Stockholms läns landsting

FOKUSRAPPORT

Behandling med hyperbar syrgas (HBO) vid Karolinska Universitetssjukhuset

Treatment with Hyperbaric Oxygen (HBO) at the Karolinska University Hospital

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Författare - Authors

Folke Lind

Gunnar Öhlén

Viveka Lindén

Bengt M Eriksson

Claes Frostell

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Det medicinska programarbetet inom SLL

Det medicinska programarbetet i Stockholm syftar till att patienter, vårdgivare och beställare skall mötas för att forma en god och jämlik vård för länets 2 miljoner invånare. Kunskapen om den goda vården skall vara gemensam, tillgänglig och genomlysbar och bilda grund för bättre beslut i vården.

Arbetet bedrivs inom avdelningen Medicinskt Kunskapscentrum för stöd till kunskapsstyrning i samverkan med såväl sakkunnigorganisationen som procenter och beställare. Programarbetet bildar en gemensam arena för vårdens parter.

Fokusrapporterna syftar till att belysa angelägna utvecklingsområden inom hälso- och sjukvården genom att beskriva dagsläget och tänkbara åtgärder. De skall vara ett diskussionsunderlag i dialogen mellan politiker, beställare och producenter.

Förord

Hyperbarmedicinsk oxygenbehandling har funnits i Sverige i mer än 50 år. 2006 installerades en modern enhet för hyperbar oxygenbehanding (HBO) utrustad och bemannad för intensivvård dygnet runt vid Karolinska Universitetssjukhuset i Solna. I samband med detta förelåg ett behov av att definiera indikationerna för HBO-behandling och det uppdrogs åt ansvariga för verksamheten att skriva en så kallad fokusrapport. Inom Stockholms läns landsting utgör fokusrapporter en sammanställning av aktuell kunskap och ett diskussionsunderlag i dialogen mellan beställare, politiker och producenter.

En grupp etablerades 2006 som har arbetat med frågan helt självständigt. De har sammanställt evidens inom aktuella terapiområden. Ett nationellt förankringsarbete har genomförts inom Svensk Förening för Anestesi och Intensivvård.

Evidensvärderingarna i fokusrapporten skiljer sig emellertid från de som gjorts i Socialstyrelsens ”Nationella riktlinjer för diabetesvården 2010”. HBO-behandling anses där utgöra en forskningsfråga. I den aktuella fokusrapporten framgår att ”texten *inte* utgör en komplett klinisk expertuppfattning om HBO och fullständig konsensus var inte möjligt att uppnå trots den begränsade mängden av författare”. Fokusrapporten är skriven och sammanställd som ett vårdprogram. Den har dock *inte* accepterats som sådant inom Stockholm läns landsting och rapportens rekommendationer ska uppfattas som författargruppens.

Med tanke på den volym av behandlingar som redan genomförs vid Karolinska Universitetssjukhuset har Kommittén för kunskapsstyrning (KUST) inom SLL rekommenderat systematiska protokollförda studier av samtliga behandlade patienter för att generera ökad kunskap inom området.

Stockholm i maj 2011

Gunnar Öhlén

Ordförande i Specialitetsrådet för Akut omhändertagande

Elisabeth Persson

Ordförande Stockholms Medicinska Råd

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0. Inledning – Introduction in Swedish

Syfte

Sedan 1991 har ANOPIVA kliniken vid Karolinska Universitetssjukhuset i Solna ansvarat för den hyperbarmedicinska verksamheten i länet. Inom Stockholms läns landsting (SLL) har det funnits ett behov av att bättre förstå indikation, resultat och andra aspekter på området, vilket föranledde ett uppdrag år 2006 till det Medicinska programarbetet i SLL att arbeta fram en Fokusrapport. Detta sammanföll med ett internt behov inom Karolinska Universitetssjukhuset, att med stöd av en gemensam referensgrupp, bättre definiera det hyperbarmedicinska uppdraget. Behovet har understrukits av att nya forskningsrön påverkar indikationer för HBO. Utanför Sverige finns exempel på HBO-verksamhet baserad på indikationer som inte accepterats i vårt land. Detta har skapat debatt.

Rapporten är skriven på engelska, med en kort svensk sammanfattning, då mycket av den vetenskapliga redovisningen och de flesta utbildningar sker på engelska och genomförs i nära internationell samverkan. HBO-verksamheten vid Karolinska Universitetssjukhuset utgör därtill en akut och elektiv resurs för hela Östersjöområdet.

Arbetsgrupp och förankring

Fokusrapportens nationella referensgrupp, med stöd från erfaren medarbetare i SBU, (se nedan och kapitel 2) har sammanträtt 1–2 gånger per år sedan år 2006. Sammankallande har varit ANOPIVA-kliniken på Karolinska Universitetssjukhuset, där Hyperbarmedicin finns som en sektion. Konsensus har till alla delar inte varit möjligt att uppnå trots den begränsade mängd av författare.

En referensgrupp för Hyperbarmedicin finns inom Svensk Förening för Anestesi och Intensivvård (SFAI) med ansvariga läkare för HBO verksamheterna vid Sunderby sjukhus i Luleå, Blekingesjukhuset i Karlskrona, Helsingborgs lasarett, Sahlgrenska Universitetssjukhuset Östra i Göteborg, Uddevalla sjukhus samt Karolinska Universitetssjukhuset. Fokusrapporten kan komma att tjäna som en nationell kunskapsbas.

Författare – Authors

Folke Lind, MD, PhD, Dept of Anaesthesia, Surgical Services and Intensive Care, Karolinska University Hospital, Stockholm

Gunnar Öhlén, MD, PhD; Dept of Emergency Medicine, Karolinska University Hospital, Stockholm

Viveka Lindén, MD, PhD; Dept of Paediatric Anaesthesia and Intensive Care; Karolinska University Hospital, Stockholm

Bengt M. Eriksson, MD; Dept of Anaesthesia, Surgical Services and Intensive Care Karolinska University Hospital, Stockholm

Claes Frostell, MD, PhD; Dept of Anaesthesia, Surgical Services and Intensive Care, Karolinska University Hospital, Stockholm

Members of the HBO reference group 2010 (alphabetical order):

Britt Arrelöv, MD, PhD Medical advisor Strategic Medical Issues Stockholm County Council	*Britt Arrelöv,* överläkare Specialist Allmänmedicin Medicinskt sakkunnig Avdelningen för Övergripande Vårdfrågor Stockholms läns landsting
Kerstin Brismar, MD, PhD, Professor Dept of Endocrinology & Diabetology Karolinska University Hospital, Solna	*Kerstin Brismar,* Professor, överläkare Kliniken för Endokrinologi, Metabolism och Diabetes Karolinska Universitetssjukhuset, Solna
Anders Ekbom, MD, PhD, Professor Clinical Epidemiology Unit Department of Medicine Karolinska Institutet	*Anders Ekbom,* Professor, överläkare Institutionen för Medicin, Solna (MedS) Enheten för klinisk epidemiologi Karolinska Institutet
Hans Grönkvist, MD, Surgeon Commander Specialist Orthopedic surgery Swedish Armed Forces (ret).	*Hans Grönkvist,* Marinläkare Specialist ortopedi Kommendörkapten, Försvarsmakten. (pens.)
Lennart Iselius, MD, PhD, Associate Professor Specialist General Surgery Division director of Clinical Neurosciences Karolinska University Hospital	*Lennart Iselius,* Docent, överläkare Chef Huvuddivisionen Karolinska Universitetssjukhuset Stockholm
Stefan Lundin, MD, PhD, Professor Dept of Anesthesiology and Intensive Care Institute of Clinical Sciences Sahlgrenska Academy Sahlgrenska University Hospital, Gothenburg	*Stefan Lundin,* Professor, överläkare Anestesi, Operation och Intensivvård Sahlgrenska Universitetssjukhuset Göteborg
Claes-Roland Martling, MD, PhD Head Central Intensive Care Dept of Anaesthesia, Surgical Services & Intensive Care Karolinska University Hospital, Solna	*Claes-Roland Martling,* Docent, överläkare Centrala intensivvårdsavdelningen (CIVA) Karolinska Universitetssjukhuset, Solna Stockholm
Tiit Mathiesen, MD, PhD, Professor Department of Neurosurgery Karolinska University Hospital,Solna	*Tiit Mathiesen,* Professor, överläkare Neurokirurgiska kliniken Karolinska Universitetssjukhuset, Solna
Britt Nordlander, MD, PhD, Associate Professor Secretary Swedish Society of Medicine Dept of Otorhinolaryngology Karolinska University Hospital, Solna	*Britt Nordlander,* Docent, överläkare Sekreterare i Svenska Läkaresällskapet Öron-, näs- och halskliniken Karolinska Universitetssjukhuse, Solna
Nina Rehnqvist, MD, PhD, Professor Professor Cardiology Karolinska Institute Chairperson the Swedish Council on Technology Assessment in Health Care	*Nina Rehnqvist,* Professor, överläkare Professor i kardiologi vid Karolinska Institutet Ordf SBU – Statens Beredning för Medicinsk Utvärdering Stockholm
Marie Wickman, MD, Professor Professor. Dept of Reconstructive plastic surgery, Division director of Medicine & Surgery 1 (e.g. Transplants, Gastroenterology, Endocrinology) Karolinska University Hospital	*Marie Wickman,* Professor, överläkare Chef MK1-divisionen Karolinska Universitetssjukhuset

1. Sammanfattning – Summary in Swedish

Hyperbarmedicinsk verksamhet har funnits i Sverige i mer än 50 år. Sedan 1991 har ANOPIVA kliniken vid Karolinska Universitetssjukhuset i Solna ansvarat för verksamheten och rustat upp och bemannat den till en av världens mest moderna enheter för hyperbar oxygen (HBO) behandling, med en stor rektangulär intensivvårdstryckkammare och fyra monokammare. Samarbete finns med andra enheter inom och utom Sverige.

Karolinska Universitetssjukhuset HBO-behandlar patienter från Stockholms län, från mellersta och norra Sverige samt från utlandet med dygnet runt beredskap för akuta behandlingar av dykarsjuka, luftembolier, kolmonoxidförgiftning samt livshotande infektioner. Årligen genomförs ca 3000 behandlingar fördelat på ca 150 patienter där majoriteten av behandlingarna är elektiva och utförs på inneliggande eller polikliniska patienter med postoperativa infektioner och komplikationer till strålbehandling mm. En typisk HBO-behandling kan ta 100 min och en behandlingsserie omfattar ofta en behandling under 20–40 vardagar. I svåra fall, ofta intensivvårdspatienter, ges två HBO-behandlingar per dag, även helgtid, varvat med diagnostik, operationer, dialys och intensivvård enligt vårdprogram.

Historiskt sett är ca 15–25 procent av HBO-behandlade intensivvårdspatienter utomlänsfall, men i och med att de vetenskapliga grunderna för HBO-indikationerna blivit tydligare och detta resulterat i kliniska vårdprogram inom och utom SLL, förutses ett ökat remissflöde under de närmaste åren. Med nuvarande HBO-resurser kan, med begränsat personaltillskott, denna volymökning klaras. En begränsande faktor är bristen på intensivvårdsplatser. Under det senaste året har ett antal patienter från SLL närliggande landsting hänvisats till Göteborg pga brist på intensivvårdsplatser. Vad avser elektiva HBO-indikationer finns det en potentiell volymökning på sikt.

En svårighet för lokal utförare av HBO och remittenter är förändringar i ersättningssystem för vård och behandling. I det system som tillämpas inom SLL kan en remittent få ekonomiskt ansvar för patienter med HBO-indikation asymmetriskt mellan olika år och gällande budget. Situationen kan liknas vid den avseende patienter med lång vårdtid på intensivvårdsavdelning, där särskild beställarersättning utgår vid vårdtider >5 dygn. Under 2009 omsatte HBO-verksamheten totalt 17,6 mkr, under 2010 19,8 mkr. Omsättningen har tidigare varit ca 25 mkr per år, men har med striktare indikationer minskat. Karolinskas huvudavtal täckte år 2009 och 2010 ca 90% av kostnaderna och resterande 10% fördelades jämnt mellan utomlänsfakturering och vidarefakturering till övriga SLL-sjukhus. Kapitel 8 ”Clinical Statistics” ger en uppfattning om relativa fördelningen av antal patienter och HBO-behandlingar på Karolinska Universitetssjukhuset för olika sjukdomstillstånd under två decennier.

Varje HBO-behandling, om ca 100 min. i monokammare kostar 4 400 kr och behandling om ca 110 min. i intensivvårdstryckkammare kostar ca 40 000 kr. Det gör att en behandlingsserie för en nekrotiserande mjukdelsinfektion, med fyra intensivvårdsbehandlingar initialt, följt av 16 ytterligare HBO-behandlingar i monokammare, sammanlagt medfört debitering med ca 230 000 kr av kundklinik för en patient. Remittenten har på liknande sätt en kostnad

på 132 000 kr (4 400 kr x 30 monoplace kammarbehandlingar) för en behandlingsserie över 6 veckor av patient med t ex diabetesfotsår eller strålskadad blåsa eller tarm.

1. Indikationer för HBO

1. **Dekompressionssjuka, gasemboliserings** (dykarsjuka/gasembolisering inom vården)
2. **Koloxidförgiftning, brandröksförgiftning** – patient som varit medvetslös, är neurologiskt påverkad, har varit långvarigt exponerad eller är gravid
3. **Diabetesfotsår** som är infekterade och inte svarar på specialistbehandling; patienter skall remitteras via specialistfotsårs mottagning[1]
4. **Strålskadade mjukdelar,** f.f.a. i blåsa (strålcystit) och tarm (strålproktit)
5. **Osteoradionekros** (strålskadad underkäke), behandling eller profylax vid kirurgi

2. Indikationer där HBO behandling kan övervägas –

(=indikationer under fortsatt vetenskaplig utvärdering /utredning)

6. **Svår akut vävnadsischemi** – traumatiska vävnadsskador (kross-kläm skador), compartment syndrom, postoperativa komplikationer (hotade lambåer), amputationshot vid sepsis (purpura fulminans), ischemisk tarm hos nyfödda (nekrotiserande enterokolit)
7. **Nekrotiserande mjukdelsinfektioner** (gasgangrän, fasciit)
8. **Intrakraniell abscess** – bakteriella infektioner i eller anslutning till hjärna och ryggmärg
9. **Akut kraniell osteomyelit** (neurokirurgi), **kronisk refraktär osteomyelit** (ortopediska/ÖNH-infektioner), **infekterat implantat** för att behålla främmande kropp
10. **Hypoxiska problemsår**, svårläkta ischemiska sår som ej svarar på specialistbehandling

3. Ej accepterade indikationer

Till denna grupp räknas:
Stroke, hjärtinfarkt, spinal infarkt, cerebral pares, autism, multipel skleros, tinnitus (yrsel), migrän, plötslig dövhet, sportskador.

Fokusrapportens nationella referensgrupp, med stöd från SBU, har sammanträtt 1–2 gånger per år sedan år 2006, sammankallande har varit ANOPIVA-kliniken på Karolinska Universitetssjukhuset, där Hyperbarmedicin finns som en sektion. En svårighet som identifierades år 2006 var existensen av ett starkt tryck från remittenter, för expanderad service, i ett läge där osäkerhet förelåg för graden av evidens för HBO.

Ett av referensgruppens första råd till verksamhetsledningen var att inte expandera till nya, icke dokumenterade indikationer, innan de som listats som ”under fortsatt vetenskaplig utvärdering” blivit bättre kartlagda, helst med randomiserade studier. I frånvaro av sådana studier, vid ovanliga tillstånd, borde minst konsekutiv fallserie redovisas, och då helst med

[1] Evidensvärderingen skiljer sig från den som gjorts i Socialstyrelsens ”Nationella riktlinjer för diabetesvården 2010”. Rekommendationen för HBO-behandling av diabetesfotsår är en forskningsfråga och bör endast göras inom ramen för studier.

en kontrasterande fallserie från verksamhet utan tillgång till HBO. Ett andra råd var att fortsätta att erbjuda behandling i de fallserier klassade som ”under fortsatt vetenskaplig utvärdering” där ett kliniskt intryck av god effekt förelåg, men där evidens kunde anses vara svag, med utökad satsning på nationella/internationella databaser.

Ytterligare ett råd var att ingen enhet som erbjuder HBO, kan anses behöva ta på sig uppdrag att genomföra behandling på indikationer ”under fortsatt vetenskaplig utvärdering” i en situation med resursbrist, även om en remittent skulle insistera på service.

Ledningen i Stockholms läns landsting rekommenderar att systematiska protokollförda utvärderingar fortsättningsvis skall göras av samtliga patienter som behandlas av HBO-verksamheten på Karolinska Universitetssjukhuset. Vidare betonas att rapporten inte utgör ett regionalt vårdprogram för SLL utan är en fokusrapport dvs. är en sammanställning av aktuellt kunskapsläge som utgör ett diskussionsunderlag för framtida sjukvårdsplanering och underlag för fortsatta FoU-insatser och att rapportens rekommendationer är författargruppens.

2. Introduction to the Focus report activity

Treatment with hyperbaric oxygen (HBO) has continued to attract attention and invite controversy in clinical medicine. There is a significant lack of awareness of Hyperbaric Medicine and the indications for HBO for appropriate patients in the medical community. 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 and a need for a review of Hyperbaric Medicine in Stockholm was recently requested.

The Stockholm County Council has formally requested this 'Focus report'. Many such reports on various clinical topics have been solicited and presented through the years. It should therefore be regarded as a text to be read by the non-expert in Hyperbaric Medicine. It is **not** intended to be a *textbook* on HBO, of which there are several good texts available for reference. In addition, it is **not** an *exhaustive narration of all relevant papers* on HBO. Furthermore, this text does **not** constitute a complete *clinical expert opinion* on HBO, and full consensus was not possible to reach even among this limited group of authors. Most parts represent the consensus opinion of the contributors; however, every contributor does not necessarily agree with each point.

We, the authors, have contributed to the text with the intention to

(1) critically assess the experimental and clinical evidence for today accepted HBO indications
(2) draw conclusions on level of clinical evidence & strength of treatment recommendation
(3) highlight areas of broad consensus on HBO indications
(4) recommend needs for future clinical and research activity
(5) offer implications for the public health care system in the Stockholm region

Hyperbaric medicine is a large subject with 50 years of experimental research, clinical experience and consensus opinions of experts. The FOCUS report has grown in tortuous ways. The first rough manuscript was sent to an HBO reference group for critical appraisal. At each step the authors added their criticisms. Where a need was felt to guide the curious reader further, we have added references to better expand the first-rate text sources. We have attempted to guide users of clinical research information about which studies are likely to be most valid.

The most recent scientific material comes from the Oxygen & Infection symposium held in Stockholm May 7–9, 2009 where a multidisciplinary international expert group introduced clinical Hyperbaric Medicine and later exchanged clinical and scientific knowledge on the role of oxygen in infectious diseases. Lectures and panel discussions on necrotizing soft-tissue infections and the infected diabetic foot were video recorded and are easily available at (www.hyperbaricoxygen.se). A progress report of a Cochrane review on the treatment of necrotizing fasciitis with HBO is appended to this FOCUS report (Addendum 1).

We have chosen to review and discuss HBO treatment in English, using the perspective of a compound (oxygen, and more specifically: oxygen under hyperbaric conditions) to be critically evaluated from a benefit – risk ratio point-of-view. The purpose is also to introduce the reader, physician or decision maker, to the role of HBO therapy in modern medical practice, and suggest guidelines for its use.

The acknowledged indication list used at Karolinska, in Sweden and in most centers around the world, is reviewed, ending with an opinion statement. Additional clinical consideration and important studies are added for the benefit of the more demanding reader but we refer to the abundant literature available via Pub Med search *"hyperbaric oxygen"*, or in textbooks, review articles and other reports referenced.

Finally, we would like to briefly explain the existence of the 'HBO reference group', as members of this group served as additional authors/advisors of this report. The group was set up in 2006, at the request of the Chair Claes Frostell of the Dept. of Anesthesiology, Surgical Services and Intensive Care at Karolinska University Hospital, Solna. The mission of the group was to act as a critical advisory group for positioning clinical and research activity in view of relevant literature, regulatory environment and clinical practice. To date 12 meetings have been held, which has greatly assisted the further development of Hyperbaric Medicine in Stockholm. Furthermore, each member of the group was invited to state his/her more personal view of the report and the present position of HBO in general, at the end of this report. No such written input was received. The generous and expert input of all participants in this group is gratefully acknowledged.

3. Background to Hyperbaric Medicine

Oxygen (O_2) is vital to sustain life. Oxygen is a colourless, odourless 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, put simply, 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, just like the cells, 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. It may also be caused by e.g. carbon monoxide (CO) and/or cyanide (CN) poisoning.

The partial pressure of O_2 (PO_2) and nitrogen (PN_2) in inspired air, at sea level pressure (100kPa) is 21 and 78 kPa, respectively. *(The partial pressure of a gas in a gas mixture is that part of the total pressure of the mixture that is contributed by that gas)*. Medical oxygen supplementation of inhaled air (up to 100% O_2 or 100 kPa PO_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 (Bove & Davis 2004, Brubakk & Neuman 2003, Davis et al 2008). The documentation on oxygen in medicine is staggering and has since then been a mainstay of emergency care, general anesthesia and intensive care (Moon & Camporesi 2010). 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.

Hyperbaric Medicine is the clinical specialty using pressure higher than local atmospheric pressure (> 1 bar = > 100kPa) to treat diseases or injuries inside a hyperbaric chamber, where the aim is to derive therapeutic benefit from breathing gases, usually O_2, at pressures greater than one atmosphere. Alteration of atmospheric pressure for medical purposes has been used for centuries, but it wasn't until after the 2nd World War that animal and clinical trials uncovered a number of beneficial mechanisms resulting from exposure to HBO (Bakker & Cramer 2002).

Diving and hyperbaric medicine are still closely related fields which has evolved from the early years of observation and anecdote. Initial enthusiasm and lack of knowledge and experience for this new treatment resulted in some misapplication of its use. Over the past decades, Hyperbaric Medicine has grown rapidly throughout the world in accordance with "evidence-based medicine" standards, and the body of evidence to support its use is growing (Gesell 2008, Kindwall & Whelan 2008, Marroni et al 2007, Mathieu 2006, Moon & Camporesi 2010, Neuman & Thom 2008). There are indications that HBO may be indicated in other diseases as well but more scientific evidence is demanded. Jain 2009 has assembled an extensive list of references also for those conditions outside of mainstream Hyperbaric Medicine.

Gas laws. Inside the hyperbaric chamber, well-known and accepted physical gas laws will define any gas under pressure. *Boyle's law* states that at a constant temperature, the pressure

and volume of a gas are inversely proportional (p1 v1 = p2 v2). *Charles' law* ([p1 v1]/T1 = [p2 v2]/T2) explains the influence of temperature. *Henry's law* states that the amount of gas dissolved in a liquid or tissue is proportional to the partial pressure of that gas in contact with the liquid or tissue.

Normobaric oxygen (NBO), by inhaling 100% O_2 at normal barometric pressures (1 bar = 100kPa), can bring the arterial PaO_2 up to as much as 80 kPa compared to 10–13 kPa normally seen with normobaric air breathing. Oxygen first aid is used in the pre-hospital setting, in injured scuba divers or fires with CO /CN poisoning.

Hyperbaric oxygen (HBO) *is a "short-term, high-dose O_2 inhalation and diffusion therapy", delivered systemically via airways and blood, achieved by having the patient breathe O_2 intermittently within a pressurized chamber.* The dosage limits for HBO therapy is determined by O_2-toxicity side effects, mainly to the central nervous system. Safe time-dose limits have been established for HBO exposure. The treatment is usually given at a pressure of 2.4–2.8 bar (240–280 kPa), the total procedure including safe compression/ decompression usually takes less than 2 hours. This dose is 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 given over an 8-week period.

Therapeutic benefit may result from the mechanical effects of increased pressure directly with improved oxygenation, or by its physiological / pharmacological effects. Harmful side effects may also arise from these two mechanisms (Moon & Camporesi 2010, Neuman & Thom 2008).

The cellular and cardiovascular effects of HBO give it all the properties of a pharmaceutical drug.

Topical oxygen therapy should NOT be confused with HBO given systemically via O_2 inhalation. "Topical HBO" involves O_2 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 (Feldmeier et al 2005).

Clinical Hyperbaric Medicine grew out of the problems met by divers exposed to high pressures. Decompression illness is a widely accepted HBO indication whereas similar damage from hospital aquired, accidentally introduced, gas bubbles is less generally recognized. 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 (Fife 2004). Hospital aquired 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 tumour sensitisation 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 tumour recurrence may be reduced (Bennet et al 2008).

Hyperbaric chambers with special technology and medical team staffing for "24/7" emergency services is required. The treatment is carried out in one of two ways. **Monoplace chambers**, acrylic single person chambers pressurized with O_2, or **multiplace chambers** of steel designed to hold two or more people pressurized with air. Patients treated in a Multiplace chamber breathe O_2 via an mask, hood system, or when intensive care is needed, with the help of a ventilator.

At Karolinska, we use both chamber techniques with hyperbaric facility safety, operation and maintenance of support systems, according to international guidelines, regulations and standards (Workman 1999). See addendum 1 for details on HBO chamber technology and HBO practice at the Karolinska and www.ECHM.org for "A European Code of Good Practice for HBO Therapy".

Side effects, contraindications & precautions. Overall, HBO therapy is extremely safe with the appropriate indications, supervision and knowledge of diving medicine (Moon & Camporesi 2010, Neuman & Thom 2008). "Diving" in the dry environment of a chamber is somewhat similar to in-water diving, but pressure changes are slower. Inside medical staff may as divers acquire "bubble-related disorders" which necessitates appropriate safety measures and dive tables to avoid decompression sickness. Fire is an extremely rare, although disastrous consequence in any closed environment. Special precautions, procedures and fire protection system are required since O_2 readily fosters combustion (Workman 1999). Claustrophobia may cause confinement anxiety in a few percent of the population and mild sedation may be needed initially.

The most common side effect (Boyle´s gas law) is barotrauma, or squeeze in the ears or sinuses, during compression if the patient has difficulty equalizing the pressure. Expanding gas during decompression can also cause barotrauma, tracheal damage or air embolism. A pneumothorax occurring at pressure is an example of a very rare but potentially dangerous complication.

Increased PO_2 in the blood and tissues (Henry´s gas law), the basis for therapeutic HBO, can cause acute O_2 toxicity with CNS "O_2 seizures" or progressive, reversible myopia, after a series of HBO treatments (see 5.4). Oxygen toxicity also limits available HBO treatment time in emergencies, imposing a need for intermittent HBO treatment 2–3 times per day.

Contraindications are relative few. Untreated pneumothorax is a contraindication unless experienced personnel accompany such a patient into the multiplace chamber with equipment to treat the problem. Some drugs with negative O_2 interaction also raise concerns such as, Bleomycin, Doxorubicin (Adriamycin), Cis-Platinum or Disulfiram (Antabuse) (Kindwall & Whelan 2008).

Hemodynamically unstable patients require particular risk-benefit evaluation and close supervision due to e.g. O_2-induced systemic vasoconstricton with changes in preload and afterload. During HBO patients with hypervolemia and/or reduced left ventricular function is in danger of acute cardiogenic pulmonary edema, especially if treated supine in a monoplace chamber. Patients in septic shock risk hypovolemia after HBO when vasoconstriction and thoracic blood pooling goes away. Short-term, reversible hypoxemia, frequently seen immediately after HBO due to atelectasis and changes in central hemodynamics, should be avoided by monitoring, O_2 supplementation and lung recruitment.

Ventilation, whether spontaneous or mechanically ventilator assisted in the intensive care patient, is hampered by the increased gas density of gas at depth. Flow resistance is almost doubled at 2,8 bar. This does not affect O_2 uptake but can lead to inadequate ventilation of the lungs (hypoventilation) and increased levels of carbon dioxide (CO_2) in the blood and tissues (hypercapnia). Ventilation should be controlled and CO_2 levels monitored during HBO treatment of the intensive care patient because CO_2 retention increase cerebral blood flow and the risk of O_2 seizures.

Scientific Societies, Guidelines 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 (Davis & Hunt 1977). The Swedish Society for Anesthesia and Intensive care (Svensk Förening för Anestesi och Intensivvård, SFAI) www.sfai.se has established a list of HBO indications (Lind et al 2005) which are updated yearly.

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, HBO is recognized by medicare as a reimbursable treatment based on the UHMS indication list (Gesell 2008). 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 (Marroni et al 2004).

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.

Several useful textbooks outline the physiological principles that constitute the basis for understanding the clinical implications for HBO treatment (Davis & Hunt 1977, Bakker & Cramer 2002, Bove & Davis 2004, Fife 2004, Mathieu 2006, Neuman & Thom 2008, Kindwall & Wheelan 2008, Jain 2009, Moon & Camporesi 2010).

Video lectures and panel discussions in the field of Hyperbaric Medicine are available on www.hyperbaricoxygen.se. They were recorded in May 2009 at the European Committee for Hyperbaric Medicine (ECHM) Conference “Oxygen & Infection” and the preceding "5th Karolinska Postgraduate Course in Clinical Hyperbaric Oxygen Therapy. Lectures range from basic mechanisms to evidence based medicine in individual HBO indications. The latest randomized controlled clinical trials are presented and some of the controversial topics in the field of oxygen and infection are evaluated.

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4. Pharmacokinetics of oxygen

A short outline of O_2 transport from the air we breathe into the mitochondria of the cell is provided to facilitate an understanding of the clinical indications for O_2 therapy and how the clinician can best individualize therapy for a patient. It is important to realize that O_2 transport in the body is driven by the partial pressure of oxygen (PO_2). HBO is therefore the only treatment option available to reach supranormal oxygenation in the tissues and may sometimes be the only way to correct tissue hypoxia in order to limit organ dysfunction and improve outcome.

4.1. Ventilation and diffusion in the lung

Oxygen is the second most common gas forming the normal external air (20.9%), preceded only by nitrogen (78.1%). The partial pressure of oxygen in the inhaled dry air is 21 kPa. As the air reaches the alveolar level it mixes with carbon dioxide and the gas becomes fully saturated with water in the functional residual capacity, the only compartment in the body with any significant O_2 storing capacity. Pressure drops further as O_2 diffuses across the alveolar wall mainly because of "shunting", Diffusion of O_2 into the pulmonary capillary blood is driven by the partial pressure gradient of O_2 between the alveoli (PAO_2) of approximately 14.5 kPa and that in the pulmonary blood. Ventilated alveoli rapidly exchange gas with perfused capillaries. The diffusion barrier is extremely thin so the PO_2 of pulmonary end-capillary blood is usually about 13 kPa in young healthy adults breathing air. In elderly, healthy individuals, the alveolar/arterial PO_2 difference rises to about 5 kPa and is still higher in lung diseases.

