# Die Hyperbare Sauerstofftherapie (HBO)

## als Therapiekonzept in der

# Neurochirurgie

## Bestrahlungsfolgen, Tumortherapie, Hirnabszess, Hirnödem

## in den Druckkammerzentren

## des VDD e.V.

Verband Deutscher
Druckkammerzentren

## Zusammenstellung von Informationen für Ärzte

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Lampl et al. Hirnabszess
UHMS Committee report Hirnabszess
UHMS Committee report Osteomyelitis (auch spinal, cranial)

## Einführung:

Aufgrund von in vitro und tierexperimentellen Studien ergibt sich eine klare Behandlungsrationale für die adjuvante Anwendung der hyperbaren Sauerstofftherapie (HBO) auch bei in ihrer Heilung gestörten oder gefährdeten zentralen und peripheren Nervenstrukturen. Infrage kommen in erster Linie folgende Störungen:

- Ödeme, postoperativ, traumatisch, radiogen
- Betrahlungsfolgen
- Infektionen
- HBO als supportive Therapie in der Tumorbehandlung

Bei all diesen Störungen ist eine Hypoxie und / oder ein erhöhter Sauerstoffbedarf gegeben. Grundsätzlich ist es naheliegend bei Mangel an Sauerstoffversorgung diesen zu verbessern. Insbesondere hyperbarer Sauerstoff ist aufgrund physikalischer Gesetzmäßigkeiten (Gasgesetze – insbesondere nach Henry) in der Lage schlecht perfundierte Weich- und Knochengewebe zu oxygenieren. Damit werden schlecht versorgte Gewebe erhalten und dem Fortschritt von Nekrosen Einhalt geboten. Zusatzbelastungen wie Operationen und Verletzungen werden besser toleriert.
Die an der Heilung beteiligten Zellsysteme werden aktiviert und die Heilung der betroffenen Gewebe beschleunigt bzw. bei Sauerstoffmangel erst ermöglicht.

## Ödemreduktion:

Der ödemreduzierende Effekt der HBO wird in vielen medizinischen Bereichen auf Evidenzklasse bis 1b angewendet: u.A. Crush-Kompartment Syndrom, radiogene Ödeme (Mamma, Extremitäten).

## Bestrahlungsfolgen:

Bestrahlte Gewebe sind im Zeitverlauf nach Radiatio zunehmend hypozellulär, hypovaskulär und damit immer auch hypoxisch. Mit Evidenzklasse 1b wird die HBO zur Linderung von Bestrahlungsfolgen eingesetzt (Strahlenproctitis, -cystitis, Osteoradionekrose etc.)

Die Evidenzlage für die Anwendung der HBO in diesem Kontext für neurologische Störungen ist auf Fallberichte und Fallserien (Evidenzklasse III) beschränkt. In Anbetracht von Rekrutierungsproblemen für Studien und die große Varianz der klinischen Strahlenfolgen lässt sich in absehbarer Zeit keine Verbesserung der Studienlage erwarten. In Anbetracht der experimentellen Grundlagen und der teils auf Evidenzlevel 1a (Cochrane) liegenden klinischen Ergebnisse bei der Anwendung der HBO bei Strahlenfolgen in anderen Bereichen besteht jedoch eine schlüssige Behandlungsrationale auch für die Anwendung im neurologischen Bereich.

## Supportive Tumortherapie:

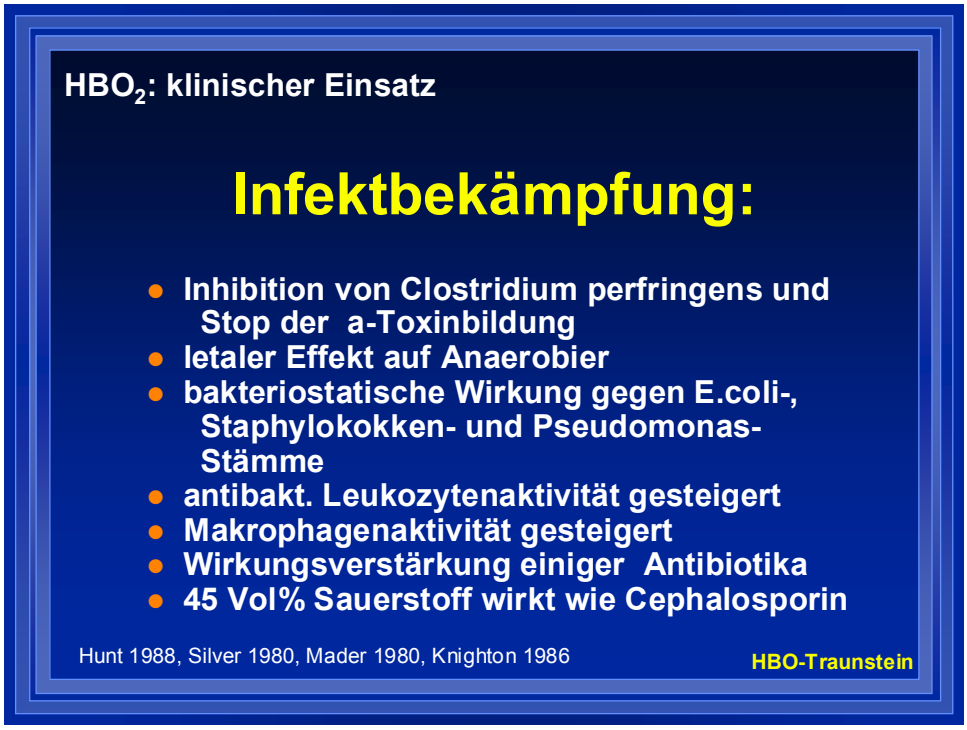
In der neurologischen, neurochirurgischen Tumorbehandlung ergeben sich Einsatzgebiete für die hyperbare Oxygenation.

Die Frage nach einer möglichen **Förderung von Tumorwachstum**, Förderung von Metastasierung und Förderung von Rezidiven wurde eingehend in vitro, tierexperimetell und in klinischen Studien untersucht (Literatur bitte anfordern).
Schlussfolgerung aus den Tierversuchen mit einer großen Bandbreite von Tumor Typen und Histologie: kein oder sogar reduzierender Effekt der HBO auf Tumorwachstum oder Metastasierung
Schlussfolgerung aus klinischen Untersuchungen zur Tumoracceleration:

- Studien, die einen wachstumsfördernden Effekt der HBO zeigen umfassen 72 Patienten.
- Studien mit keinem oder wachstumshemmendem Effekt der HBO umfassen > 3000 Patienten. (Sminia 2006)
- Wegen Bedenken, dass die HBO die Wahrscheinlichkeit von Tumorrezidiven oder Metastasen bewirken könnte, sollte man Patienten die Aussicht auf Linderung durch HBO haben diese Therapie nicht vorenthalten' (Feldmeier et al., UHM 30, 1-18, 2003 (Metaanalyse))

