Practical Application of Hyperbaric Oxygen Therapy

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ABSTRACT

Hyperbaric Oxygen Therapy (HBOT) can be viewed as the new application of an old, established technology to help resolve certain medical problems. HBOT continues to attract attention and invite to controversy in clinical medicine. 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. 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 other indications, the use of HBOT is mainly based on theoretical reasoning and animal models, while clinical evidence is often based on case series comparing outcomes in centres with hyperbaric facilities or with historical controls. The field is advancing, and the general understanding of pathophysiology in many diseases has improved. 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. Despite the gradual growth, there have been advances and retreats in this field of medicine that continues to be both a stimulant and restricted area of scientific knowledge.

1.0. 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) [1].

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 [2].

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 other conditions than Decompression illness (DCI) only started about 50 years ago, when the Dutch cardiac surgeon *Ite Boerema* reported on the use of hyperbaric oxygen during pediatric 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, however many were based on little or no evidence [2].

Recently, randomized controlled trials (RCTs) were performed for specific indications and evidence on certain indications has appeared. The field is advancing, and the general understanding of pathophysiology in many diseases has improved. However, the therapy requires additional resources such as highly specialized staff and expensive facilities.

2.0 HYPERBARIC OXYGENATION THERAPY: BRIEF 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. At a depth of 10 meters pressure is approximately 2 ATA, and every additional 10 meters of depth corresponds to about one extra ATA [3].

Hyperbaric Medicine goes back a long way, since its history derives from the history of diving which dates back to ancient times. The history of Hyperbaric Medicine has been closely linked with the development of technology for underwater activities and the advance in knowledge about the physical laws and physiological mechanisms of breathing oxygen at pressures above atmospheric pressure.

As early as the 17th century, strong airtight vessels combined with pumps capable of compressing air could be produced and were sporadically even used as treatments for various conditions [4-5]. Treatments with compressed air were introduced empirically, for the first time in 1662, by *Henshaw*, a member of the English clergyman, who has designed for this purpose, a watertight compartment, the "*domicilium*", equipped with a pair of organ bellows, by which it was inflated with air or deflated [6].

The last quarter of the nineteenth century saw the development of important scientific work in this area of knowledge, highlighting the name of Paul-Bert who systematized theoretical, physical and physiological bases of hyperbarism.

Serious hyperbaric therapy, only began in the late 19th century, as a treatment of *"caisson disease"*, a frequent illness in workers involved in large construction projects (bridges, tunnels) where they had to work in hyperbaric conditions while labouring in 'caissons'[4,7].

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 [4] and for a long time *"caisson disease"*, or decompression sickness (DCS) as it was later called, remained the main therapeutic indication for hyperbaric therapy. Mortality from this disease, also called "bubble disease", that originally ran as high as 25%, was greatly reduced thanks to recompression therapy with normal air [8].

Halfway the 20th century, the use of normal air was replaced by the use of either pure oxygen or specific mixtures of gases, and HBOT established itself as standard therapy for all types of decompression illness (DCI) caused by diving, aviation or of iatrogenic origin.

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 ("*Steal Ball Hospital"*), the largest ever, was built by *O.J. Cunningham* [4, 5]. Serious medical interest, however, quickly faded.

The interest of Military Medicine by physiological and pathophysiological changes related to the practice of activities in underwater environments and in the treatment of injuries associated with these, would contribute significantly to demystify and to the implementation of this therapy [6]. 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. However, medical interest was only revived and hyperbaric oxygen therapy would only be introduced in clinical practice, with scientifically credible basis, after the experimental studies carried out and reported by *Boerema* in 1956 [4, 9] His reports marked the beginning of a proliferation of hyperbaric chambers in hospitals around the world.

New and sometimes bizarre indications were proposed. 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) [1] and the European Committee for Hyperbaric Medicine (ECHM, www.echm.org) [10], 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 [11], 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 (O_2) is vital to sustain life. Oxygen is a colorless, odorless and tasteless gas that constitutes about 21% of the air we breathe. The body cannot store O_2 in any way, so the cells rely on a continuous supply of O_2 in order to generate the energy, which keeps them alive. Hypoxia is a lack of O_2 that leads to deterioration and eventually cell death. Depending on where in the body these cells are situated, parts of the body, will also deteriorate and die. Hypoxia can occur when breathing a hypoxic gas mixture, at high altitudes or because of failure of the lungs, heart, circulatory system or diffusion through tissues [12].

Medical oxygen supplementation of inhaled air (up to 100% O_2), available for clinical use since the 1st World War, has long since been accepted as a sine qua non in many areas of clinical medicine or diving and aviation medicine. The documentation on oxygen in medicine is staggering and has since then been a mainstay of emergency care, general anesthesia and intensive care.

When the therapeutic use of medicinal O_2 is discussed, a distinction is made between normobaric O_2 (NBO) and hyperbaric (HBO) O_2 delivery.

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. HBOT involves breathing oxygen in a pressurized chamber in which the atmospheric pressure is raised up to three times higher than normal

Hyperbaric Oxygen Therapy (HBOT) is a treatment, in which a patient breathes near 100% oxygen intermittently, while inside a treatment chamber at a pressure higher than sea level pressure (i.e. > 1 ATA). It can be viewed as the new application of an old, established technology to help resolve certain medical problems [1]. In certain circumstances, it represents the primary treatment modality while in others it is an adjunct to surgical or pharmacologic interventions.

HBOT can be defined as a "short-term, high-dose O_2 inhalation and diffusion therapy", delivered systemically via airways and blood, achieved by having the patient breathe O2 intermittently within a pressurized chamber. The dosage limits for HBOT is determined by O_2-toxicity side effects, mainly to the central nervous system. Safe time-dose limits have been established for HBO exposure [12].

The treatment is usually given at a pressure of 2.4–2.8 bar. The total procedure including safe compression / decompression usually takes less than 2 hours. Treatment can be repeated 2–3 times a day for critically ill patients. The number of treatments given depends on the medial condition and the prescribed treatment program, ranging from a few acute treatments in the first days up to 40 sessions or more given during a several-week period [12].

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, treatment tables have been devised. In practice, however, the choice of treatment schedules has often been empirical, at least in the past [11, 13].

Three primary mechanisms are believed to be involved in HBO 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 [14]. 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 [15].