4.2. Oxygen transport in the blood/ hemodynamics

At normobaric pressure, almost all O_2 carried in blood is reversibly combined with hemoglobin (Hb) and only a small amount exists in physical solution in plasma. The Hb has multiple O_2 binding sites. The quantity of O_2 combined with Hb is dependent on PO_2 in a fixed but non-linear (sigmoid) relationship. A blood PO_2 of at least 50kPa, which is achieved by inhalation of 70% O_2, is required to effect complete 100% saturation of hemoglobin in arterial blood (Nahas et al 1952). When fully saturated with four O_2 molecules Hb turns bright red seen as arterialized blood (oxyhemoglobin) and each gram of Hb binds 1.31 ml of O_2. As the oxygen is unloaded the oxyhemoglobin changes in color to the "venous" bluish purple of deoxyhemoglobin. This can easily be seen in blood vessels near the skin surface (cyanosis) of nailbeds, lips and mucous membranes.

During normal air breathing at sea level the O_2 dissolved in blood plasma amounts to 3 ml per litre of blood and the Hb in arterial blood is 98 % saturated with O_2, and the resting tissues extract 50 to 60 ml of O_2 per litre of blood if perfusion is normal.

With 100% O_2 administered at normobaric pressure, the amount of O_2 dissolved in the blood increases to 15 ml per litre. With HBO it can reach 50 ml per litre (McMahon TJ et al 2002) which is adequate to satisfy the tissue requirements without any contribution from the O_2 that is bound to Hb.

The arterial and pulmonary arterial hemodynamics and oxygen delivery/extraction in normal humans are altered by 3 bar hyperbaric O_2 exposure (Weaver et al 2009). Cardiac output is decreased by 18%, mainly by a decrease in heart rate, and the systemic peripheral vascular resistance is slightly increased. Pulmonary arterial pressure and pulmonary vascular resistance are decreased, 19 and 48%, respectively. Arterial and mixed venous PO_2 increases to 230 and 50 kPa, respectively, with almost fully saturated haemoglobin in the mixed venous blood drawn from the PA catheter.

The human brain with its high energy consumption (making up only 2–3% of body weight) receives 15% of the cardiac output and consumes 20% of the oxygen uptake of the whole human body (Clark & Thom, 2003). During HBO at 3.5 bar (350 kPa) in 16 healthy men, the arterial and venous internal jugular blood PO_2 average 280 and 10 kPa, respectively (Lambertsen et al 1953, Lambertsen 1978). Most of the physically dissolved O_2 (6.5 vol %) was given up to the brain tissue by a 25 % reduction in brain blood flow caused by a 55% increase in cerebral vascular resistance. This shows that the regulation of blood flow to the brain closely matches oxygen consumption.

4.3 Oxygen diffusion into the tissues

Looking at oxygenation in relation to the partial pressures of O_2 it is evident that O_2 travels through the body, from the lungs to the cells, via a transport chain known as the “oxygen cascade” (Fig1). After transport via the arterial blood to the capillary bed O_2 diffuses into the tissue and across the interstitial and intracellular fluid to the mitochondria within the cell where the majority (90%) of O_2 is consumed. Each cell creates and replenishes its supply of ATP mainly through aerobic respiration by using O_2 as the final electron acceptor in the electron transport chain.

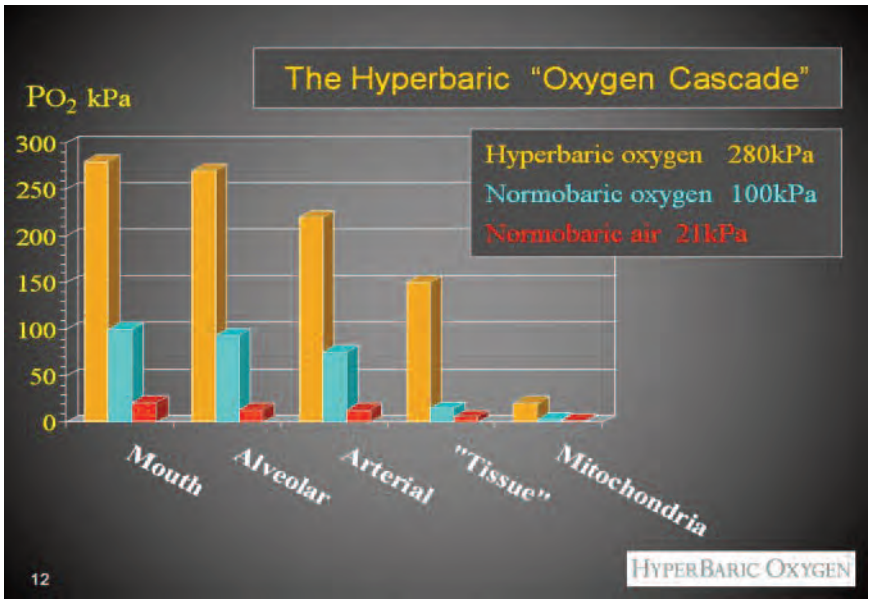

Fig 1. The Hyperbaric “oxygen cascade”. Inspired O_2 moves down a partial pressure (PO_2) gradient from the ambient air/gas we breathe, through the respiratory tract, the alveolar gas, into the blood and out into the tissues and to the mitochondria in the cells. The inspired PO_2 can be increased from “normobaric air” (21 kPa) with increased O_2 fraction 100% “normobaric oxygen” (100kPa) or with increased O_2 fraction 100% and pressure “hyperbaric oxygen” (280 kPa).

Oxygen supply and demand varies from one tissue to another, and even from one cell to another depending on a balance among factors such as arterial PO_2, blood flow, capillary density (or intercapillary distance) and tissue metabolic rate. Muscle tissue has small intercapillary distances and high O_2 consumption. In subcutaneous tissue, the intercapillary distances are greater and the consumption of O_2 is relatively low. Slow healing tissues such as subcutis, tendon, fascia, and bone then become dependent on PO_2 in blood and tissue and, to a lesser degree on the concentration of Hb in blood (Gottrup et al 1987).

Trauma, inflammation and infection can cause ischemia due to injured or obliterated microcirculation and edema with increased diffusion distances. Since the distance of O_2 diffusion from the capillaries into the tissues and mitochondria is governed by PO_2 in the blood and hence in the inspired gas HBO may then be the only way to increase PO_2 sufficiently to drive oxygen diffusion and correct tissue hypoxia. Sepsis is also a disorder of the microcirculation where shunting and regional dysoxia can become a major problem and HBO is the only treatment option available to reach supranormal oxygenation of the tissues in case of severe soft tissue infections.

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5. Pharmacodynamics of oxygen

5.1 Oxygen supply and storage

The normal adult O_2-consumtion at rest is 250 mL/minute. Oxygen is vital to life and must be continuously supplied to the tissues. The role of O_2 in the metabolism of the mammalian body is profound and complex. Oxygen therapy is like a two-edged sword: at one edge, O_2 is essential for human survival, while at the other edge it may become toxic with prolonged use at an elevated partial pressure.

The body reserves of dissolved O_2 are small (only about 1.5 L when breathing air) and will only last a few minutes before the O_2 tension at the mitochondrial level falls below the critical level. Sensitive tissues, such as the brain and myocardium, cannot tolerate hypoxia for more than a few minutes before serious and permanent tissue damage is inflicted. Because of this narrow tolerance margin the O_2 supply to the blood must be maintained at all times. The only significant storage of O_2 available in the body is the functional residual capacity of the lungs. With NBO and HBO this 2–3 liter safety reservoir of O_2 may last 10–20 minutes before hypoxemia and cardiac arrest occurs. This method of pre-oxygenation is used routinely before anesthesia induction and gives extra security against airway complications.

5.2 Ischemia, Hypoxaemia and Hypoxia

Ischemia means inadequate microvascular blood flow.
Hypoxaemia may be defined as a relative deficiency of O_2 tension in the arterial blood.
Hypoxia refers to a state when O_2 supply to the tissues is inadequate to sustain aerobic metabolism.

Brain cells are particularly sensitive to hypoxia. Symtoms appear suddenly and progress rapidly. They include impaired judgment, incoordination, headache, slurred speech, confusion, euphoria, drowsiness and tunnel vision and as hypoxia is aggravated continuing to loss of vision, muscle weakness and loss of consciousness with circulatory collapse as the end stage. There is considerable interpersonal variation in susceptibility to hypoxia. A PaO_2 below 4.8 kPa (36 mmHg) is associated with overt signs of cerebral hypoxia and neurological damage.

The heart is also sensitive to hypoxia: the myocardial O_2 reserve is minimal and the myocardial fibers rapidly loose their contractile force: heart rate increases at first, peripheral vascular resistance falls and cardiac output increases. Severe hypoxia can produce bradycardia and, ultimately, circulatory failure (Miller 2010).

Lack of O_2 transport at the microvascular level may cause cell and tissue death. (Davis et al 2008, Miller 2010). Diving related disorders with air or gas embolism block the microvasculature and cause edema both of which give rise to ischemia and hypoxia. Ischemia and hypoxia is also a characteristic of acute trauma and wounded tissue (for example: crush injury). Hypoxia may also be the consequence of poor O_2 utilization at the tissue level (for example: circulatory shock) or at the cell level (for example: cyanide poisoning) (Neuman & Thom 2008).

Microvascular deficiencies cause many chronic diseases. Adequate O_2 delivery to wounded tissue is vital for optimal healing and resistance to infection. Progressive endothelial injury after high-dose ionizing irradiation leads to loss of capillaries, ischemia and hypoxia. Diabetic lower extremity wounds, artery insufficiency ulcers, venous stasis ulcers and pressure ulcers are other common chronic non-healing wounds caused by ischemia (Fife 2004, Fife et al 2009).

5.3 Oxygen toxicity

The normal utilization of O_2 for energy production is associated with formation of O_2-free radicals; short-lived intermediates such as superoxide anion, singlet O_2, hydroxyl radical, and hydrogen peroxide. If unopposed, these highly reactive substances will initiate oxidative damage, including enzyme inhibition, lipid peroxidation, and oxidation of compounds containing sulphydryl groups, which ultimately afflicts all components of the cells (Clark & Thom 2003).

Oxygen dependent endogenous mechanisms exist for defense against oxidative damage and O_2 toxicity occurs when this defense mechanism is overwhelmed. It is now apparent that the same O2 pressures required to sustain life would cause lethal O_2 poisoning in the absence of these mechanisms. The basic mechanisms of O_2 toxicity and opposing antioxidant defenses are described in recent textbooks (Neuman & Thom 2008) and the difference between NBO and HBO on NO release and what form the toxicity takes is now being explored (Allen et al 2009). Hyperbaric O_2 toxicity usually manifests in one of two forms; either as acute CNS "O_2 seizures" or as ocular manifestations with reversible myopia occurring after a series of HBO treatments. Pulmonary O_2 toxicity is generally not a clinical HBO problem.

5.4 HBO Mechanisms; Physical, physiological and pharmacological effects

– HBO 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. A century of 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 not only improves local host immune response causing clearance of infection in hypoxic tissues, it also stimulates increased vascular density and wound metabolism with enhanced tissue growth. The net result is improved local tissue oxygenation and healing. The sound physiological basis for HBO was well established already in the first textbooks on "Hyperbaric Oxygen Therapy" (Davis & Hunt 1977, 1988).

– HBO 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 (Mathieu 2006, Neuman & Thom 2008, (Thom 2009).

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

Elimination of gas. HBO increase the resolution rate of air or gas bubbles. The gases goes 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.

Increased blood O_2–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 oxyhemoglobin. This may help restore tissue O_2 tensions back to normal or supranormal levels in hypoperfused tissues.

Increased O_2 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.

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.

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.

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

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.

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.

5.5 HBO and Carcinogenesis

There is no evidence that HBO promotes recurrence of malignancy or enhance malignant growth or metastases. A history of malignancy is not a contraindication for HBO therapy. A review of the literature, including a large number of clinical reports over the years, suggests that the risk is low (Feldmeier et al 2003). Similarly, the published literature on tumour angiogenesis mechanisms and other possible mechanisms of cancer causation or accelerated growth provides little basis for worries. Malignant angiogenesis appears to follow a different pathway than angiogenesis related to wound healing.

5.6 HBO and interactions with chemicals and drugs

Oxygen interacts with several chemicals in vitro as well as in vivo. High O_2 fraction, including HBO, may further impair the damage caused by lung toxic agents such as Paraquat, Nitrofurantoin, and Bleomycine, (for details see Gram 1997). HBO and drug interactions have recently been reviewed (Kindwall & Whelan 2008, ch. 12).

Studies on the effects of hyperbaria or hyperbaric hyperoxia on the disposition of drugs are still sparse but most studies do not demonstrate significant effects of hyperbaric or hyperoxic conditions on pharmacokinetics of drugs eliminated by the kidney or the liver in dogs or humans (Rump et al 1999 a,b).

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6. Preclinical studies on HBO

Sixty years of basic HBO studies on tissular, cellular or subcellular level and controlled animal experiments show strong evidence of beneficial action. A Pub Med search on "Hyperbaric Oxygen" gives much new information each month. Experimental data supporting the efficacy of HBO treatment for the list of accepted indications are summarized below.

6.1 Decompression sickness (DCS) and air/gas embolisms

Large systematic animal studies support the use of HBO as the primary treatment for DCS and gas embolism (Francis & Mitchell 2003, van Hulst et al 2005). Basic studies support the use of HBO through a number of mechanisms. Bubbles shrink more rapidly (Hyldegaard & Madsen 1994) when 100% O_2 is given. Also it may help prevent cerebral edema, reduce the adherence of leukocytes to damaged endothelium and reduce performance deficit after DCS (Martin JD and Thom SR, 2002).

6.2 Carbon monoxide poisoning and smokeinhalation

HBO maximizes O_2 delivery to tissues to reverse cellular acidosis. Even without hemoglobin, HBO can oxygenate exsanguinated pigs with only saline in the cardiovascular system (Boerema I, et al 1960). However, carbon monoxide (CO) pathophysiology is more complex than merely a blocked O_2 transport and pure tissue hypoxia. First, CO binds to haemoglobin. Dogs transfused with 80% COHb up to 60% COHb does not suffer adverse reactions even though the blood was transfused from dogs that had been killed by CO (Goldbaum et al 1975). Second, CO extravasates into the tissues where it binds to myoglobin and other heme proteins in the cells. In particular it is toxic for the mitochondria, inhibiting the cytochrome c oxidase of the human mitochondrial chain for at least three days (Miro et al 1998, Alonso et al 2003). Third, animal studies indicate that tissue injury results from a combination of hypoxia/ischemia, ATP depletion, excitotoxicity, oxidative stress, and immunological responses and support a view that CO exposure causes acute inflammatory events in humans (Thom et al 2010).

HBO attenuates the cascade of events causing tissue damage and neurological sequelae. In animal models of CO-poisoning, HBO bring about more rapid improvement in cardiovascular status, lower mortality, and a lower incidence of neurological sequelae (Jiang et al. 1997). Compared to normoxia (air breathing), HBO but not NBO, significantly reduce the formation rate of brain edema, prevent intracranial pressure increase, reduced neurological dysfunction and improved short term outcome by increasing survival time and survival rate. In rat brains, HBO prevents CO-mediated oxidative injury, lipid peroxidation and leukocyte adherence to brain microvascular endothelium by inhibiting neutrophil B2 integrin adhesion (Thom 1993). In addition, regeneration of inactivated cytochrome oxidase is accelerated (Brown & Piantadosi 1989, 1992) thus relieving pure CO-induced hypoxic stress of the mitochondria. Similarily, HBO, but not NBO, has been shown to improve mitochondrial oxidative processes during CN poisoning (Takano et al 1980). In the rat model acute CO poisoning causes intravascular neutrophil activation due to interactions with platelets and HBO prevents immune-mediated delayed neurological dysfunction following CO poisoning (Thom et al 2006).

6.3 Diabetic foot ulcers

HBO exerts a dose-dependent stimulation of human fibroblast proliferation (Hehenberger et al 1997), which may be explained by an HBO-induced up regulation of fibroblast growth factor receptors (Buras et al 2001) working through a NO dependent pathway (Reenstra 2009). In an animal wound model Sheikh et al (2000) found that vascular endothelial growth factor (VEGF) levels in the wounds significantly increase with HBO by approximately 40% 5 days after inflicting the wound. HBO has a dose-dependent effect on angiogenesis by increasing the VEGF production (Hopf et al 2005). In diabetic mice, hyperoxia enhances the mobilization of circulating endothelial progenitor cells from the bone marrow to the peripheral circulation (Gallagher et al 2007) essential in vasculogenesis and wound healing (Liu & Velazquez 2008). Hyperbaric oxygen stimulates vasculogenic stem cell growth and differentiation (Milovanova et al 2009).

6.4 Soft-tissue radiation injury (hemorrhagic proctitis/cystitis)

HBO increase vascular density and cellularity in bone and irradiated skin and soft tissues (Marx 2008). In humans, this effect can be seen as an increase in transmucosal O_2 tension levels almost up to normal non-irradiated tissue tensions in patients treated for ORN (Marx 2008, Thorn et al 1997).

This neo-angiogenesis can also be an effect of increased stem cell mobilization (Thom 2009).

HBO may also reduce the early inflammatory response following radiation injury where ICAM-1 receptors are invoved since HBO downregulates endothelial ICAM-1 receptors induced by hypoxia and hypoglycemia (Buras et al 2000). In a murine model of small bowel radiation damage HBO given prophylactically has been shown to reduce fibrosis (Feldmeier et al 1995, 1998).

6.5 Osteoradionecrosis

Osteoradionecrosis is a hypoxic, hypocellular and hypovascular tissue injury of the irradiated bone. Angiogenesis is induced by 20 HBO treatments in an irradiated rabbit mandible model in a dose-dependent fashion. An increased vascular density with a series of HBO towards normality 1.00, (fig.2 below), as assessed by angiography, was seen in 42 rabbits with an irradiated mandible (6 groups of 7 rabbits). As evident from the fig. 2, page 28, the higher the oxygen pressure the better the vascular density response, with no apparent effect of 100% O_2 (100kPa) at normal ambient pressure (Marx RE et al 1983,1990, 2008).

In irradiated bone, HBO improves bone turnover, bone formation and bone maturation capacity. HBO also develop the capacity for osseo-integration of implants with improved bone metal contact and a significant increase in the force necessary to unscrew implants. This has been elegantly shown in a number of well-controlled animal experiments using for example vital microscopic chamber, bone harvest chamber, bone densitometry and titanium screw implants in irradiated tissues by Prof. Granström and colleagues in Gothenburg (Johnsson et al 1993, 1999, 2000, Granström 1998).

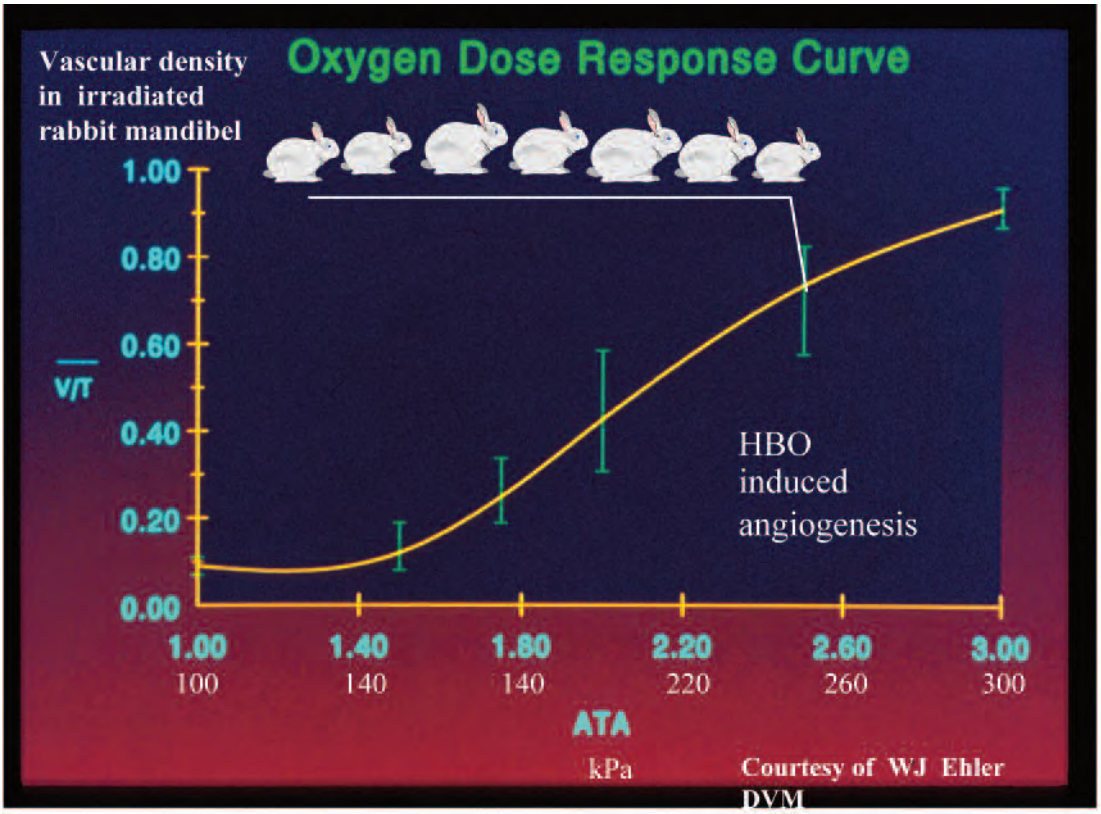

Fig. 2 courtesy of Ehler.

6.6 Severe acute ischemic conditions

Surgical and physiological observations in an experimental chamber have been done (Illingsworth et al 1961). 30 animal studies have shown efficacy of HBO in preserving both pedicled and free flaps in multiple models. These models looked at arterial, venous, and combined insults in addition to irradiated tissues. While improvement was observed regardless of the type of vascular defect, those with arterial insufficiency and radiation injury showed the greatest improvement. The importance of prompt onset of HBO after surgery for best results was emphasized already in the classical paper from Karolinska by Jurell & Kaiser (1973).

A large number of animal experimental studies also report beneficial effects of HBO on compartment syndrome (Bartlett et al 1998, Strauss et al 1996), flaps and various types of transferred tissues with prolonged ischemic periods (Friedman et al 2006).

HBO can stop or reduce ischemia-reperfusion related injury in skin grafts & flaps and a number of different organs also after prolonged ischemia, one example being in muscle as shown by Haapaniemi et al. (1996) from Linköping, Sweden. They interestingly enough found that one HBO treatment could reverse a 3 hour warm tourniquet ischemia in the rat hindlimb but that it took repeated HBO to counteract a 4 hour IR injury. After 4 hours of ischemia, the changes in levels of the intracellular muscle compounds adenosine triphosphate, phosphocreatine, and lactate were less in HBO treated rats. HBO also modulates anti-oxidant enzyme activity in postischemic skeletal muscle (Bosco et al 2007). Animal

studies further suggest that a reperfusion injury is diminished by suppression of neutrophil-endothelial adhesion in a dose dependant manner (Buras et al 2000, Buras & Reenstra 2007, Zamboni et al 1989, Thom 2004).

6.7 Severe necrotizing soft tissue infections (gas gangrene & fasciitis/myosiitis)

Infected tissues are hypoxic and severe soft tissue infections are often called “necrotizing” due to their particular aggressive nature. Tissue dies and becomes “necrotic” while the septic inflammatory response threatens to kill the host. There is a strong physiological rationale as well as experimental evidence of significant therapeutic benefit, ranging from animal models to basic data supporting the use of HBO (Mader et al 1987, Park et al 1992, Buras 2006). HBO increase tissue oxygenation with enhanced “host defense” via leukocyte mediated killing of bacteria and potentiate the effects of antibiotics (Allen DB and Maguire JJ, 1997).

Most of the early experimental research on the activity of HBO in infections involved anaerobic infections, clostridium perfringens in particular. In animal models (mice, rabbits, guinea pigs, dogs) of gas gangrene, and other multimicrobial bacterial acute necrotizing infections, HBO has been found to be effective in decreasing morbidity, mortality and improve wound healing with the best results obtained when HBO is combined with surgery and antibiotics. (Bakker, 2002, Hirn M et al,1992, 1993, Zamboni et al 1997). A combination of HBO, surgery and antibiotics lead to better results than any of these treatment modalities alone as elegantly shown in a comparative study on experimental Clostridium perfringens infections in a traumatized dog hind limb model (see fig from Demello et al 1973).

Therapy	n	Mortality
HBO	**12**	**100 %**
Surgery	**12**	**100**
HBO + Surgery	**13**	**100**
Antibiotics	**20**	**50**
HBO + Antibiotics	**20**	**45**
Surgery + Antibiotics	**20**	**30**
HBO + Surgery + Antibiotics	**20**	**5 %**

The combined treatment with penicillin and HBO exerts at least additive effects in both decreasing bacterial counts in vivo and increasing survival in a murine model of streptococcal myosiitis (Zamboni et al 1997). HBO reduces neutrophil-endothelial adhesion and has also been found to reduce mortality in intra-abdominal infections and multimicrobial sepsis animal models (Thom et al 1986, Muhvich et al 1988, Luongo et al 1998, Bitterman & Muth 2004, Buras et al 2006). HBO also attenuates the expression of iNOS in zymosan or LPS-treated animals (Imperatore et al 2004, Pedato et al 2003) which restores vascular resistance and arterial pressure in animals with septic shock. HBO reduces systemic vascular dysfunction, oxidative stress, and mortality in LPS-stimulated septic rats (Lin et al 2005).

6.8 Intracranial abscess

The PO_2 of bacterial abscesses is low (Simmen & Blaser 1993). The same can be observed in steel net cages implanted subcutaneously into rabbits where infection of the cage fluids with gram-negative aerobic bacteria cause a marked hypoxia (PO_2 0.6 vs 8.3 kPa), acidosis (pH 6,9 vs 7,3) and reduced aminoglycoside efficacy with increased number of remaining viable bacteria (Rylander et al 1981).

In 1965 David Ingvar published animal experiments in treating focal cerebral ischemia with HBO. HBO can oxygenate ischemic tissue, reduce brain edema and has beneficial effects on cellular metabolism and intracranial pressure from various experimental models (Ingvar & Lassen 1965, Sukoff et al 1968, Moody et al 1970, Miller et al 1970).

In intracranial infections, HBO can intermittently overcome the diffusion barrier and hypoxic milieu protecting the bacteria from white blood cell phagocytosis. Improved circulation and oxygenation can improve the effects of antibiotic agents (Park et al 1992).

Anaerobes account for the vast amount of isolated bacteria in intracerebral abscesses and HBO exerts bacteriostatic or bactericidal effects depending on microorganism antioxidant defense mechanisms.

Hyperbaric oxygenation provides protective effects against systemic oxidative stress and mortality in animals with septic shock (see 5.3). HBO protects against endotoxin-related neuronal activation and oxidative stress in the brain stem nuclei in rats; in a LPS-induced brain damage rat model (Lin & Wan 2008).

6.9 Acute cranial osteomyelitis, chronic refractory osteomyelitis, infected implants

Animal experiments using microelectrodes to measure pO_2 in normal healing, infected tissues and in tissues containing foreign material have demonstrated marked hypoxia especially when infected foreign material was present (Silver 1977). The effects of hypoxia and hyperoxygenation on bacteria, antibiotic activity and host defense mechanisms has been extensively reviewed (Park et al 1992), and HBO can restore normal cellular processes that are compromised by infection and hypoxia. The O_2 supply to an area of bacterial invasion is essential for effective leukocyte killing of microorganisms (Knighton et al 1986, Allen et al 1997).

In the rabitt's osteomylitic bone, blood flow is reduced and pO_2 is far too low, rarely exceeding 3 kPa, for effective phagocytic intracellular killing of bacteria. HBO can restore the intramedullary bone pO_2 in rabbits with infected osteomyelitic bone (Mader et al 1987, Esterhai et al 1986). In a rabbit models of osteomyelitis with *staph aureus* inoculum a proportional relationship between pO_2 and phagocytic killing was found with the best effect when the intramedullary pO_2 reached 20–100 kPa (Mader et al 1980).

Typically, slime producing (biofilm) pathogens are associated with osteomyelitis and im-

plated devices and other chronic refractory infections such as staphylococcus and pseudomonas, and it has been shown in both Klebsiella and Pseudomonas biofilm that the pO_2 reaches zero kPa when the O_2 diffusion distance is too great (Anderl et al 2000, Walters et al 2003). During HBO, this biofilm diffusion barrier and hypoxic environment protecting the bacteria from phagocytosis, can be overcome intermittently by improved O_2 transport and diffusion. Likewise, oxygenation of biofilm and surrounding tissues can improve the effect of antibiotic agents.

Hypoxia also decreases antibiotic activity and HBO augments the bactericidal effects in the aminoglycoside class of antibiotics, as well as in other antibiotics such as vancomycin, quinolones, trimetoprim/sulfa and nitrofurantoin (Park et al 1992). The bactericidal effect of Tobramycin was improved in a rabit model of *Ps. aeruginosa* osteomyelitis when pO_2 was increased from anaerobic to aerobic and HBO levels (Mader et al 1987, 2008).

Bone healing is also improved by HBO (Mader et al 2008). This has been demonstrated in animal models of osteomyelitis (Strauss et al 1982). HBO promotes resorption of necrotic bone and "bone turnover" since osteoclast & osteblast function is oxygen-dependent (Granström et al 1998). HBO also improve bone-metal contact, increase the force necessary to unscrew implants etc (see 6.5 above) which may be of importance when treating infected implants.

6.10 Hypoxic problem wounds

Severe hypoxia, as commonly noted in problem wounds and other tissue injuries, is not compatible with optimal tissue repair since O_2 plays an important role in each phase of the wound healing processes (Hunt & Davis, 1988). Wound bed hypoxia inhibits fibroblast proliferation, collagen production, angiogenesis and bacterial killing (Hopf & Rollins 2007, Thackman et al 2008). Fibroblast proliferation increases in a dose-dependent manner between 1 and 2,5 bar O_2 in both normal diabetic skin fibroblasts and those from a chronic wound (Hehenberger et al 1997). Periodic hyperoxia/HBO has a dose dependent effect on angiogenesis (Hopf et al 2005), it controls infection, reduces inflammation, enhances perfusion and promotes tissue repair. Chronic wounds appear stuck in the inflammatory phase. In a rat ischemic wound model (Zhang et al 2008), HBO was found to improve wound healing. Analysis of extract from ischemic wound tissue demonstrated significantly reduced neutrophil infiltration and attenuated cell apoptosis.

There is a synergistic effect of systemic hyperbaric oxygen and growth factors and other signals to regulate signal transduction pathways (Tandara & Mustoe 2004) and oxygen stress per se has been shown to mediate some of the effects (Thom 2009). Lactate and oxygen together stimulate angiogenesis and matrix deposition (Hunt et al 2008). In a mouse model, circulating stem/ progenitor cell (SPC) recruitment and differentiation in subcutaneous matrigel were stimulated by HBO, and by a physiological oxidative stressor, lactate. In combination, HBO and lactate had additive effects. By causing an oxidative stress, HBO activates a physiological redox-active autocrine loop in SPCs that stimulates vasculogenesis. Thioredoxin system activation leads to elevations in HIF-1 and -2, followed by synthesis of HIF-dependent growth factors (Milovanova et al, 2009).