**sonstige Einsatzgebiete der adjuvanten HBO in der Radio – Onkologie:**
Strahlenproktitis (Evidenzlevel = 1b)
Strahlencystitis (Evidenzlevel = 2)
bei drohender Cystektomie (Evidenzlevel = 1)
radiogenes Mammaödem (Evidenzlevel = 3)
Strahlennekrosen im ZNS (Evidenzlevel = 3)
Glioblastome zur Strahlensensibilisierung (Evidenzlevel = 3)
Strahlensensibilisierung spez. bei Rezidivcarcinomen (Evidenzlevel = 3)
rez. Neuroblastom IV (mit G-BA Akzeptanz) (Evidenzlevel = 1a)
Vor Dental-Implantation und Impantation von Knochenankern im bestrahlten Gebiet (Evidenzlevel = 2)
Osteoradionekrose speziell Mandibula (Evidenzlevel = 2)
Osteoradionekrose sonst (Evidenzlevel = 3)

## HBO zur adjuvanten Infektionsbehandlung:



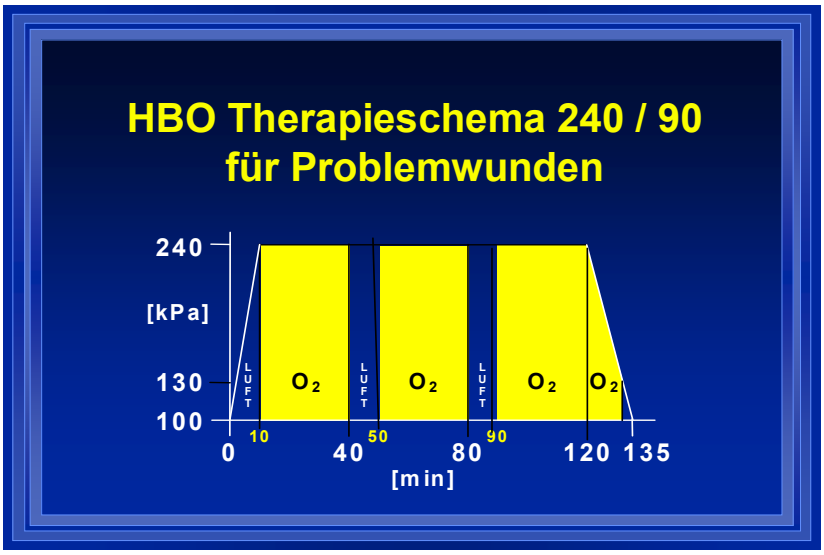

Hyperbarer Sauerstoff wirkt direkt sowohl auf Aaerobier wie auch Aerobier (die Radikalentoleranz der Bakterien ist unterschiedlich). Die Evidenz für den Einsatz reicht bis zu 1a. Insbesondere bei problematischer Lage von Hirnabszessen und bei multiplen Hirnabszessen bietet die HBO eine gute adjuvante Alternative. Hier, wie auch bei sonstigen schwer beherrschbaren Infektionen an Knochen und Weichteilen erfolgt Anwendung der HBO international.

In der Folge bieten wir eine Zusammenstellung von Literatur zu diesen Themen ohne Anspruch auf Vollständigkeit. Auch auf dem Gebiet der Hyperbarmedizin werden laufend neue Erkenntnisse veröffentlicht und zunehmend die positiven klinischen Erfahrungen durch gute Studien untermauert. Mittlerweile liegen Studien bis zur Evidenzklasse 1a vor.

Die hyperbare Sauerstofftherapie bietet insbesondere bei unzureichender Wirkung der üblichen Behandlungsmethoden und nachgewiesener oder anzunehmender Hypoxie einen weiteren Therapieansatz, der häufig mit Erfolg eingesetzt wurde. Die HBO Therapie erfolgt in neurochirurgischen Bereich adjuvant unter Fortführung der etablierten Maßnahmen.

## Behandlungsprotokoll

Problemwundenschema mit täglicher 90-minütiger 100%iger Sauerstoffatmung bei 2,4 bar über maximal 60 Tage (siehe Committee Report der UHMS).



Kohshi,-K : [**Hyperbaric oxygen therapy for neurologic emergency and neurosurgical diseases: a systematic review of the literature**] J-UOEH. 2003 Dec 1; 25(4): 419-33

I have reviewed reports concerning neurologic emergency and neurosurgical diseases adjunctively treated with hyperbaric oxygen (HBO) therapy. Some clinical studies indicate the favorable effects of HBO therapy on the events at an **ultra-acute stage of brain ischemia**. This therapy has been used in the treatments of other neurologic emergency diseases, such as **brain and spinal injury**, **carbon monoxide intoxication**, **decompression illness** involving the central nervous system and so on.
Some reports clarify that patients with **malignant gliomas** have a prolonged survival by radiotherapy after HBO therapy. In addition, I have applied HBO preexposure to **radiosurgical treatments** for recurrent and brain stem gliomas. HBO therapy enhances the effects of some **chemotherapeutic** agents such as platinum drugs and nitrosoureas. Especially, the therapeutic effect of carboplatin, one of platinums, is improved by HBO therapy in recurrent malignant tumors. Although **radiation-induced brain injury** is the most serious problem after radiosurgery, HBO therapy controls this condition and its progression. **Wound infection** after intracranial or spinal surgery is well controlled by anti-infectious drugs combined with HBO therapy.

Now HBO therapy is an important therapeutic option in the fields of neurologic emergency and neurosurgery. However, high-quality randomized controlled trials that evaluate the short- and long-term risks and benefits of HBO therapy are necessary to better inform clinical decisions.

Record 4 of 16 - MEDLINE(R) on CD 2003 Part A

# Strahlenbedingte Optikusschäden

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# Fallbericht

# Sehverlust nach Strahlentherapie

## Fallbeschreibung:

Weiblich, 56 Jahre,

Zustand nach Operation und Bestrahlung eines Oberkiefercarcinoms re. 7 Jahre zuvor.

Re Auge erblindet in Verlauf eines Jahres,

Li Auge verschlechtert sich schrittweise mit mehrjähriger Verzögerung

Kommt zur hyperbaren Sauerstofftherapie auf Anraten der Radioonkologen zur Linderung der Strahlenfolgen.

## Therapie :

29 x HBO nach dem „Problemwundenschema“ TS 240-90

Komplikation: Tubenbelüftungsstörung erfordert Paukendrainage um den erforderlichen Druckausgleich in den Ohren zu erreichen

Sonst ereignislos

## Ergebnis:

Das Sehvermögen des li Auges bessert sich im Verlauf von 20% auf 80%

Das re. Auge bleibt blind

Therapieende nach fehlender weiterer Verbesserung

Boschetti M, De Lucchi M, Giusti M, Spena C, Corallo G, Goglia U, Ceresola E, Resmini E, Vera L, Minuto F, Ferone D.: **Partial visual recovery from radiation-induced optic neuropathy after hyperbaric oxygen therapy** in a patient with Cushing disease. Eur J Endocrinol. 2006 Jun;154(6):813-8.