Treatment can be carried out in either a monoplace or multiplace chamber and the choice of chamber typically depends on the capacity needs and the conditions being treated. The monoplace chamber accommodates a single patient; the entire chamber is pressurized with near 100% oxygen, and the patient breathes the ambient chamber oxygen directly. The multiplace chamber holds two or more people (patients, observers, and/or support personnel) and is pressurized with compressed air while the patients breathe near 100% oxygen via masks, head hoods, or endotracheal tubes.

Hyperbaric chambers are considered medical devices. To use a hyperbaric chamber, in USA, a Food and Drug Administration (FDA) clearance is required. FDA clearance of a device for a specific use means FDA has reviewed valid scientific evidence supporting that use and determined that the device is at least as safe and effective as another legally U.S.-marketed device.

Some publications described a therapy delivering topical oxygen at high flow rates locally to the wound surface, sometimes mistakenly calling this HBOT [13]. Topical oxygen therapy should not be confused with HBOT given systemically via O_2 inhalation. "Topical HBO" involves application over a wound bed by the use of a plastic bag in an attempt to force O_2 into tissues at pressures only slightly higher than normal sea level pressure. This therapy causes insignificant O_2 perfusion and higher pressures surrounding an extremity would create a detrimental tourniquet effect with ischemia and hypoxia.

3.0 HBO MECHANISMS: PHYSICAL, PHYSIOLOGICAL AND PHARMACOLOGICAL

Therapeutic benefit may result from the mechanical effects of increased pressure directly with improved oxygenation, or by its physiological / pharmacological effects. The cellular and cardiovascular effects of HBO give it all the properties of a pharmaceutical drug [12].

HBOT is simply intermittent, short-term, high-dose O_2 inhalation therapy to achieve hyperoxygenation via the blood. Treatment of tissue hypoxia often remain the main therapeutic value of HBO therapy. Inadequate oxygenation often occurs in tissue compromised by traumatic injury, infection, inflammation, ischemia and edema where one or more HBO treatments can be life-, limb- and tissue saving.

HBO acts as a drug with a wide range of beneficial mechanisms including dose-dependent pharmaceutical effects on e.g. inflammation, angiogenesis and wound healing. Research in O_2 administration has established that the effects are dose-related, and that the hyperbaric environment not merely provides the opportunity to give higher O_2 doses than can be achieved at sea level. A series of HBO treatments improves local host immune response causing clearance of infection in hypoxic tissues, and also stimulates increased vascular density and wound metabolism with enhanced tissue growth. The net result is improved local tissue oxygenation and healing.

HBOT is limited by O_2 toxicity, yet oxidative stress is fundamental in the HBO signal transduction cascades to mediate e.g. wound healing, in infection and to ameliorate post ischemic and inflammatory injuries. A steadily growing body of evidence provides a broader scientific basis for understanding the mechanisms of action for HBO listed below.

a) Compression of bubbles. HBOT helps relieve obstruction and restore perfusion because gas volumes trapped in the body diminish in proportion to the pressure (Boyle's law).

b) Elimination of gas. HBO increase the resolution rate of air or gas bubbles. The gases go into solution in proportion to the partial pressure of the gas (Henry's law). The elimination of dissolved nitrogen is enhanced by breathing 100% O_2.

c) Increased blood O2–carrying capacity. HBO doubles the blood-O_2 carrying capacity by an increase in O_2 physically dissolved in the blood. At 2.8 bar the tissue O_2 requirements can be supplied entirely by O_2 in physical solution since five vol.% of O_2 is dissolved in the blood, the same amount normally delivered by oxy-hemoglobin. This may help restore tissue O_2 tensions back to normal or supra-normal levels in hypoperfused tissues.

d) Increased O2 diffusion distance into the tissues. HBO increases the driving forces for O_2-diffusion. A 9–16 fold arterial pO_2 increase permits a 3–4 fold increase in O_2-diffusion distance into the tissues spherically from functioning capillaries. Intermittent correction of hypoxia, across the barriers created by edema and poor perfusion, can support basic metabolic requirements and maintain cellular integrity and function. This may help salvage limbs and marginally perfused tissues. Bacterial hypoxic/anoxic biofilm may be oxygenated.

e) Vasoconstriction and edema reduction. HBO causes a general vasoconstriction, mainly in healthy, non-ischemic tissues, causing a direct decrease in e.g. brain edema and intracranial pressure. Edema is also diminished through reduced extravasation and restoration of cell ion pump function. Improved rheology with increased red blood cell deformability and blood O_2-carrying capacity preserve oxygenation.

f) Anti-inflammatory effects. HBO reduces leukocyte-endothelial cell adhesion in injured tissues by HBO induced down regulation of cell adhesion molecules. HBO ameliorates the ischemia-reperfusion injury of organs such as the brain, skeletal muscle, liver, small intestine and testicle.

g) Anti-microbial effects. HBO improves host immune response. Leukocyte bacterial killing capacity is enhanced. The growth of anaerobic organisms is inhibited. Clostridial alphatoxin production is stopped. Antibacterial and antifungal effects of antibiotics are improved e.g. aminoglycosides, vancomycin, amphotericin B.

h) Angiogenesis/Vasculogenesis. HBO increases vascular density. New capillaries are formed in selected ischemic or poorly perfused wounds, e.g. after irradiation injury or in the diabetic foot. HBO increase the mobilization of endothelial progenitor cells "stem cells" from the bone marrow into peripheral blood. Microcirculation and oxygenation improves after a series of HBO treatments. The increased vascular density remains stable in clinical long-term follow up.

i) Wound healing. HBO improves wound metabolism. Wound healing is O_2-dependent and rate-limited by its availability at the cellular level, such as the collagen matrix formation needed for angiogenesis. HBO stimulates a variety of growth factor mediated wound-healing processes. HBO has dose-dependent effects on fibroblast proliferation, angiogenesis, inflammation and antioxidant defense systems.

4.0 ACCEPTED INDICATIONS BY HYPERBARIC MEDICAL SOCIETIES

4.1 Introduction

Clinical Hyperbaric Medicine grew out of the problems met by divers exposed to high pressures. Decompression illness is a widely accepted HBOT indication. Several categories of illness clearly benefit from HBO and promising results are seen in other diseases. Maintenance of tissue oxygenation is central to intensive care and HBO is sometimes the only way to correct tissue hypoxia in order to limit organ dysfunction and improve outcome in some groups of critically ill patients.