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7. HBO indications

HBO is the primary therapy for decompression sickness, gas embolism, CO poisoning and smoke inhalation. In all other indications, mainly ischemic and / or infected surgical conditions, it is an important adjunct to other treatments, such as antibiotics and surgery.
A multidisciplinary approach with referral for HBO from specialist clinics is recommended. A patient with diabetic foot ulcer ought to be referred to HBO through a comprehensive diabetes foot care clinic first after appropriate evaluation and care. The same patient may however be referred by a surgeon or orthopedic specialist because of a severe necrotizing limb or life threatening soft tissue infection.

The Swedish Society for Anesthesia and Intensive Care (Svensk Förening för Anestesi och Intensivvård, SFAI) has published a list of recommended indications for HBO use within Sweden, which is corresponding to Karolinska University Hospital HBO practice (www.sfai.se). These recommendations have been revised in 2009 with addition of the level of clinical evidence (1–4) for each indication from human studies following EBM (evidence-based medicine) procedures.

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

In addition, the strength of HBO treatment recommendation (A–C) is given, based on the quality of research data and the clinical ”directness” of the data, additional experimental evidence, and clinical experience and consensus opinions of experts. The HBO treatment recommendation (A–C) published by ”The Swedish Society for Anesthesia and Intensive Care” is neither used, nor accepted by Socialstyrelsen; The National Board of Health and Welfare in Sweden or by SBU; The Swedish Council on Technology Assesment in Health Care.

A. HBO “should” be provided to eligible patients
B. HBO “ought to” be provided to eligible patients
C. HBO “may” be provided to eligible patients

The acknowledged indication list used at Karolinska University Hospital, in Sweden and in most centers around the world, is reviewed, ending with a reference group opinion statement using the above-mentioned grading systems for recommendations in order to achieve evidence-based clinical guidelines for HBO treatment.

HBO indications

Evidence-based clinical practice guidelines listed according to the level of clinical scientific evidence (1-4, see above page), with treatment recommendation (A–C).

Recommended

7.1	Decompression Sickness and Air/Gas Embolisms	Level 4	A
7.2	Carbon Monoxide Poisoning and Smoke Inhalation	Level 2	A
7.3	Diabetic Foot Ulcer[1]	Level 2	A
7.4	Soft-tissue Radiation Injury - Hemorrhagic Proctitis/Cystitis	Level 2	A
7.5	Osteoradionecrosis	Level 3	B

”Under investigation”

7.6	Severe Acute Ischemic Conditions	Level 3	B–C
7.7	Severe Necrotizing Soft Tissue Infections - Gas Gangrene & Fasciitis/ Myosiitis	Level 3	B–C
7.8	Intracranial Abscess	Level 3	C
7.9	Acute Cranial Osteomyelitis, Chronic Refractory Osteomyelitis, Infected Implants	Level 3	C
7.10	Hypoxic Problem Wounds	Level 3	C

Not acceptable indications

“Not acceptable” HBO Indications are listed due to lack of evidence of effectiveness, or at least fair evidence that HBO is ineffective. Additional indications will not be dealt with in more detail in this Focus report.

- Sudden Deafness, Tinnitus, Migraine
- Cerebral Pareses, Autism, Multiple Sclerosis
- Heart- Brain- Spinal Infarcts
- Sports Injuries

[1] The national guidelines for treatment of diabetes mellitus 2010, recommend that HBO therapy for diabetic foot ulcer is a therapy "Under investigation". "Nationella riktlinjer för diabetesvården 2010 (only in Swedish)" published by The National Board of Health and Welfare in Sweden.

Recommended HBO indications (7.1- 7.5)

7.1 Decompression sickness (DCS) and air/gas embolisms; (diving related & iatrogenic)

General

Gas bubbles released upon decompression cause decompression sickness (DCS). When divers surface too rapidly the partial pressure of N_2 dissolved in the tissues may exceed the ambient atmospheric pressure sufficiently to form gas bubbles in the blood and in the tissues. These bubbles have the potential of occluding blood vessels and damaging the vascular endothelium.The embolic occlusive process results in varying degrees of ischemia and inflammation in the affected parts of the body (Francis & Mitchell, 2003). Similarly, rapid ascent from sea level to over 5.500 m can result in high altitude DCS or aviation DCS. Decompression sickness may produce mild problems such as rash or joint/musculoskeletal pain or be more serious resulting with paralysis, confusion, convulsions, and ultimately death secondary to blockage of vital blood vessels.

Air or gas embolism may occur during compressed gas diving. In diving medicine, arterial gas embolism is usually considered a consequence of pulmonary barotrauma with lung overexpansion during rapid ascent due to Boyle´s law. However, arterialization of venous gas can also occur from right-to-left passage of venous gas emboli through a patent foramen ovale or overloading the gasbubble filtering capacity of the pulmonary vascular bed (Butler & Hills 1985, Neuman 2003), and it may even occur without breathing compressed gas during deep repetitive breath-hold diving (Tamaki et al 2010). Neurological symptoms from gasembolism with unilateral motor weakness, sensory numbness or other “stroke-like” symptoms usually occur during ascent or soon after a dive whereas symtoms from DCS may be delayed.

Iatrogenic venous and arterial gas embolism can occur from many in-hospital related procedures. They have been reported in almost all areas of clinical and surgical practice e.g. cardiopulmonary bypass surgery, angioplasty, laparoscopy, neurosurgery, mechanical ventilation, central venous catheter placement and haemodialysis. Venous gas bubbles may obstruct the pulmonary circulation and put a strain on the right ventricle. Gas can also cross over to the arterial side through a right-to-left intracardiac shunt and/or through the pulmonary vasculature. The diagnosis is not easy to establish in anesthetized patients. Sudden neurological and/or cardio-respiratory symptoms during an invasive procedure should lead to the suspicion of venous or arterial gas embolism (Moon & Camporesi 2010). Manifestations of arterial gas embolism include loss of consciousness, confusion, focal neurological deficits, cardiac arrhythmia or ischemia. Manifestations of venous gas embolism include hypotension, tachypnea, hypocapnia, pulmonary oedema and cardiac arrest.

HBO treatment

Recompression therapy with HBO is the standard for treatment of DCS and air/gas embolisms, but there is no randomized controlled trial evidence. Long clinical experience has

shown that recompression in a hyperbaric chamber, in conjunction with 100% O_2 breathing and subsequent slow decompression to sea level according to standardized HBO tables gives the best outcome and promotes the most rapid, complete removal of gas bubbles. Its efficacy has been validated by extensive clinical experience and scientific studies (Bennet et al 2010, Marroni et al 2007, Moon 2008 a,b).

Treatment with recompression and HBO should be started as soon as possible to alleviate symptoms and increase the "wash out" of tissue gas. The pressure reduces the bubble volume (Boyle's law) and increases the rate at which the gas moves out of the bubble into physical solution in the surrounding blood or tissues (Henry's law). The gas is then eliminated through the blood and the lungs during the extended decompression. HBO is also thought to counteract or reduce the effects of an inflammatory cascade caused by bubble-endothelial interactions.

It is paramount that a patient suffering from acute DCS and/or air/gas embolism is rapidly brought to HBO services with properly experienced personnel and suitable critical-care equipment. First line therapy is O_2 inhalation and fluid resuscitation with emergency evacuation of divers via 112. Avoid hypoventilation and use supine, resting position with 30% head elevation to minimize brain edema. Helicopter transfer at low altitude (<300m) or a pressurized aircraft should be used, if available, since higher altitude may exacerbate symptoms. It is likely that urgent HBO treatment will result in a better outcome, particularly in severe cases. However, in the literature patients arriving as late as 24 hours after decompression and air/gas embolism have been treated with some degree of success.

HBO protocol

Recompression to 2,8 bar with close to five hour HBO therapy according to the U.S. Navy Table 6a, is universally accepted and recommended as first treatment of both DCS and gas embolism. The table may be extended by extra O_2 periods at 2,8 and /or 1,9 bar if the clinical response is judged to be suboptimal.

Daily repetitive HBO treatments of shorter duration, at 2.4–2.8 bar, have been shown to further improve the ultimate outcome in patients with neurological deficits. HBO is recommended until there is no further objective evidence of stepwise improvement, typically after no more than 1–2 HBO treatments, but occasionally up to 5–10 treatments (Marroni et al 2007, Moon R. 2008).

Additional clinical considerations

First aid normobaric 100% O_2 breathing enhances the elimination of dissolved gas/N_2 in bubbles, tissues and blood and may help oxygenate ischemic tissues. Some patients with neurological manifestations may rapidly respond to O_2 breathing. However, gas "bubbles" can damage the endothelium and initiate a variety of inflammatory and thrombotic processes causing secondary oedema and ischemia. Clinical experience has shown that it is important to treat these patients urgently with HBO as secondary deterioration may occur due to an inflammatory response. Spinal DCS is a typical example where the patient, after an initial period of recovery, may become permanently paraplegic due to late onset edema and ischemia of the spinal cord.

Rehydration and fluid resuscitation through infusion of colloid solutions or drinking is accepted to optimize the microcirculation.

Helium O_2 mixtures (Heliox), usually 50/50 and deeper recompression to 4 bar according to a French Commercial treatment table (COMEX 30) may be tried in severe cases, e.g. patients who have been diving deep (> 4bar) or who fails to show the desired improvement after the first 20 min O_2 period (Bennet et al 2010).

Nonstereoidal anti-inflammatory drugs (Tenoxicam, 20mg daily for 7 days) have been shown to significantly reduce the number of repetitive treatments needed from a median of 3 in the placebo group to 2 HBO sessions in the NSAID group (Bennet et al 2003). However, recovery was not improved.

Anticoagulant therapy. Due to risk of hemorrhage of infarcted tissues in the brain and spinal cord anticoagulant therapy is not generally indicated (Muth & Shank 2000). For patients with lower limb immobility, venous thromboembolism prophylaxis with low molecular weight heparin s.c. is indicated (Moon 2008).

"Test of pressure" with 20 min HBO at 2,8 bar can be used to differentiate less severe (non-CNS) symptoms of DCS with pain due to musculo-skeletal injury or some other problem. If there is no change in symptomatology one may decompress and continue with other diagnostics/ therapy. If patient symptoms improve with HBO, or deteriorate on decompression, HBO treatment for DCS should be continued.

Critical assessment and conclusion: Decompression sickness (DCS) and air/gas embolisms; (diving related & iatrogenic)

- The evidence level (see page 40) can be classified as 4, as no randomized study is available, and will likely not be undertaken since the prosecution of randomized controlled trials is highly problematic in this area.
- The panel agrees that HBO therapy is universally accepted as standard practice in decompression sickness and air or gas embolism for which there are limited alternative treatment options. This is based on good theoretical and experimental evidence, long-standing use and clinical consensus. On the same rationale, it can be concluded that HBO is a valuable and effective treatment in the management of non diving related victims of gas-embolism, therefore we have chosen treatment recommendation = A
- Thresholds for initiating HBO-therapy and the size of this effect remains unclear and continue to leave room for opinionated statements. The panel agrees that systematic long-term follow-up studies are needed to improve the quality of care for these patients. Consideration should be given to establish a large national (probably multinational) database.

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7.2 Carbon monoxide poisoning and smoke inhalation

General

Carbon monoxide (CO) poisoning is the most frequent cause of poison related death in the world. CO is a colorless, odorless, tasteless, non-irritating and highly diffusible gas. CO is primarily generated by incomplete combustion in faulty furnaces, stoves and heaters as well as is part of car/truck/motor exhaust gases. The amount of CO absorbed in the body depends mainly upon the inspired CO concentration, length of exposure (soaking) and physical activity. The signs and symptoms of poisoning are highly variable, depending on the acuity and duration of the exposure.

In all humans, small amounts of CO are present and are important for multiple physiological functions, including neurotransmission. Exogenous exposure to amounts of CO above physiological levels can result in a protective or adaptive response (Bauer & Pannen 2009) but exposure to even higher levels results in toxic effects. Toxic exposures can cause inflammation, followed by hypoxia, although there is uncertainty regarding the range of CO exposures above which inflammation occurs (Weaver 2009, Thom 2009).

CO-poisoning causes hypoxic stress due to its affinity for haemoglobin, myoglobin, and (with significant hypoxia) other vital hemoproteins such as the cytochrome a-a3 and p-450 in the mitochondrial respiratory chain. In CO victims, mitochondrial cytochrome c oxidase remains inhibited several days after admission (Miró et al 1998). In CO poisoning from smoke inhalation there is a synergistic toxicity induced by cyanide at the cellular level (Norris et al 1986). The cells must switch to anaerobic metabolism leading to anoxia, lactic acidosis, and eventually to cell death (Piantadosi 2002, Weaver 2009).

The cardiovascular and nervous systems are the two organ systems most susceptible to CO poisoning. Vasodilatation causes hypotension and increased intracranial pressure. Hypoxic brain damage predominates in the cerebral cortex, cerebral white matter and basal ganglia, especially in the globus pallidus (Prockop & Chichkova 2007). The damage is related not only to the direct intra- and extracellular hypoxic states but also to acute inflammatory events (Thom et al 2010). Acute CO poisoning cause a significant increase in blood neutrophil count (Schnittger et al 2004) which may lead to secondary tissue damage and neurological sequelae.

Delayed encephalopathy with all kinds of neuro-psychiatric symptoms such as mental impairment (concentration, attention, language, learning, memory), motor dysfunction, depression, dementia, or psychosis may also develop between 2 and 28 days after complete recovery from initial hypoxic injury (Choi 1983, Chang et al 2010).

COHb values has always been said to correlate poorly with clinical outcomes. Acute exposures may give minimal symptoms despite high COHb levels in the sleeping patient rescued from a fire whereas the partying victim from a nightclub fire may die “instantly” on the scene due to asphyxia. Children are generally most severely poisoned when a family is intoxicated, probably due to their increased metabolism. Long term exposure, “soaking”,

allow extravasation of CO and manifest itself with severe toxicity, profound metabolic derangements, tissue damage and rhabdomyolysis with risk of acute kidney failure. COHb values therefore has to be interpreted individually and it is often wise to get the correct information regarding exposure, initial symptoms etc. from the scene of the accident.

HBO treatment

First line therapy for CO-poisoning is O_2 inhalation, preferably HBO. Tissue oxygenation can be restored through O_2 dissolved in the plasma and accelerated dissociation of CO from Hb, myoglobin and other haeme proteins. The half-life of COHb is dramatically reduced; from 4–5 hours in subjects breathing room air, to 80 100 min breathing 100% oxygen, to 20 min or less with HBO. Dissociation of CO from other vital hemoproteins such as cytochrome c oxidase is also facilitated; improving electron transport and cellular energy state (Piantadosi 2002, Weaver 2009), however the dissociation half-lives from haeme proteins other then Hb remains unknown.

A large number of clinical retrospective cohort studies report positive results with HBO as compared with literature and historical controls. In reported series of CO-poisoned patients, clinical recovery among patients treated with HBO improved beyond that expected from using NBO both in terms of mortality and neurological morbidity.

There are five prospective clinical trials published of which two are double-blind randomized trials.

1) **Raphael et al** (1989) found no significant benefit when 2 bar HBO was compared with NBO. The lack of effect may be due to the fact that only mild CO intoxications patients without loss of consiousness were included, and more than half were treated more than 6 hours after intoxication and at an unconventionally low HBO pressure of 2 bar.

2) **Ducasse et al** (1995) and 3) **Thom et al** (1995) in single-center non-blinded randomized trials found significantly better outcomes when HBO at 2,5–2,8 bar pressure within 6 hours of poisoning was compared with NBO. No severely intoxicated patients were included for ethical reason.

4) **Scheinkestel et al** (1999), enrolled all poisoned patients regardless of poisoning severity in a double-blind randomized study at a major australian trauma center. They used an unconventional HBO and NBO protocol where CO intoxicated patients received up to 3–6 days of single daily HBO or NBO treatment plus supplemental 100% O_2 via mask or ventilator between treatments. No oxygen toxicity data was reported from this flawed clinical and experimental design. Only cognitive outcomes from a few days after CO poisoning was reported, no 1 month or long-term data was given and only 46% of patients returned for the 1-month evaluation. The authors concluded that HBO therapy was not of benefit and may have worsened the outcome. They did not recommend its use in CO poisoning. The study has been heavily criticized for using an O_2 toxic protocol and lack of long term follow up but has been used in Cochrane analyses (Juurlink et al 2005) and other systematic reviews from the same Australian toxicology group (Buckley et al 2005) with

continued controversies surrounding the value of HBO in CO victims (Wolf et al 2008). The limitations of the study by Scheinkestel, et al. render it uninterpretable for clinical decision-making.

5) **Weaver et al.** 2002 is the only randomized, double-blind, placebo controlled clinical trial which addresses long-term neurological sequelae after CO poisoning. They enrolled all CO poisoned patients regardless of poisoning severity. In a well designed and executed single-center trial using monoplace chambers, patients with acute CO poisoning were randomly assigned to either HBO (2,8 bar) or NBO treatment followed by two HBO or two placebo (air) sessions within a 24-hour period. Neuropsychological tests were carried out immediately after chamber sessions one and three, and 2 weeks, 6 weeks, 6 months, and 12 months after enrollment. The trial was stopped after the third of four scheduled interim analyses, at which point there were 76 patients in each group. The primary outcome was cognitive sequelae six weeks after CO poisoning which was found to be less frequent in the HBO group (19 of 76 [25.0 %]) compared with the NBO group (35 of 76 [46.1 %], P = 0.007). Long-term neurological sequelae were also found significantly reduced in the HBO group at 6 month- and one year follow up.

HBO protocol

Patients with CO poisoning are treated at 2,8 bar pressure for 110 minutes. Repetitive treatments are given with two additional sessions at 2,4-2,8 bar within the first 24 hours. Subsequent treatments may be given daily until there is no further improvement in cognitive function.

In deeply comatose patients or victims with myocardial depression, where a short treatment evidently is not capable of reversing the clinical symptoms and intracellular dysfunction (e.g. stunned heart) the first treatment can be prolonged.

HBO treatment may also be considered in patients who have delayed neuropsychiatric abnormalities (sequelae) on neuropsychometric testing even several days after intoxication (Chang et al 2010).

NBO should be administered over 6–12 hours in all less severely CO- poisoned patients.

Additional clinical considerations

Smoke inhalation in closed spaces should be considered as combined CO- and cyanide poisoning, to which severe chemical and thermal irritation of the airways may have been added. The fire also consumes O_2 and produces CO_2, which worsen the hypoxic stress even further. This is why surviving victims from fires seldom have prolonged CO exposure, risk immediate cardiac arrest and are difficult to resuscitate. Removal from the toxic environment and 100% O_2 breathing via face mask, demand valve, or assisted breathing /laryngeal tube is the cornerstone emergency treatment of CO- and smoke inhalation victims. Hydroxocobalamin cyanide antidote and NBO should be administered already at the scene of the accident. Smoke inhalation victims with witnessed cardiac arrest have a dismal prognosis

and should according to our own and others experience not be referred for HBO (Hampson & Zmaeff 2001). Burn and critically ill patients may be safely treated but require acute transport (ambulance or helicopter) and hyperbaric services with properly experienced personnel and suitable critical-care equipment (Lind 1993).

CO-poisoning in pregnant women is of special concern as the foetus is at increased risk of death, foetal malformations and intellectual retardation. The severity of foetal poisoning is difficult to detect /assess. It is known that the foetal haemoglobin has a greater affinity to CO than adult haemoglobin. It is therefore universally recommended to treat all CO-poisoned pregnant women with HBO. An evaluation of maternal and foetal outcome after HBO treatment of CO-poisoning was recently done by Mathieu-Nolf et al (2007) who carried out a detailed follow-up on 501 (90%) cases treated with HBO within 24 hours of CO exposure, over a 22-year period. Maternal outcome was death in two patients (0.3%), not statistically different from that of non-pregnant CO poisoned women. 476 pregnancies (95%) ended with delivery of a normal baby. Foetal loss occurred in 14 cases (3,3%) and malformations were observed in 11 babies (2.5%), a rate not statistically different from that seen in the general (reference) population. There was a 3.2 fold increase in stillbirth ($p<0.001$) when compared to the general population and therapeutic abortion is not recommended.

Risk factors for CO sequelae. Many patients continue to experience cognitive impairments in memory, attention and executive function after CO poisoning. In 163 patients not receiving HBO, 68 (42%) manifested sequelae in a six year follow-up study (Weaver et al 2007). A multivariable analysis was carried out using univariate results with (n=75) and without (n=163) HBO to determine risk factors for 6-week cognitive sequelae from CO poisoning and risk modification with use of HBO. The authors concluded that HBO is indicated for patients with acute CO poisoning who are 36 years or older or have exposure intervals greater than or equal to 24 hours. In addition, subgroup analyses support that patients with loss of consciousness or COHb levels greater than or equal to 25% warrant HBO.

Critical assessment and conclusion: Carbon monoxide poisoning and smoke inhalation

- The evidence level (see page 40) can be classified as 2, as one high-quality randomized study with adequate long-term follow-up is available supported by two less well performed randomized studies with appropriate protocols. Other less well-performed studies present controversial or contradictory conclusions.
- The rationale from a pathophysiological standpoint can be considered compelling with theoretical and experimental evidence of beneficial effects. Treatment recommendation = A.
- Thresholds for initiating HBO-therapy, number of treatments and the use and length of normobaric oxygen treatment is unclear and continue to leave room for opinionated statements.
- The majority of panel members agreed to recommend HBO if the patient is recently (within 24 hours) exposed to smoke or CO, is comatose or has a history of loss of consciousness due to exposure to CO, is pregnant (regardless of CoHb) or has a documented high (>20 %) CO-Hb level.
- The panel agreed that systematic long-term follow-up studies via a national database are needed in general to improve the quality of care for these patients. Consideration should be given to establish a large national (probably multinational) database.

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7.3 Diabetic foot ulcers

General

People with diabetes mellitus and non-healing foot ulcers have a very low quality of life and a high probability for amputation due to infection and ischemia. Diabetic foot is a major health problem which each year affects around 5% of the diabetic population, 15% will develop a foot ulcer in their lifetime and only two-thirds eventually heal and up to 28 % may result in some form of amputation (Hinchliffe et al 2008). In fact, the amputation rate is estimated to be 8–24 times higher than that in the general population (Fosse et al 2009). The death rate after major amputation (above or below knee) is significantly increased with a 1-year and 5-year survival rate of only 69 % and 31 %, respectively (Aulivola et al 2004). The impact of diabetic foot disease is substantial. Ulcer care is responsible for a large proportion of the cost of healthcare for people with diabetes and a below knee amputation carries a large cost for the patient and society (Apelqvist 2008). Patients with diabetic foot ulcer suffer from multiorgan disease. Factors related to outcome are correspondingly complex (Gershater et al 2008).To put the Diabetes Epidemic in perspective, it has been estimated that in U.S.A. every 24 hours there are: 4,100 people diagnosed with diabetes, 120 people who enter end-stage kidney disease programs, 55 people who go blind and 230 lower extremity amputations (Vinicor 2006).

Infection in the diabetic foot varies from superficial cellulitis to deeper infection of the soft tissue and bone. Underlying osteomyelitis occurs in up to two-third of the patients (Lavery et al 2009). *S. aureus* is the commonest cultured organism. Chronic wounds are often polymicrobial, with Gram negative bacilli, anaerobic and multi-drug resistant organisms. The underlying principle of the infected diabetic foot is to detect the bacteria and treat aggressively (Edmonds 2009). In Europe, 58 % of individuals' foot ulcers have signs of infection at admission, and one-third have signs of both peripheral artery disease and infection. The relapse rate for diabetic foot ulcers is 66% over 5 years and approximately 12% of people with ulcers progress to lower extremity amputation (Prompers et al 2007).

The clinical diabetic foot can be defined as infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degree of peripheral vascular disease in the lower limb. Because of the complexity of factors related to outcome the treatment requires an aggressive multidisciplinary approach in a comprehensive diabetic foot care clinic including antibiotics, wound care with cleansing and the use of dressings to maintain a moist wound bed, pressure relief and strategies for maintaining optimal blood glucose levels, adequate nutrition etc. Diagnostic procedures include plain radiography, MRI, duplex angiography and bone sampling for microbial cultures. Revascularisation by surgical by-pass or via angioplasty of stenoses and occlusions, debridement of dead tissues and surgical removal of a dead or infected digit may also be required.

HBO treatment

HBO has been used for decades as it seems to accelerate the rate of healing, reduce the need for amputation, and increase the number of wounds that are completely healed on

long-term follow-up (Abidia et al 2003, Faglia et al 1996, Kalani et al 2002). Additionally, there appears to be potential saving in the total cost of treatment for each patient (Abidia et al 2003, Cianci & Hunt 2008).

In 1999, the American Diabetes Association endorsed the use of HBO in severe diabetic wounds that fail to respond to traditional approaches. The Centres for Medicare and Medicaid Services in USA stated in 2002 that there was adequate evidence to conclude that HBO is clinically effective, reasonable and necessary in the treatment of certain diabetic lower limb-threatening wounds (Wagner grade III or higher and recalcitrant to 30 days of appropriate wound treatment). HBO was graded as "Level I" treatment in "Guideline for the treatment of diabetic ulcers" supported by the Wound Healing Foundation (Steed et al 2006).

More than 110 studies can be found of which 6 are randomized controlled trials and 2 are comparative cohort studies. Over the past decade there have been over 10 published independent evidence-based reviews (Kranke et al 2004, Warriner & Hopf 2008, Hinchliffe et al 2008, Goldman 2009). The best evidence exist for HBO treatment of the ischemic, infected (Wagner III or worse) diabetic foot ulcer suggesting that HBO best be used in an adjunctive role together with optimized patient and wound care including appropriate antibiotics and surgery (Warriner & Hopf 2008). A systematic review of the effectiveness of many different interventions to enhance the healing of chronic Diabetic foot ulcers found evidence that HBO may reduce the incidence of major amputation and sufficient data to justify use of HBO where the necessary facilities are available (Hinchliffe et al 2008). Another systematic review (Goldman 2009) concluded that there was a high level of evidence that HBO reduces risk of amputation in the diabetic foot population by promoting partial and full healing of problem wounds. For patients with diabetic foot ulcers complicated by surgical infection, HBO significantly reduces chance of amputation and improves chance of healing.

A new, well designed, single-centre prospective randomised double-blind study on HBO therapy in 75 diabetics with chronic foot ulcers has recently been published (Löndahl et al 2010). The study was designed to primarily look at ulcer healing to intact skin in 94 diabetic patients with chronic foot ulcers. Inclusion criteria: Diabetes Mellitus patients with Wagner grade 2–4 foot ulcer at or below ankle with duration of more than 3 months despite best medical care at a Swedish Diabetes Foot Clinic (Helsingborg, Lund or Malmö) for at least two months and further vascular intervention ruled out by a vascular surgeon. The effects of > 35 HBO (2,5 bar) sessions were compared to > 35 placebo sessions (air breathing at 2,5 bar). Patients from both groups were simultaneously treated in a multiplace chamber (≤ 8 sitting patients) for 90 minutes per day, 5 days a week, for 8 weeks up to 40 sessions. Treatment was carried out on an outpatient basis. With 1-year follow up, there is evidence that HBO increases wound healing and lead to an increased tissue oxygenation (Löndahl et al 2010). TcPO2 seems to be a better predictor for outcome than toe-blood pressure or ankle-brachial index (Löndahl 2010, personal communication).

It seems clear that in a center of excellence of both HBO and diabetic foot care, like the one in Lund, HBO can help heal refractory wounds (Lipsky and Berendt 2010).

HBO protocol

Patients with (infected) diabetic foot ulcers are treated daily at 2,4–2,5 (2,8) bar pressure for 100 minutes, 1–(2) times/day, 5–(7) days per week in the total number of 30–40 sessions. Minor amputations and other surgical procedures or wound dehiscence may occasionally extend the series up to 60 sessions.

Additional clinical considerations

Predictive factors and major amputation rates for HBO treated foot ulcers (Kaya et al 2009). A total of 184 consecutive patients were treated with HBO therapy as an adjunct to standard treatment modalities for their diabetic foot ulcer. Of these patients, 115 (63%) were completely healed, 31 showed no improvement and 38 underwent amputation, nine major amputations (below knee) and 29 minor amputations. No major amputation was applied to Wagner grades 2 and 3. The amputation rates in grades 4 and 5 were 4.9 and 70.0%, respectively. Major amputations were associated with the Wagner grade ($p < 0.0001$) and with the age of the patients ($p = 0.028$). According to the authors HBO can help to reduce the major amputation rates in diabetic foot ulcer.

Factors influencing the outcome of lower-extremity diabetic ulcers treated with HBO therapy (Fife et al 2007). Five hyperbaric facilities supplied data on 1,006 patients. A sixth clinic served as a validation sample for the regression-based prediction model, and later additional data were added. The severity of lower-extremity lesions was assessed upon initiation of HBO using the modified Wagner scale, and the outcome described as healed, partially healed, not improved, amputated, or died. Overall, 74% of patients improved (granulated or healed). Factors significantly relating to outcome included renal failure, pack-year smoking history, transcutaneous oximetry, number of HBO treatments, and interruption of treatment regimen. Number of treatments per week and treatment pressure (2.0 vs. 2.4 bar) were not significant factors in outcome. These data suggest that HBO treatment should be an important adjunctive therapy to heal lower-extremity lesions, especially those with a Wagner grade 3 or worse. In practise this means an infected deep wound with abscess and infected bone/osteitis (grade 3), a localised gangrene of forefoot or heal (grade 4) or a gangrene of entire foot (grade 5).

Transcutaneous oximetry ($TcPO_2$) can help select patients and predict a beneficial response to HBO. $TcPO_2$ measurement is a valuable and helpful non-invasive method for patient selection, follow-up and treatment monitoring (Wattel et al 1991, Mathieu et al 2006). It uses a Clark's polarographic heated electrode with PO_2 measured as a current generated by O_2 electrochemical reduction in proportion to the number of O_2 molecules entering the chamber through transcutaneous diffusion. In adults, $TcPO_2$ is a reliable index of local blood flow (Hauser & Shoemaker 1983). $TcPO_2$ seems to be a better predictor for outcome than toe-blood pressure or ankle-brachial index (Löndahl 2010, personal communication).

Hypoxic $TcPO_2$ values, i.e. $PO_2 < 5,3$ kPa (40 mm Hg) in adjacent areas of a wound, are valuable as inclusion criteria for selection of patients who will respond to HBO (Fife et al 2009). Breathing 100% O_2 at normal pressure can improve the accuracy in predicting successful healing; periwound $TcPO_2$ values > 7 kPa (50 mm Hg) predict healing. Hyperbaric

$TcPO_2$ values > 27 kPa (200 mm Hg) gives the most accurate predicition of a reversible critical ischemia and a 74% reliable cut off value for a beneficial response to HBO (Fife et al 2009).

However, $TcPO_2$ is a more accurate predictor of failure to heal than success. The prognosis is poor if $TcPO_2$ is low and unresponsive to HBO and revascularization is not possible. A lack of an increase in hyperbaric TcPO2 values > 13 kPa (100 mm Hg) predicts failure to heal with HBO (Wattel 1991, Mathieu et al 2006).