Department of Endocrinological and Metabolic Sciences and Center of Excellence for Biomedical Research, University of Genoa ans San Martino Hospital, Italy.

Here we describe the **case** of a 41-year-old woman with a history of Cushing disease who had previously undergone unsuccessful **neurosurgery**, followed by **stereotactic radiosurgery**. More than **4 years after this treatment**, she presented severe visual impairment, which started in the left eye and was documented by neuro-ophthalmic evaluation. Radiological assessment by contrast-enhanced magnetic resonance (MR) imaging initially suggested the diagnosis of glioma of the optic nerve and the patient started corticosteroid treatment (first with prednisone, 80 mg/day, followed by dexamethasone, 8 mg/day). Despite the therapy, vision in the left eye rapidly worsened until light was no longer perceptible; similar symptoms and signs also developed in the right eye, evolving to complete temporal hemianopsia.

The clinical evidence was confirmed by the rapid progression of the MR picture, which showed homogeneous enhancement of the chiasm and optic nerves. On the basis of these findings, the original diagnosis of glioma was excluded, and radiation-induced optic neuropathy was diagnosed.

As corticosteroids had proved inefficacious, hyperbaric oxygen (HBO) therapy was promptly instituted and vision steadily started to improve. This improvement was documented and confirmed by the progressive recovery of the visual field in the right eye and the changes in the sequential follow-up MR scanning.

Optic neuropathy is an infrequent but dramatic complication of radiation therapy. Symptoms develop, on average, 12 months after treatment, and the onset may be acute and characterized by the progressive loss of vision in one or both eyes. HBO has already been used to treat this complication, but its efficacy is still controversial.

Here, in addition to describing this particular case, which presented a significantly delayed radiation injury of the optic pathways, we provide a brief literature review and discuss some important points.

PMID: 16728540 [PubMed - indexed for MEDLINE]

# Strahlenbedingte Hirnschäden

Ohguri T, Imada H, Kohshi K, Kakeda S, Ohnari N, Morioka T, Nakano K, Konda N, Korogi Y.: Effect of **prophylactic hyperbaric oxygen treatment for radiation-induced brain injury after stereotactic radiosurgery** of brain metastases. Int J Radiat Oncol Biol Phys. 2007 Jan 1;67(1):248-55.

Department of Radiology, University of Occupational and Environmental Health,
Iseigaoka, Kitakyushu, Japan. ogurieye@med.uoeh-u.ac.jp

PURPOSE: The purpose of the present study was to evaluate the prophylactic effect of hyperbaric oxygen (HBO) therapy for radiation-induced brain injury in patients with brain metastasis treated with stereotactic radiosurgery (SRS).

METHODS AND MATERIALS: The data of **78 patients** presenting with 101 brain metastases treated with SRS between October 1994 and September 2003 were retrospectively analyzed. A total of 32 patients with 47 brain metastases were treated with prophylactic HBO (HBO group), which included all 21 patients who underwent subsequent or prior radiotherapy and 11 patients with common predictors of longer survival, such as inactive extracranial tumors and younger age. The other 46 patients with 54 brain metastases did not undergo HBO (non-HBO group). The radiation-induced brain injuries were divided into two categories, white matter injury (WMI) and radiation necrosis (RN), on the basis of imaging findings.

RESULTS: The radiation-induced brain injury occurred in 5 lesions (11%) in the HBO group (2 WMIs and 3 RNs) and in 11 (20%) in the non-HBO group (9 WMIs and 2 RNs). The WMI was less frequent for the HBO group than for the non-HBO group ($p = 0.05$), although multivariate analysis by logistic regression showed that WMI was not significantly correlated with HBO ($p = 0.07$). The 1-year actuarial probability of WMI was significantly better for the HBO group (2%) than for the non-HBO group (36%) ($p < 0.05$).

CONCLUSIONS: The present study showed a potential value of prophylactic HBO for the radiation-induced WMIs, which justifies further evaluation to confirm its definite benefit.

**(retrospektive Fallauswertung mit “Kontrollgruppe”)**

PMID: 17189073 [PubMed - indexed for MEDLINE]

Cihan YB, Uzun G, Yildiz S, Dönmez H.: Hyperbaric oxygen therapy for **radiation-induced brain necrosis** in a patient with primary central nervous system lymphoma. J Surg Oncol. 2009 Dec 15;100(8):732-5.

Department of Radiation Oncology, Kayseri Training and Research Hospital, Kayseri, Turkey. cihany@erciyes.edu.tr

A 45-year-old man who developed brain radionecrosis in the right frontal and left temporoparietal lobes after receiving whole brain radiotherapy and stereotactic radiosurgery for primary central nervous system lymphoma. Since high dose steroid treatment failed and he declined to undergo surgery, he was referred to hyperbaric oxygen (HBO) therapy.

Both clinical and radiological findings improved after HBO therapy. Steroid requirements were also reduced.

HBO therapy may have a potential value in treatment of brain radionecrosis.



PMID: 19722227 [PubMed - indexed for MEDLINE]

**sihe auch unter 3. Hirnödem**

# Radiogenes Hirnödem

Pérez-Espejo MA, García-Fernández R, Tobarra-González BM, Palma-Copete JD, González-López A, De la Fuente-Muñoz I, Salinas-Ramos J, Felipe-Murcia M, Martínez-Lage JF, Fernández-Pérez J, Romero JM.: [Usefulness of hyperbaric oxygen in the treatment of **radionecrosis and symptomatic brain edema after LINAC** radiosurgery]. Neurocirugia (Astur). 2009 Oct;20(5):449-53.

[Article in Spanish]
Servicios de Neurocirugía. Hospital Universitario "Virgen Arrixaca". Murcia. España.

Radionecrosis with brain edema is a complication of radiosurgery.

Three female patients harbouring frontal pole, petrous and parasagital parietoocipital meningiomas respectively who had been treated with LINAC radiosurgery are presented. Those patients developed, between two and eight months later, a severe symptomatic radionecrosis with a huge brain edema resistant to the usual steroid therapy.
Only after 40 sessions of hyperbaric oxygen, a good remission of the lesions was obtained. There are few cases reported in the literature with such a good outcome.

Consequentely, this therapy must be taken into account to treat this type of radiosurgical complication before considering surgery.

PMID: 19830367 [PubMed - indexed for MEDLINE]

Lynn M, Friedman WA: Hyperbaric oxygen in the treatment of a **radiosurgical complication**: technical case report. Neurosurgery. 2007 Mar;60(3):E579; discussion E579

Department of Neurosurgery, University of Florida, Gainesville, Florida 32610, USA.

OBJECTIVE: Hyperbaric oxygenation is a rarely used method of treatment for steroid-refractory **radiation-induced edema after stereotactic radiosurgery**. We present its successful implementation for a radiosurgical complication after the treatment of a deep, large arteriovenous malformation. We also review the literature on hyperbaric oxygenation for radiation-induced complications.

