze kamers in appendix bij te voegen
Overweegt uw ziekenhuis momenteel de aankoop en installatie van een nieuwe hyperbare zuurstofkamer Indien ja, welke	☐ Ja ☐ Neen ☐ monoplace ☐ duoplace ☐ multiplace : |__|__| aantal patiënten zittend |__|__| aantal patienten liggend gewoon bed |__|__| aantal patienten liggend intensief bed Vermoedelijk jaar van aankoop: |__|__|__|__|

Indicaties waarvoor hyperbare zuurstoftherapie toegepast wordt + gemiddeld aantal sessies

Opm: Indien u de hyperbare zuurstofbehandelingen in een database registreert, dan mag u ons ook de (geanonimiseerde) database opsturen. Bij het KCE verzekeren we u een discrete en anonieme behandeling van de data. De data zullen ook enkel voor deze studie gebruikt worden en niet verder verspreid worden voor ander gebruik.

Voor welke indicaties gebruikt uw ziekenhuis hyperbare zuurstoftherapie (zowel ambulant als gehospitaliseerd) **U mag de hiernavolgende indeling (1 t.e.m. 16) gebruiken, of indien u dat verkiest, uw eigen indeling.**	
1. CO intoxicatie	Aantal gevallen in het laatste volledige jaar*: ⌊___⌋⌊___⌋ *Mogen we u vragen telkens het aantal gevallen in 2006 in te vullen, of indien deze niet beschikbaar zijn, van een ander jaartal, namelijk: 20 ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋
2. Decompressieziekte na duikongevallen in initiële behandeling	Aantal gevallen in het laatste volledige jaar: ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋
3. Ischemische ulcers of gangreen bij diabetische patiënten	Aantal gevallen in het laatste volledige jaar: ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋
4. Ischemische ulcers of gangreen bij niet-diabetische patiënten	Aantal gevallen in het laatste volledige jaar: ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋
5. Arteriële gasembolie	Aantal gevallen in het laatste volledige jaar: ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋
6. Afstervingsinfectie van zacht weefsel met anaerobe of gemengde bacteriële infectie (myonécrose, afstervend fasciites, cellulites)	Aantal gevallen in het laatste volledige jaar: ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋
7. Intracraniaal, pleuro-pulmonair of lever abces	Aantal gevallen in het laatste volledige jaar: ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋
8. Verplettering/Verbrijzeling van ledematen (open fracture type II gustilo B en C)	Aantal gevallen in het laatste volledige jaar: ⌊___⌋⌊___⌋ Gemiddeld aantal sessies per patient ⌊___⌋⌊___⌋

9. Chronische refractaire Osteomyelitis	Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋ Gemiddeld aantal sessies per patient ⌊__⌋⌊__⌋
10. Brandwonden 2° graad en >20%	Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋ Gemiddeld aantal sessies per patient ⌊__⌋⌊__⌋
11. Radio-geïnduceerde verwondingen	Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋ Gemiddeld aantal sessies per patient ⌊__⌋⌊__⌋
12. Neuroblastoom stadium IV	Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋ Gemiddeld aantal sessies per patient ⌊__⌋⌊__⌋
13. Plotselinge doofheid	Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋ Gemiddeld aantal sessies per patient ⌊__⌋⌊__⌋
14. Cysteuse pneumatose van de ingewanden	Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋ Gemiddeld aantal sessies per patient ⌊__⌋⌊__⌋
15. Oftalmologische pathologieën	Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋ Gemiddeld aantal sessies per patient ⌊__⌋⌊__⌋
16. Andere indicaties	☐ Ja ☐ Neen Zo ja, voor welke indicaties: Aantal gevallen in het laatste volledige jaar: ⌊__⌋⌊__⌋

Totaal aantal behandelde patiënten per jaar

Hoeveel patiënten in totaal worden gemiddeld jaarlijks behandeld met Hyperbare zuurstoftherapie in uw ziekenhuis	⌊__⌋⌊__⌋⌊__⌋ patiënten/jaar
Gemiddelde duur per sessie	⌊__⌋⌊__⌋ minuten

Kostprijs voor de patiënt

Opmerking: de kostprijsgegevens worden geanonimiseerd voor onze studie. In geen geval zal een kostprijs per ziekenhuis worden gepubliceerd. Er wordt een gemiddelde, minimum en maximum berekend over gans België en enkel deze geaggregeerde cijfers worden gepubliceerd

Hoeveel betaalt de patiënt per sessie? Hoeveel wordt hiervan terugbetaald? Wat wordt aan het RIZIV aangerekend?	1e dag: 2e dag: 3e en volgende dagen:

Bedankt voor uw medewerking

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