The cost-effectiveness and budget impact of HBO has been estimated for Canada (Chuck et al. 2008) using a decision model comparing adjunctive HBO with standard care alone. The population was a 65-year-old cohort with Diabetic Foot Ulcers (DFU). The time horizon was 12 years taken from a Ministry of Health perspective. The health status was a healed wound with or without a minor amputation, an unhealed wound with no related surgery, and a major lower extremity amputation. Efficacy data were based on outcomes reported in studies included in a literature review. Cost and capacity needs for treating DFU patients in Canada were estimated using prevalence data from the literature, and cost and utilization data from government records. The 12-year cost for patients receiving HBO was CND$ 40,695 compared with CND$ 49,786 for standard care alone. Outcomes were 3.64 quality-adjusted life-years for those receiving HBO and 3.01 years for controls. Estimated cost of treating all prevalent DFU cases in Canada was CND$ 14.4–19.7 million/year over 4 years. If seven-person HBO chambers were used, a further nineteen to thirty-five machines would be required nationally. The authors concluded that adjunctive HBO for DFU is cost-effective compared with standard care.

Critical assessment and conclusion: Diabetic foot ulcers

- The evidence level (see page 40) can be classified as 2, as one high-quality randomized study with adequate long-term follow-up is available supported by several less well performed randomized studies with appropriate protocols, resulting in our treatment recommendation = A. However we note that our recommendation is not in agreement with the present statement issued from the National Board of Health and Welfare Sweden – Socialstyrelsen:" Nationella riktlinjer för diabetesvården 2010- stöd för styrning och ledning (only in Swedish)" ("National recommendation for treatment of diabetes mellitus 2010".) http://www.socialstyrelsen.se/publikationer2010/2010-2-2
- The most trusted effect from using HBO is enhanced wound healing but there is also documented effects on diabetic limb preservation with reduced major amputation rates in ischemic and infected (Wagner III or worse) diabetic foot ulcers
- The rationale from a pathophysiological standpoint can be considered compelling with theoretical and experimental evidence of beneficial effects
- The majority of panel members agreed that a recommendation to use HBO can be issued in ischemic, infected (Wagner III or worse) diabetic foot ulcers and in wounds refractory to specialized foot care
- HBO is an adjunctive therapy, not a substitute for standard treatments, and should only be used as part of a multidisciplinary approach with optimized patient and wound care strategies including appropriate antibiotics and revascularization procedures. All other use of HBO in diabetic patients remains investigational
- Thresholds for initiating HBO-therapy are clear. Transcutaneous oximetry can help select patients and predict a beneficial response to HBO
- The number of HBO treatments is unclear, and continue to leave room for opinionated statements
- The panel agreed that systematic long-term follow-up studies via a national database are needed in general to improve the quality of care for these patients. Consideration should be given to establish a large national (probably multinational) database.

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7.4 Soft-tissue radiation injury - hemorrhagic proctitis/cystitis

General

Cancer is a significant global health problem often treated with radiation therapy. Dosing is limited not only by acute inflammatory changes in previously healthy tissues but also by delayed slowly progressing obliterative damage to the microcirculation developing months to years after radiation therapy. The pathophysiology of "delayed" radiation injury is that of endarteritis with loss of capillary bed and tissue fibrosis. The result is a hypovascular, hypoxic tissue with impaired potential for tissue repair. Because radiation-induced capillary loss is progressive rather than transient, wound or tissue break down in previously irradiated tissue is usually chronic and nonhealing.

Radiation therapy of prostate, rectal, cervical, bladder, breast and head & neck cancers may cause complications from the rectum (proctitis), bladder (cystitis), colon (enteritis), anogenital region, breast/ chest wall or in the soft tissue of the head & neck referred to by us as "soft-tissue radiation injury". Laryngeal radionecrosis can lead to dysphagia and respiratory obstruction. Irradiated skin develops painful, necrotic wounds that do not heal with standard wound care.

Hemorrhagic radiation proctitis is a potential complication after pelvic irradiation but is most commonly seen in men with prostate cancer. It presents with tenesmus, bleeding, diarrhea or constipation, and rectal pain. There may be stricture or ulcer formation, abscesses, or fistulae. Some patients will develop intractable or massive bleeding from rectum that will require repeated hospital admissions and blood transfusions. First line therapy includes conservative measures such as medications (sulfacrate, steroids), intrarectal formalin, and laser therapy of telangiectasias. Surgery is reserved for severe cases that develop fistulae, abscesses or strictures.

Hemorrhagic radiation cystitis is most commonly seen in women with cervical cancer due to its close proximity to the urinary bladder. Inflammatory changes after pelvic radiotherapy causes chronic fibrosis and progressive endarteritis in poorly oxygenated bladder submucosal and muscular tissues, with eventual tissue scarring. This can potentially lead to bladder mucosal sloughing and severe blood loss requiring frequent blood transfusions. Conventional treatment includes many remedies including intravesical 4% formalin installation. In refractory cases, it may involve cystectomy, nephrostomies and death.

HBO treatment

HBO induced angiogenesis improves regional tissue oxygenation in previously irradiated hypoxic and scarred submucosal tissue. In a large semi quantitative review of 71 reports, involving 1193 patients across eight different tissues, clinically significant improvements from HBO were found in the majority of patients, where conservative treatment had previously failed to improve symptoms (Feldmeier JJ and NB Hampson et al. 2002). Results varied between tissue types, with neurological tissue being most resistant to improvement. Only seven of 71 reports indicated a generally poor response to HBO.

In a Cochrane review (Bennett el al 2005) of six randomized and pseudo-randomized clinical trials with 447 patients (some involving osteoradionecrosis), HBO was suggested to be associated with improved outcome for people with late radiation tissue injury affecting tissues of the head, neck, anus and rectum. There was no such evidence of any important clinical effect on neurological tissues.

HBO treatment of hemorrhagic radiation proctitis has usually been reserved for patients who have failed previous conservative therapies. In a recent analyses of 199 cases summarized from clinical publications on HBO treatment of proctitis, colitis and enteritis (Feldmeier & Packard 2008), 80 (41%) showed complete resolution while 169 (86%) experienced at least partial response to therapy. Only 14% failed to respond at all.

Recently, a well controlled randomized blinded trial with cross-over design and long-term follow up was published on the effects of HBO treatment of patients with refractory chronic radiation induced proctitis (Clarke et al 2008). Out of 150 patients enrolled 116 could be analyzed using the SOMA-LENT scoring systems for radiation injuries/complications. Primary outcome was the score after the initial 30–40 treatments of HBO at 2 bar or 30–40 sham treatments in chamber breathing air at 1.1bar. Patients in the HBO arm showed a statistically increased improvement ($p=0.0019$) with 88.9% responders compared to 62.5% in the sham control group ($p=0.00009$). The absolute risk reduction was 32% and the numbers needed to treat (NNT) was 3. A substantial improvement occurred also in the sham group after unblinding and open crossover to active HBO therapy. The mean scores remained relatively stable through 1 year and showed a trend to additional and sustained improvement through year 5. The improved healing response with HBO persisted over an extended follow-up period (average of 2-year, minimum 1 year) with continued improvement over time. The bowel specific quality of life improved with suggestions of enhanced cost effectiveness. There were little or no side effects of HBO.

HBO treatment of hemorrhagic radiation cystitis can also improve outcome in patients resistant to conservative treatment. In the past forty years there have been numerous positive publications, mainly retrospective studies, on HBO in hemorrhagic radiation cystitis, with beneficial results in 18 out of 19 studies, with either partial or complete response in 196 (76%) of the 257 patients (Feldmeier & Packard 2008). Hematuria, a dominant symptom can be relieved in many cases and frequency and incontinence improved in some cases. In a prospective study on 40 patients where the only measure to be considered was cystectomy (Bevers et al 1995), there was a high rate of response to HBO (20 sessions at 3 bar for 90 min, 5-6 times per week). Hematuria stopped in 30 patients, was improved in 7 and failure of treatment was only seen in 3 patients. There were a considerable number where the improvement was maintained long term with a high rate of bladder preservation.

A double-blind study on radiation cystitis by Clarke and coworkers, similar to the one on proctitis, is currently recruiting patients.

HBO protocol

Patients with radiation tissue injury are treated at 2,4–2,5 bar pressure for 100 minutes, in 30–40 sessions. Post operative complications and infections are initially treated at 2,8 bar.

Additional clinical considerations

Early intervention with HBO, within 6 months of hematuria onset, is associated with a greater therapeutic response rate according to a retrospective study on 60 patients with radiation-induced hemorrhagic cystitis treated at 2.4 bar 90 minutes for an average of 33 (range 9–63) HBO treatments (Chong et al. 2006). When treated within 6 months of hematuria onset, 96% (27 of 28) had complete or partial symptomatic resolution (P = 0.003). All 11 patients with previous clot retention had clinical improvement when treated within 6 months of hematuria onset (P = 0.007). After a minimum of 12 months follow-up, 80% (48 patients) had either total or partial resolution of hematuria. Prior intravesical chemical instillation did not affect the clinical outcome. Patients who had undergone primary, adjuvant, or salvage external beam pelvic radiotherapy showed response rates of 81%, 83%, and 78%, respectively (P = 0.950). The authors concluded that these results show that delivery of HBO within 6 months of hematuria onset is associated with a greater therapeutic response rate. Treatment efficacy was independent of the timing of radiotherapy.

HBO response rate improve with number of HBO treatments. The HBO protocol differs between hyperbaric facilities. To study if the clinical response depends on the rate of administration of HBO treatments, details of patients treated for radiation enteritis/proctitis (n = 65) and cystitis (n = 94) at a single institution were reviewed by Hampson et al (2007). The authors concluded that soft tissue radionecrosis of the gastrointestinal tract or bladder is effectively treated with HBO, has a higher response rate if at least 30 treatments are administered, and is equally responsive to rates of hyperbaric treatment ranging from 3 to 7 or more treatments per week.

Surgery in radiation-compromised tissues has an increased complication rate (cf ORN below) because wound healing and white blood cell activity is oxygen dependent. In a prospective single center study, (Marx 1999), 160 patients scheduled for major soft tissue surgery or flap introduced into tissue radiated to a dose of 64Gy or greater were divided into two groups; to receive 20 pre- and 10 postoperative HBO treatments (n=80) or control (n=80). Wound infections and wound dehiscence was significantly reduced in the HBO group from 24% to 5% and 48% to 11%, respectively. Delayed wound healing was also highly significantly reduced from 55% in the control group to 11% in the 20/10 HBO group. In our experience, postoperative complications and infections in irradiated tissues can also be treated successfully with HBO. (Neovius et al 1997, Larsson et al 2002). Randomized studies on postoperative radiation complications do not exist.

HBO enhanced radiation therapy, a major research field in the 1960's, is now again a developing field of clinical Hyperbaric Medicine that warrants further investigation. Mortality and tumour recurrence may be reduced when HBO is used as a radiosensitizer in hypoxic tumour cells (Bennet et al 2008). Japanese researchers have developed a new

approach with administration of radiotherapy immediately (20–30 minutes) after HBO when the ischemic and hypoxic tumour remains oxygenated whereas healthy well-perfused tissues have come back towards normal. By using this treatment window for radiation, the side effects in healthy tissues can be limited and it is much simpler than to irradiate during ongoing HBO therapy, through a Monoplace chamber plexiglas hull. In a non-randomized study, two groups of patients with newly diagnosed malignant gliomas with evidence of residual tumour were compared; 15 patients were irradiated within 15-30 min following HBO (2.5 bar; 60 min) and 14 patients were conventionally irradiated without HBO at another hospital. At 2–76 months clinical and neuro-imaging follow-up, 11 of 15 patients (73%) showed a complete or partial response vs. 4 out of 14 patients (29%) in the control group (Koshi et al 1999). Median survival time was doubled for the HBO group.

Gamma fractionated stereotactic radiotherapy on recurrent high-grade gliomas after HBO therapy appears to confer a survival benefit for patients with recurrent high-grade gliomas (Koshi et al 2007).

HBO for hemorrhagic cystitis after hematopoietic stem cell transplantation (not a radiation injury). HBO seems also to be safe and effective in pediatric patients. In a multicenter study Cesaro et al. (2003) assessed the incidence and the treatment of hemorrhagic cystitis in 1218 pediatric patients, with a mean age of 10.8 years, who underwent hematopoietic stem cell transplantation. After a median of 23 days 44 patients (3.6%) developed hemorrhagic cystitis. Significantly better results were achieved with HBO compared with prostaglandin therapy ($P = 0.02$) in the treatment of grade II - III hemorrhagic cystitis.

HBO in in BKV-associated hemorrhagic cystitis (not a radiation injury). BKV is a human polyomavirus causing widespread infection in childhood and remains latent in the host; it is believed to cause hemorrhagic cystitis and nephritis in immuncompromised patients. HBO has also been suggested to be beneficial in BKV-associated hemorrhagic cystitis refractory to intravenous and intravesical cidofovir (Focosi et al 2009).

HBO for interstitial cystitis (not a radiation injury). Van Ophoven et al (2006) conducted a double blind, sham controlled study to evaluate the safety, efficacy and feasibility of HBO for interstitial cystitis. Twentyone patients were randomized to 30 HBO sessions at 2.4 bar for 90 minutes or to 1.3 bar (sham), breathing normal air. HBO resulted in a sustained decrease of interstitial cystitis symptoms. They concluded that HBO appears to be a safe, effective and feasible therapeutic approach to interstitial cystitis.

Critical assessment and conclusion: Soft-tissue radiation injury – hemorrhagic proctitis/cystitis

- The evidence level (see page 40) can be classified as 2, as one high-quality randomized study with adequate long-term follow-up is available supported by less well performed randomized studies and many cohort studies.
- The majority of panel members agreed to recommend HBO if the patient has a history of radiation therapy and subsequent local organ damage due to this, and the aim is to reduce clinical symptoms of proctitis and /or cystitis. Treatment recommendation = A.
- There is less evidence that HBO is associated with improved outcome in other soft-tissue radiation injuries as well, and for prophylaxis and treatment to optimize outcome after surgery in radiation-compromised tissues, where HBO may be justified in selected patients.
- The rationale from a pathophysiological standpoint can be considered compelling with theoretical and experimental evidence of beneficial effects. The most trusted effect from using HBO is enhanced angiogenesis demonstrated to occur over time in hypoxic, hypocellular and hypovascular radiation damaged tissues.
- The panel agreed that systematic long-term follow-up studies via a national (multinational) database are needed in general to improve the quality of care for these patients.
- HBO for tumour sensitisation to radiotherapy is an interesting field in oncology research but remains experimental

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7.5 Osteoradionecrosis (ORN)

General

Head and neck cancer patients get bone and soft-tissue damage after radiotherapy. In addition to targeted tumor cells, radiation unavoidably destroys normal cells and blood vessels. Though any bone and soft tissue can be involved the mandible is by far the most common site for osteonecrosis (dead bone) because the main arterial supply of the mandibular body is through the inferior alveolar artery, whereas the remaining bones of the head and neck receive highly redundant periosteal and muscular perforators.

Osteoradionecrosis (ORN) is defined as an area of non-healing exposed bone in a patient with a history of radiation therapy that persists for more than three months without any evidence of tumour recurrence. The incidence of "non-healing exposed bone" depends on the dose of irradiation and varies from 0–9% in the literature. The majority of these cases heal conservatively but 15 % become "chronic" and even progressive ORN with involvement of soft-tissues (Feldmeier & Packard 2008). A "simple" dental extraction in an irradiated mandible may cause a non-healing lesion with denuded bone. The ORN may progress to a fracture of the jaw requiring mandibulectomy with complex, extensive and expensive surgical reconstructive work.

In the 80s, ORN was demonstrated to primarily be an avascular "aseptic" necrosis rather than the result of infection (Marx 1983a). HBO was introduced in the multidisciplinary bony reconstruction procedures, to increase the vascular density, so that the hypoxic, acellular matrix in the postirradiated field is changed to a more normoxic situation (Marx 1983b).

HBO treatment

A series of HBO treatments creates a capillary angiogenesis that improves the radiation damaged tissue in the jaws in a dose dependent fashion. By using HBO pre- and postoperatively, together with an aggressive surgical approach, the salvage rate for ORN and its complications was increased dramatically (Marx 1983b). Many papers, mostly case series, have been published with good results when HBO has been used according to the so called "Marx protocol" (see below); which is a multidisciplinary surgical and hyperbaric staged management of mandibular ORN (Feldmeier & Packard 2008, Freiberger et al 2009).

The only prospective randomized clinical trial published on HBO treatment of ORN failed to report a positive outcome (Annane et al 2004). The Annane study has received massive critizism (Feldmeier & Packard 2008) stating that e.g. it did not follow the Marx protocol with proper surgical removal of necrotic bone. This study has created a debate in recent years where HBO for ORN in general has been questioned (Teng and Futran 2005).

HBO therapy was recognized as an adjunctive treatment for ORN by the Consensus Conference in Lisbon, Portugal, 2001 with European Committee for Hyperbaric Medicine & European Society for Therapeutic Radiology and Oncology. The experimental evidence was found to be of highest evidence level and while recognizing that there were no randomized

studies there was a considerable body of evidence to support the view that HBO is effective in improving ORN of the mandible in 72–92% of patients when conservative measures fail to allow healing (Consensus conf. 2001).

In a prospective randomized trial, prophylactic HBO was shown to reduce the risk of ORN following tooth extraction in an irradiated field (Marx et al 1985). In 74 patients who had received a radiation dose of at least 68 Gy, the 37 patients who received 20 pre + 10 post extraction HBO treatment prophylaxis and no penicillin did better than the 37 patients assigned to penicillin alone control group. Of 135 teeth removed in the control group, 11 patients (29.9%) developed ORN compared with the 156 teeth removed in the HBO group with 2 (5,4%) cases of ORN (P=0.005). HBO has also shown to be valuable in the prohpylaxis of ORN as well as a stimulator of osseointegration when installing dental inplants in full-dose irradiated tissue (Granström 1998, Granström et al 1999, Feldmeier & Packard 2008).

HBO therapy has been used for several decades as an adjunct to appropriate surgery in the treatment and prophylaxis of ORN. In the USA, authoritative bodies such as the National Cancer Institute (1990), the Federal Drug Administration, the Centers for Medicare and Medicaid Services (2006) recommend and support its use (Feldmeier & Packard 2008). A Cochrane review concluded that there is some evidence that HBO improves outcome in late radiation injury affecting bone and soft tissues of the head and neck and in preventing ORN following tooth extraction in an irradiated field (Bennet et al 2005).

HBO protocol

ORN treatment protocol (Marx 30/10 protocol). Patients with radiation damaged tissue and exposed bone are treated at 2,4–2,5 bar pressure for 100 min in chamber time. Most of the HBO usually is given before surgical intervention. Thirty HBO treatments are given preoperative followed by 10 or more postoperative HBO treatments depending on surgery and assessment up to a total of 40 or even 60 sessions (Marx 2004).

ORN prevention protocol (Marx 20/10 protocol). HBO prophylaxis before tooth extraction or dental implants in irradiated (>60Gy) jaw is usually referred to as a "20/10 protocol" with 20 sessions of HBO at 2.5 bar for 90 minutes on 100% oxygen prior to surgery, followed by 10 such sessions after surgery (Marx 2004).

Additional clinical considerations

The Marx protocol uses a staging system for classifying and planning treatment (Marx 1983b) which is largely accepted throughout the oromaxillofacial surgery community. It includes an oral surgeon to extirpate necrotic bone in stage 1, or who work together with the E.N.T. and plastic surgeons for resections and reconstructive surgery in stages 2 & 3, depending on clinical severity and response to previous therapy. Basically, in full dose irradiated patients, no surgery should preferably be attempted in the jaw before the first 30 HBO treatments have provided sufficient angiogenesis to support surgical wounding and then HBO should be resumed as soon as possible after surgery.

- Stage 1 - Exposed alveolar bone: 30 HBO treatments before the patient is reassessed and staged according to the extent of improvement achieved; bone exposure, granulation, and resorption of nonviable bone. If a favourable response is obtained an additional 10 treatments may be considered.
- Stage 2 - A patient who formerly was Stage I with incomplete response or failure to respond: Carry out transoral sequestrectomy with primary wound closure followed by an additional 10 HBO treatments.
- Stage 3 - A patient who fails stage II or presents with an orocutaneous fistula, pathological fracture, or an ORN extending to the inferior border of the mandible: 30 HBO treatments followed by transcutaneous discontinuity mandibular resection of the necrotic bone, mandibular fixation and wound closure, followed by 10 or more postoperative HBO treatments.

Microbial biofilms may also play a role for the disease process as recently shown in patients with osteonecrosis of the jaws secondary to bisphosphonate therapy; ONJ (Sedghizadeh et al 2008). Bone samples from sequestrectomy procedures in four patients with active ONJ were evaluated with histopathological techniques and scanning electron microscopy. The bone specimens showed large areas occluded with microbial biofilms comprising mainly bacteria and yeast, embedded in extracellular polymeric substance suggesting a role for microbial biofilms in the disease process (Sedghizadeh et al 2008). Microbial biofilms were seen in the deeper cavities of the bone and not just the surface exposed to the contaminated oral cavity. Biofilms greater than 50 micrometer in thickness were observed. The bacteria identified in all the bone specimens comprised of Gram-positive and Gram-negative organisms, and included aerobes, although anaerobes and facultative anaerobes dominated. Yeast and candida species were also evident in all cases. Traditional microbial culturing and antibiotic sensitivity techniques are not applicable to biofilm mediated diseases. The authors concluded that these findings have important clinical and therapeutic implications and may suggest a role for microbial biofilms in the disease process of ONJ (Sedghizadeh et al 2008). Robert Marx introduced the new important concept of ORN pathophysiology (1983a) that ORN is a hypoxic-hypovascular-hypocellular tissue and not a primary infection of irradiated bone. He stated that the surface microorganisms identified by culture techniques or tissue staining only played a contaminant role in ORN since he could not find any organisms in the deep so-called “infected bone” of ORN (Marx 1983a). This was in contrast with both superficial and deep findings of microorganisms in osteomyelitis and infected bone grafts. Maybe we now have to rethink this conclusion that ORN is an aseptic necrosis and consider the possibility that microbial biofilm may also be involved in the disease process of ORN (Sedghizadeh et al 2008). For example, in addition to a staged surgical approach and hyperbaric oxygenation of avascular hypoxic biofilm and tissues, Stage 1 and 2 ORN could then perhaps benefit from antibacterial and antifungal medication to help achieve resolution. Biofilm research in ORN patients is warranted on the basic science and clinical level to help provide further insight or rationale for improved therapeutic interventions.

Critical assessment and conclusion: Osteoradionecrosis (ORN)

- The evidence level (see page 40) can be classified as 3, as no adequate high-quality randomized study is available. One randomized trial on profylactic HBO was found to prevent ORN after tooth extraction in the iradiated mandible. Another negative randomized study on HBO treatment of ORN has been criticized for serious design flaws that limit interpretation. Treatment recommendation = B.
- The rationale from a pathophysiological standpoint can be considered compelling with theoretical and experimental evidence of beneficial effects in irradiated bone. Among these, angiogenesis and increased bone turnover and maturation.
- The majority of panel members agreed to recommend HBO for prevention and treatment of ORN when used according to an established multidisciplinary protocol.
- The panel agreed that systematic long-term follow-up studies via a national (international) database is needed to improve the quality of care for these patients.
- Biofilm research on the basic science and clinical level in ORN patients may help provide further insight or rationale for improved therapeutic interventions

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Indications under investigation 7.6 – 7.10

7.6 Severe Acute Ischemic Conditions

General

Low tissue PO_2 is a common clinical problem in surgical sites and wounds suffering from severe acute ischemia (too little blood flow) such as crush injury, skeletal muscle-compartment syndrome and failing grafts and flaps. Acute peripheral trauma leads to vascular damage, edema, ischemia and hypoxia causing a gradient of tissue injury. High energy traffic accidents with open tibial fractures and severe soft tissue injury of the lower leg "crush injury" are especially difficult to treat. Vessel injury is important to repair because already after 2–4 hour's warm ischemia the injury may be enlarged due to an inflammatory response often called "ischemia-reperfusion (I-R) injury". Posttraumatic edema with low oxygen tension also has detrimental effects on wound-healing and infection control. As oxygen tension falls, WBC killing becomes compromised in the often heavily contaminated tissues, which predisposes for infection (Lindström et al 1998). Gustilo's classification of open fractures is often used to grade the severity of these fractures since it provides guide treatment options and prognostic indications:

Gustilo's classification of open fractures		Complication rate	
Type	Mechanism	Infection	Amputation
I	Small laceration <1cm	minimal	
II	Large laceration but minimal soft tissue damage	3%	
III	Crush Injuries		
	A: Sufficient soft tissue to close wound	4%	
	B: Flaps or grafts required to cover bone	52%	16%
	C: Major vessel injury	42%	42%

Compartment syndrome is another severe ischemic condition with obliterated circulation and oxygenation when compartment pressures exceed the capillary perfusion pressures. A continuum of injury can occur even after fasciotomy. Skin grafts and reconstructive flaps may also fail because of inadequate perfusion with hypoxia with risk of I–R injury. Oxidative killing, can be profoundly impaired by poor blood perfusion and oxygenation.

HBO treatment

Patients with acute severe ischemic conditions after trauma or surgery may benefit from HBO based on sound pathophysiological rationale and theoretical and experimental evidence.

Although each case is unique, a key factor to necrosis is hypoxia and HBO may help salvage the situation in an acute hypoxic phase and the I-R phase. HBO can enhance O_2 transport and diffusion to overcome a decreased, but not obliterated, perfusion. Tissue PO_2 may be returned to sufficient levels for survival in threatened tissues and allow the host defenses to function properly. HBO may also reduce edema and has anti-inflammatory effects on the ischemia reperfusion (IR) syndrome (Zamboni & Baynosa 2008). The host response to infection and ischemia become compromised if tissue PO_2 falls below 4–5 kPa /30–40 mmHg (Strauss 2008). A series of HBO treatments may help wound healing and infection in the compromised host or help prepare irradiated or infected tissues for further surgery.

Crush injury. A number of clinical observational reports have described benefit of HBO in extremity trauma (Strauss 2008) but only as an adjunct to surgery after appropriate resuscitation, macrovascular repair, fracture fixation/stabilization, and fasciotomy in compartment syndrome.

Garcia-Covarrubias et al (2005) did a systematic review of the literature. Nine reports fulfilled the inclusion criteria with approximately 150 patients. Most documents were retrospective, uncontrolled, and case series lacking a standardized methodology (class III). There was one prospective, double blind, controlled randomized trial (Bouachour et al 1996). The authors determined that eight of nine studies showed a beneficial effect from HBO with only one major complication. They concluded that adjunctive HBO is not likely to be harmful and could be beneficial if administered early.

Grafts and flaps. A randomized single-blinded study (with intention to treat analyzes, but no sham treatment) was published in Lancet (Perrins 1967) on a group of 48 patients received split-thickness skin grafts. Compared with the control group the graft survival rates were higher in the 24 patients treated with 7 postoperative HBO sessions given at 2 bar for 2 hours; first on the same evening and then twice daily for three days. Total or near total take was achieved in 64% of hyperbaric treated grafts as compared with only 17% of the controls ($p<0.01$).

A number of clinical observational reports have described benefit of HBO in skin grafts and reconstructive flaps, which fail because of inadequate perfusion and hypoxia (Bowersox et al 1986, Zamboni & Baynosa 2008). In a review, Friedman et al (2006) analyzed the available literature on the use of HBO for composite grafts, skin grafts, random flaps, distant flaps, and free flaps. Although there is a significant amount of animal data supporting the application of hyperbaric oxygen for grafts and flaps (see above 6.7) there is very little clinical information other than case reports and case series to support its use. In another recent review Goldman (2009) concluded that there is a low to moderate level of evidence that HBO promotes successful "take" of compromised flaps and grafts.

HBO protocol

Patients with severe ischemic conditions after trauma or surgery can be treated at 2,8 bar pressure for 110 minutes, 1–2 times/day in the first 24 hours, followed by 1–2 times/day. HBO should be started as soon as feasible and continued in agreement with referring physician according to clinical response.

Additional clinical considerations

Postoperative HBO improves tissue perfusion (peak dopper signal) and oxygenation ($TcPO_2$) after reamed intramedullary nailing of tibia fractures (Lindström et al 1998). In a randomized prospective study on 20 consecutive patients with uncomplicated, closed and simple, tibial shaft fractures, HBO (2.5 bar, 90 min daily) was given 5 days postoperatively, the first session 1 h postop. Doppler and $TcPO_2$ were evaluated before surgery and then daily 4–6 hours after HBO. Whereas no difference was seen in a. tibialis anterior doppler values between the two groups, here was a statistically significant improvement in a. tibialis posterior values in the nailed legs in the HBO treatment group after the first postoperative day that remained significantly higher throughout the study. A significant improvement in $TcPO_2$ values, measured from the skin adjacent to the fracture, was also seen in the HBO group (6 kpa) as compared with the control group (4kpa) from day 2 until day 5. HBO was suggested to improve arterial blood flow and oxygenation in the deep posterior compartment and locally in the skin adjacent to the fracture. The authors conclude that this beneficial effect of HBO may be of crucial importance in the adjuvant treatment of severely crushed legs with critical local ischemia.

Hyperbaric Oxygen in Lower Limb Trauma (HOLLT)
www.HOLLT.org/www.clinicaltrials.gov.
The Karolinska University hospital is presently one of the participating centers in an ongoing international multi-centre randomized (non-blinded) controlled trial investigating the potential for HBO to reduce complications and improve outcomes after lower leg injuries involving a fracture of the tibia with severe soft tissue injury. The trial, coordinated by the Alfred Hospital Trauma center in Melbourne Australia, now has 38 patients included. So far, april 2010, 12 Stockholm patients with severe lower leg fractures (Gustillo III) have been identified and randomized into the protocol. They receive standard trauma care, in accordance with local protocols, or standard care plus a course of 12 HBO sessions, commencing as soon as possible after the initial surgery and continuing twice a day for three days and then once a day for 6 days. The surgeons are blinded as to treatment allocation until after first trauma surgery. Radiological examination will be carried out by blinded assessors and unlike the Bouachour trial (1996) we have a 2-year “long-term” follow up including questionnaires such as. SF 36 quality of life. Inclusion of patients is slow because on average one patient every 2–3 months fits the inclusion criteria in large cities with modern safety standards such as Stockholm and Melbourne.

Critical assessment and conclusion: Severe Ischemic Conditions

- The evidence level (see page 40) can be classified as 3, as only one small well-designed randomized study exist to support the use of HBO therapy in crush injuries, and other prospective randomized studies and cohort studies are limited in design. Overall, there is little firm evidence from well-conducted studies for the broad group of "severe acute ischemic conditions". The same can however be said for any other therapy. Treatment recommendation = B-C.
- A majority of panel members can consider the rationale for HBO from a patho-physiological standpoint compelling and logical but not proven. The panel noted some support from experimental studies.
- Any use of HBO should be considered 'under investigation' until more data are available, and no clear recommendation to administer HBO as an adjunctive measure can at present be issued. A minority of panel members saw the evidence grading differently.
- More rigorous studies with improved methodological design in different settings and examining more varied outcomes are required to provide more generalized evidence to confirm a positive effect and the panel agreed that any final judgment should be reserved until more conclusive evidence is available. It was noted that an adequate randomized study on lower limb crush injury is presently recruiting patients.
- The panel agreed that systematic longterm follow-up studies are needed. Consideration should be given to establish a large national (probably multinational) prospective cohort study including centers with expertise and experience with these infections both with and without adjunctive HBO.