CLINICAL PRESENTATION: A 25-year-old man underwent radiosurgical treatment for a large arteriovenous malformation. Three years later, substantially smaller remaining nidus was retreated. Five months after that treatment, the patient developed edema around the nidus and hemiparesis. This problem was refractory to high-dose steroids.

INTERVENTION: The patient underwent a course of 25 hyperbaric oxygenation treatments. Within 1 month, the edema and hemiparesis had improved, allowing steroids to be tapered. A follow-up examination 1 year later revealed complete thrombosis of the arteriovenous malformation and minimal neurological deficit.

CONCLUSION: This technical case report adds to the few studies in the literature suggesting that hyperbaric oxygenation therapy, in conjunction with a slow steroid taper, is a reasonable addition to the treatment armamentarium for radiation-induced cerebral edema associated with clinically evident neurological deficits.

PMID: 17327770 [PubMed - indexed for MEDLINE]

Wanebo JE, Kidd GA, King MC, Chung TS: Hyperbaric oxygen therapy for treatment of **adverse radiation effects after stereotactic radiosurgery** of arteriovenous malformations: case report and review of literature. Surg Neurol. 2009 Aug;72(2): 162-7; discussion 167-8. Epub 2008 Sep 11.

BACKGROUND: Adverse radiation effects are a known complication after the use of SRS for AVMs, although it is difficult to predict which patients will manifest with these side effects. Treatment of swelling due to ARE is usually medical, but refractory cases may require surgical decompression.

CASE DESCRIPTION: This report presents a case of a patient who experienced AREs after SRS (edema, headaches, and nausea) that failed to respond to steroid treatment but was successfully treated with HBO. The treatment characteristics of this and of 5 other cases of radiation injury after SRS for AVM managed with HBO therapy are reviewed, and the pathophysiology is discussed.

CONCLUSION: Hyperbaric oxygen therapy provides a therapeutic option to treat AREs following SRS of cerebral AVMs.

# Hyperbaric oxygen therapy for late radiation tissue injury (Review)

Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C

THE COCHRANE COLLABORATION®

Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C: **Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database** Syst Rev. 2005 Jul 20; (3): CD005005. Update in Cochrane Database Syst Rev. 2012;5:CD005005

Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital, Barker Street, Randwick, New South Wales, Australia, 2031. m.bennett@unsw.edu.au

**Abstract**

**BACKGROUND:**

Cancer is a significant global health problem. Radiotherapy is a treatment for many cancers and about 50% of patients having radiotherapy with be long-term survivors. Some will experience LRTI developing months or years later. HBOT has been suggested for LRTI based upon the ability to improve the blood supply to these tissues. It is postulated that HBOT may result in both healing of tissues and the prevention of problems following surgery.

**OBJECTIVES:**

To assess the benefits and harms of HBOT for treating or preventing LRTI.

**SEARCH STRATEGY:**

We searched The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 3, 2004, MEDLINE, EMBASE, CINAHL and DORCTHIM (hyperbaric RCT register) in September 2004.

**SELECTION CRITERIA:**

Randomised controlled trials (RCTs) comparing the effect of HBOT versus no HBOT on LRTI prevention or healing.

**DATA COLLECTION AND ANALYSIS:**

Three reviewers independently evaluated the quality of the relevant trials using the guidelines of the Cochrane Handbook Clarke 2003) and extracted the data from the included trials.

**MAIN RESULTS:**

Six trials contributed to this review (447 participants). For pooled analyses, investigation of heterogeneity suggested important variability between trials. From single studies there was a significantly improved chance of healing following HBOT for radiation proctitis (relative risk (RR) 2.7, 95% confidence Interval (CI) 1.2 to 6.0, P = 0.02, numbers needed to treat (NNT) = 3), and following both surgical flaps (RR 8.7, 95% CI 2.7 to 27.5, P = 0.0002, NNT = 4) and hemimandibulectomy (RR 1.4, 95% CI 1.1 to 1.8, P = 0.001, NNT = 5). There was also a significantly improved probability of healing irradiated tooth sockets following dental extraction (RR 1.4, 95% CI 1.1 to 1.7, P = 0.009, NNT = 4). There was no evidence of benefit in clinical outcomes with established radiation injury to neural tissue, and no data reported on the use of HBOT to treat other manifestations of LRTI. These trials did not report adverse effects.

**AUTHORS' CONCLUSIONS:**

These small trials suggest that for people with LRTI affecting tissues of the head, neck, anus and rectum, HBOT is associated with improved outcome. HBOT also appears to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field. There was no such evidence of any important clinical effect on neurological tissues. The application of HBOT to selected patients and tissues may be justified. Further research is required to establish the optimum patient selection and timing of any therapy. An economic evaluation should be also be undertaken. There is no useful information from this review regarding the efficacy or effectiveness of HBOT for other tissues.

PMID: 16034961 [PubMed - indexed for MEDLINE]

Auszug aus:

# HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF RADIO-INDUCED LESIONS IN NORMAL TISSUES

**CONSENSUS CONFERENCE**
**Long Version**
**Jointly held by:**
**EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY - ESTRO**
**AND**
**EUROPEAN COMMITTEE FOR HYPERBARIC MEDICINE - ECHM**
*October 19-20th, 2001*
*Lisbon – Portugal*

Pasquier et. al. Radiotherapy and Oncology 72 (2004) 1-13

## Introduction

Surgery, radiation therapy and cytotoxic chemotherapy are the principal methods employed in the treatment of cancer. Although all have achieved considerable advances in the attainment of cure all are associated with a risk of morbidity and mortality. Radiation therapy differs from the other two modes of treatment in that its most serious associated morbidity tends to occur months and commonly years after treatment when management is often difficult and unsatisfactory.

It has been estimated that within the European Union there are five million people alive at five years or more after having received radiation therapy as the principal or as an adjuvant method of treatment. Although the large majority are fit and well with little or nothing to relate to the treatment given, troublesome symptoms may be present in up to 5% due to late radiation changes. Perhaps as many as 1%, that is, 50,000 people, may have serious problems, which are resistant to simple methods of treatment. Major surgery may be required as well as prolonged hospital care. Personal and social problems may be very distressing and commonly those affected are unable to pursue gainful employment.

Because a dominant feature of post-radiation change is the obliteration of small blood vessels leading to hypoxia, hyperbaric oxygen has been employed in the care of these patients. In the past forty years there have been many publications reporting benefit in studies, which have included some thousands of patients. Because the literature is dominated by case series containing modest numbers and by case reports and because there have been few randomised trials, there is considerable uncertainty as to the place of hyperbaric oxygen in the management of radiation morbidity. The importance of the problem led the European Society of Therapeutic Radiology and Oncology and the European Committee for Hyperbaric Medicine to jointly organise a Consensus Conference, so that the evidence could be reviewed and guidance drawn up as to clinical practice.