In less critical conditions, a series of HBO treatments can help achieve 1) infection control 2) new blood vessels and 3) wound healing. Hospital acquired infections may be treated and promising results are seen in surgical-site infections with implants and/or multi-resistant bacteria. HBO may also be used to treat, or try to prevent radiation injury complications. HBO is the only well proven drug that can achieve angiogenesis (blood-vessel formation from pre-existing vessels) or vasculogenesis (spontaneous blood-vessel formation). HBO for tumor sensitization to radiotherapy, i.e. improve radiotherapeutic killing of hypoxic cancer cells by administration of radiotherapy immediately after HBO, will only be dealt with briefly in this report. This is another developing field of clinical Hyperbaric Medicine especially for oncology where mortality and tumor recurrence may be reduced.

4.2 Scientific Societies and HBO Indications

HBO indications have been only slightly redefined over the past 40 years despite the fact that the collection of evidence has increased with number of experimental and clinical studies since the first published textbook.

Several medical societies are active in the world of Hyperbaric Oxygenation Therapy. The *European Committee for Hyperbaric Medicine* (ECHM) - www.echm.org - and the *Undersea and Hyperbaric Medical Society* (UHMS) in the United States - www.uhms.org - set the international HBO standards and HBO indication, based on the most up to date research and medical knowledge to date. In USA, HBOT is recognized by medicare as a reimbursable treatment based on the UHMS indication list. Whereas UHMS create a new Committee report every 3rd to 4th year, in Europe ECHM hold international consensus conferences and workshops with recognized experts to evaluate the literature and current data to create an updated list of accepted indications for HBO treatment.

4.3 Underwater and Hyperbaric Medical Society (UHMS) Accepted Indications

The North America based "Undersea and Hyperbaric Medical Society" (UHMS), formerly the Undersea Medical Society founded in 1967, is the largest society in this field of activity. 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 [1].

Table 1- Conditions accepted by UHMS in 2003 (Source: UHMS) [1]

	Conditions accepted
1	Air or gas embolism
2	Carbon Monoxide poisoning (whether or not complicated by cyanide poisoning)
3	Clostridial Myositis and Myonecrosis (Gas gangrene)
4	Crush injuries, compartment syndrome and other acute ischemias
5	Decompression Sickness
6	Enhancement of Healing in Selected Problem Wounds
7	Exceptional anemia
8	Intracranial abscess
9	Necrotizing soft tissue infections
10	Refractory osteomyelitis
11	Delayed radiation injury including soft tissue and bone necrosis
12	Skin grafts and flaps
13	Thermal Burns Thermal Burns

At the present moment, 14 indications are approved uses of hyperbaric oxygen therapy as defined by the Hyperbaric Oxygen Therapy Committee of UHMS (Table 2). Sudden deafness was included on the UHMS list only in 2011.

Table 2 - Conditions accepted by UHMS in 2011 (Source: UHMS) [1]

	Conditions accepted
1	Air or Gas Embolism
2	Carbon Monoxide Poisoning Carbon Monoxide Poisoning Complicated By Cyanide Poisoning
3	Clostridial Myositis and Myonecrosis (Gas Gangrene)
4	Crush Injury, Compartment Syndrome and Other Acute Traumatic Ischemias
5	Decompression Sickness
6	Arterial Insufficiencies: Central Retinal Artery Occlusion Enhancement of Healing In Selected Problem Wounds
7	Severe Anemia
8	Intracranial Abscess
9	Necrotizing Soft Tissue Infections
10	Osteomyelitis (Refractory)
11	Delayed Radiation Injury (Soft Tissue and Bony Necrosis)
12	Compromised Grafts and Flaps
13	Acute Thermal Burn Injury
14	Idiopathic Sudden Sensorineural Hearing Loss (approved on October 8, 2011 by the UHMS Board of Directors)

Thirteen uses of a hyperbaric chamber for HBOT have been cleared by FDA. They include treatment of air or gas embolism (dangerous "bubbles" in the bloodstream that obstruct circulation), carbon monoxide poisoning, decompression sickness (often known by divers as "the bends"), and thermal burns (caused by heat or fire).

4.4 European Committee for Hyperbaric Medicine (ECHM) Accepted Indications

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 (Table 3) [16]. 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.

Table 3 - Indication accepted by the ECHM in 2004 (Source: ECHM) [10]

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

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.

Annex A1 contains detailed information about the 7th ECHM Consensus Conference held in 2004, where this List of accepted HBOT indications was approved. Methodology followed to analyze different pathologies is included, as well as tables containing accepted and non accepted indications and the corresponding levels of Recommendation and Evidence.

5.0 EVIDENCE FOR CLINICAL EFFECTIVENESS

5.1 Introduction

Since the late nineteen-fifties HBOT has been increasingly used for indications other than decompression illness (DCI) [4, 7, 11] For most of these indications, serious evidence is at best scarce.

Part of this lack of evidence is due to the fact that randomized controlled trials are more difficult to conduct for HBOT indications since these conditions are too complex to allow for easy randomization, or by the fact that these conditions are sometimes so life threatening that inclusion of the patient in a properly randomized controlled trial (RCT) would be considered unethical [16].

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. [17] or by placing intervention and control patients in the same hyperbaric chamber, raising the pressure but administering different mixtures of gasses [18, 19].

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.

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.

In 2004 the European Committee for Hyperbaric Medicine organized its 7th European Consensus Conference on Hyperbaric Medicine in Lille (France), to make recommendations on which indication to endorse [16]. 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 4.

Table 4 - 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.)

5.2 Literature Searches on Clinical Effectiveness

Tue European Committee for hyperbaric Medicine (ECHM) - www.echm.org - and the Undersea and Hyperbaric Medical Society (UHMS) in the United States - ww.uhms.org - set the international HBO standards and HBO indication, based on the most up to date research and medical knowledge to date.