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7.7 Severe Necrotizing Soft Tissue Infections-Gas Gangrene & Fasciitis/ Myosiitis

General

Severe, **Necrotizing Soft Tissue Infections (NSTI)** are vicious because of the rapid progression of tissue necrosis, systemic toxemia, septic inflammatory response and multi-organ failure. NSTI is a dramatic and life-threatening illness but the speed, depth of invasion and outcome depend on the virulence of the bacteria and the host defense. NSTI requires expert surgery and critical care with appropriate antibiotics (Endorf et al 2009). Those who survive these devastating infections usually have significant morbidity, frequently undergoing multiple surgical debridements and possibly even amputation. Hospital costs alone are substantial with mean costs reported from 60,000 to 115,000 USD (Endorf et al 2008, Widjaja et al 2005).

Mortality rates of 20% to 40% are still reported even in relatively recent published case series including early aggressive surgical intervention and a multidisciplinary approach to treatment, with little evidence of a substantial improvement over the last forty years (Jallali et al, 2005, Levine and Manders 2005, Endorf et al 2008, Bennet et al 2009).

Gas gangrene (Clostridium myosiitis/myonecrosis) is caused by anaerobic, spore-forming, bacteria from the *Clostridium species*, with Cl. *Perfringens type A* found in 95% of cultures (Bakker 2002a). *Clostridium* spores are everywhere and can be found in the majority of open trauma wounds. With low tissue PO_2 they may start a vicious circle and kill the host. Among 20 exotoxins, alpha-toxinis is the most lethal being profoundly hemolytic and tissue-necrotizing, liquefying muscle and causing renal tubules necrosis. The result is profound hypoxemia and fatal septic shock.

Necrotizing fasciitis (NF) /myosiitis is a rapidly progressive, life-threatening, deep-seated soft tissue infection. Rapid bacterial proliferation in the fascia is followed by leukocyte infiltration and tissue death and in worst cases with involvement of the muscle (myosiitis/ myonecrosis). Progressive thrombosis of the blood vessels in the fascia leads to occlusion of the perforating skin vessels and secondary cutaneous ischaemia and gangrene (Bakker 2002b). Bacterial endotoxins, exotoxins and protease enzymes degrade fat and the extracellular matrix, resulting in rapid and extensive tissue damage and severe systemic toxicity. Streptococcal myosiitis, with severe systemic toxicity, is difficult to distinguish from clostridial myonecrosis (gas gangrene). In media alerts the *Streptococcus pyogenes* bacteria *(group A Strep.)* is often named “flesh-eating” or “killer bug”. In clinical medicine terms such as “streptococcal toxic shock syndrome” is used.

Necrotizing fasciitis has been subdivided into type 1 polymicrobial NF, and type 2 *group A streptococcal* necrotizing fasciitis (Levine & Manders, 2005). The *streptococcal* group of bacteria seems to play a very important role in fasciitis producing a rapidly spreading hypoxic inflammatory milieu into which many other bacterial species can invade. However, the whole population of mixed aerobic-anaerobic bacteria can be found in wound cultures but

and there is synergy between the bacteria in mixed infections. The facultative aerobic organisms lower the O_2 tension and redox potential of the tissue, which promotes an environment for anaerobic organism growth. The anaerobic organisms impede phagocyte function in the host immune response, which favors aerobic bacterial growth. These infections can also produce exotoxins such as enzymes that destroy tissue constituents (hyaluronidase, proteinase, collagenase) and allows for movement along fascial planes or toxins that cause localized coagulation (coagulase) (Bakker 2002b).

Necrotizing fasciitis may arise in any anatomical location and may be labelled specifically. "Cervical necrotizing fasciitis", begins with a dental infection or tonsillitis/peritonsillitis and may cause a threatened airway. The infection may spread along fascial planes into the mediastinum "mediastinitis", up towards the base of the skull or out to the extremities or on to the torso. In the perineum, Jean-Alfred Fournier 1883 gave name to the process "Fournier's gangrene" which often strikes the diabetic compromised host following an anorectal or cutaneous infection. It often starts with a red and swollen scrotum and a diagnostic "black spot", a necrosis of the overlying skin. The infection very rapidly spreads along fascia planes on the abdominal and gluteal regions requiring aggressive, extensive and repeated debridement. Early tissue biopsies give almost 100% streptococcal cultures in Fourniers gangrene although it is often referred to as type 1, "polymicrobial" necrotizing fasciitis (Bakker 2002b).

The typical patient has a history of some kind of surgery or trauma - sometimes just a day or two before the onset of symptoms. Host related factors such as diabetes, peripheral vascular disease, malignancy, malnutrition, IV drug use, alcoholism, etc. also contribute to the initiation and progression of disease. The initial presentation of soft tissue infections can be non-specific but often includes localized pain (dolor) out of proportion to the wound. Heat (calor), redness (rubor), and swelling (tumor) are the other classical local signs of inflammation. Eventually, there may be bullae or blister formation, exudates and crepitation and the skin may turn red to purple. The presence of crepitation, and/or radiographic evidence of gas in the subcutaneous tissue, does not necessarily mean anaerobic clostridial gas gangrene since there are many other gas-producing organisms. Systemic signs may include high fever with an altered mental status that can rapidly deteriorate; tachycardia, hypotension and shock with hemodynamic collapse followed by multi-organ failure and other signs of systemic toxicity and generalized inflammatory response. Early lab values can show metabolic acidosis, leukocytosis, anemia, thrombocytopenia, coagulopathy, myoglobinemia and myoglobinuria, and liver or kidney dysfunction, especially when the muscles are engaged. The progression to life threatening necrotizing infection can be very rapid (hours).

If not recognized early and treated aggressively with empiric antibiotic therapy and surgery, these infections can rapidly progress to septic shock, multi-organ failure and death. The different anatomical regions bring many specialists together for a multidisciplinary approach to produce best results.

Treatment

HBO have been claimed to be the cornerstones of therapy for this potentially devastating

condition for over half a century together with aggressive, early tissue-saving debridement's along with broad-spectrum antibiotic therapy directed at presumed causative agents. Surgical treatment includes excision of necrotic fascia, compromised skin and subcutaneous tissue and multiple debridements within the first days. Tissue saving surgery is preferred and generally recommended. Old "war-time surgery" such as excision of all subcutaneous tissue, "down to fascia" even when not necrotic or amputation, cause significant morbidity. Amputation may sometimes still be used in catastrophies or in the individual patient to save lives. No double-blind prospective controlled studies exist and adjunctive HBO as part of the protocol in NSTI is still controversial.

The potential therapeutic benefits of HBO, given once or twice per day, are related to O_2 diffusion via the blood into the vicinity of injured or infected hypoxic tissues (Korhonen 2000). HBO intermittently alleviate tissue hypoxia and restores cellular metabolism and host immune defences and the bactericidal effect action of various antibiotics, e.g. aminoglycosides is augmented (Park et al 1992). HBO helps marginally viable tissues survive and establish a demarcation line between necrotic and viable tissues (Bakker 2002a,b). HBO also exerts secondary pharmacological effects on inflammation and wound healing.

Brummelkamp, Boerema and co-workers in Amsterdam (1961) first reported the use of HBO in the treatment of gas gangrene. In the first textbook on HBO, chapter "Current therapy of gas gangrene", (Heimbach et al 1977) HBO treated case series of over 800 cases showed an overall mortality rate of 22–27% and a case fatality rate from the primary infection of 13–15%. They concluded that HBO as an adjunct to the multi-organ, intensive care approach, resulted in a dramatic increase in the number of lives and the amount of tissue that can be saved. The Swedish experience 1964–1977 from Lund University hospital of 30 gasproducing infections treated with HBO gave a 15% mortality in the group of clostridium infections; 2 patients died out of 14 cases and 6 were amputated (Tönjum et al 1980).

In gas gangrene HBO has been claimed to be more important than surgery initially because tissue PO_2 over 30 kPa stops Clostridial alpha-toxin production which inhibits their systemic effects, improving cardiovascular status and the patient's general condition (Bakker 2002a). Rapid initiation of HBO with a minimum of 3–4 HBO sessions in the first 24–48 hours get the infection under control and the patient can be brought out of shock. Conservative surgery aimed at reducing oedema related compression with ischemia and hypoxia by e.g. fasciotomies is combined with subsequent debridement of dead tissue only so that amputation can be more conservative or may be avoided (Bakker 2002a). In the original Dissertation by Bakker 1984 totalling 409 cases of clostridial gas gangrene, mortality was 12% with the worst outcome seen in referrals and all 48 patients who died did so within the first 26 hours. Primary HBO before primary surgery reduced amputation rates from 50% to 18% (Bakker 2002a).

In necrotizing soft tissue infections such as Fourniers gangrene the addition of HBO, as part of a well-functioning multidisciplinary program of surgery and antibiotics, was also introduced in the 1960s. Encouraging results have been reported for decades (Bakker 2002b, Clark & Moon 1999, Elmqvist Stenberg et al 2004, Escobar et al 2005, Hirn 1993, Jallali 2005, Larsson et al 2009, Wilkinsson 2004, Zamboni et al 1997). Yet, HBO remains con-

troversial as there are no large controlled prospective cohort- or randomized study trials demonstrating its efficacy. The same can however be said for any other therapy.

In a progress report of a Cochrane review (Bennet et al 2009), included as an addendum to this report and available as video presentation from an international conference in Stockholm (www.hyperbaricoxygen.se), the clinical evidence for the effectiveness of HBO in the treatment of necrotizing fasciitis was recently examined. Mortality rates ranging from 6% to 76% were seen in historical controls (NSTI cohort studies) contrasting with HBO case series with generally lower mortality rates (range 0 to 43%). Nine clinical comparative trials were identified, published over a 20-year period between 1985 and 2005, in total including data on 330 patients, 187 receiving HBO and 143 controls. A meta-analysis of these nine individual studies is shown in Fig. 4 (addendum 2). Out of 187 cases treated with HBO 33 died (17.6%), versus 49 dead (34.3%) in 143 controls. This difference is statistically significant and they conclude that the weight of evidence favors the application of HBO for necrotizing soft tissue infections.

The authors recognize that the overall result should be interpreted with caution due to the lack of prospective cohorts or randomized studies. Since the designing and execution of randomized controlled trials is highly problematic in this area they urge that consideration be given to establishing a large multicoated (probably multinational) prospective cohort study including centers with expertise and experience with these infections both with and without adjunctive HBO. A carefully prepared prospective data collection would likely provide a useful guide to practice and take away some of the biases possible in the data presently available.

HBO protocol

Patients with fasciitis/ myosiitis are treated at 2,8 bar pressure for 110 minutes, 2–3 times/ day in the first 24 hours, after that 1–2 times/day depending on clinical improvement. Patients with clostridium infections may initially be HBO treated more aggressively than other NSTI infections, and HBO may be given prior to surgery, but each case is individually assessed.

Additional clinical considerations

Clostridial myonecrosis or "gas gangrene, has historically, been associated primarily with combat injuries. Clostridium spores are everywhere and can be found in the majority of open trauma wounds. Yet, this is now an uncommon infection. With low tissue PO_2 these clostridium spores may start a vicious circle and kill the host. Anaerobic bacteria such as Clostridium require a lowered partial pressure of O_2 or decreased tissue redox potential to survive. These species can thrive within contaminated wounds with crushed, necrotic and ischemic edges. War time surgery has taught us to leave dirty wounds open. Historically Karolinska Institutet was founded in 1810 on a Royal decree to quickly train Army Surgeons working among wounded soldiers in the field, after the terrible losses suffered by the Swedish army during the 1808–1809 Finnish War against Russia. Gas gangrene, historically also associated with 1st world war "trench foot", is nowadays very rare but the prognosis is still bad since it often hit the compromised patient.

Morbidity in necrotizing soft-tissue infections: Difference in patients treated at burn centers and nonburn centers. Endorf et al 2008 investigated the referral patterns and difference in mortality for 10 940 NSTI patients treated at burn centers and nonburn centers 2001 to 2004. They used an American national inpatient database from 37 states, and ICD 9 codes for necrotizing fasciitis, gas gangrene, and Fournier's gangrene. Mortality in 1409 NSTI patients treated in specialized American burn centers, related to number of organ systems in failure, was 5% (zero), 27% (one), 41% (two) and 77% (three or more organ failures). In comparison, 9531 patients treated for NSTI at nonburn centers had 4, 17, 39 and 48 % mortality, respectively. Surprisingly, there was a *significantly poorer outcome in the burns center groups*, which the authors suggested to be attributable to greater severity of infections in a higher risk population at the burns centers. Patients at burncenters were more likely to have been transferred from another institution and statistics showed that those patients were worse off compared to patients admitted directly to the burns centers. Patients treated at burn centers had significantly more surgical procedures, longer total length of stay (22.1 vs 16.0 days) and higher hospital charges ($101,800 vs $68,500).

Cervical necrotizing fasciitis (CNF) begins with a dental infection or tonsillitis/peritonsillitis and the threatened airway and difficult anatomical region brings many surgeons and anesthesia/intensive care specialists together. Cervical necrotizing fasciitis is a serious, rapidly progressive infection along fascia planes that sometimes involves skin, subcutaneous and muscle tissue with a relatively high mortality rate of up to 25 % or more.

We have previously reported the outcome of the first 13 cases- all survived (Elmqvist Stenberg et al 2004). We have recently enlarged the material to 52 patients treated with HBO according to these guidelines at the Karolinska University hospital from 1998 to 2008 (Larsson et al 2009). Medical charts were retrospectively analyzed in 31 males and 21 females; age 19 – 89 (mean 52±16) with 48 of the 52 patients treated in the intensive care unit. Forty-nine of the fifty-two patients recovered, all deaths were in the intensive care group. *Streptococcus milleri* group *bacteria* were the predominant pathogens found in initial tissue cultures.

Streptococcus pyogenes bacteria, in media alerts often named "flesh-eating" or "killer bug" and in clinical medicine terms like "streptococcal toxic shock syndrome" is used. The anaerobic *streptococcus Milleri* group bacteria found as part of the normal flora in the mouth, throat, GI tract and genital tract also produces toxins, inflammation (Fujiyoshi et al 2001) and toxic shock-like syndrome and is, according to the Karolinska experience also commonly found in cervical necrotizing fasciitis (Elmqvist Stenberg 2004). Analyses of tissue biopsies from patients with necrotizing fasciitis reveal massive recruitment of neutrophils and monocytes to the infectious site further compromising oxygenation. Soluble M1 protein of *Streptococcus pyogenes* triggers potent T cell activation and the hyperinflammatory response (Påhlman et al 2008). This may contribute to the profound pathophysiological consequences seen in severe streptococcal infections.

The intensive care patients had an APACHE II score of 3-37 (mean 16±8), a mean time on ventilator 12 (±11) days, 34/48 (71%) were treated with inotropic drugs and 8/48 (16,7%) with inotropic drugs and dialysis. Mean length of stay in intensive care in Karolinska University Hospital was 16,6 (±18,6) days. Expected mortality rate according to APACHE II score for septic patients would have been 26 %, our 90 day mortality rate was 6,2 %. Our case series demonstrates that patients with CNF treated according to the Karolinska Hospital guidelines including HBO have an outcome with a 90 day mortality considerably lower than that indicated by their APACHE II score (Larsson et al 2009).

Similar experience with better than expected statistics using HBO in a multidisciplinary protocol has been reported from Copenhagen (Skovsen et al 2010). They found a reduced mortality in 85 consecutive patients treated 2005-2007, 6% ICU mortality and 9.5 % one-month mortality as compared with the expected 38 % mortality from SAPS II and APACHE II scoring.

These results are particulary interesting in view of the high mortality rates in other studies of NSTI despite treatment at specialty care facilities such as burn centers (Endorf 2008). Patients treated at Stockholm and Copenhagen regional trauma, HBO centers were also more likely to have been transferred from another institution with higher severity of infections, at a later stage of the disease when previous surgical and antibiotic treatment regimens had failed.

Karolinska multidisciplinary HBO protocol for NSTI. Although at Karolinska, the general surgeon is “soft-tissue infection leader” (c.f. trauma leader), other specialists soon take over the responsibility. ENT surgeons are familiar in the surgical exploration of infections in the head and neck region. They work closely with thoracic, neuro- , orthopedic and plastic-reconstructive surgeons when the infection spreads into the mediastinum “mediastinitis”, up towards the base of the skull, out to the extremities or the torso. Urologists and gynecologists are often involved in their field of interest. Karolinska University Hospital has since 1995 used multidisciplinary agreed upon guidelines to ensure rapid recognition of the diagnosis and treatment of these patients. The guidelines advocate a multidisciplinary approach with diagnostic cultures; antibiotics (imipenem/cilastatin and clindamycin and, if in septic shock, one dose of gentamicin); early extensive, tissue-saving debridement; HBO therapy for intermittent oxygenation of infected hypoxic tissues and frequent CT scans to assess the need for repeated surgical intervention.

Critical assessment and conclusion; Severe necrotizing soft tissue infections- gas gangrene & fasciitis/ myosiitis

- The evidence level (see page 40) can be classified as 3, with treatment recommendation = B-C, as no well-designed randomized study exist, and will likely not be undertaken soon, and there is a lack of common "nomenclature and disease specification".
- Overall, there is little firm evidence from well-conducted studies to support the use of HBO therapy for severe necrotizing soft tissue infections-gas gangrene and fasciitis/myosiitis. The same can however be said for any other therapy.
- We only have access to a large number of case series, and a few clinical comparative trials, which suggests there may be an overall benefit of the application of HBO pre- and postoperatively in gas gangrene and postoperatively in other necrotizing soft tissue infections as part of an aggressive resuscitation program including surgery and broad spectrum antibiotics.
- A majority of panel members can consider the rationale for HBO from a pathophysiological standpoint compelling when a clostridium infection is present, and logical but not proven in other NSTI infections. The panel noted some support from experimental studies.
- Any use of HBO should be considered 'under investigation' until more data are available, and no clear recommendation to administer HBO as an adjunctive measure can at present be issued. A minority of panel members saw the evidence grading differently.
- More rigorous studies with improved methodological design in different settings and examining more varied outcomes are required to provide more generalised evidence to confirm a positive effect and the panel agreed that any final judgment should be reserved until more conclusive evidence is available.
- The panel agreed that systematic longterm follow-up studies are needed. Consideration should be given to establish a large national (probably multinational) prospective cohort study including centers with expertise and experience with these infections both with and without adjunctive HBO.
- The utilization of common nomenclature and datasets by the various regional subspecialty databases will facilitate the eventual linking of these databases and the creation of a comprehensive database that spans conventional geographic and subspecialty boundaries.

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7.8 Intracranial Abscess

General

The disorders considered in treatment of intracranial abscess include spontaneous, traumatic and postoperative brain abscesses as well as subdural and epidural empyemas. Adequate abscess drainage and appropriate antimicrobial therapy remain the cornerstones of proper treatment of this condition. In the absence of controlled clinical trials, the choice of antibiotics for the treatment of brain abscess is based on the antibacterial spectrum of the agents available, the ability of such agents to penetrate into the abscess, and the findings of case reports and some retrospective clinical studies (Jansson et al 2004).

Despite modern diagnostic tools, surgery and antibiotics, abscesses and empyemas still have very serious prognosis: death in 5–30% and mild to moderate morbidity up to 54% of the survivors (Jansson et al 2004, Tonon et al 2006, Carpenter et al 2007, Gutiérrez-Cuadra 2009). Hampson (2008) found an average mortality of 20%, when summing up 21 studies from 1981 onwards, with a trend towards a decrease in death rate. Mortality is 79% in fungal cerebral zygomycosis infections (Roden et al 2005).

HBO treatment

HBO has multiple mechanisms that may be of value (cf 5.8) for intracranial abscesses where there is a sub-optimal efficacy of standard therapy in hypoxic, acidotic tissues. HBO oxygenate tissues and can help reduce increased intracranial pressure and perifocal brain swelling. HBO can help prevent anaerobic bacterial growth, improve neutrophil oxidative killing, improve antibiotic function and get infection control from the organisms commonly found in this difficult to treat condition.

Kutlay et al (2005) reported a prospective study on stereotactic aspiration combined with antibiotic and HBO therapy. They achieved infection control and healing for all 13 patients with 0% recurrence rate with average follow up of 9,5 months. Kurschel et al (2006) reported successful outcome in 5 children with brain abscesses. Hampson (2008), doing a literature review, reported one death (1,5 % mortality) in a total of 66 cases of cerebral abscesses treated with HBO.

In view of the high mortality and morbidity reported in the literature, an intracranial abscess is an accepted indication in the UHMS guidelines (Hampson 2008). Candidates for HBO are patients who have multiple abscesses, who have an abscess that is in a deep or dominant location, whose immune systems are compromised, in whom surgery is contraindicated, who are poor candidates for surgery, and who exhibit inadequate response despite standard surgical and antibiotic treatment. These recommendations are used by the Centers for Medicare and Medicaid Services and other third party payers in USA for determining reimbursement.

The Karolinska experience of 56 consecutive intracranial abscesses treated with HBO was recently presented at the Oxygen & Infection Conference in Stockholm, May 2009 (Mat-

hiesen et al 2009). The mean age was 47 years, with children down to one year included. One fourth had spontaneous or traumatic origin the rest were postoperative complications. The addition of HBO to standard therapy was found to be very effective with a rapid clinical improvement and with little side effects, but for the risk of barotrauma encountered in one patient. The 6-month mortality was 0 % with no severe morbidity and only one case of moderate disability. In addition, 10 spinal / epidural empyemas were successfully treated with infection control and no mortality. However, our results should encourage a prospective observational trial together with other regional neurosurgical centers in Sweden and abroad.

HBO protocol

Patients with cerebral abscesses are treated at 2,5–2,8 bar pressure for 100 minutes, 1–2 times/day, usually for up till 10–20 sessions, occasionally more. The course of HBO sessions is individualized depending on the clinical history, clinical response as well as radiological findings, the pathogen found, available effective antibiotics and whether osteitis or foreign material is present.

Additional clinical considerations

Antibiotic or antimycotic therapy recommendations is based on knowledge of the likely pathogens, the antimicrobial spectrum of available agents, their penetration into the abscess fluid, and individual reports of efficacy of antimicrobial regimens. No double-blind randomized clinical trials have compared the efficacy of different antibiotics for treatment of brain abscesses. The clinical documentation up to now relies on case reports and some retrospective clinical studies in which patients are given several different treatments (Jansson et al 2004). Prospective controlled trials of antibiotic therapy for brain abscesses are unlikely to be undertaken. Since the disease is rare, it is not likely there will be a sufficient number of patients to enroll in a clinical trial that will be able to detect differences between treatment regimens with a reasonable magnitude of statistical power. The same can be said for HBO where it would also be ethically difficult to perform a hyperbaric sham control in these very sick patients.

HBO in fungal intracranial abscesses. Zygomycosis or mucormycosis with cerebral involvement is a rare but increasingly frequent life-threatening infection caused by opportunistic fungi of the class Zygomycetes (e.g. Mucor). It causes an infection of the vessel wall of various organs in immunocompromized patients including those with poorly controlled diabetes, trauma/burns, organ transplants and hematological malignancies and neutropenia. Aggressive surgical debridement of all infected tissues and lengthy administration of antifungals (Amphotericin B) is standard therapy. Mortality is 62% with rhinocerebral zygomycosis and 79 % with cerebral zygomycosis (Roden et al 2005).

HBO is used as an adjunctive treatment for zygomatosis due to the sub-optimal efficacy of standard therapy in hypoxic, acidotic tissues. John et al (2005) reviewed a few small case series and found a high rate of survival (86%) among the 28 HBO treated patients published, of which 21 (75%) had rhinocerebral involvement. They also found a higher rate of survival after prolonged courses of HBO (median 24 HBO sessions, range 9–85). The very good

results may in part be due to publication bias and survival bias, respectively. They conlude that HBO offers a theoretically promising approach for the treatment of zygomycosis and that additional studies are required to assess the optimal timing and dose of HBO (John et al 2005).

Another recent review concluded that, although there appears to be a scientific rationale for adjunctive HBO in the treatment of zygomycosis, the clinical evidence is only anecdotal and does not allow for conclusions about its general clinical efficacy, nor about host- or disease specific conditions of patients who may benefit from it (Tragiannidis & Groll 2009).

Critical assessment and conclusion – Intracranial abscess

- The evidence level (see page 40) can be classified as 3, with treatment recommendation = C, as no randomized study is available, and only a few cohort studies support the clinical effect of HBO.
- A rationale from a pathophysiological standpoint can be argued. Thresholds for initiating HBO-therapy and the size of this effect remains unclear and continue to leave room for opinionated statements.
- Any use of HBO should be considered ‘under investigation’ until more data are available, and no clear recommendation to administer HBO as an adjunctive measure can at present be issued. A minority of panel members saw the evidence grading differently.
- The panel agreed that more rigorous studies with improved methodological design in different settings and examining more varied outcomes are required to provide more generalised evidence to confirm a positive effect and that any final judgment should be reserved until more conclusive evidence is available.
- The panel agreed that systematic long-term follow-up studies via a national database are needed in general to improve the quality of care for these patients. Consideration should be given to establish a large national (probably multinational) prospective comparative cohort study including centers with expertise and experience with these infections both with and without adjunctive HBO.

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7.9 Acute Cranial Osteomyelitis, Chronic Refractory Osteomyelitis, Infected Implants

General

Osteomyelitis is an infection of the bone and /or bone marrow that remains difficult to treat. It is a complex disease that is often associated with high morbidity and considerable health care costs. The extremities with the long bones of tibia and femur and the foot (especially in diabetic patients) are common sites for osteomyelitis. Cranial, spinal, mandibular and sternal osteomyelitis also deserve special attention since their anatomical location may lead to difficult and life threatening infections. Bacteria reach bone through the bloodstream (bacteremia) or secondary to a contiguous focus of infection such as penetrating trauma, or surgery. Contiguous-focus osteomyelitis is commonly seen in patients with diabetes mellitus and often involves polymicrobic infections in the feet, while hematogenous osteomyelitis often occurs in the long bones, commonly in children.

Bone necrosis and bone destruction occur early in the course of osteomyelitis, leading to a chronic process and eliminating the host's ability to eradicate the pathogens. The presence of poorly vascularised tissues, the adherence to bone structures and implants, and a slow bacterial replication rate are recognized as important factors for the persistence of the infection. The gold standard of diagnosis for osteomyelitis is to obtain a biopsy specimen and culture it for the infecting organism. One species in particular, *Staphylococcus aureus*, is able to cause an acute bone infection even with a low inoculum. Through its arsenal of virulence factors and aided by its ability to develop antibiotic resistance rapidly, S. aureus progresses to a chronic, biofilm-mediated infection (Costeron 2005, Brady et al 2006).

Wound infections remain the most frequent and costly complications of surgery. Once a chronic infection develops, bacterial clearance cannot be attained by the host immune system or antimicrobial therapy. At this point, surgical removal of the implant or focus of infection is “gold standard” usually necessary for complete infection resolution. Antibiotic treatment is usually started on an empiric basis and then modified according to the results of cultures and sensitivity tests. Surgical treatment is often staged and consists of debridement, obliteration of dead space, adequate soft tissue coverage, restoration of blood supply, and stabilization (Lazzarini et al 2002, Calhoun & Manring 2005).

Treatment of acute cranial or spinal osteomyelitis is particularly challenging and involves adequate antimicrobial therapy and rapid surgical debridement of all necrotic tissues and urgent implant removal due to the risk of spread of the infectious diseases into the nervous system. Following craniotomy, the bone flap is devascularized and devitalized and at increased risk for infection. The standard of care for post craniotomy infections includes antibiotics, repeat craniotomy with removal of bone flap/implant and secondary reconstruction with acrylic implant which involves two major additional surgeries. Spinal infections require antibiotics, repeated surgical debridement and lavage without removal of implanted hardware in most circumstances due to instability. This makes it more difficult to eradicate the infection. Malignancy, radiation therapy, chemotherapy, repeated surgery, tissue transplants and

implants can create an environment where the tissue is hypoperfused and hypoxic, which is fertile ground for infection and makes treatment even more difficult.

HBO treatment

Chronic Refractory Osteomyelitis

The first reports on beneficial therapeutic effects with the use of HBO in chronic refractory osteomyelitis stem from the 1960´s (Slack et al 1965) followed by in vitro and in vivo experimental research uncovering its many mechanisms (see 5.6 above). The decreased oxygen tensions found in infected bone may be elevated to normal or above-normal bone oxygen tensions by HBO (Mader et al 1980, Niinikoski & Hunt 1972). Oxygen tensions above 4–5 kPa are necessary for neovascularization in an ischaemic environment, and neutrophils also require similar levels of tissue oxygen to destroy bacteria by oxidative killing mechanisms.

While no randomized clinical trials exist, the majority of published human case series and prospective trials support HBO as a safe and adjunctive therapy in the management of chronic refractory osteomyelitis (Hart 2008, Lentrodt et al 2007). Goldman (2009) after reviewing all data found that HBO is associated with remission of about 85% of cases of refractory lower extremity osteomyelitis, but that a randomized controlled trial is lacking to clarify extent of effect. He concluded that there is moderate evidence that HBO, in combination with a comprehensive program of surgery and antibiotics, promotes remission and healing in chronic osteomyelitis. The use of HBO in chronic refractory osteomyelitis of the sternum and other locations than the lower extemities has also been reported (Shields et al 2010). The theory and limited clinical evidence supporting the role of HBO therapy in the treatment of acute or chronic sternal wound infections have recently been reviewed (Mills and Bryson 2006).

Acute Cranial Osteomyelitis

Since 1996, some 200–300 patients have been treated with HBO at the Karolinska University Hospital for neurosurgical infections as an adjunct to antibiotics and, if possible, in order to avoid repeat surgery.

The first 36 consecutively HBO treated patients were published in 2002 (Larsson et al 2002), recently republished by Neurosurgery 2009. A strict, “avoidance of surgery” criteria was used to define a positive outcome; Infection control and healing without removal of bone flaps or foreign material, with a minimum of 6 months of follow-up monitoring, were considered to represent success. Successful results were achieved for 27 of the 36 patients (71%), with a mean follow-up period of 27 months, including 23 patients who did not require removal of bone flaps/implants or a secondary reconstruction. A sub group analysis was done; In Group 1 (uncomplicated first time cranial wound infections), all infections resolved and 12 of 15 patients (80%) achieved healing with retention of bone flaps. In Group 2 (complicated cranial wound infections, with risk factors such as malignancy, radiation injury, repeated surgery, or implants), all except one infection resolved, 10 of 16 (62%) without surgical intervention, three of four bone flaps and three of six acrylic cranioplasties could be retained. In Group 3 (spinal wound infections), all infections resolved,

5 of 7 without removal of fixation systems. The two failures were not primarily attributable to poor HBO response. One patient with good HBO response left the hospital due to drug addiction and discontinued HBO treatment. The other patient was classified as failure because the fixation material was removed 4 months after HBO treatment, after healing of the wound and fracture, because of migration of the screws. There were no major side effects of HBO treatment. If clearance of infection alone would have been the outcome 35 of 36 (97%) patients had a positive outcome including a case of MRSA wound infection that could be cured by HBO therapy alone, without antibiotics. Side effects to HBO were minimal. It was concluded that HBO therapy is a safe medical treatment for postoperative neurosurgical cranial and spinal infections. It is an alternative to standard surgical removal of infected bone flaps. It is also a powerful therapy for more complex infections involving multiple risk factors, such as radiotherapy and foreign material. Our results indicate that HBO therapy can reduce the need for reoperations and can probably improve outcomes and reduce overall costs. (Larsson et al 2002, 2009).