## Format of the Conference

After listening to evidence, a jury drawn from authorities in the areas of medicine concerned, were asked to answer six questions covering the field of concern. The jury and those attending the conference were informed by two highly detailed literature reviews:

**(i)** Radio-Induced Lesions in Normal Tissues: Incidence, Risk Factor and Conventional Treatment. Dr David Pasquier, Centre Oscar Lambret, Lille, France

**(ii)** Hyperbaric Oxygen Therapy in Radionecrosis (A review of the literature). Dr Jorg Schmutz, Hyperbaric Center, Basel, Switzerland

Nine experts prepared written reviews often with the assistance of colleagues and gave presentations which extended through the whole of the first day of the conference:

**(iii) Professor Michael Baumann**
Carl Gustav Carus, Dresden, Germany
Incidence, risk factors and cost of radio-induced lesions in normal tissues.
Written review by: Baumann, M. Holscher, T.

**(iv) Professor Bernard Dubray**
Centre Henri Becquerel, Rouen, France
Pathophysiological basis of radiation-induced lesions in normal tissues.
Written review by: Dubray, B. Lefaix, J-L. Martin, M. Delanian, S.

**(v) Professor Gosta Granstrom**
Goteborg Universitat, Goteborg, Sweden
Pathophysiological basis for HBO in the treatment of healing disorders in radio-injured normal tissues. Written review by: Granstrom, G.

**(vi) Professor Johannes Van Merkesteyn**
Leiden University Medical Center, The Netherlands
Hyperbaric oxygen therapy in the treatment of osteo-radionecrosis.
Written review by: Van Merkesteyn, J

**(vii) Professor A J Van der Kleij**
Academic Medical Center, Amsterdam, The Netherlands
Hyperbaric oxygen therapy in soft tissue radionecrosis. Radio-induced cystitis. Written review by: Van der Kleij, A J. De Rijke, T. Hulshof, M.

**(viii) Dr F Roque**
Hospital da Marinha, Lisboa, Portugal
Hyperbaric oxygen therapy for late radio-induced intestinal lesions.
Written review by: Roque, F. Saraiva, A. Simao, G. Sousa, A. Torres, P. Sampaio, J.

**(ix) Professor J Yarnold**
Institute of Cancer Research, Sutton, Surrey, UK
Hyperbaric oxygen therapy in soft tissue radionecrosis: Radiation-induced myelitis and plexopathy. Written review by: Yarnold, JR. Gothard, L.

**(x) Professor John Feldmeier**
Medical College of Ohio, USA
Hyperbaric oxygen: Does it have a cancer causing or growth enhancing effect? Written review by: Feldmeier, J.

**(xi) Dr A Marroni**
Centro Iperbarico Ravenna, Italy
A cost-benefit evaluation of hyperbaric oxygen use in tissue radio-induced lesions. Written review by: Marroni, A. Longobardi, P. Cali Corleo, R.

After each presentation there was a vigorous discussion amongst the 150 attendees who were physicians and surgeons with an interest in hyperbaric oxygen or radiation oncologists.

On the second morning there was a three-hour session of the jury. The members were:

**Stanley Dische, President**
Professor in Oncology – Centre for Cancer Treatment – Mount Vernon Hospital – UK
**Dirk Bakker**
Professor of Surgery – Academic Medical Center – Amsterdam – The Netherlands
**Karl Hartmann**
Department of Radiation Oncology – University of Dusseldorf – Germany
**Ferran Guedea**
Head of the department of Radiation Oncology – Institut Catala d'Oncologia – Barcelona – Spain
**Joaquim Gouveia**
Director Hospital Cuf-Descobertas/Former Director Instituto Portugues de Oncologia – Lisboa - Portugal
**Eric Lartigau,** ESTRO General Secretary
Professor in Radiation Oncology – Centre Oscar Lambret – Lille – France
**Daniel Mathieu,** ECHM General Secretary
Professor in Critical Care Medicine – Centre Hospitalier Universitaire – Lille – France
Advising the jury were –
**David Pasquier**
Centre Oscar Lambert – Lille – France
**Jorg Schmutz**
Hyberbaric Center – Basel – Switzerland

After the meeting of the jury there was an immediate report to the conference by the President of the Jury. A written report was drafted by the President and circulated to all members of the jury for comment, addition and deletion before presentation for publication.

# Conference Report

The jury discussed all the evidence put before it and came to recommendations for clinical practice. In assessing the quality of the evidence, the scale:

1 (strong)
2 (convincing evidence)
3 (existing but weak evidence) and
4 (anecdotal evidence) was employed

The jury were grateful to the eleven reviewers who worked so hard to collect and analyse the evidence, which they had considered. These valuable reviews, which were at a high standard of scholarship, will be published on the web of ESTRO (www.estro.be), so as to be generally available. In this report the reviews will be referred to by the Roman numbers as noted above.

## Question 1:

***What are the incidence and the cost of the radio-induced lesions in normal tissues?***

The jury was grateful to Professor Michael Baumann for his review of the subject. It was the modification of the late effects by use of hyperbaric oxygen that was the concern of the meeting and the incidence was much influenced by the definition and grading of the late changes. There was unfortunately no internationally agreed grading system but the greatest experience was with the RTOG/EORTC system available for over thirty years and the LENT-SOMA, which was developed from it and published in 1995. Other systems such as the Franco Italian glossary and the dictionary approach had been proven of value in randomised clinical trials. International agreement as to the definition of morbidity would advance knowledge in the field. The Mitre Meeting held in Brussels in December 2000 effectively reviewed systems, which might be employed in routine practice. There was to be a meeting in Florida in April 2002 to try to make further advance in this field. The Conference gave its encouragement towards the pursuit of agreement in this area.

The hardest evidence as to the incidence of morbidity is contained in reports of randomised controlled clinical trials but some can be gained from reports of consecutive series. These have been reviewed by Dr Pasquier [i] and the incidence figures varied very widely according to definition and site. Even with one site a common range was from less than 1% to over 30%. There was no doubt that the incidence of late damage using the older techniques of radiotherapy, particularly the use of ortho-voltage apparatus, was considerable and has reduced with the employment of high energy equipment, with improvements in patient immobilisation, the introduction of precise planning using simulators and with greater precision in dose definition and delivery. Further improvements, such as advanced planning so that treatment is "conformal" to the tumour target volume and the use of intensity modulated radiotherapy, should spare normal tissue damage.

There were, on the other hand, developments in oncology, which might reverse this trend. "Conformal" radiotherapy has encouraged the attainment of higher tumour doses and inevitably some normal tissues will be included. The concomitant administration of cytotoxics where an adjuvant effect is likely to increase the incidence of late damage and the quantitative importance of these drug radiation interactions are difficult to predict. An increasing use of major surgery for restoration of function or for salvage of advanced recurrent disease is also associated with a high risk of morbidity when a heavily irradiated area is operated upon.

The maximum tolerable radiation dose is often set as that which produces an incidence of 5% of moderate or severe late damage. The number of patients with severe damage that is resistant to simple measures is likely in actual fact to be much smaller. However, a prevalence of 1% does represent a very large number of patients in need of care.