Relevant literature is also present in Medline, Embase, and the Cochrane Database of Systematic Reviews (CDSR). Information about ongoing clinical trials can also be searched in the Cochrane Central Register for Controlled Trials. All human randomized controlled trials and meta-analyses published in the field of Hyperbaric Medicine can be found on www.hboevidence.com, a useful searchable citation database with links from all citations to a standardized, one-page critical appraisal of the methodological quality and results of each trial. Web links to additional international organizations and sites can be found on either of the links above and the vast amount of HBO publications via a PubMed web search using "hyperbaric oxygen" as key word.

6.0 EVIDENCE AND HBOT RATIONALE FOR SPECIFIC INDICATIONS

The structure of this chapter is mainly based on the indications that were accepted by the European consensus conference [16], but other indications have been added when sufficient evidence is available for an assessment. For each indication is summarized the description of the condition, the summary of the evidence and the rationale for HBOT.

6.1 Carbon Monoxide (CO) Intoxication

6.1.1 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 colorless and odorless 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 hemoglobin (but also to intra- and extracellular haeme containing proteins), is much greater than that of oxygen, forming carboxy-hemoglobin (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-hemoglobin level, but recent investigations have established that systemic oxidative stress can arise from CO exposure and cause perivascular and neuronal reperfusion injury [13]. The most vulnerable organs are the brain and the heart.

6.1.2 Summary of the evidence and HBOT rationale

This indication was accepted by the ECHM consensus conference as a type 1 recommendation supported by level B evidence 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) [16]. 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 [13]. The UHMS recognizes, however, that additionally studies are required to clearly define benefits, optimal treatment indication, optimal pressure, timing and number of sessions (one or more) [13].

The rationale for hyperbaric oxygenation therapy is that this rate of dissociation of CO from hemoglobin could be expected to be greater that with normobaric oxygenation therapy, and several historical and laboratory studies support this view [13].

Neither for hyperbaric nor for normobaric oxygen therapy, RCTs evaluating the short term effects on CO poisoning have been carried out.

6.2 Decompression Accidents

6.2.1 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 [13]. 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 [11, 13].

6.2.2 Summary of the evidence and HBOT rationale

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.

The rationale for treatment with hyperbaric oxygen (HBO) includes immediate reduction in bubble volume, increasing the diffusion gradient for inert gas from the bubble into the surrounding tissue, oxygenation of ischemic tissue and reduction of Central Nervous System edema. It is also likely that HBO_T has other beneficial pharmacological effects, such as a reduction in neutrophil adhesion to the capillary endothelium. The efficacy of administration of oxygen at increased ambient pressure (hyperbaric oxygen, HBOT) is widely accepted, and HBOT is the mainstay of treatment for this disease.

6.3 Gas Embolism

6.3.1 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 pulmonary barotrauma. It has also been described during normal ascent in divers with predisposing lung pathology or traumatically [13]. 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 [20, 21]. Other than through diving accidents and trauma, there may also be iatrogenic causes for gas embolism, such as accidental air injection, surgical accidents and hemodialysis. Clinical manifestations are variable and in general much more serious with AGE compared to VGE.

6.3.2 Summary of the evidence and HBOT rationale

The rationale for HBOT in AGE is similar to the one for decompression illness, but again, evidence is mainly historical. For AGE, HBOT is recommended by the UHMS even after initial recovery. It is, however, not recommended for asymptomatic VGE [13]. The ECHM does not formally differentiate between AGE and VGE in their recommendations [16].

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 [13].

6.4 Anaerobic or Mixed Anaerobic-Aerobic Bacterial Infections

6.4.1 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 [13] 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.

6.4.2 Summary of the evidence and HBOT rationale

In all of these indications, HBOT is recommended as part of the therapy in addition, obviously, of antibiotics, surgery and supportive therapy [13, 16]. Solid results from RCTs are lacking and evidence for therapy is mainly based on belief and pathophysiological reasoning. Major retrospective clinical studies indicate that the lowest morbidity and mortality are achieved with initial conservative surgery and rapid initiation of HBO therapy. Results decline progressively when HBO therapy is delayed. Early aggressive surgery and delayed HBO treatment lead to a significantly higher mortality and morbidity than when HBO is administered promptly [1].

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 [13]. Because of the rapidity of gas gangrene evolution it is recommended to start therapy as soon as the condition is recognized. In humans, clinical observational studies concluded that lowest mortality and morbidity was achieved with initial conservative surgery and rapid initiation of HBOT [13].

For intracranial abscess there have been several observational case series suggesting a better prognosis with HBOT. 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 data [22] and on the fact that this has become accepted practice [13].

6.5 Acute Soft Tissue Ischemia

6.5.1 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.

The UHMS includes in its recommendation the crush injuries, compartment syndrome and other acute tissue ischemia and also the compromised skin grafts and flaps.

6.5.2 Summary of the evidence and HBOT rationale

The ECHM recommends (type 1, level B) HBOT as adjuvant therapy in post-traumatic crush injuries with open fractures. 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. Both organizations recommend the measurement of transcutaneous oxygen pressure as an index to define indications and evolution of treatment (ECHM type 1, level B recommendation).

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 [13].

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 [13]. Small RCT's have been conducted.

6.6 Post-Radiotherapy Tissue Damage (SOFT Tissue and Bones)

6.6.1 Short description of the condition

Cancer is a frequently occurring disease and often radiotherapy is part of the treatment. The injuries caused by ionizing irradiation can be severe. They are generally subdivided into acute, sub-acute or delayed reactions [13]. 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 [13]. Radiation lesions are typically associated with endarteritis, tissue hypoxia and secondary fibrosis.

6.6.2 Summary of the evidence and HBOT rationale

The impact of hyperbaric oxygen in terms of its beneficial effects is likely to involve all three of the above mechanisms in irradiated tissues: 1) Hyperbaric oxygen stimulates angiogenesis and secondarily improves tissue oxygenation; 2) Hyperbaric oxygen reduces fibrosis; and 3) Hyperbaric oxygen is likely to mobilize and stimulate an increase of stem cells within irradiated tissues. The third mechanism is at this point putative and remains to be proven in radiation damaged tissues.

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 [13, 16]. 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 1 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.

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 [13], while clinical evidence is often collected by location or organ system.

A series of small RCTs have been conducted and some Cochrane reviews have dealt with this series of indications. The Cochrane review from 2005 [23], 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.

6.7 Delayed Wound Healing

6.7.1 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. 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 [13].