In 2006 we doubled the material and evaluated and reported the first 72 consecutive patients treated for neurosurgical infections (Larsson et al 2006) with similar positive results.

HBO protocol

Patients with osteomyelitis are treated at 2,4–2,8 bar pressure for 100 minutes, 1 –(2) times/day in the total number of 30–40 sessions. Surgical procedures or delayed wound closure due to dehiscence may occasionally extend the series up to 60 sessions.

Additional clinical considerations

HBO is a safe and useful adjuvance in complex situations in the treatment of deep postoperative infections in paediatric "scoliosis" patients with neuromuscular spine deformity (Larsson et al 2011). Six consecutive children (age 1,5 to 16 years) with scoliosis and/or kyphotic deformities of the spine due to myelomeningocele with tethered cord developed postoperative infections in 2003–2005. The most common cultures from the location of the deep postoperative wound infection were *Enterococcus, Pseudomonas* and *Staphylococcus,* all typical slime-producing (biofilm) pathogens associated with implanted devices. These patients had long operative procedures with detethering of the spinal cord followed by correction of the spine deformity with extensive hardware implanted for stabilization. Removal of instrumentation or high pressure irrigation was not an alternative due to a destabilized spine, extensive intradural neurosurgical procedures and poor soft tissue quality. Litterature still reports severe functional deterioration from repeated surgery with long convalescent periods, and with our previous experience with infection control after HBO treatment of adult patients with infected spinal implants (Larsson et al 2002) HBO was added to the regime also in children.

With HBO added to antibiotic treatment according to their bacterial cultures as advised by specialists in infectious diseases, infection control and healing was reached in three months. Side effects of HBO treatment were minor. During the 3–6 year follow-up no removal of implants or major revisions were needed and radiological bony fusion was seen without any signs of loosening (Larsson et al 2011).

Long-term positive outcome after HBO treatment of bacterial spinal osteomyelitis in six patients was recently reported (Ahmed et al 2009).

Biofilm theory can guide the treatment of device-related orthopaedic infections (Costerton & Manring 2005). Adherent bacterial colonization is involved in the pathogenesis of osteomyelitis (Gristina et al 1985). Direct observations of the surfaces of orthopaedic prostheses that have failed and of bone affected by osteomyelitis, with and without the presence of prosthesis, have shown that the bacteria that cause these infections live in well-developed biofilms. The bacteria and fungi within these matrix-enclosed surface-associated communities are protected from host defenses and antibiotics, and clinical experience has shown that they must be removed physically before the infection can be resolved. The biofilm etiology of these diseases demands new diagnostic methods because biofilm cells typically do not grow on agar plates when recovered by scraping or swabbing (Costerton & Manring 2005). Cells within these sessile communities go through a phenotypic change that make them resistant to conventional antibiotics and they adopt a matrix-protected mode of growth that renders them almost immune to attack by antibodies or by phagocytes. It is suggested that much of the tissue damage in chronic biofilm infections is caused by "frustrated phagocytosis," and it is known now that inflammation in response to the presence of biofilms is a major cause of tissue damage in chronic infections (Costerton et al 1999). Certain bacteria rapidly form matrix-enclosed biofilms on available surfaces, with preference for inert materials and dead tissues. Once the biofilms have developed and matured, the clinician is faced with an implacable foe. The low doses achieved by systemic antibiotic therapy may alleviate symptoms caused by planktonic bacteria that leave the biofilms during acute exacerbations, but the sessile cells of the biofilm are not affected, and they continue to damage tissues by stimulating inflammatory reactions of the host (Costerton & Manring 2005).

Staph aureus and *Ps. aeruginosa* are typical, slime-producing (biofilm) pathogens, associated with osteomyelitis and implated devices and other chronic refractory infections. It has been shown in both *Klebsiella* and *Ps. aeruginosa* biofilm that the pO_2 approaches zero kPa when the O_2 diffusion distance of the biofilm becomes too great (Anderl et al 2000, Walters et al 2003). Animal experiments using microelectrodes to measure pO_2 in normal healing, infected tissues and in tissues containing foreign material have demonstrated marked hypoxia especially when infected foreign material was present (Silver 1977). During HBO, this biofilm diffusion barrier and hypoxic milieu protecting the bacteria from phagocytosis, can be overcome intermittently by improved O_2 transport and diffusion, and the effects of antibiotic agents can simultaneously be improved.

Critical assessment and conclusion: Acute Cranial Osteomyelitis, Chronic Refractory Osteomyelitis, Infected Implants

- The evidence level (see page 40) can be classified as 3, with treatment recommendation = C, as no randomized study is available, and only a few cohort studies support the clinical effect of HBO.
- A rationale from a pathophysiological standpoint can be argued. Thresholds for initiating HBO-therapy and the size of this effect remains unclear and continue to leave room for opinionated statements. The panel noted some support from experimental studies.
- Any use of HBO should be considered 'under investigation' until more clinical data are available, and no clear recommendation to administer HBO as an adjunctive measure can at present be issued. A minority of panel members saw the evidence grading differently.
- The panel agreed that more rigorous studies with improved methodological design in different settings and examining more varied outcomes are required to provide more generalised evidence to confirm a positive effect and that any final judgment should be reserved until more conclusive evidence is available.
- The prosecution of randomized controlled trials in neurosurgical infections with implants is highly problematic since golden standard states that they should be removed.
- The panel agreed that systematic long-term follow-up studies via a national database are needed in general to improve the quality of care for these patients. Consideration should be given to establish a large national (probably multinational) database (prospective comparative cohort study) including centers with expertise and experience with these infections both with and without adjunctive HBO.
- The utilization of common nomenclature and datasets by the various regional subspecialty databases will facilitate the eventual linking of these databases and the creation of a comprehensive database that spans conventional geographic and subspecialty boundaries.

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7.10 Hypoxic problem wounds

General

Chronic wounds, often leg ulcers, are a significant socioeconomic health care problem. This indication refers to selected patients with "chronic" refractory arterial insufficiency ulcers, that do not heal with standard wound care. They include calciphylactic or vasculitis ulcers which are often painful, necrotic and infected. Non-healing amputation stumps is another example of hypoxic, often infected, problem wounds. Surgeons try hard to amputate as far distal as possible to preserve function. HBO is generally not indicated for venous leg, decubitus or pressure ulcers where bandaging and off-loading remains crucial for successful outcome. Diabetic foot ulcers (7.3), irradiated skin ulcers (7.4), failing grafts and flaps (7.6) which are also "hypoxic problem wounds" are considered in separate sections above. Underlying osteomyelitis (7.9) must also be considered in chronic non-healing wounds.

A wound is an opening in the skin that does not heal with regular medical treatment. Wounds may fail to heal for a variety of reasons including the use of corticosteroids, smoking, persistent infection, persistent cancer, unrelieved pressure and underlying hypoxia within the wound bed. If left untreated or unhealed, wounds can turn into more serious conditions, which may require amputation or cause a life-threatening infection.

A fundamental clinical observation is that wounds do not heal in tissues that do not bleed, and they almost always heal in tissue that bleed extensively. Similarily, infections are rarely seen in well perfused regions of the mouth or anogenital regions despite wounding and worst possible bacterial contamination. Continuous supply of O_2 to the tissue through microcirculation is vital for the healing process and for resistance to infection. Hypoxia inhibits the wound healing process by blocking fibroblast proliferation, collagen production, and capillary angiogenesis (Hopf & Rollins 2007). Hypoxia also increases the risk of infection (Hunt & Hopf 1997).

Smoking, through its toxic constituent's nicotine, carbon monoxide, and hydrogen cyanide, cause tissue hypoxia, attenuates the neutrophil oxidative burst (Sørensen et al 2004), and may jeopardize wound healing and surgery (Jensen et al 1991, Silversten 1992) with post-operative infections and complications.

HBO treatment

Healing is O_2 dependent (Hunt & Hopf 1997) and HBO can oxygenate ischemic wounds. Infections which exacerbate tissue hypoxia may be treated. A series of HBO treatments can increase angiogenesis, fibroblast proliferation and collagen formation within the wound creating a rich vascular bed for healing with or without skin grafting (Thackham et al 2008).

One prospective randomized double-blind study has been published on chronic leg ulcers (Hammarlund and Sundberg 1994). In a small but well controlled group of patients with venous leg ulcers (n=16) treated weekdays at 2,5 bar for 90 min they found a 35.7% decrease in wound area after 6 weeks in the HBO group as compared with a 2.7 % decrease in the hyperbaric placebo air group (n=0.0004). No long-term outcome was given.

Numerous scientific reports, mostly cohort studies, have shown promising results with HBO in the care of selected compromised patients with complex hypoxic wounds (Gesell 2008, Hunt & Hopf 1997, Sheffield & Fife 2008, Zamboni et al 2003). Because the goals of HBO for wound healing include infection control, cellular proliferation and angiogenesis, HBO is generally carried out daily for a minimum of 30 treatments. In 2004, a Cochrane report did not find routine HBO treatment of chronic non-diabetic wounds justified without further scientific trials (Kranke et al 2004). In 2006, guidelines for the treatment of arterial insufficiency ulcers and diabetic ulcers, established by request of the Wound Healing Society in the USA, supported the use of adjunct HBO for ischemic diabetic wounds, but recommended further investigation for ischemic non diabetic ulcers (Hopf et al 2006). A recent evaluation of published clinical evidence on wound healing and limb salvage (Goldman 2009) found high level of evidence that HBO improves healing and reduces risk for amputation in diabetic foot ulcers; and moderate level of evidence that HBO promotes healing of arterial ulcers, calciphylactic and refractory vasculitic ulcers, as well as refractory osteomyelitis.

HBO protocol

Patients with hypoxic (infected) problem wounds are treated at 2,4–2,5 (2,8) bar pressure for 100 minutes, 1–(2) times/day, 5–(7) days per week in the total number of 30–40 sessions. Based on the response to therapy and surgical intervention, extended courses of therapy may be indicated.

Critical assessment and conclusion: Hypoxic problem wounds

- The evidence level (see page 40) can be classified as 3, with treatment recommendation = C, as only a small randomized study is available, and only a few cohort studies support the clinical effect of HBO.
- A rationale from a pathophysiological standpoint can be argued. Thresholds for initiating HBO-therapy and the size of this effect remains unclear and continues to leave room for opinionated statements. The panel noted some support from experimental studies.
- Any use of HBO should be considered ‘under investigation’ until more clinical data are available, and no clear recommendation to administer HBO as an adjunctive measure can at present be issued. A minority of panel members saw the evidence grading differently.
- The panel agreed that more rigorous studies with improved methodological design in different settings and examining more varied outcomes are required to provide more generalised evidence to confirm a positive effect and that any final judgment should be reserved until more conclusive evidence is available.
- The panel agreed that systematic long-term follow-up studies via a national database are needed in general to improve the quality of care for these patients. Consideration should be given to establish a large national (probably multinational) database (prospective comparative cohort study) including centers with expertise and experience in wound care practice both with and without adjunctive HBO.

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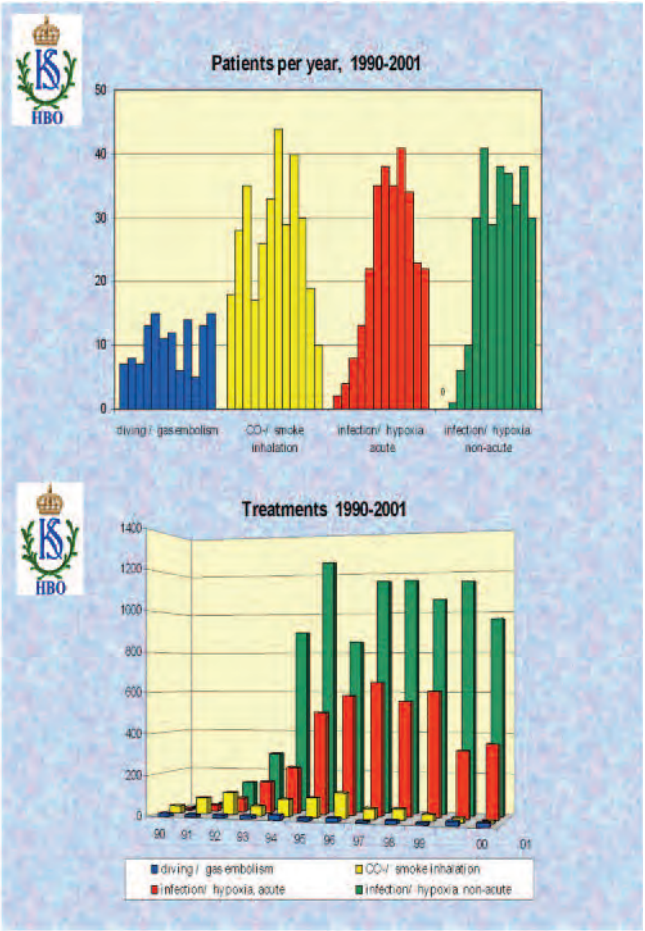
8. Clinical statistics, Stockholm

A hypo- and hyperbaric research chamber (Kockums) was built 1965 for research purposes for the clinical physiology department at the Karolinska hospital. HBO treatments began in the late 1960s as an occasional treatment for non critical care diving injuries or CO poisoned patients. Occasionally a comatose patient could be treated when anesthesia intensive care staff was available. The lack of standardized protocols, equipment and personnel led to suboptimal HBO availability and care.



The Department of Anesthesiology & Intensive Care assumed responsibility over the HBO facilities in the early 1990s. The development from 1990 until 2001 is given in the figure beside the text. Going from one to two Monoplace chambers in 2004 can be discerned in the number of non-acute patients and treatments given.

The clinical statistics from 2000 to 2008 in number of treatments per year for eight separate indications are given and briefly commented on below. Since 2003 we have carried out approx 3000 treatments per year for 130–140 patients of which 300 were intubated intensive care patients in the ICU chamber named NEMO.

The statistics has been split in two grafts; one contains indications where the main reason for HBO was to treat ischemia and hypoxia (fig 2); the other was to treat infection and hypoxia (fig 3). The ten indications reported above have been condensed into eight; the two radiation injury indications have been coupled into one, likewise the diabetic foot and hypoxic problem wound has been joined into one group.

8.1 HBO indications based on treatment of ischemia & hypoxia

Diving/gas embolism. The number of divers treated has remained more or less constant over the years. Despite a huge increase in sports diving, we still see only approximately 10 divers per year including one or two iatrogenic gas embolism. These often very young patients are treated as emergencies with an initial prolonged 5 hour treatment table. They require a very limited number of HBO treatments, often only one, making the number of treatments low and difficult to analyse in the statistics below. The occasional "bad outcome" involves drowning or severe iatrogenic air embolism with global anoxic brain damage. Approx 5–7 sport divers per year die in Sweden for this reason, most of whom never reach the hospital alive.

CO poisoning & smokeinhalation. The number of CO victims has decreased since its peak in 1996 when 44 patients were treated. This is a result of a decrease in suicide attempts using the car exhaust system since the catalyst of exhaust fumes was introduced reducing CO significantly, but may also be due to less referrals. Approx. 10 patients per year are referred nowadays, mainly fire victims, and often by helicopter transport. They usually receive three HBO treatments before being transported back to their referring hospital.

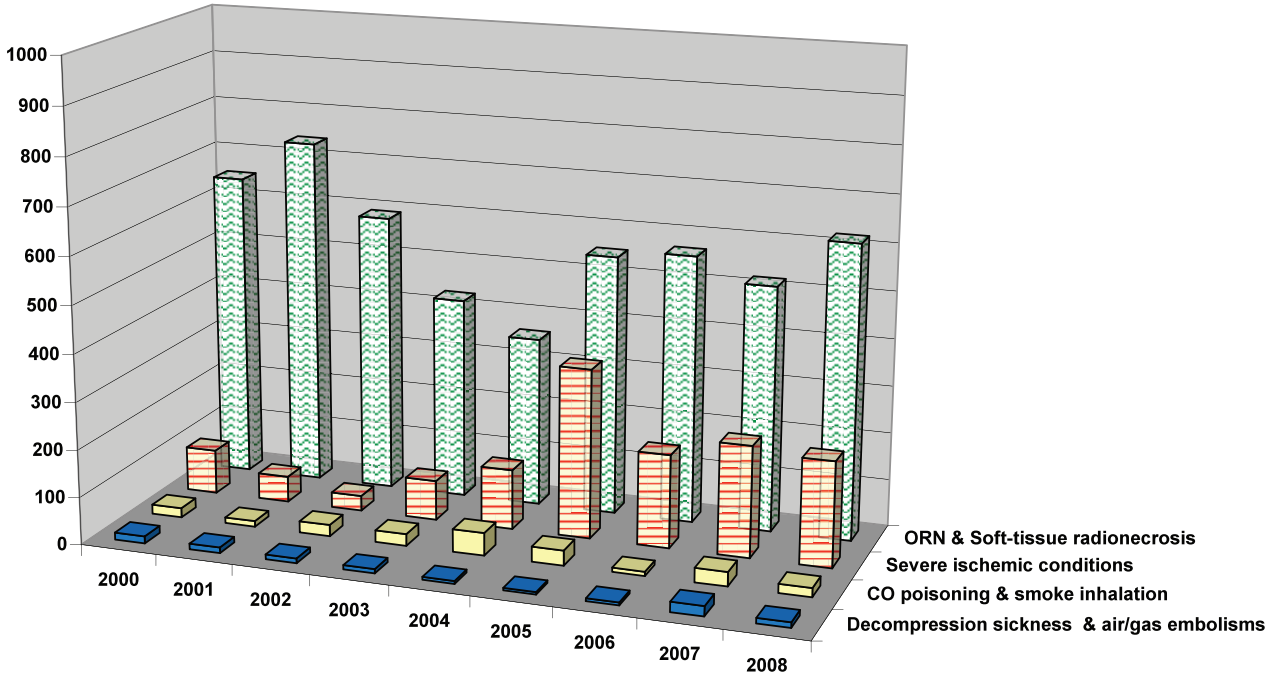


Fig 2. HBO indications based on treatment of ischemia & hypoxia

Severe acute ischemic conditions. This mainly surgical group of patients are like most emergencies referred from hospitals within the region with various types of trauma and postoperative complications, e.g. crush injuries, blast injuries, degloving injuries and failing flaps, has remained relatively constant over the years. On average one septic patient/child with "purpura fulminans" and life or limb threatening ischemia/ infection is treated per

year. Since 2007 we have been part of an international trial on severe open lower leg fractures with high-energy crush and /or vascular injury (HOLLT- Hyperbaric Oxygen in Lower Limb Trauma, see 7.6 above).

Osteoradionecrosis (ORN) & Soft-tissue Radionecrosis (Haemorrhagic Proctitis/Cystitis). These patients are typically "out-patients" with late radiation injury after cancer treatment with complications of the jaw, bladder or intestines or other problematic wounds of significant severity and socioeconomic costs. The number of patients and treatments has remained more or less stable over the years and many patients are not referred.

8.2 HBO indications based on treatment of infection & hypoxia

Diabetic foot ulcer & Hypoxic problem wounds. These patients are usually referred and treated as elective patients via an endocrinology or other specialist clinic. The orthopaedic specialist is often involved because of osteitis or minor amputations and revisions. They may start as in hospital patients if there is a severe soft-tissue infection. The number of patients and treatments has remained more or less constant over the years with only a few patients being treated annually.

Severe necrotizing soft-tissue infections. This remains the largest intensive care group of patients, since 1995 when we formally introduced the Karolinska multidisciplinary protocol for severe soft-tissue infections. Daily HBO treatments, 1-2 times over several days, give large number of HBO treatments compared with the occasional diver or CO poisoned patient. HBO is also logistically difficult to manage when there is need for surgical debridements, CT diagnostics, intensive care with inotropic and ventilatory support, and perhaps dialysis. The new large rectangular ICU chamber has improved safety and hygiene. It has saved valuable patient time and reduced personnel overtime considerably with its close proximity to the ICU and the possibility of treating more than one patient at a time safely. HBO treatments can also be given in a monoplace chamber if no ventilator, ICU inotropic support or "hands-on" requirements are needed.

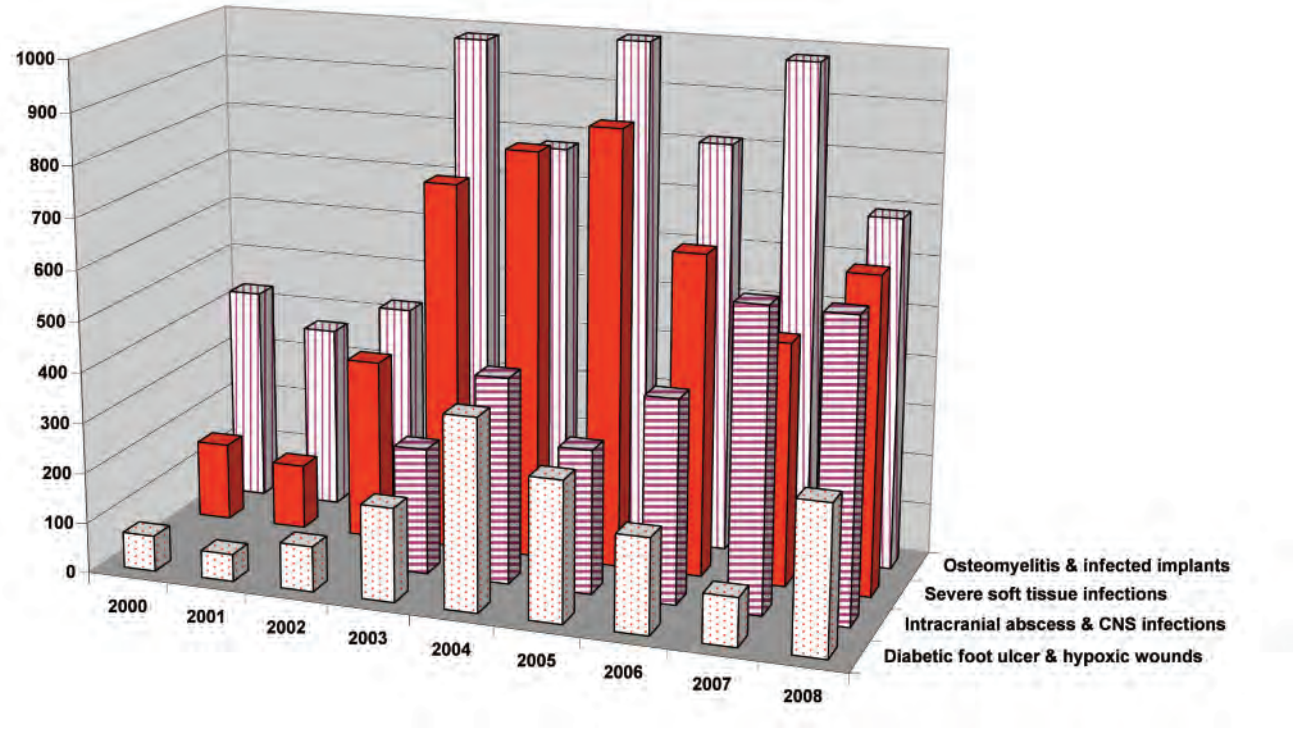


Fig 3. HBO indications based on treatment of infection & hypoxia

Intracranial Abscess. Since 2003 approx. 60 patients have been treated for severe infections in the brain or outside of the dura mater with exceptional clinical results. The majority are initially bed ridden and treated as "in-hospital" patients. The typical patient rapidly improve and can be treated as outpatients for the completion of the HBO series considered necessary for infection control.

Acute Cranial Osteomyelitis, Chronic Refractory Osteomyelitis, Infected Implants
Since 1996, some 200-300 patients, many of those being children, have been treated with HBO at the Karolinska University Hospital for neurosurgical infections as an adjunct to antibiotics and the possibility of avoiding repeat surgery. This includes refractory infections with antibiotic resistant bacteria, implants with biofilm producing bacteria, etc. The results were extremely good with little side effects and near to 100% infection control in the follow up material so far evaluated. In approximately 2/3 to ¾ of the material repeat surgery can be avoided and implants remain intact long term. Most patients are treated in Monoplace chambers, in the most part as outpatients.

9. Summary & Recommendations

As a therapeutic modality, Hyperbaric Medicine edges closer to the mainstream of modern medical practice. Laboratory investigations support the firm physiological basis for the utilization of HyperBaric Oxygenation (HBO). Recently published controlled and randomized studies provide the much needed clinical validation for some of the HBO indications and have therefore been labeled “recommended” but many indications, especially in the field of surgery, lack sufficient randomized clinical studies and has been marked HBO indications “under investigation”.
In this report it has been shown that there are several indications for treatment with HBO where sufficient evidence favors HBO in selected cases, either as a primary therapy or as part of a protocol including appropriate surgery, antibiotics etc. Specialist referrals are compulsory and the diabetic foot patient should for example firstly be assessed at and then referred through a comprehensive diabetic foot care clinic.

Recommended HBO indications

- Decompression Sickness and Air/Gas Embolisms
- Carbon Monoxide Poisoning and smoke inhalation
- Diabetic Foot Ulcers
- Soft-tissue Radionecrosis (Hemorrhagic Proctitis/ Cystitis)
- Osteoradionecrosis

HBO indications ”under investigation”

- Severe Acute Ischemic Conditions
- Severe Necrotizing Soft Tissue Infections (Gas Gangrene & Fasciitis/ Myosiitis)
- Intracranial Abscess
- Acute Cranial Osteomyelitis, Chronic Refractory Osteomyelitis, Infected Implants
- Hypoxic Problem Wounds

For historical reasons, there is continued controversy around the field of Hyperbaric Medicine. This is mainly due to the fact that the use of O_2 never entered the market and clinical medicine through rigorous clinical testing such as adequate trials and preclinical screening amongst other tools. This in turn may explain that lucrative HBO treatment can continue on many indications that lack adequate scientific support and where HBO is **not** indicated.

Not acceptable indications

- Sudden Deafness, Tinnitus, Migraine
- Cerebral Pareses, Autism, Multiple Sclerosis
- Heart- Brain- Spinal Infarcts
- Sports Injuries

However this aspect of Hyperbaric Medicine should not exclude HBO from serious discussions and rigorous testing, where evidence based medicine is possible to establish. A great deal of peer reviewed data has been published on the subject of Hyperbaric Medicine and a large number of laboratory investigations and randomized clinical trials are ongoing, but more funding, especially for clinical research is anyhow needed.

As in all areas of medicine, HBO activity should only be maintained on indications that can be documented by randomized clinical studies and in diseases for which there are limited alternative treatment options supported by good theoretical and experimental evidence, long-standing use and clinical consensus. On rare indications, e.g. where compassionate treatment is argued for critically ill patients, at least case-series should be collected for future reference with contrasting patient series from other medical centers. There are now data suggesting a benefit from health economic point of view on at least some indications for HBO. Among these, we note acoute osteomyelitis with or without implants (Larsson et al 2009, 2011) and diabetic foot ulcers (Abidia et al 2004, Cianci & Hunt 2008). Obviously, such data need to be further assembled and evaluated.

We, the authors, strongly recommend that the Stockholm County Council continue to insist on state-of-the-art clinical follow-up on all HBO activity sponsored by public funding. Development of national and preferably international databases for systematic long-term follow-up studies of HBO indications “under investigation” should include regional centers with expertise and experience of trauma, surgical infections and postoperative complications, to improve the overall quality of care for these patient groups and to identify cost-effective treatment programs, with or without HBO. With this approach, Hyperbaric Medicine supported by public funding, may better establish itself as a potent and beneficial therapeutic option/adjuvant in selected cases.

Addendum 1: The treatment of necrotising fasciitis with hyperbaric oxygenation – Progress report of a Cochrane review

Michael Bennett[1], **Denny Levitt**[2] and **Ian Millar**[3]
[1] Prince of Wales Hospital and University of NSW, Sydney, Australia;
[2] Centre for Altitude Space and Extreme Environment Medicine, University College London, UK;
[3] The Alfred Hospital, Prahan, Melbourne, Australia.

Introduction

This presentation will briefly outline the rationale for the use of hyperbaric oxygen therapy (HBOT) in the treatment of necrotising soft tissue infections (NSTI) before examining in detail the clinical evidence for the effectiveness of such therapy. The authors are in the process of performing a systematic review of the comparative evidence through the Cochrane Collaboration and our progress to date will be summarised.

NSTIs are a rare group of soft tissue infections characterized by rapidly progressive necrosis of the fascia and subcutaneous tissue with relative sparing of the underlying muscle [1]. Necrotizing fasciitis may occur in a wide range of anatomical locations and it has been labelled specifically when it occurs in certain locations [2–4]. One of the more common presentations, for example, is in the perineum where the process is called 'Necrotising Fasciitis' (NF) or Fournier's gangrene following an early description of the condition in the scrotum and penis by the French venereologist Jean-Alfred Fournier in 1883 [5]. In fact, the description of scrotal gangrene has been variously attributed to Avicenna in 1025, Baurienne in 1764 and others but those early cases were not fulminant. For example, Baurienne described a case involving a boy who had been gored by an ox, but recovered after scrotal incisions [6]. The most historically prominent sufferers from this condition may have been Herod the Great and the Roman emperor Galerius [7].

Fulminant tissue necrosis is usually accompanied by generalized toxicity, which may progress to shock and multiple organ failure. Without prompt recognition and immediate aggressive management, it is often rapidly fatal. When treated, the fatality rate is reported between 10% and 70% with little evidence of a substantial improvement over the last forty years (see Table 1).

The initial event in the onset of NF is the entry of bacteria into the fascia, which may be an apparently 'spontaneous' event or secondary to either trauma or surgery. Rapid bacterial proliferation in the fascia is followed by polymorphonuclear leukocyte (white cell) infiltration and liquefactive necrosis (tissue death). Progressive thrombosis (occlusion) of the blood vessels in the fascia leads to occlusion of the perforating skin vessels and secondary

Author(s) and year		Cases (n)	Death rate (%)
1970	Rea and Wyrick	44	30
1972	Stone and Martin	63	76
1981	Kaiser and Cerra	20	40
1981	Rouse et al	27	73
1982	Oh et al	28	36
1983	Miller	15	27
1983	Majeski and Alexander	30	33
1984	Stamenkovic and Lew	19	42
1984	Spirnak et al	20	45
1985	Pesa and Howard	33	33
1985	Freischlag et at	21	35
1987	Sudarsky	33	6
1990	Clayton et al	57	18
1992	Wang and Shih	18	33
1993	Francis et al	25	24
1995	McHenry	65	29
2000	Brandt	37	24
2003	Korkut	45	20

Table 1: Case series reporting fatality rates from necrotising soft tissue infections where hyperbaric oxygen was not used

cutaneous (skin) ischaemia and gangrene [8, 9]. The extent of skin necrosis is often considerably less than the fascial involvement and this can lead to inadequate debridement if the pathological process is not appreciated (Figure 1).