The risk factors are similar over all sites and include the total radiation dose, the overall time, the biological effective dose which takes into account fraction size and the overall time, the volume irradiated, the use of a combination of external beam with an implantation or intracavitary procedure, a high dose rate with brachytherapy, tumours adjacent to or involving bone, the presence of infection, the use of surgery and the occurrence of trauma.

Although we need better data concerning the incidence of late damage due to radiotherapy in routine practice the level of evidence to support the observations about incidence which we have made is extensive and certainly can be regarded as being at level 1/2.

Professor Baumann could find very little useful evidence to answer the question concerning the cost of morbidity. Dr Marroni, in his contribution [xi] concerned with cost effectiveness, has reviewed two papers from the United States concerned with mandibular radionecrosis where the average

yearly costs of care reached $140,000 Much of the cost was due to hospitalisation and drugs and these figures did not include costs due to loss of work and care at home. Dr Marroni presented data from Italian hospitals suggesting that over 3000 patients in the year 2000 were discharged with a diagnosis of “radio-lesions of the mandible and soft tissues» and these did seem to represent a high cost to the Italian Health Service. Dr Marroni also gave some evidence suggesting that hyperbaric oxygen treatment would considerably reduce the cost. The jury had some uncertainty about the reliability of this data but it did give some support to the view that the costs of care for radionecrosis were extremely high and that these might be reduced with the use of hyperbaric oxygen. Overall the current evidence was regarded to be at level 3, that is, weak.

## Question 2:

***What tissue changes induced by radiotherapy lead to impaired healing in radioinjured normal tissues?***

When heavily irradiated tissues are examined at an interval of months or years after treatment the characteristic findings are a cellular depletion, fibrosis and a reduction in vascular density with marked narrowing of the small blood vessels. There is therefore hypoxia due to the vascular changes. Professor Granstrom [v] described the changes, which may be observed in irradiated tissue.

Professor Bernard Dubray reviewed the subject and stressed the inter-relationship between these three types of change. The exact mechanism of production of these changes is undoubtedly complex and incompletely understood. Molecular biology has shown that hypoxia could trigger altered gene expression leading to a whole range of effects. Use of hyperbaric oxygen in these circumstances may also lead to complex changes, which may not all be favourable.

There is laboratory and clinical evidence that interstitial fibrosis and necrosis can, at least in part, be reversed by drugs such as exogenous SOD or a combination of Pentoxifylline and vitamin E. The mechanism whereby the benefit is gained remains obscure and Professor Dubray expressed the need for better knowledge of radiation induced late damage in normal tissues

## Question 3:

***What is the rationale for Hyperbaric Oxygen Therapy in the treatment of radioinduced lesions in normal tissues?***

This subject was fully reviewed by Professor Granstrom (v). He considered papers, which gave evidence that there could be an increase in vascular density in irradiated skn and soft tissues after treatment with hyperbaric oxygen. There was further evidence using bone densitometry that new bone formation capacity could be increased. In a controlled study in rabbits where implants had been performed there was evidence of a significant increase in the force necessary to unscrew implants. In another animal study hyperbaric oxygen increased the capacity for osseo-integration. Further it has been found that hyperbaric oxygen could stimulate bone maturation.

Experimental studies of animals with myocutaneous flaps showed significantly increased vascularity with hyperbaric oxygen. It was found that steep oxygen gradients stimulated macrophage angiogenesis factor and macrophage derived growth factor. Bone healing in mice was enhanced.

There was evidence at a similar level which suggested that in patients, hypoxia was a major component of delayed wound healing because a reduced fibroblast activity and less efficient

production of collagen. Hyperbaric oxygen inducing a temporary increase in the oxygen supply stimulated angiogenesis and modified fibrosis.

The jury considered there was a real rationale for hyperbaric oxygen to be used in radiation-induced morbidity as gained from these studies. The evidence was at level 1 and level 2.

## Question 5:

***May hyperbaric oxygen therapy play any role in the prevention of radio-induced tissue lesions?***

**b) Surgery in irradiated tissue**

Considerable evidence was brought before the jury that post operative complications could be reduced by the use of hyperbaric oxygen when major surgery was planned in previously irradiated patients. Wound infections and dehiscence were significantly reduced as well as delayed wound healing reported as serious. No randomised controlled study has however taken place. The jury felt it was an area where hyperbaric oxygen may well have a place but the evidence remained weak ( **level 3**) in the absence of a randomised controlled trial published in peer-reviewed journals, which is always necessary when a measure for prevention is being assessed.

## Question 6

***Is hyperbaric oxygen therapy cost effective in these indications?***

An important consideration in a patient with malignant disease was the possibility that there could be a harmful effect of hyperbaric treatment. Professor Feldmeier gave us a most interesting review of this subject. The question first arose over forty years ago when patients were being treated by radiotherapy in hyperbaric oxygen chambers. Dr Feldmeier effectively reviewed the subject and showed that the evidence that hyperbaric oxygen disseminated tumour and led clinically to a higher incidence of distant metastasis was extremely weak and the jury were convinced that this was not a problem. In patients who suffered post-radiation phenomenon the large majority were, of course, free of tumour so this was not a problem to even consider.

The evidence produced in reviews (iii) and (xi) has already been considered. The jury felt that there was so little hard evidence in this field that it was not possible to reach a conclusion. Costs of hyperbaric therapy could be measured but even here it was necessary to consider the personal and social costs as well as that of the actual treatment. The cost of radiation morbidity itself is obviously high but until real data was available it was not possible to determine whether hyperbaric oxygen would truly have a cost-saving effect. Their impression was that this would be the case but presently this could not be substantiated by hard evidence.

# postoperatives Hirnödem

# The effect of hyperbaric oxygen on clinical outcome of patients after resection of meningiomas with conspicuous peritumoral brain edema

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ABSTRACT

Objective: The goal of this study was to determine the effect of hyperbaric oxygen therapy on the clinical outcome of patients after resection of meningiomas with conspicuous peritumoral brain edema (PTBE).

Patients and methods: 232 patients with intracranial meningiomas and conspicuous PTBE were allocated to the $HBO_2$ Group or the Control Group (116 in each group). The Karnofsky Performance Score (KPS), the focal brain edema and the encephalomalacia in the operative region, as well as the number of patients with neurological deficits were compared statistically between the two groups at different times after the Operation.

Results: On the third day after Operation, the KPS and focal brain edema in the operative region between the $HBO_2$ Group and the Control Group were not significantly different ($p>0.05$), but 15 days after surgery, compared with the Control Group, the KPS of the HBO2 Group appeared obviously higher ($p<0.05$), and the focal brain edema in the operative region was definitely smaller ($p<0.05$). Six months after surgery, the volume of encephalomalacia in operative region and the number of patients with neurological deficits in the HBO2 Group were significantly less than those in the Control Group ($p<0.05$).

Conclusion: HBO2 therapy is effective in reducing edema formation and neurological deficits after resection of meningiomas with conspicuous PTBE.