6.7.2 Summary of the evidence and HBOT rationale

The rationale for the use of HBO is based on the fact that, despite wounds are by nature hypoxic, the oxygen tensions from surrounding tissue is normally adequate to support normal healing of wounds.

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 [13, 16]. Those two indications are for the ECHM type 2, level B recommendations [16]. In addition HBOT is accepted for selected non-healing wounds caused by inflammatory processes (ECHM type 3, level C recommendation) [16].

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. A Cochrane review from 2004 assessed the evidence for HBOT in chronic wounds [24].

6.8 Chronic Refractory Osteomyelitis

6.8.1 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 [13].

6.8.2 Summary of the evidence and HBOT rationale

There is evidence that HBOT enhances osteogenesis [1]. Remodeling of bone by osteoclasts is an oxygen-dependent function. Consequently, inadequate oxygen tensions inhibit microscopic debridement of dead, infected bone by osteoclasts. HBOT can restore physiologic or provide supra-physiologic oxygen tension in hypoxic bone environments, thus osteoclast function in infected bone can be improved.

HBOT has been shown to be effective in acutely reducing tissue edema, lowering intra-compartmental pressures and ameliorating the detrimental effects of inflammatory reactions [1]. Over the longer term, HBOT can be used to promote new collagen formation and capillary angiogenesis in both hypoxic bone and surrounding tissues [1]. By creating a sustained increase in arterial perfusion of previously hypoxic bone and soft tissues, HBOT can reduce susceptibility of these tissues to recurrent infection and necrosis.

HBOT as adjuvant therapy (next to antibiotics, nutritional support and surgical intervention) has been advocated since the nineteen sixties. The ECHM supports this indication as a type 2, level C recommendation [16]. Most evidence, however, comes from in vitro and in vivo animal studies [13]. Clinical studies are limited to a few retrospective and uncontrolled case studies [13]. No Cochrane reviews are available for this indication. The evidence for this indication is mainly consensual.

6.9 Post-Anoxic Encephalopathy

6.9.1 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.

6.9.2 Summary of the evidence and HBOT rationale

The potential beneficial effects of HBO on cerebral anoxia have been described and they apply particularly well to cases of post-hanging anoxic encephalopathy. Clinical studies have shown that HBO provided immediately after rescue is associated with rapid and complete recovery except when there was cardiac/circulatory arrest on rescue [25].

HBOT is considered optional in the ECHM guidelines (type 3, level C recommendation) and is not mentioned in the UHMS guidelines [13, 19]. No Cochrane reviews are available for this indication. A review of Chinese trials, 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 [26].The evidence for this indication is mainly consensual.

6.10 Thermal burns

6.10.1 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 most common mechanisms of burn injury are flame and scalding, and the upper extremity, head and neck are the most common body areas involved (1).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 [13].

6.10.2 Summary of the evidence and HBOT rationale

Goals of burn treatment include survival of the patient with rapid wound healing, minimal scarring and abnormal pigmentation, and cost-effectiveness. The optimal outcome is restoration, as nearly as possible, to the pre-burn quality of health and psychological well-being [1]. Therapy of burns, therefore, must be directed toward minimizing edema, preserving marginally viable tissue, protecting the microvasculature, enhancing host defences, and promoting wound closure.

Adjunctive HBOT therapy can benefit each of these problems directly, and shows promise in the treatment of inhalation injury but the use of hyperbaric oxygen therapy as part of the treatment of thermal burns is far from being universally accepted.

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.

A Cochrane review from 2004 identified five RCTs, and two of those fulfilled inclusion criteria [27].All trials in this review, however, were considered of poor methodological quality and heterogeneous in patients and outcomes. In general, the authors concluded that little evidence supports the effectiveness of HBOT in the management of thermal burns. In view of the current available knowledge, hyperbaric oxygen therapy should only be administered according to strict protocols of utilization, optimizing the possible benefits while avoiding any extra risk.

6.11 Hearing disorders

6.11.1 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. The incidence is estimated at 5 to 20 cases per 100,000 annually. However, the incidence may be higher, as many cases are likely unreported. Additionally, it has been estimated that as many as 65% of cases may resolve spontaneously. ISSHL is classicaly defined as a hearing loss of at least 30 dB in 3 consecutive audiometric frequencies over 72 hours or less The most common clinical presentation involves an individual experiencing a sudden unilateral hearing loss, tinnitus, a sensation of aural fullness and vertigo.

The hearing loss is due to pure damage of the cochlea. and The aetiologies and pathologies of ISSHL remain unclear. Because of its rapid onset a vascular cause has been suspected, although other pathophysiological mechanisms have been described. Four main theories are proposed to explain this disturbance: vascular, viral, round window rupture and auto-immune disorders. Although these hypotheses are controversial, the most likely cause involves impaired oxygen delivery to the organ of Corti.

Treatment for ISSHL is generally designed to improve blood circulation and oxygenation of the inner ear. This can be restored with hyperbaric oxygen therapy.Assessing treatment is complex due to the high rate of spontaneous recovery [27].

6.11.2 Summary of the evidence and HBOT rationale

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. The cochlea and the structures within it require a high oxygen supply. HBOT may therefore be able to reverse this hypoxia [11].It has been used since the nineteen sixties for this indication with conflicting results.

Controlled studies have demonstrated a greater degree of hearing improvement when patients receive early intervention with HBOT and oral steroids concomitantly. The use of HBOT for the treatment of ISSHL is Class IIa (AHA Evidence-Based Scoring System) with an "A" Level of Evidence.

While there is a large body of literature comparing therapeutic interventions for the treatment of ISSHL, only a small number of controlled studies have been performed. There is no clear consensus for the treatment. More than 60 protocols have been described. However, when the three most prominent and efficacious treatments (steroids, vasodilators and HBOT) were reviewed by meta-analyses, only HBOT received a positive, objective, critical review (Cochrane Review, 2010).

6.12 Acute ophthalmological ischemia

6.12.1 Short description of the condition

Central retinal artery occlusion (CRAO) is a relatively rare emergent condition of the eye resulting in a sudden interruption of the blood supply to the retina, causing unilateral loss of vision. Usually occurring between ages 50 to 80, is sometimes preceded by transient episodes of vision loss (amaurosis fugax) [29].This disease is most often caused by embolism of the retinal artery. The vision loss is usually dramatic and permanent and the prognosis is poor. Patients particularly at risk include those with giant cell arteritis, atherosclerosis, and thromboembolic disease. Attempted treatment is based on medical treatment trying to improve perfusion of the retina. A wide variety of treatment modalities have been tried with little to no success, with the exception of hyperbaric oxygen therapy.