The key therapeutic intervention is immediate and radical surgical debridement of all dead tissue. It has been consistently shown that delay to the first surgical debridement is associated with increased mortality rate [10–15]. Surgery should be accompanied by the prompt commencement of broad-spectrum antibiotics and appropriate high-dependency supportive care.

Even with early aggressive surgical intervention, mortality rates are in the region of 30% to 40% in relatively recent published case series [3, 4, 16]. Furthermore, patients frequently require multiple extensive debridements and are not uncommonly left with large soft tissue deficits. Prolonged hospital stays and rehabilitation are often required. Thus NF is a condition that incurs significant morbidity and both early and late mortality.

High dose oxygen therapy has been advocated as an adjunctive measure in the treatment of NSTI. Hyperbaric oxygen therapy (HBOT) results in greatly increased arterial oxygen content and thus tissue oxygen pressure (PtO_2). The precise details of oxygen dose vary between studies, but the majority involve 60 to 90 minutes of exposure to oxygen at pressures of between two and three atmospheres. Full critical care monitoring, including invasive blood pressure and central venous pressure (CVP) monitoring, may be required during treatment, as might mechanical ventilation. Only facilities capable of intensive care should treat these patients. Whilst critical care can be safely and effectively undertaken using a monoplace chamber, the use of multi-occupant chambers may be preferable as this permits constant medical supervision inside the chamber by critical care nurses and doctors.

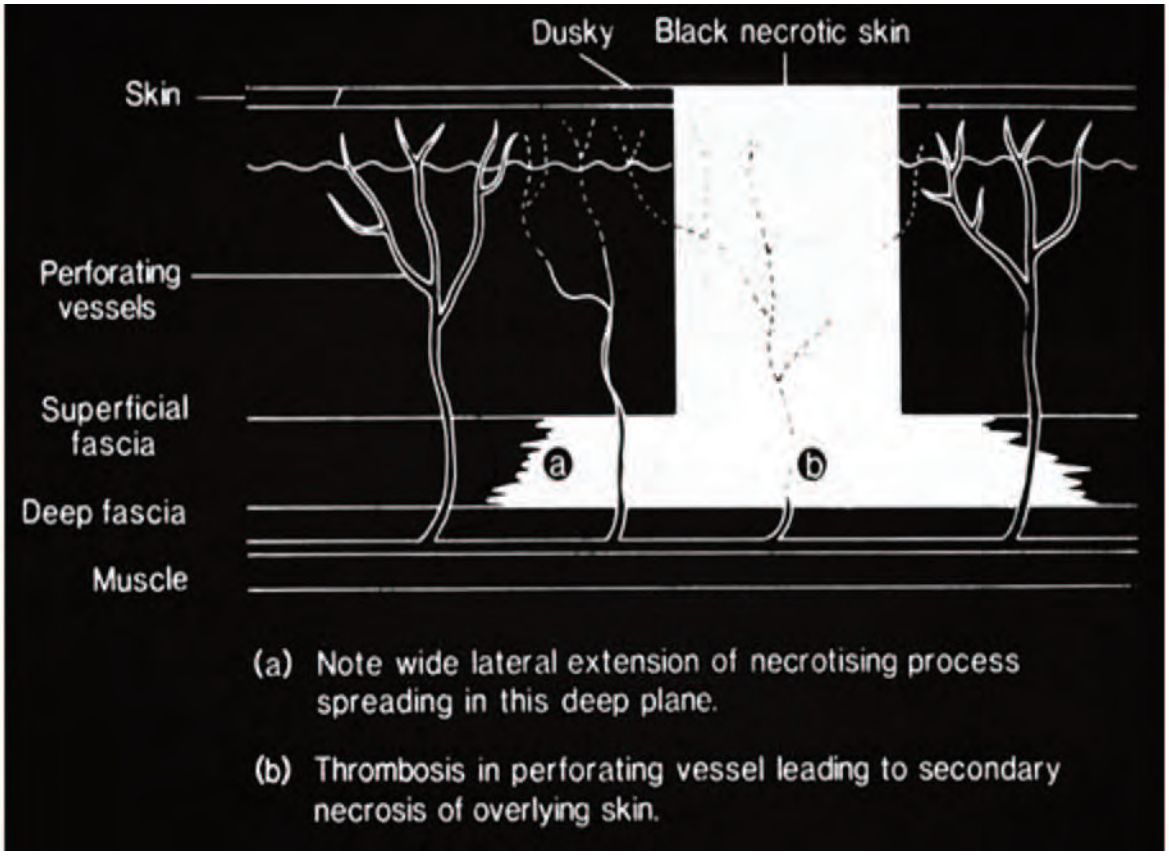


Figure 1. Progress of the necrotic process in necrotising fasciitis. Deep necrosis extends beyond the apparent skin necrosis.

Rationale for the use of hyperbaric oxygen therapy

Infected, necrotic fascia with disrupted vasculature is oedematous and relatively hypoxic [17]. HBOT increases tissue oxygen tension in NSTI with the aim of salvaging critically ischaemic areas [18]. Furthermore, hyperoxia potentiates antibiotic efficiency, improves white cell killing efficacy, and is anti-inflammatory; all of which may improve outcomes [16, 19–24]. These apparently contradictory mechanisms are explained with reference to the effective dose of this complex drug at the site of action. None however, have been conclusively shown to be important in the clinical setting, and many of these factors will likely be operating simultaneously to produce any clinical benefit.

In general, we can identify some mechanisms that may operate through the gross elevation of tissue oxygenation, and others that may result from the restoration of hypoxic tissue to a more normal state.

Consequences of gross hyperoxia

The administration of hyperbaric oxygen results in very high blood partial pressures of oxygen – during a 2ATA treatment we might expect an arterial oxygen tension of 1,000 to 1,200 mmHg, for example [25]. Such high tensions have a number of consequences.

Hyperoxic vasoconstriction
Hyperoxia mediated vasoconstriction will maintain oxygen delivery while limiting tissue oedema– particularly in those hypoxic areas of the advancing wound. For example, in one study of the retinal vasculature, hyperoxia caused a decrease in retinal blood flow between 29% and 34% ($P < 0.001$) [26]. Other tissues where this effect has been demonstrated include the brain, kidney and skeletal muscle [27, 28]. The mechanism is probably inhibition of nitric oxide (NO) mediated vasodilatation. This has been investigated extensively in the rat brain, where at least one mechanism appears to be the inhibition of Nitric Oxide by superoxide anions [29]. One elegant possibility is that vasoconstriction may only be active outside the target region, and may be associated with a beneficial diversion of blood to the target area in a reverse steal phenomenon.

Reduction in leucocyte adherence
Hyperoxia is also of some efficacy in tissue injury via inhibition of the binding and subsequent activation of leucocytes to damaged vascular endothelium. There is strong experimental evidence that this is mediated through an inhibition of B2 integrin function [23] and this seems to be a consequence of HBOT doses of 2.8 to 3.0 ATA rather than 2.0 ATA [30]. The prevention of leucocyte activation ultimately reduces ischaemia-reperfusion injury and subsequent lipid peroxidation. Indeed, the basic mechanisms of HBOT seem to involve a complex balance between the generation of reactive oxygen species and the up-regulation of antioxidant defences [30] – it is not known to what extent this mechanism might be of importance in NF.

Despite reductions in leucocyte adherence, there is experimental evidence that HBOT does not result in immunocompromise. HBOT does not reduce neutrophil viability or functions such as degranulation or phagocytosis [30, 31], and a number of sepsis models suggest HBOT has a beneficial effect [31, 32]

Bacteriostasis
In infections caused by anaerobic and facultative organisms, the achievement of a sufficiently high tissue PO_2 may cause increased bacterial vulnerability through a direct bacteriostatic or bacteriocidal effect. For example, oxygen at 3ATA (304 kPa) is bacteriocidal for Clostridium perfringens. Indeed this was the original rationale for treating gas gangrene. Closer inspection of the data, however, reveals that 18 hours of oxygen at 3ATA is required to kill the bacteria.

Of greater probable relevance is that the germination of spores and elaboration of toxins is inhibited at 2ATA for shorter periods. Similarly, HBO is bacteriostatic to E coli at 2ATA and Mycobacterium tuberculosis at intermittent exposures at 2.9ATA [33] [Jain 1996]. Such bacterial effects are probably secondary to a combination of direct toxic effects of oxygen free radicals, synergism with certain antibiotics and enhancement of the host immune system (as described below).

Osmotic reduction in tissue oedema
One other intriguing possibility has recently been postulated by Hills- the osmotic effect of high arterial oxygen tensions [34]. Soft-tissue infection results in ischaemia and hypoxia.

This leads to malfunction of capillary membranes the development of oedema, with subsequent worsening of tissue hypoxia, more leaking of fluid from capillaries and more oedema. Hills maintains this vicious cycle may be broken more at the point of oedema than at the more traditionally accepted point of hypoxia.

Hills' proposal is that, while arterial oxygen tensions are greatly raised during HBOT, the tissue level of oxygen is not greatly increased. This leads to an effective steady state gradient of oxygen between arterial blood and the site of oxygen consumption in the tissues – and this gradient will promote fluid reabsorption into the vascular compartment by the osmotic effect of oxygen. Hills calculates the effect of typical arterial oxygen tensions during HBOT as an approximately 8.5% increase in plasma oncotic pressure, although this may be an underestimate. It is the unique nature of oxygen, by which it is consumed in the tissues, that allows the long-term maintenance of an 'oxygen pump' effect. The proposed effect is illustrated in Fig 2.

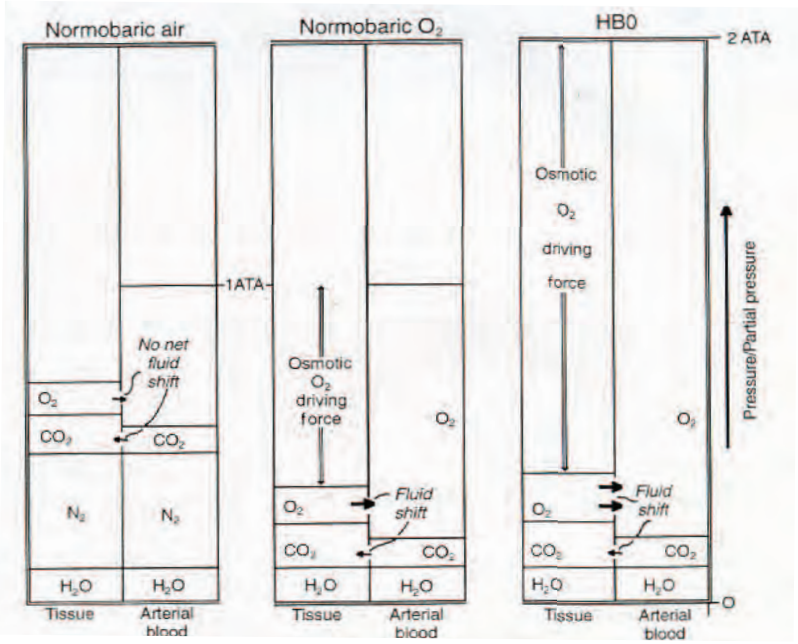


Fig 2. The osmotic oxygen pump during HBOT. Tensions of various gases present in arterial blood and tissues during air and oxygen breathing. From [34].

Treatment tables designed for the maximisation of oxygen tensions have traditionally used a treatment pressure of 2.8 ATA (283.6 kPa). This is the maximum oxygen pressure compatible with both a reasonable treatment time and an acceptable incidence of cerebral oxygen toxicity. Typically, such tables employ a treatment pressure of 2.8 ATA for 90 to120 minutes, giving the inside attendant a decompression obligation.

Consequences of restoring normoxia

NSTI render the host tissue profoundly hypoxic at the advancing margin of infection. The hypoxic environment is highly advantageous to many of the causative organisms. Anaerobes and facultative anaerobes continue to function, producing toxins that further disable the host, while the host immune mechanisms are profoundly incapacitated. While all wounds are

hypoxic to some degree, and hypoxia is an important stimulus to the normal immunological response to wounding and contamination, when the wound is located in a wider area of hypoxia these responses are no longer possible. Hypoxia in these conditions may be profound and disabling.

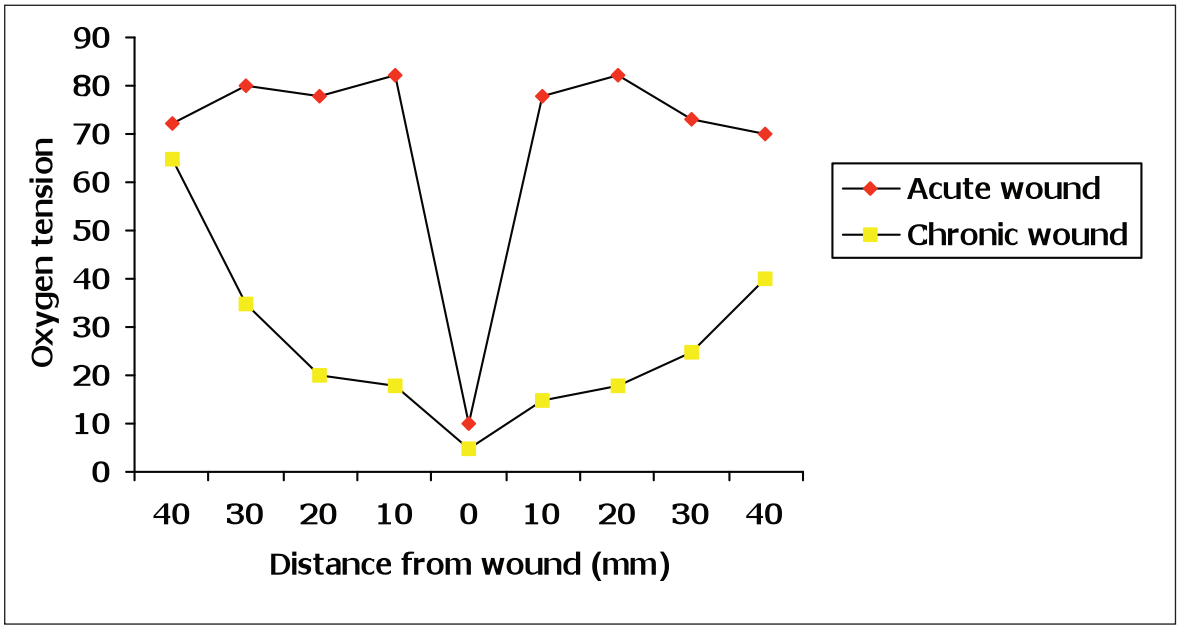
A number of key elements can be identified where oxygen may play an important role in limiting tissue destruction. Leucocytes are intimately involved with the clearance of debris and foreign material (including bacteria) from the wound area. Many such functions are exquisitely sensitive to oxygen. For example, the process of phagocytosis involves consumption of oxygen in an 'oxidative burst' [21]. Although such processes are possible at remarkably low tissue oxygen tensions, improving oxygenation within the physiologic range often dramatically improves the efficiency of such activity. Allen has shown that oxygen tensions between 40 and 80 mmHg are required to maintain activity at 50% of maximum in the NADPH-linked oxygenase responsible for this respiratory burst. To work at 90%, tensions as high as 400 mmHg may be required [35].

For NSTI patients, once the acute infection is resolved, there begins a long recovery phase. In the face of significant tissue destruction the application of supplemental oxygen may remain crucial. A direct effect of raising wound oxygen tension is on the fibroblast. Migration is inhibited at low tensions and the production of collagen through the hydroxylation of proline and lysine is very oxygen sensitive [36]. The enzyme responsible needs 20 mmHg of oxygen to reach 50% of maximum activity, and 150 mmHg to reach 90% [37].

Finally, raising wound PO_2 may also stimulate angiogenesis in a somewhat counter-intuitive way. Hypoxia is the single most powerful stimulus to angiogenesis under normal conditions. However, some evidence exists to suggest that, rather than the absolute value of tissue oxygen, it may be the tension gradient over the healing area that is of prime importance. In many problem wounds there are reasons why the oxygen tension in tissues surrounding the wound will also be low, thus eliminating a point at which tension drops sharply. Such gradients can be created by the administration of hyperbaric oxygen, converting the ‘oxygen profile’ of an hypoxic wound into that resembling an acute wound, as shown in Figure 3. The marginal tissue following a NSTI may be compromised in this way and HBOT is given in an attempt to maximize tissue salvage. A complementary view is that it is the falling tension following treatment that forms the direct stimulus to enhance new vessel growth. Further, some experimental data exists to suggest that HBOT enhances the expression of angiopoietin-2 and induces angiogenesis through RNA transcriptional stimulation via a nitric oxide stimulating pathway [38].

Because the recovery phase is about wound healing rather than the achievement of bacteriostatic oxygen tensions, treatment after the initial phase tends to consist of lower doses of oxygen. Generally, we apply maximum pressures of between 2.0 and 2.4ATA (14 m equivalent depth of seawater or 243.1kPa) for 90 minutes daily.

Fig 3 Transcutaneous oxygen tension in acute and chronic (hypoxic) wounds (from the author).



Note the steep oxygen gradient near the wound edge in an acute wound in normal tissue. The administration of HBOT produces this oxygen profile in hypoxic tissues.

Summary

HBOT may act through the effect of pressure or through metabolic and chemical effects of oxygen. Hyperoxic mechanisms are mainly credited for intravascular effects or effects in vessel rich tissues without vascular compromise. In wound healing and other hypoxic conditions, restoration of normal tissue oxygen tensions may be the more important and achievable mechanism.

Treatment tables have been developed largely empirically, but do reflect the appropriate dose for the mechanisms discussed above. As with all pharmacological agents, there is a requirement for demonstrating the appropriate dosing schedule to maximize efficacy while minimizing toxicity.

Adverse effects

The administration of HBOT is associated with some risk of adverse effects, although for the most part these are minor and reversible at the end of therapy.

The most common adverse event is pressure-induced damage (barotrauma) to the middle ear, which occurs in approximately 4% of treatments [39]. In the vast majority of cases barotrauma is self-limiting and has no long-term effects on hearing[40]. In ventilated patients, tympanostomies (holes in the tympanic membrane) may be performed prior to HBOT under local anaesthetic to prevent the occurrence of middle ear barotrauma. Pressure-induced damage to the inner ears, lungs, sinuses, teeth have been reported but are extremely rare; a recent prospective study reported no cases in 11,376 HBOT treatments [39]. HBOT may cause acute brain oxygen toxicity, which presents with seizures and occurs in approx-

imately 0.03% of HBOT treatments [39, 41]. Seizures terminate if oxygen is removed and their occurrence does not confer any long-term risk of seizures. HBOT may cause pulmonary oxygen toxicity, resulting in a cough, but this does not affect lung function test results during a typical clinical course [39, 42]. A temporary worsening of short-sightedness occurs in up to 70% of patients, but this usually resolves by 10 weeks [43, 44]. Claustrophobia occurs in a minority of patients [39]. Thus, although serious adverse events are rare, hyperbaric oxygen therapy cannot be regarded as an entirely benign intervention.

Evidence-basis for the use of HBOT

The above discussion suggests there is some biological plausibility for the use of HBOT in NSTI. The experimental evidence is summarised below.

Animal experiments

Although HBOT had been used in the treatment of NSTI due to clostridial organisms since the early 1960s, it was not until 1973 the first focussed animal work was published by Demello et al where an experimental model of clostridial myonecrosis was created by inoculation into the traumatised hind legs of dogs[45]. Demello then treated the dogs with various combinations of surgery, antibiotics and HBOT. The results are summarised in Table 2. Combination therapy using all three modalities was clearly the most successful strategy.

Other animal models have suggested similar success from combination therapies where HBOT is a component [46, 47] – although, of less direct relevance, others used HBOT prophylactically rather than therapeutically[48], and others did not suggest benefit with the addition of HBOT [49].

Therapy	N	Mortality (%)
HBOT	12	100
Surgery	12	100
HBOT + Surgery	13	100
Antibiotics	20	50
HBOT + Antibiotics	20	45
Surgery + Antibiotics	20	30
HBOT + Surgery + Antibiotics	20	5%

Table 2. Survival in dogs infected with Clostridium perfringens in a traumatised hind limb (from [45])

Clinical evidence

HBOT has been used as an adjunctive treatment in necrotizing soft tissue infections since the 1960s when it was proposed to treat anaerobic infection by the Dutch surgeon, Brummelkamp [50]. However, the non-random evidence supporting the use of HBOT is conflicting.

Case series where HBOT has been employed have been reported since 1961. These are summarised in Table 3.

Many of these case series have reported significantly lower mortality than the (often contemporary) series where HBOT was not used. While this is of interest and has fuelled the continuing interest in HBOT for these infections, no direct comparison is possible. There

Table 3. Case series where HBOT has been used for NSTI.

Author	Country	Anatomical Site	N	Mortality (%)
Hirn 1993	Finland	Perineal	11	1 (9)
Pizzorno et al 1997	Italy	Perineal	11	0 (0)
Korhonen et al 1998	Finland	Perineal	33	3 (9)
Dahm et al 2000	USA	Perineal	38	3 (8)
Gurdal et al 2003	Turkey	Perineal	28	2 (7)
Gozal et al 1986	Israel	Mixed	16	2 (12)
Skacel et al 1992	Australia	Mixed	24	6 (25)
Elliot et al 1996	USA	Mixed	198	50 (25)
Torda et al 1997	Australia	Mixed	34	5 (15)
Takahira et al 2002	Japan	Mixed	7	3 (43)
Escobar et al 2006	USA	Mixed	42	5 (12)
Mathieu et al 1995	France	Cervical	45	10 (22)
Langford et al 1995	USA	Cervical	6	0 (0)
Whitesides et al 2000	USA	Cervical	12	0 (0)
Stenberg et al 2004	Sweden	Cervical	13	0 (0)

are simply too many potential biases to such an analysis – particularly due to preferential publication of good results and bias by expertise (see discussion below).

Trials where clinical results following the addition of HBOT are compared to results in the same facility or geographical area hold out some hope of a meaningful comparative analysis. Previous reviews of HBOT for NSTIs have highlighted the absence of truly randomised trials in this area and have described the generally positive results in non-random comparative trials. The combination of the results of these cohort reports into a single meta-analysis has been suggested in the past, but not acted upon. We registered our interest in doing so through the Cochrane Collaboration and here report for the first time some preliminary findings.

Systematic review of the comparative evidence

We reviewed the evidence concerning the use of HBOT as an adjunctive treatment for necrotizing fasciitis (NF). Specifically, we wanted to address the questions ‘does the administration of HBOT reduce mortality or morbidity associated with NF’ and ‘what are the adverse effects of HBOT when treating NF’?

Controversy

Systematic reviews (SRs) are playing an increasingly prominent role in clinical decision-making. Traditionally, and where heterogeneity between studies appears acceptable, SRs of the randomised evidence have included meta-analysis in order to produce numerical estimates of effectiveness. It is much less clear if such an approach should be contemplated for comparative trials where the patients are allocated by any other method.

There are a number of reasons why one might wish to do this. Most commonly, there is

simply no alternative. In reviewing the evidence for HBOT in NF, for example, there are no randomised data, and any conclusions at this stage will need to be based on non-random studies. Another potential advantage is that non-random studies are more likely to include the full spectrum of patients, and may therefore be more generalisable to the population at large. This has been argued as the justification for a number of SRs of the non-random literature [51].

A number of quality checklists have been suggested to assist with assessing the reliability of data from individual trials, and one such checklist is summarised in Table 4 [51]. Comparing the conclusions from RCT versus non-random studies of acupuncture for chronic headache, one group concluded that while RCTs in general report patients and outcomes more precisely, many non-random studies are comparable in this regard and non-random studies are associated with higher response rates [51]. These authors believe that the 'traditional' approach over-emphasises methodology and disregards some clinical aspects.

Table 4. A possible checklist for quality of non-random comparative studies. Adapted from [51]

Feature of the report?	Comment
Sampling method clear?	Are all relevant patients likely to have been included?
Diagnosis well-described and clear?	What mix of NSTIs is included?
Patients characterised well?	Age, co-morbidities, severity score
At least one clinical outcome?	Case fatality, major amputation
Other therapy well described?	Surgical approach, antibiotics, ICU?
At least 90% of cases have outcome reported	Why are cases missing form analysis?
Historical or contemporary comparison?	

In fact, one might go further and try to define those clinical situations where randomised trial data might not be required to drive therapeutic decisions. Black suggested the following criteria [52]:

1. **Unnecessary.** When the effect is dramatic and nears universal (all or nothing – e.g. recompression for decompression illness, or insulin for diabetic coma)
2. **Inappropriate.** When the disease or outcome is very rare (e.g. randomisation may reduce effectiveness (e.g. surgical expertise) or outcomes are very long-term (e.g. therapy for loosening of artificial hip joints).
3. **Impossible.** Clinician refusal to participate (e.g. HBOT for osteoradionecrosis), unethical (e.g. cardiac transplant versus medical management) or where there are legal obstacles.
4. **Inadequate.** Areas where there is low external validity (e.g. dependent on surgical technique).

With regard to the use of HBOT for NSTI, we might reasonably suggest that because physicians might refuse to participate, randomisation is impossible in most centres where HBOT is available and also approaching inappropriate because the disease is so relatively rare, it is difficult to see a trial of any power being undertaken within a reasonable period

of time. Sometimes these attitudes can change with considerable rapidity. An example in our experience is the treatment of pelvic soft tissue radiation injury. One prominent group of potential referrers to POWH went from a position of complete scepticism to enthusiastic support over a six month period following the chance referral of a single patient who did well. Any period of 'clinical equipoise' was short-lived indeed.

In the area of infectious diseases, one of the most famous relevant accounts is the landmark paper by Abraham et al concerning the use of penicillin [53]. This report revolutionised modern medicine on the basis of a case series of five.

The major problem with the combined analysis of non-random trials lies in the distinction between causality and association. Meta-analysis of observational studies can exaggerate and compound errors – one such analysis, for example, showed an association between cigarette smoking and suicide risk. Rather than concluding that smoking causes suicide, it is far more likely that the two are associated because they have common underlying causes [54]. Unfortunately, implausibility does not protect us well from spurious claims and researchers are surprisingly adept at explaining unexpected findings[55].

Both methodologically and from example, case-control studies are much more likely subject to misleading results due to selection biases (both how the cases and their controls were identified), and it seems appropriate that even greater caution should be exercised when drawing conclusions from this type of study [55]. For this reason, we have limited our analysis to cohort studies only.

The authors accept the analysis that follows should be subject to considerable scepticism. Inevitably, the included trials will be subject to biases – both knowable and unknowable. Given that this data is likely to be the best available for the foreseeable future, we felt an analysis with appropriate caveats was both of interest and a worthwhile guide to future research efforts. Others have supported the use of similar analyses on the basis that the alternative is a return to highly subjective narrative reviews [55].

Methods

We included all comparative trials that compared the effect of HBOT with no HBOT in the treatment of necrotizing fasciitis in children or adults. We included any HBOT administered in a monoplace or multiplace chamber at pressures between 1.5 and 3 atmospheres for 60 minutes or more, at least once a day. The comparator therapy was no HBOT treatment. Any additional therapy performed concomitantly must have been applied in both groups. We accepted any antibiotic and surgical regimens designed to control the infection.

Our primary outcome was case fatality during the presenting admission. We also collected data on case fatalities at any time, major amputation rate, number of surgical debridements, functional outcomes and quality of life measures, ventilator days, hospital length of stay, costs and adverse events.

In January 2009 we searched the Cochrane Central Register of Controlled Trials (CENTRAL) *(The Cochrane Library)*, MEDLINE, CINAHL,EMBASE and the Database of Randomised

Controlled Trials in Hyperbaric Medicine (DORCTHIM, M Bennett). The search strategies used will shortly be available in the Cochrane database (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). In view of the confusing and varied nomenclature in the field of necrotizing fasciitis, these searches contain a wide variety of search terms including: necrotizing fasciitis, Fournier's gangrene, necrotizing soft tissue infection, haemolytic streptococcal gangrene, progressive synergistic bacterial gangrene, suppurative fasciitis, acute dermal gangrene, Meleney's ulcer, Cullen's ulcer, hospital gangrene, and synergistic necrotizing cellulitis.

In addition, we performed a systematic search of specific hyperbaric literature sources including hand searching of relevant hyperbaric textbooks [56-59]; hyperbaric journals *(Hyperbaric Medicine Review, South Pacific Underwater Medicine Society Journal, European Journal of Hyperbaric Medicine, Aviation Space and Environmental Medicine Journal)*; and the conference proceedings of the major hyperbaric societies (Undersea and Hyperbaric Medical Society, South Pacific Underwater Medicine Society, European Undersea and Baromedical Society, and International Congress of Hyperbaric Medicine).

One author (MB) was responsible for searching for and identifying potentially eligible studies, while two authors (DL and IM) examined the search results and identified studies for inclusion. The identified studies were retrieved as full text and reviewed independently by DL and IM.

Meta-analysis

We undertook an analysis using RevMan 5.0 software (Cochrane 2008), using relative risk (RR) with 95% confidence intervals to measure treatment effect and precision for proportions (dichotomous outcomes). As an estimate of the clinical relevance of any difference between the experimental and control interventions, we calculated the number needed to treat to benefit (NNT) using Catmaker version 8.5.0.321 (Catmaker).

Differences between studies in the key characteristics of the participants, interventions, or outcome measures (clinical heterogeneity) were assessed and consideration given to the appropriateness of pooling results and meta-analysis. In the absence of prohibitive clinical heterogeneity, differences in the reported effects (statistical heterogeneity) were assessed. Statistical heterogeneity was assessed using the I^2 statistic [60]. We considered that statistically important heterogeneity is likely when the I^2 is greater than 40%. We addressed publication bias with a funnel plot, examining for signs of asymmetry.

If data are available, we considered subgroup analysis on the basis of the time of onset to time of first treatment, severity of illness at outset, location of NF (limb versus trunk), age (children versus adults) and intercurrent illness.

Results

Included studies

Combining all searches yielded a total of 2,193 citations of potential interest. MB scanned all results and eliminated 1,326 citations that were clearly not human trials of therapy for a NSTI, or were clearly duplicated citations. The remaining 867 citations were examined in

more detail. Of these, 825 were discarded, leaving 42 reports. Of these, 33 were rejected (21 no comparator group, five duplicate reports, five reviews with no new data and two reporting insufficient data), leaving nine clinical reports for inclusion in this review (Table 5).

These reports were published over a 20 years period between 1985 and 2005 and in total include data on 330 patients, 187 receiving HBOT and 143 control. Both the dose of oxygen per treatment session and for the total course of treatment varied between studies. The lowest dose administered was 2.4 ATA for 90 minutes daily [61], while the highest dose was 2.8 ATA for 60 minutes three times daily [62]. All trials described urgent and extensive debridement of necrotic tissue with the administration of multiple broad spectrum antibiotics.

Seven of the nine reports included HBOT and non-HBOT patients enrolled over the same time period. In these studies either the physician responsible for the case made the decision to refer for HBOT, or the therapy was available in some included centres but not others. The other two reports were historically controlled with some patients presenting prior to the establishment of a local hyperbaric service (see Table 5) [63, 64].

Table 5. Characteristics of comparative studies.