## INTRODUCTION

Meningiomas arise from arachnoidal cells in the meninges, constitute about 13.4-38% of intracranial tumors in adults and are generally benign [1]. With developments in microtechnique and radiological technology, free survival rates have increased significantly [2-3]. However, despite benign histopathology, peritumoral brain edema (PTBE), a well-known associated pathology, often accompanies meningiomas. PTBE in meningioma may increase peri-operative mortality and morbidity [4], and may induce a variety of complications, such as palsy, mental disturbance (dysnesia), epilepsy and encephalomalacia.

Hyperbaric oxygen therapy (HBO2T) has been positively linked with the reduction of brain edema and the improvement of neurological deficits [5-7]. The purpose of this study was to help determine the effects of HBO2T on the reduction of brain edema and the improvement of neurological deficits after the resection of meningiomas with conspicuous PTBE.

## CLINICAL MATERIAL AND METHODS

232 patients (98 males, 134 females) with supratentorial meningiomas treated surgically at the Affiliated Hospital of North Sichuan Medical College from July 2003 to December 2009 were enrolled into the study. Ages of the patients ranged from 20 to 70 years. All cases were confirmed, upon admission, by CT scan or MRI to be unilateral meningiomas and conspicuous PTBE. The histological diagnosis and the WHO grade were verified through laboratory testing after surgical resection. Exclusion criteria included the following:

1) Patients whose medical condition was not compatible with HBO2 therapy, such as those with severe psychiatric symptoms or epilepsy;
2) Patients having severe systemic disease, such as hypertension or diabetes;
3) Patients with subtentorial or multiple tumors;
4) Patients with obsolete PTBE;
5) Patients who experienced an unexpected event resulting in severe neurological lesion, such as cenencephalocele.

**TABLE 1— *The comparison of charneteristics in two groups***

| Items | HBO2 Group | Control Group | Statistical test, significance |
|---|---|---|---|
| **GENDER** | | | |
| M | 50 | 48 | $X^2 = 0.071, p = 0.790$ |
| F | 66 | 68 | |
| **LOCATION** | | | |
| convexity | 46 | 47 | $X^2 = 0.959, p = 0.966$ |
| cerebral falx | 22 | 24 | |
| anterior cranial fossa | 11 | 10 | |
| middle cranial fossa | 7 | 5 | |
| crista sphenoidalis | 26 | 24 | |
| suprasellar | 4 | 6 | |
| **SUBTYPES*** | | | |
| WHOI | 104 | 106 | $X^2 = 0.201, p = 0.654$ |
| WHOII—III | 12 | 10 | |
| AGE (Years) | | | |
| Mean (SD) | 48.33 (14.52) | 49.51 (15.12) | $t = 1.284, p > 0.05$ |
| **Volume of PTBE($cm^3$)** | | | |
| **Mean** (SD) | 65.39 (11.58) | 60.87 (10.87) | $t = 1.675, p > 0.05$ |
| **Volume of tumor($em^3$)** | | | |
| **Mean** (SD) | 125.35 (25.54) | 121.98 (24.65) | $t = 1.538, p > 0.05$ |
| **KPS** | | | |
| Mean (SD) | 95.43 (12.85) | 96.06(13.14) | $t = 1.462, p > 0.05$ |

*WHO classification of meningiomas: cormnon benign (WHO I), atypical (WHO II) and malignant (WHO III ).

The preoperative and postoperative function status of patients was measured with the Karnofsky Performance Score (KPS). The volume of the tumor, PTBE, the focal brain edema of the operative region and the encephalomalacia in the operative region were calculated six months after surgery, by measuring its three largest perpendicular diameters. The tumor had assumed an ellipsoid shape, although most tumors have a more irregular outline *(see the for mula below).*

$$V-=1/2abc$$

`V' represents the volume of the tumor, PTBE, the focal brain edema of the operative region or the encephalomalacia operative regain; 'a, b, c' represent the three largest perpendicular diameters respectively.

All the patients underwent gross total resection of the tumor under a surgical microscope during the first operation. Dehydration, anti-epileptic, infection prevention and symptomatic treatment were provided for patients after surgery. Three days after surgery, the function status of patients was evaluated with KPS, and a CT scan was performed to calculate the volume of the focal brain edema in the operative region.

232 patients were randomly allocated to the HBO2 Group or Control Group (116 in each group). Every patient obtained a random number upon admission. All 232 random numbers were sorted from least to greatest; the first 116 patients were enrolled in the HBO2 Group, and the latter 116 in the Control Group. The control group received conventional therapy only, as described above, and the HBO2 Group received early $HBO_2$ treatment in addition to conventional therapy.

The patients were placed in a monoplace HBO2 chamber that was pressurized to 2 ATA (atmosphere absolute) over a 20-minute period, maintained at pressure for 20 minutes and then slowly depressurized over a 20-minute period. Each patient received at least 20 HBO2 sessions, one session per day, unless severe complications occurred, clinical condition worsened, the patient re-entered surgery or died during the treatment procedure.

The study protocol was approved by the Medical Ethics Committee of the hospital. Before study, infomied consent was obtained from all patients and their relatives.

Averages and variances reported in *Results* were expressed as the means SEMs. $\chi^2$ test for numeration data and T-test for measurement data via SPSS version 11.5 were performed. Statistical significance was established at a probability value of less than 0.05 in all analyses.

**FIGURE 1_The variances of KPS among preoperative, the third day after operation and the fifteenth day after operation.**

smaller in the $HBO_2$ Group than in the Control Group — 34.58±5.19cm$^3$ in the HBO2 Group versus 47.12±6.37 cm$^3$ in the Control Group (t--8.930, p<0.01) *(Figure 2 below*

**The encephalomalacia in the operative region and the neurological deficits**

Six months after surgery, 97 cases in the HBO2 Group and 105 cases in the Control Group received a follow-up CT scan, and the volume of the encephalomalacia in the operative region were revealed to be smaller in the $H80_2$ Group than that in the Control Group — 8.95±2.34 cm$^3$ in the $HBO_2$ Group versus 13.89+3.67 cm$^3$ (1-2.223, p<0.05). The typical cases were demonstrated in Figure 3 *(Page 112)*. Fifteen cases in the HBO2 Group and 28 cases in the Control Group had neurological deficits such as epilepsy, incomplete paralysis, aphasia, which was significantly different (x2=14.76, p=0.01).

## RESULTS

**The participant characteristics**

There were no significant differences between the two groups in terms of the age, the gender, the volume and the location of tumor, the preoperative KPS, the volume of the PTBE tumor and the histological subtype at the time of entry *(Table I, facing page)*.

**The postoperative KPS**

The KPS an the third day after the Operation was 75.83+13.68 in the $HBO_2$ Group versus 75.25+12.99 in the Control Group, which was not significantly different between the two groups (t=1.837, p>0.05). When compared with the preoperative KPS, the KPS an the third day after operation decreased definitely. Fifteen days after the operation, the KPS of the HBO2 Group was higher than that of the Control Group — 9.5.43±15.61 in the HBO2 Group versus 88.39+14.97 in the Control Group (i=3.921, p<0.05) *(Figure 1, above)*.