6.12.2 Summary of the evidence and HBOT rationale

The visual signs and symptoms of vascular occlusive diseases of the retina are dependent on both the particular vessel occluded, the degree of occlusion, the location of the occlusion, and the presence or absence of a cilioretinal artery. Normally, the choroidal circulation supplies the majority of the oxygen to the retina. Under normoxic conditions, approximately 60% of the retina's oxygen comes from the choroidal circulation. Under hyperoxic conditions, the choroid is capable of supplying 100% of the oxygen needed by the retina [1].

In considering the effect of treating CRAO with supplemental oxygen, four key factors determine success: 1) therapy must be initiated before the retinal tissue is irreparably damaged; 2) the degree of occlusion of the blocked vessel may vary; 3) some patients may not respond to oxygen therapy, even if it is initiated promptly, if the level of occlusion is at the ophthalmic artery; 4) an adequate partial pressure of oxygen must be maintained to keep the retina viable until circulation is restored. The aetiology of the arterial occlusion (thrombosis, embolus, arteritis, vasospasm) has also been described as affecting outcome [1].

The ECHM considers HBOT optional in acute ophtalmological ischemia (type 3, level C recommendation) [16]. The indication is also mentioned in the UHMS guidelines)[13]. From retrospective comparisons of case series no reliable evidence about the benefits of HBOT could be found in people with acute retinal ischemia. Again, it is concluded that RCTs are feasible and should be carried out.

6.13 Neuroblastoma stage IV

6.13.1 Short description of the condition

Neuroblastoma is a cancer that arises in immature nerve cells and affects mostly infants and children. Stage IV is a primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs [30].

6.13.2 Summary of the evidence and HBOT rationale

Hypoxia is recognized as a major cause of failure of radiotherapy. In clinical oncology, several treatment modalities have been applied to overcome tumour hypoxia either by increasing the oxygen delivery to

tumour cells (ie carbogen and HBO) or by combined treatment with oxygen mimicking agents to sensitize hypoxic cells (ie misonidazole). Radiation enhancement by HBOT in the treatment of patients with recurrent Neuroblastoma stage IV seems to be the most promising indication of that approach.

According to the ECHM, adjuvant HBOT for this indication should be considered although no RCTs are available to support this [16]. The UHMS does not mention this indication)[13].

6.14 Pneumatosis Cystoides Intestinalis

6.14.1 Short description of the condition

Pneumatosis Cystoides Intestinalis (PCI) is a rare disease characterized by multiple gas-containing cysts in in the bowel wall. The diagnosis is currently best obtained by plain abdominal radiography or ultrasonography and specifically delineated by computer tomography.It is a radiographic finding and not a diagnosis, as the etiology varies from benign conditions to fulminant gastrointestinal disease [31].

Primary pneumatosis intestinalis is extremely rare. The underlying pathology can be gastrointestinal, pulmonary or immunological. The cysts are thin walled and break easily. Spontaneous rupture gives rise to pneumoperitoneum.

6.14.2 Summary of the evidence and HBOT rationale

Surgical intervention is indicated only in acute complications, such as perforation, peritonitis, bowel necrosis, or tension pneumoperitoneum. Several reports have indicated the advantages of hyperbaric oxygen therapy in the management of pneumatosis cystoides intestinalis. It is stressed that HBOT is effective if it is continued until cyst resolution has occurred and not just until symptomatic improvement. Results obtained from HBOT in patients with PCI have been favorable and promising.

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 (type 3, level C recommendation).[9] The UHMS guidelines do not mention this indication.

6.15 Exceptional anaemia

6.15.1 Short description of the condition

Patients who have marked loss of red blood cell mass by hemorrhage, hemolysis, or aplasia run the risk of lacking adequate oxygen carrying capacity by blood. The more quickly the severe anaemia develops, the less tolerant the patient may be of the insult [1]. In the United States, HBOT for severe anaemia has had a long-standing approval for use.

6.15.2 Summary of the evidence and HBOT rationale

Where safely available, 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 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.

Not surprisingly, the indication of anemia is only accepted by UHMS in exceptional cases where the patient cannot receive or refuses to accept a transfusion [16], but this indication is not withheld by ECHM [16]. The evidence for this indication is mainly based on animal models and on small human case series and case reports [13]. A review of this observational evidence found generally positive results. [32],

HBOT provides a way in severe anaemia to successfully correct accumulating oxygen debt in untransfusible patients [1]. Both by the support of animal work and human clinical experience evidence-based analysis firmly supports the use of HBO as a treatment option in severe anaemia. using AHA, NCI-PDQ, and BMJ evidence-based criteria.

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

Apart from the previously mentioned accepted indications by ECHM, UHMS or both, there is a multitude of other indications, often based on little or no evidence, where treatment is mainly experimental. This group of Miscellaneous indications is detailed in **Annex B1**.

7.0 GENERAL CONCLUSIONS

Hyperbaric Medicine goes back a long way, since its history derives from the history of diving which dates back to ancient times.HBOT can be viewed as the new application of an old, established technology to help resolve certain medical problems. 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.

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. 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.

There is empirical evidence and wide consensus, on the efficacy of HBOT in the treatment of a few life threatening conditions i.e. decompression illness 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 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.

The field is advancing, and the general understanding of pathophysiology in many diseases has improved. Over the course of the past 2 decades, a constant number of scientific papers of EBM standards have been published, resulting in a progressively increasing acceptance of HBOT as a valuable adjunctive medical treatment in a given number of diseases. 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.

According to ECHM, some questions must be regarded about the research in Hyperbaric Medicine for the next future and some Recommendations (**Annex C1**) were issued concerning this matter: 1) it is strongly recommended that personnel of hyperbaric facilities will associate into multi-disciplinary teams with specialist in other fields and basic scientists; 2) it is strongly recommended that medical staff involved in Hyperbaric Medicine receive training in basic and clinical research methods on a continuously regular base; and 3) it is strongly recommended the establishment of a directory of centers and teams involved in clinical and basic research related to hyperbaric medicine.