Author	Allocation	Site of infection	Patients	HBOT	Standard therapy
Barzilai 1985 [65]	Physician choice. HBOT not standard	All perineal, lower abdomen	34 to 63 yrs. 18% septic shock, 27% diabetes	2–4 sessions. No details	Wide excisions. Gentamicin, clindamycin, penicillin
Riseman 1990 [63]	Before and after chamber available	18/29 perineal/ abdo Some clostridial	14 to 88 years. 21% septic shock, 41% diabetes	90 mins, 2.5 ATA to total of 10	Early and extensive debridement. Aminoglycocides, clindamycin, penicillin
Brown 1994 [66]	Physician choice	All abdo/perineal Mixed group of infections.	Apache scores 12 HBOT v 16 control	90 mins, 2.5 to 3ATA until no necrosis (4–7 sessions)	Debridement, appropriate antibiotics
Shupak 1995 [67]	Physician choice	Site of infection unclear, 86% trunk	16 to 85 years. 57% diabetes 16% septic shock. Apache 11 HBOT and 9 control	90 mins, 2.5ATA until no further necrosis for 2 treatments	Extensive debridement, broad spectrum antibiotics
Hollabaugh 1997 [61]	Only if available at the case hospital	All perineal	Age 27 to 87, 38% diabetes	90 mins, 2.4ATA for 14 days	Prompt surgical management, broad spectrum antibiotics
Niezgoda 2003 [68]	Physician choice	All truncal	No details	No details	Debridement, antibiotics, VAC dressing
Wilkinson 2004 [62]	Not stated – probably physician choice	Mixed group of NSTI	Diabetes 34%	60 min, 2.8ATA until necrotising process resolved	Debridement, antibiotics not specificed
Mindrup 2005 [69]	Physician choice	All perineal disease	Septic shock 6, diabetes 69%	Variable dose from 30 to 90 min, 2.4 to 3 ATA, 1 to 3 daily	Urgent debridement and antibiotics
Ayan 2005 [64]	Before and after chamber available	All perineal	Diabetes 41%, 10 'unconscious'	90 mins, 2.5ATA daily for 3 to 10 days	Urgent debridement and antibiotics (implied only)

Outcomes

All studies reported case fatality rate during the presenting admission and several reported the number of debridements, hospital and ICU lengths of stay and a variable degree of data on the microbiology of the infections. Most series contained the usual mix of diabetics, alcoholics and other immunocompromised patients. The number of patients in each group, case fatality rates and the odds of dying if given HBOT are summarised in Table 6.

Some of these retrospective cohort studies report a significant reduction in case fatality rate with adjunctive HBOT (Hollabaugh 1998; Riseman 1990; Wilkinson 2004; Ayan 2005), whilst others report no change in mortality (Barzilai 1985; Brown 1994; Shupak 1995; Niezgoda 2003; Mindrup 2005). Given the low power of these studies individually, this variability in the estimate of effect is not surprising.

Table 6. Included comparative studies with estimates of effect on fatality rate. OR = odds ratio (odds of dying if given HBOT compared to odds of dying if given no HBOT). *Hollabaugh reported a significant difference in case fatality using a one-tailed test.

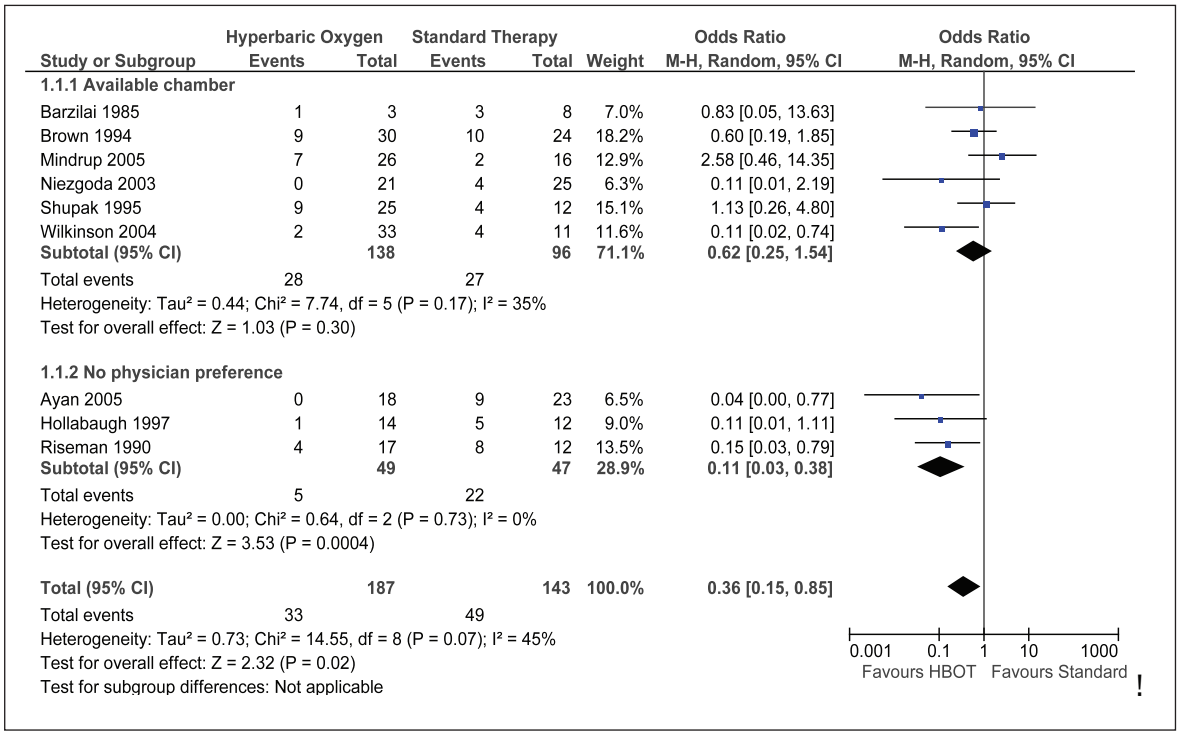
Author	Country	HBO/non-HBO n/n (total)	Mortality HBO (%)	Mortality Control (%)	Odds ratio (95%CI) P-value
Barzilai 1985	Israel	3/8 (11)	1 (33)	3 (38)	OR0.83 (0.01 to 24.1) P = 0.99
Riseman 1990	USA	17/12(29)	4 (23)	8 (66)	OR 0.15 (0.03 to 0.79) P = 0.03
Brown 1994	Canada	30/24 (54)	9 (30)	10 (42)	OR 0.60 (0.19 to 1.85) P = 0.4
Shupak 1995	Israel	25/12 (37)	9 (36)	4 (25)	OR 1.13 (0.26 to 4.8) P = 0.99
Hollabaugh 1997*	USA	14/12 (26)	1 (7)	5 (42)	OR 0.11 (0.01 to 1.11) P = 0.07
Niezgoda 2003	USA	21/25 (46)	0 (0)	4 (16)	OR N/A (0 to 1.72) P = 0.11
Wilkinson 2004	Australia	33/11 (44)	2 (6)	4 (36)	OR 0.11 (0.02 to 0.74) P = 0.03
Mindrup 2005	USA	26/16 (42)	7 (27)	2 (13)	OR 2.6 (0.46 to 14.4) P = 0.44
Ayan 2005	Turkey	18/23 (41)	0 (0)	9 (39)	OR N/A (0 to 0.49) P = 0.003

A meta-analysis of these individual studies suggests there may be an overall benefit of the application of HBOT (Figure 4). 33 out of 187 (17.6%) of the cases treated with HBOT died, versus 49 out of 143 of the cases that did not receive HBOT (34.3%). This difference of 16.7% is statistically significant (Odds of dying with HBOT are 0.36, 95%CI 0.15 to 0.85, P = 0.02). This analysis suggests that given the average risk of dying across these studies, we might expect to treat six patients with NF in order to prevent one death (95%CI 4 to 14).

The analysis in Figure 4 is divided into two subgroups in an attempt to identify at least one potential source of bias. The upper five studies are those where a chamber was available, and the physician in charge had the opportunity to use HBOT if he or she wished to do so.

These studies do not, overall, suggest a benefit from HBOT (OR 0.62, 95%CI 0.25 to 1.54, P = 0.3). The lower three studies are those where a chamber was not available at the time or place where the control patients were treated. These three studies do suggest a benefit overall (OR 0.11, 95%CI 0.03 to 0.38, P = 0.0004).

Figure 4. Forest plot for the odds of dying if given HBOT versus not given HBOT. The studies are divided into subgroups based on whether or not the physicians could choose to refer to HBOT or whether HBOT was un-available for part of the study period.



Discussion

Our analysis suggests a benefit from the use of HBOT for the treatment of NSTI, particularly Fournier's gangrene (NF). Pooling the data from nine small comparative trials suggests the odds of dying if HBOT is added to standard therapy are about 0.36. This overall estimate of effect should be interpreted with great caution, however.

The use of meta-analysis for the pooling of non-randomised data is highly controversial and may give the impression of a precision not reflective of the true nature of the data. Previous commentators have advocated for the judicious use of such analyses, whilst equally eminent clinical epidemiologists have argued that such an analysis is never justified. It does not appear likely that this controversy will be settled in the foreseeable future.

For the present then, we must decide how to approach the clinical evidence for the use of HBOT. There is broad consensus that the most rational approach to choosing between therapeutic options is a thorough critical appraisal of the best evidence available. This is the basic principle of 'evidence-based medicine' that Sackett has defined as *'the integration of best research evidence with clinical expertise and patient values'* [70]. The best research

evidence is the series of comparative cohort studies considered in the analysis above. Different commentators have used this evidence – often selectively – to reinforce their opinion concerning the usefulness or otherwise of HBOT. It is difficult to conceive of how we might use the totality of this evidence in an unbiased way.

One approach would be to avoid formal data synthesis and simply list all the trials and their individual characteristics for the individual reader to interpret. Whilst avoiding the biases of the reviewer, this leaves the reader free again to form any conclusion their preconceptions desire! A second approach is to attempt an analysis of quality across the cohort studies and give greater weight to those studies where quality is higher. One such scheme was summarised above [51]. No quality scale or checklist has been validated for this purpose.

Using the Linde checklist (adapted for the clinical situation under discussion) and simply awarding a point for each item on the checklist that each report satisfies, suggests that the highest quality reports are Riseman 1990 (6 points) and Barzilai 1985, Brown 1994, Hollabaugh 1997 and Ayan 2005 (5 points), whilst the lowest scoring report is Niezgoda 2003 (3 points). It is not obvious that such a scoring system advances our understanding of the situation.

In this report, we have chosen to present the pooled data by meta-analysis. This is the best evidence available and we note with interest that the overall suggestion is one of significant clinical benefit. However, this pooled estimate of effect may be seriously biased by several factors.

Among the most often discussed are publication bias, selection bias, historical bias and expertise bias. Publication bias is widely understood. Authors are simply more likely to report, and have accepted by journals, accounts that suggest significant benefits or reinforce the commonly held understanding of a situation. In the case of HBOT for NSTI, one might put the argument that hyperbaric physicians are more likely to report comparative studies that support the use of HBOT. It is also possible that the same is true for those not inclined to refer patients to HBOT. Potential examples of both could be identified among the nine reports included here.

Selection bias is a distinct possibility in those reports where the physician could choose to refer to HBOT or not, and this was the basis for our subgroup analysis in Figure 4. One might argue this bias in either direction. Responsible physicians might preferentially refer the worst cases for HBOT on the basis that the less serious cases are likely to do well with ‘conservative’ management alone. On the other hand, it is also possible that the worst cases, where patients arrive shocked and unstable with extensive disease, are those least likely to reach a chamber. In our analysis, there was more heterogeneity between studies when physicians could choose or withhold hyperbaric referral and this may suggest different biases operating across these studies.

Those three studies where, if HBOT facilities were available, all cases were referred to HBOT show a more consistent benefit from HBOT (Figure 4). Comforting though this may be for supporters of HBOT, two of the three studies included here used historical controls.

This may lead to a bias toward success of the more 'modern' approach to therapy. The sophisticated support available in the ICU, new antibiotics and a greater appreciation of the importance of good early debridement may all operate to improve survival in the more recently reported patients within a series. It may be that the arrival of a hyperbaric service on site simply coincided with improving general care.

Finally, all of these reports may reflect a bias by expertise. Many centres where HBOT is available attract a high proportion of the NSTI cases within a geographical area. NSTIs are relatively rare and best practice demands early and decisive therapy from surgeons, infectious disease specialists and the intensive care staff. It may simply be that a higher case load, as a result of secondary referrals to a hyperbaric centre, result in improved outcomes that may be attributed to the HBOT itself.

Conclusions

We believe the weight of evidence to favour the application of HBOT for NSTI. However, the evidence is weakened by the lack of prospective cohorts or randomized studies. The possibility of bias cannot be discounted and our overall result should be interpreted with caution.

The prosecution of randomized controlled trials is highly problematic in this area. The best course is likely to lie in the establishment of a large multicentre (probably multinational) prospective cohort study including centres with expertise and experience with these infections both with and without adjunctive HBOT. The advantage of a carefully prepared data collection prospectively would avoid some of the biases possible in the data presently available and would likely provide a useful guide to practice. We urge that consideration be given to establishing such a study.

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Addendum 2: History and practice of Hyperbaric Medicine in Stockholm

The history of hyperbaric medicine goes back to the 17th century when innovations aimed at improving diving techniques and equipment led to the theory that pressurized air could be used as a therapeutic modality. The discoveries by Pascal (1653) and Boyle (1661) concerning hydrostatics, barometric pressure and pressure/volume relationships laid the basis for the development by Henshaw (1662) in London of the domicilium, a sealed chamber within which the pressure could be altered. This chamber was used to treat pulmonary diseases with the simple principle that acute conditions would benefit from increased air pressure, while those suffering more chronic ailments would profit from decreased air pressure. In the 18th century, Black (1755) discovered carbon dioxide and Scheele (1772) and/or Priestly (1775) discovered oxygen. Despite the discovery of oxygen in the 1770s, treatment with hyperbaric oxygen (HBO) instead of simply hyperbaric air was not put into practice until the mid 20th century.


ÉTUDE CLINIQUE
DE L'EMPLOI ET DES EFFETS
DU
BAIN D'AIR COMPRIMÉ
DANS LE
TRAITEMENT DES MALADIES DE POITRINE
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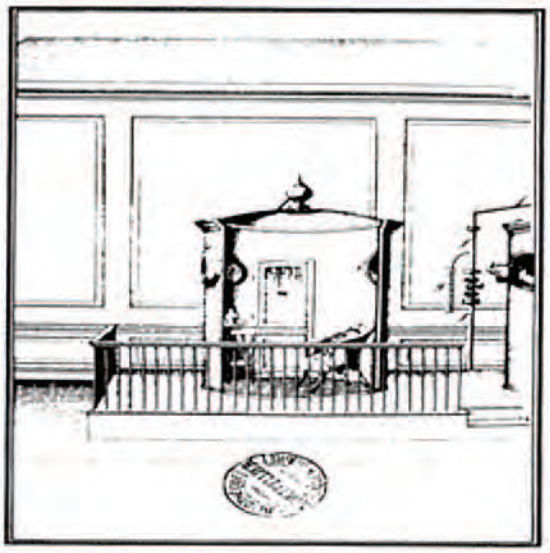
LE CATARRHE CHRONIQUE, L'ASTHME ET LA PHTHISIE PULMONAIRE
PAR
EUGÈNE BERTIN
PARIS
MONTPELLIER



In 19th century Europe the use of the hyperbaric air chamber as a treatment modality increased, especially for pulmonary diseases. The first chamber opened in Montpellier, France by E. Tabarié in 1840.

Through support of the Swedish government and Anders Retzius at the Karolinska Institute, Professor Oskar Theodor Sandahl (1860) opened the first Medico-pneumatic centre with four *hyperbaric chambers in Stockholm*. Among several indications, pulmonary diseases and infections with problematic oxygenation were treated with a "hyperbaric air bath". The unit was closed some 20 years later due to financial problems.

In the 1870s, a French surgeon named Fontaine built the first mobile hyperbaric operating theatre where the amount of oxygen carried in the patient's bloodstream during the administration anaesthesia was increased. This allowed for deeper anaesthesia (N_2O) without a precipitous drop in blood oxygen levels as typically happened with surgically acceptable depths of anaesthesia at that time.

The work of Paul Bert in the 1870s led to the discovery of the relationship between nitrogen bubbles and decompression sickness/"the bends". His work "La Pression Barométrique (1878) is one of the foundations of hyperbaric medicine. He also discovered some of the toxicities of hyperoxygenation on the central nervous system. In 1895, Haldane demonstrated that a mouse could be kept alive during CO intoxication by exposure to HBO. Haldane also created the first decompression tables for divers while working for the Scottish Royal Navy.

In the USA in the 1920s, Cunningham observed that patients with cardio-respiratory disease secondary to influenza were worse off at higher altitude. He began treating cyanotic patients secondary to pulmonary infections with great success. However, many other indications were tested but undocumented. He built the largest "steel ball" chamber in 1927 in Cleveland with 72 rooms on 6 floors. His results were questioned and his unit was closed down.

The modern era of HBO began in the late 1950s with Professor Boerema, a cardiac surgeon at the University of Amsterdam, who conceived the idea that babies with congenital heart disease (blue babies) could be placed in a pressurized chamber and ventilated with 100% oxygen. This would serve to "drench" the tissues with oxygen; thereby allowing the heart to be stopped while the abnormality, such as an atrial septal defect, could be repaired under direct vision. His scientific publication 1960, "Life without blood" is classic where he demonstrated that HBO could oxygenate exsanguinated pigs with only saline in the cardiovascular system. The same year he introduced HBO clinically to extend cardiac arrest during open-heart surgery. This led to the opening of many large chambers for thoracic surgery throughout the world, a technique no longer needed after the invention of heart-lung machines. Other indications, such as the treatment of gas gangrene, carbon monoxide poisoning, gas embolism and wound healing began to be elucidated.

In Stockholm Per Olof Barr, MD, PhD was one of the world pioneers in HBO in the treatment of diabetic wounds. After research at the Karolinska Institute and a clinical period at the Karolinska hospital he opened a clinic for HBO and wound healing at Rosenlunds hospital, Stockholm with four monoplace chambers working 'under pressure' in the 1980s. Within the field of oncology researchers also began to look at HBO as a radio sensitizer since it was well-known that hypoxic tumour cells are less sensitive to radiation, whereas well-oxygenated tumour cells are as much as three times more sensitive to radiation cell death. The science behind HBO began to be supported not only by clinical observations but also through the rigors of laboratory studies.

Unfortunately, the credibility of hyperbaric medicine has been tarnished over the years by indiscriminate and inappropriate use of HBO for a variety of medical conditions.

Scientific organizations involved in the field of Diving and Hyperbaric Medicine.

With renewed interest in HBO scientific societies began to emerge to codify the practice of hyperbaric medicine. In 1963 the first International Congress of Hyperbaric Medicine (ICHM) took place in Amsterdam under the auspices of the Founding President, Professor Boerema. The European Undersea Biomedical Society, formed in 1965 had its first annual scientific meeting in Stockholm 1973. Professor Carl-Magnus Hesser from the Karolinska Institute in Stockholm was the first president. The name was later changed to European Undersea and Baromedical Society (EUBS). In the USA, the Undersea Medical Society (UMS) was formed in 1967, later changing its name to Undersea and Hyperbaric Medical Society (UHMS). The name changes reflect the rapidly growing clinical interest in HBO physiology and therapy. Both EUBS and UHMS give annual scientific meetings and have an international membership.

In 1991, the European Committee for Hyperbaric Medicine (ECHM) was founded for the purpose of understanding, promoting and improving the level of quality of hyperbaric medicine. Both the UHMS and the ECHM have created guidelines for the use of HBO therapy based on the most up to date research and medical knowledge to date.

The Swedish Hyperbaric Medical Association (SHMS) was formed in the 1980s with the prime target of promoting science and education through a yearly two-day meeting alternating between the HBO centres in Sweden. This meeting is given jointly with the HBO Nurses Association of Sweden. In the Swedish Society for Anesthesia and Intensive care (Svensk Förening för Anestesi och Intensivvård, SFAI), a special HBO reference group for Hyperbaric Medicine was formed in 1995. It consists of the anaesthesiologists in charge of the separate HBO centres in Sweden. Its main task has been to create a list of established indications for HBO use within Sweden.

Hyperbaric chamber technology and HBO Practice at the Karolinska University Hospital

The present day Karolinska University Hospital, with a total of 15,000 employees and 1600 hospital beds, is the result of a 2004 merger between the former Huddinge University Hospital south of Stockholm and the Karolinska Hospital in Solna in the northern part of Stockholm. The Karolinska University Hospital is also closely affiliated with the Karolinska Institute located immediately adjacent to the Karolinska Solna site. Karolinska, Solna has during the past decade become the major trauma hospital in the region and sees the most complicated patients, including crush injuries, burns, inhalation injuries, diving accidents etc. Unlike many other trauma centers, the Karolinska incorporates paediatric care with the Astrid Lindgren Children's Hospital located immediately adjacent to the adult trauma facilities. It incorporates all specialties involved in trauma care including a centrally located heliport and hyperbaric medicine.

In 2006, a new state-of-the-art chamber replaced the old one and has placed the Karolinska at the forefront of modern hyperbaric medicine. It is one of six hospitals in Sweden with a hyperbaric multiplace chamber equipped for intensive care. With 24-hour emergency ser-

vices, it is the busiest emergency / intensive care hyperbaric facility in Sweden and presently meets the needs for more than half of the Swedish population, approx 5 million people. It services several regional hospitals for emergency treatment of carbon monoxide poisoning, smoke inhalation, gas embolism, decompression sickness (the bends), crush injuries, severe soft-tissue infections and other post-operative infected and hypoxic conditions.

HBO chamber "delivery systems"

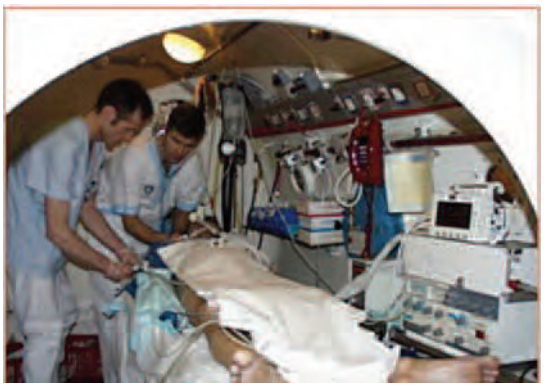
Karolinska has for decades used the two main types of therapeutic hyperbaric chambers or "HBO delivery systems" used globally; the large steel "multiplace chamber" most common in Europe and Australia, and the smaller acrylic "monoplace chamber" most common in USA and Japan. The old multiplace chamber and premises have been replaced in recent years by newly renovated, modern facilities located adjacent to surgical wards, the intensive care, heliport, emergency department and trauma unit.

Multiplace Hyperbaric Chamber

In general, the multiplace chamber is compressed with air and the patients are provided with oxygen via an individualized delivery system, such as mask, hoods or a ventilator. The patients are accompanied by hyperbaric staff members, who may enter and exit the chamber during therapy via a transfer lock or compartment. A specialized fire suppression system is required. Advantages include constant patient attendance and evaluation, particularly useful for ICU patients, and for treating multiple patients per session. Disadvantages include high capitalization and staffing costs, non-individualized treatment and risk of decompression sickness in attending staff.

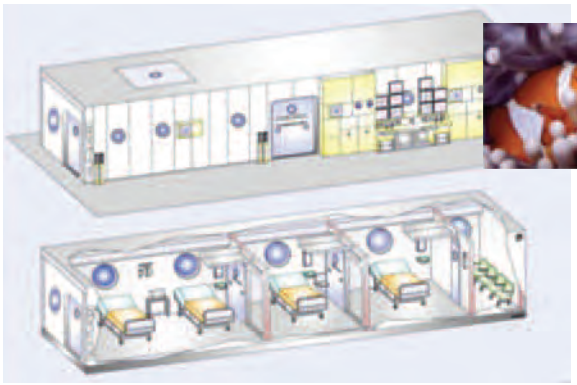
HBO treatment in a multiplace chamber has been carried out at the Karolinska, Solna since 1965 when a hypo- hyperbaric research chamber (Kockums) was built for the clinical physiology department.

ICU treatment with cumbersome loading in the old research chamber



ICU treatment inside old and new multiplace chamber

It was replaced in April 2006 when Karolinska installed the largest and most well equipped rectangular shaped intensive care chamber in the world. Our HAUX Quadro 3500 chamber system is CE marked for hyperbaric use (European conformity mark for medical devices). Its location within the trauma hospital, immediately adjacent to the ICU and heliport, also makes it unique. The chamber is a 115 ton rectangular steel chamber system capable of 300 kPa (4 bar absolute) pressurization, with two treatment compartments, a bed lock (also a treatment compartment) and a personnel lock. The chamber, named NEMO after the famous clown fish pictures on the walls, consist of two functionally totally independent chamber systems for maximal flexibility and safety. It is flexible and allows access of staff/patients, equipment, blood products and drugs while maintaining pressure in one, two or three of compartments. It allows two separate simultaneous treatment protocols. It permits accompanying doctor and nurses to attend up to four ICU patients “hands-on” with adequate intensive care monitoring and with acceptable hygiene and working environment.



The chamber design with four compartments and a flexible ventilation system allows patients with multi-resistant bacteria to be isolated and treated safely with HBO. Monitoring and correction of the patient's vital functions, i.e. ventilation, arterial and central venous pressure, fluid and electrolyte status, and diuresis can be carried out within the chamber. The patients breathe oxygen via a ventilator if they require intensive care or by means of hood or mask if awake, oxygen being dumped outside the building to minimize risk of fire. Continued development of this new intensive care hyperbaric chamber system will enable HBO therapy during resuscitation or primary trauma assessment or with ongoing continu-

ous renal replacement therapy. It will also enable to treat selected high-risk patients e.g. neurosurgical and paediatric intensive-care patients, severe trauma, extensive burn etc. In severe cases, with large medical transport risks, the patient can stay in the large lock for ICU-care inside the chamber between HBO treatments in the first precarious time period.

Monoplace Chambers

Monoplace chambers are designed for single occupancy and compressed with oxygen supplied via the hospital liquid oxygen system. No mask is needed for breathing oxygen and the acrylic shell allows the patient to watch TV or observe his or her surroundings. Advantages include cost-efficient, individualized and patient friendly delivery of HBO, especially for children. Disadvantages include fire hazard and relative patient isolation not allowing normal equipment or personnel “hands-on”. This is the reason for not treating ventilator dependent or otherwise critically ill ICU patients in the monoplace chamber. The first monoplace chamber at the Karolinska was part of the burns unit and began treatments of less critically ill, spontaneously breathing patients in 1991.

We now have four SECHRIST monoplace chambers located in a specially designed ward with up to standard hygiene and working environment, officially opened in April 2007. The large open treatment room, created by fusion of several 4-bed patient rooms, has the capacity of holding a total of 6 chambers. These chambers w ill treat stable ward patients as well as the long term treatment series of outpatients. Although monoplace chambers are designed to treat a single patient we often treat children with accompanying parent or personal.

Medical equipment

HBO treatment of critically ill patients necessitates special considerations regarding hygiene and technical solutions. Frequently, these patients require mechanical ventilation, vasoactive drug infusions, sophisticated monitoring and accurate fluid and electrolyte therapy during treatment. Since 1991 we have successfully carried out thousands of HBO treatments using: low-voltage powered Servo 900C ventilators (Siemens/ Maquet) with accompanying infrared main-stream end-tidal CO_2 analyzer 930 to avoid hypoventilation & O_2 seizures battery-powered Propaq Encore 206 monitors (Welch-Allyn).

A European code for good practice in hyperbaric oxygen therapy has been published in 2004 to set the guidelines, regulations and standards in hyperbaric medicine. In addition, we have Swedish standards (SFAI 2005) as well as local Karolinska guidelines for safe practice. Work continues with manufacturers and Karolinska Department of Clinical Engineering to have our hyperbaric ICU equipment comply with European codes and standards. Battery powered Argus 600 syringe pumps (Codan Triplus), have been tested and used for five years and new models are being tested. They function well during transport and HBO treatment also at very low flow rates used with inotropic drugs & children.

In addition to HAUX monitoring equipment, low-voltage powered General Electrics IMM, Datex Light ICU Monitor, with a 19 inch screen, is mounted in each treatment chamber. Hill-Rom and Linet intensive-care beds are used after disconnecting the transport motor battery power supply. Ongoing work with ventilators (Servo I, Maquet) and defibrillators (Physiocontrol, Medtronic) are encouraging.

Hygiene

HBO treatment of critically ill patients necessitates special hygiene procedures. Hygiene and work environment has improved with wash basins in each treatment lock and a toilet for personnel use.

A new water based nontoxic, non-corrosive, acrylic- and fire safe disinfectant has been introduced by us which seems ideal for hyperbaric use. Desisoft (Desisoft) is a broad-spectrum biocide that is effective against bacteria, spores, viruses, fungi and mould with 1–2 weeks long-lasting effects.

Personnel

The successful management of critically ill patients rests on physicians and staff specialized in diving and hyperbaric medicine. It also requires experienced personnel with resources and equipment to carry out HBO treatment in intubated, sedated critically ill or comatosed patients. Frequently, these patients require mechanical ventilation, endotracheal suctioning, chest tubes, hemodynamic monitoring, blood gas measurement, accurate vasoactive drug infusions and fluid and electrolyte therapy during treatment.

According to Swedish (SFAI) guidelines the medical HBO director should be a specialist in anesthesia- and intensive care whereas the doctor in charge of a HBO session should be MD, educated in hyperbaric and diving medicine, with a local introductory course and with relevant medical knowledge to treat acute HBO victims (e.g. anesthesia/ intensive care). Since the inside staff are “dry divers” at risk of decompression sickness, the anaesthesia intensive care specialist in charge must also be a specialist in Diving Medicine and the medical staff must be volunteers fit to dive. Swedish government regulations requires repeat “fitness to dive” medical examinations and prohibits the employer to use pregnant divers.

Personnel education, training policies and main characteristics of any essential member of the staff has been part of ECHM work since first consensus meeting 1994. A joint medical subcomission with the European Diving Techniology Committee (EDTC) was created and a full program of minimal standards for Education of Physicians was delivered in 1996. Standards for remaining members of the staff of Hyperbaric Medical Centers are in progress.

Intensive care in the hyperbaric environment

The multiplace chamber is ideally suited for HBO therapy in the critically ill patient with failing vital functions, primarily because it allows "hands-on" intensive care by an accompanying physician and/or nurse.

Time to treatment is crucial in the comatose patient such as the diver with cerebral arterial air embolism, sometimes complicated by near drowning, or the burn victim with cyanide and CO intoxication and inhalation injuries or the “toxic shock” septic patient with necrotizing fasciitis. In general, the earlier these patients with potentially life-threatening conditions are treated, the better the outcome. This stresses the importance of emergency transportation services and availability of HBO treatment centers with personnel and equipment for treating critically ill patients on a 24-hour basis. To minimize the risk of transportation the chamber should ideally be located within the ICU; in our new setting we are immediately adjacent to the Central ICU with no stairs, elevators or even thresholds to disturb the patient ICU bed transport.

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