HBOT will surely continue to attract attention and invite to controversy in clinical medicine and will remain a stimulant area of scientific knowledge and future research.

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ANNEXES

Annex A1

This annex contains detailed information about the 7th ECHM Consensus Conference held in 2004, where this List of accepted HBOT indications was approved. Methodology followed to analyze different pathologies is included, as well as tables containing accepted and non accepted indications and the corresponding levels of Recommendation and Evidence.

RECOMMENDATIONS OF THE JURY:

Introduction

The aim of the Consensus Conferences organized by the European Committee for Hyperbaric Medicine (ECHM) is to reach an agreement on how Hyperbaric Medicine should be delivered with regard to its different aspects: indications, organizational aspects, education and training of personnel, operational rules and procedures, evaluation and quality assurance, research.

The first ECHM Consensus Conference was held in Lille in 1994 and, after 2 days of intense debates, recommendations were issued. At that time, it was found that not many of these recommendations were supported by a high level of evidence according to the methodology of Evidence-Based Medicine, but as these recommendations were consensually agreed by a large number of experts, they were regarded as a good starting point for further research and experience.

Ten years have elapsed since this first Conference and a tremendous amount of work has been done in Europe and elsewhere. The time has come to review these 1994 recommendations and to elaborate a new synthesis.

The method of Evidence-Based Medicine (EBM) has gained a large agreement and is presently an integral part of modern medical practice. It is typically based on 3 axes: (1) the level of evidence (i.e. quality of available data), (2) interpretation of the evidence (i.e. what the data suggest and how concordant these data are regarding a particular problem), and (3) the type or strength of the recommended practice (i.e. the extent to which a physician is able to recommend a particular intervention on the basis of the first two considerations). This method may be used either by an individual physician or by a group of experts who could be expected to arrive at the same conclusion.

Unfortunately, this method is only applicable when high quality randomized controlled clinical studies exist. When there is a lack of data, the search for a consensus of experts is the method the most widely adopted. This method is regarded as the best surrogate to EBM method to evaluate interventions under the following circumstances. (1) Where a particular intervention, unsupported by a high level of evidence, has become universally accepted to such an extent that it would be considered a violation of accepted standards of care to deny a patient the benefit of the therapy for the purpose of a study. (2) Where the disease or condition of interest is so complex or where there are so many variables that it would be impossible to design a study sufficiently powerful to evaluate any single intervention. (3) Where the application of the therapy is so logical that it would be grossly inappropriate to consider omitting it to establish proof of efficacy. (4) Where no current higher level of evidence exists, but experts are able to report, not only from their own experiences but also by producing comprehensive literature reviews from which consensus can provisionally be reached, pending the outcome of future studies.

Even if an enormous effort has been made by the hyperbaric medicine community in order to achieve high quality clinical studies, we are forced to recognize that in our field, many questions remain without sufficient evidence to give a definite answer. During its debates, the jury was faced with a number of

conditions where the evidence was evaluated as insufficient to put them on the list of accepted indications for Hyperbaric Oxygen Therapy (HBO2). With other conditions, recent data did not convince the Jury of the efficacy of HBOT. In these cases, the Jury adopted a "conservative" attitude while awaiting future studies. However, far from discouraging us, this must be a strong stimulant to increase our research effort and improve the quality of our practice.

As for the recommendations of the first ECHM Consensus Conference, those issued by the Jury of this 7th ECHM Consensus Conference have to be looked at a new step forward and a new starting point for the next 10 years.

Methodology of 7th ECHM Consensus Conference

Consensus Conferences aim to create an objective and complete review of current literature and knowledge on a particular topic or field. This method has the advantage of involving a diverse group of experts, thus increasing objectivity. Participants in Consensus Conferences are selected from a broad range of relevant backgrounds to provide consideration of all aspects of the chosen topic and maximum objectivity. The opportunity to meet with other experts in the same field and share comments and information is also a valuable aspect of Consensus meetings.

In a Consensus Conference, experts present their review of the literature relating to a specific topic in front of a jury and an audience. Thereafter, the jury gathers in a secluded place to discuss the presentations, and presents its finding in a Consensus Statement that includes recommendations for clinical practice based on the evidence that was presented. These recommendations are published in the medical literature.

The application of Evidence-Based Medicine methodology to the consensus conference process helps the jury members to reach a consensus and strengthens the recommendation made. Thus, it is proposed each jury member assesses the literature and the evidence presented by the experts, and grades those according to their quality.

We propose each jury member uses the same grading scale, which has been extensively validated.

Basic studies (tissular, cellular or subcellular level)

1. Strong evidence of beneficial action

2. Evidence of beneficial action

3. Weak evidence of beneficial action

4. No evidence of beneficial action, or methodological or interpretation bias precluding any conclusion.

Animal studies with control group

1. Strong evidence of beneficial action

2. Evidence of beneficial action

3. Weak evidence of beneficial action

4. No evidence of beneficial action, or methodological or interpretation bias precluding any conclusion

Human studies

1. Strong evidence of beneficial action based on at least two concordant, large, double-blind, controlled randomized studies with no or only weak methodological bias.

2. Evidence of beneficial action based on double-blind controlled, randomized studies but with methodological bias, or concerning only small samples, or only a single study.

3. Weak evidence of beneficial action based only on expert consensus or uncontrolled studies (historic control group, cohort study,...)

4. No evidence of beneficial action (case report only), or methodological or interpretation bias precluding any conclusion.

ECHM Recommendations

The Jury will issue its recommendations using a 3 grade scale according to the strength each recommendation has been evaluated.

Type 1: Strongly Recommended. The Jury considers the implementation of the recommendation of critical importance for final outcome of the patient/quality of practice/future specific knowledge.

Type 2: Recommended. The Jury considers the implementation of the recommendation as positively affecting final outcome of the patient/quality of practice/future specific knowledge.

Type 3: Optional. The Jury considers the implementation of the recommendation as an option.

The Jury will also report the level of evidence which supports, in its view, the recommendation.

Level A: Recommendation supported by level 1 evidence.

Level B: Recommendation supported by level 2 evidence

Level C: Recommendation supported only by level 3 evidence.

In using such a methodology, we expect every physician reading the jury conclusions will be able to assess the strength of evidence supporting each statement and how it has to be applied in clinical practice.

Table I: List of potential and proposed indications for Hyperbaric Oxygen Therapy.

After having listened to the experts and with the assistance of literature reviewers, the Jury has graded the existing evidence using the scale used in ECHM Consensus Conferences.

Conditions where the use of HBOT was supported by level A, B or C evidence were considered as accepted indications.

Level A: At least 2 concordant, large, double-blind, controlled randomized studies with no or little methodological bias.

Level B: Double-blind controlled, randomized studies but with methodological flaws; studies with only small samples, or only a single study.

Level C: Consensus opinion of experts.

In order to make more transparent the jury discussion and decision, conditions which were not considered as accepted indications for HBOT are also reported with the Jury's evaluation of the existing evidence. The scale used in this table is an extension of that used for accepted indications.

Level D: Only uncontrolled studies with no consensus opinion of expert.

Level E: No evidence of beneficial action, or methodological or interpretation bias preclude any conclusion.

Level F: Existing evidence favors not to use HBOT.

CONDITION	ACCEPTED			NON ACCEPTED		
	Level of Evidence			Level of Evidence		
	A	B	C	D	E	F
Type I						
CO poisoning		X				
Crush syndrome		X				
Prevention of osteoradionecrosis after dental extraction		X				
Osteoradionecrosis (mandible)		X				
Soft tissue radionecrosis (cystitis)		X				
Decompression accident			X			
Gas embolism			X			
Anaerobic or mixed bacterial anaerobic infections			X			
Type II						
Diabetic foot lesion		X				
Compromised skin graft and musculocutaneous flap			X			
Osteoradionecrosis (other bones)			X			
Radio-induced proctitis / enteritis			X			
Radio-induced lesions of soft tissues			X			
Surgery and implant in irradiated tissue (preventive action)			X			
Sudden deafness			X			
Ischemic ulcer			X			
Refractory chronic osteomyelitis			X			
Neuroblastoma Stage IV			X			

CONDITION	ACCEPTED			NON ACCEPTED		
	Level of Evidence			Level of Evidence		
	A	B	C	D	E	F
Type III						
Post anoxic encephalopathy			X			
Larynx radionecrosis			X			
Radio-induced CNS lesion			X			
Post-vascular procedure reperfusion syndrome			X			
Limb replantation			X			
Burns >20 % of surface area and 2nd degree			X			
Acute ischemic ophthalmological disorders			X			
Selected non healing wounds secondary to inflammatory processes			X			
Pneumatosis cystoides intestinalis			X			
Others indications						
Post sternotomy mediastinitis				X		
Stroke				X		
Sickle cell disease				X		
Malignant otitis externa				X		
Acute myocardial infarction				X		
Femoral head necrosis				X		
Retinitis pigmentosa					X	
Tinnitius					X	
Interstitial cystitis					X	
Facial (Bell's) palsy					X	
Cerebral palsy						X
Multiple sclerosis						X
Fetoplacental insufficiency						X

Annex B1

In **Annex B1** is detailed a group of indications, apart from the previously mentioned "accepted" indications by ECHM, UHMS or both. In this group of Miscellaneous indications, often based on little or no evidence, the treatment is mainly experimental. A short summary of the evidence for each of these condition is included.

1. Acute Coronary Syndrome

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.

2. Acute Ischemic Stroke

No evidence for improved clinical outcomes when applied during the acute presentation of ischemic stroke. Evidence from the performed RCTs is insufficient but clinical benefit does not seem likely.

3. Acute Traumatic Brain injury

Very low quality evidence from small trials for a reduced risk of death, without evidence for improved outcomes in terms of quality of life.

4. Autism

Very low quality evidence from a few anecdotic case series and one very small RCT 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.

5. Cerebral Palsy

No evidence for the efficacy of HBOT for the treatment of cerebral palsy. Some small RCTs are currently being conducted for this indication.

6. Delayed onset muscle soreness and closed soft tissue injury

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. .

7. Facial Palsy

Very low quality evidence from a single small RCT for a better complete recovery and a shorter duration of symptoms using HBOT compared to prednisone therapy.

8. Fracture Healing

No evidence available for the efficacy of HBOT on fracture healing.

9. Malignant Otitis externa

No evidence available for the efficacy of HBOT when compared to treatment with antibiotics and/or surgery.

10. Migraine and cluster headache

Very low quality evidence from nine small RCTs 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.

11. Multiple sclerosis

Very low quality evidence from nine small RCTs for no beneficial effect of HBO.

12. Tinnitus

Low quality evidence from one small RCT for no beneficial effect of HBOT.

13. Tumour Sensitization to radiotherapy

Very low quality evidence from nineteen trials 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.

Annex C1

Hyperbaric oxygen therapy is a relatively recent development in the field of human medicine.

Over the course of the past 2 decades, a constant number of scientific papers of EBM standards have been published, resulting in a progressively increasing acceptance of Hyperbaric Oxygen Therapy as a valuable adjunctive medical treatment in a given number of diseases. However, the absolute number of these publications is still to be considered low, and the general quality of research is still to be improved [9,27].

According to ECHM some questions must be regarded in this matter. **Annex C1** contains Recommendations issued by the Jury of the 7th Consensus Conference (in 2004) about the research in Hyperbaric Medicine for the next future.

ECHM RECOMMENDATIONS CONCERNING THE RESEARCH IN HYPERBARIC MEDICINE FOR THE NEXT FUTURE

* It is strongly recommended that personnel (member) of hyperbaric facilities will associate into multi-disciplinary teams with specialist in other fields and basic scientists (Type 1 recommendation, level C)

* It is strongly recommended that medical staff involved in Hyperbaric Medicine receive training in basic and clinical research methods on a continuously regular base (e.g. CME). (Type 1 recommendation, level C)

* It is strongly recommended that a network of multicentric basic and clinical research is implemented. (Type 1 recommendation, level C)

* It is strongly recommended that European Ethical and Research Committees have to be continued within the European Committee for Hyperbaric Medicine with 2 priorities:

- establishment of a directory of centers and teams involved in clinical and basic research related to hyperbaric medicine.

- organization of seminars and workshops dedicated to clinical and basic research training. (Type 1 recommendation, level C)

* It is strongly recommended that information and personnel exchange policies between hyperbaric facilities are implemented (Type 1 recommendation, level C)