**The focal brain edema in the operative region**

On the third day after surgery, there were no significant differences of the focal brain edema in the operative region between the $HBO_2$ Group and the Control Group — 105.63±7.92 cm$^3$ in the HBO2 Group versus 100.99± 8.34 cm$^3$ in the Control Group (t=1.922,p>0.05). On the fifteenth day after the operation, the focal brain edema in the operative region decreased obviously, and was

## DISCUSSION

Meningiomas are primarily extra-axial tumors, physically separated by the arachnoid mater, the subarachnoidal space, the pia mater, as well as the cerebral cortex from the brain, which represent the anatomical barriers protecting the brain from edema associated with meningiomas. Despite this, peritumoral brain edema is present in approximately 60% of all cases of meningiomas [8-9].

FIGURE 2

FIGURE 2 — The variances of focal brain edema in the operative *region* between the $HBO_2$ and Control Groups.

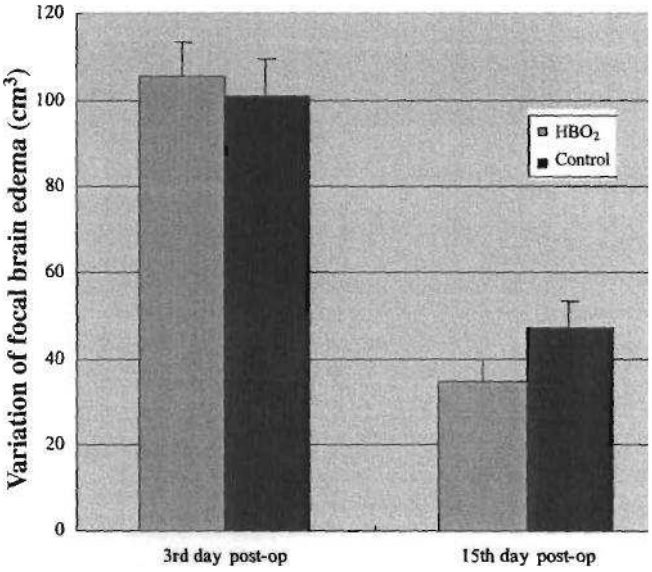

FIGURE 3 — Case 1

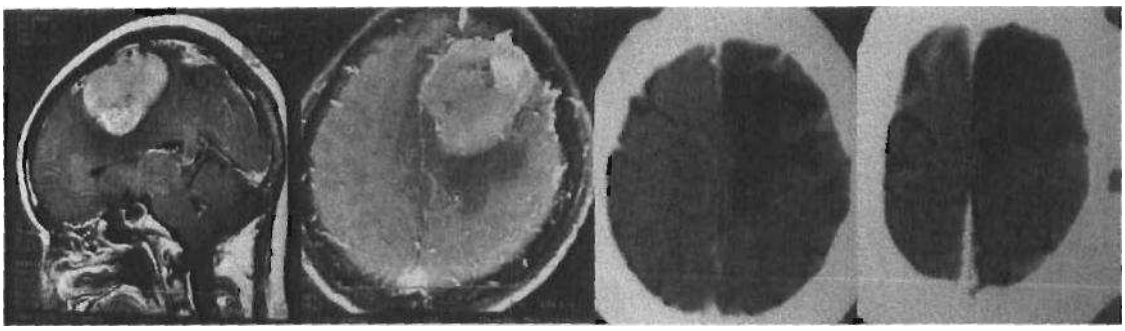

FIGURE 3 — Case 2

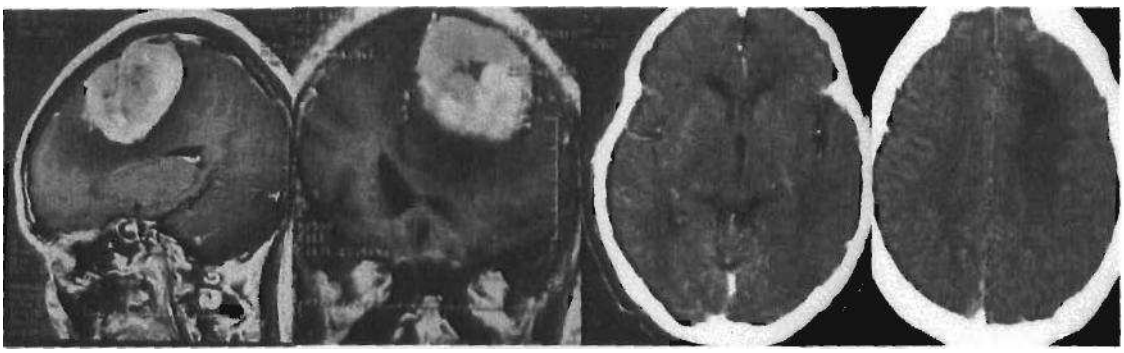

FIGURE 3 – The two cases had similar characteristics in the age, the gender, the volume and location of tumor, the preoperative KPS, the volume of PTBE tumor and the histological subtype, Case 1 received conventional therapy, and Case 2 received early HBO2 treatment in addition to conventional therapy. Half a year aber resection of the tumor, the encephalomalacia in the operative region in Case 2 was smaller than that of Case 1.

The mechanism by which meningiomas produce brain edema is as yet unclear. It is generally assumed that the brain edema associated with meningiomas is more likely vasogenic rather than cytotoxic in origin. Several leading ideas about the pathogenesis of edema associated with meningiomas are listed as follows [10]:

1) Mechanical compression of the tumor induces ischemia [11], which becomes more likely as the size of the tumor increases(12).
2) Meningiomas in venous drainage areas induce stasis and venous congestion [13]. Meningiomas associated with venous changes in sylvian veins and with dysplastic transmedullary veins showed significantly larger edemas, compared with meningiomas without involvement of these vessels [14].
3) Substances produced by the tumor appear in adjacent brain tissue, which then induce edema [15], such as the secretion of prostaglandins [16], the expression of hormone receptors(17), the secretion of vascular endothelial growth factor (VEGF)[18] and so on.
4) The disruption of leptomeningeal barrier results in extravasates from meningiomas to appear in the immediately surrounding brain tissue [19-20].
5) Ischemic alterations can be regarded as secondary, facultative phenomena in the pathogenesis of meningioma-related brain edema [10]. Meningioma-related brain edema induces ischemia of brain tissues with edema, which in turn aggravates brain edema.

Currently, the most important therapies of peritumoral brain edema are resection of the tumor, anhydration, and amelioration of cerebral circulation and metabolism. lt seems that the resection of the tumor removes the mechanical compression of the rumor and the source of secretion and venous congestion. But the resolution of brain edema is still slow after the resection of meningiomas, and in some cases, refractory brain edema occurs, which induces cellular necrosis, the softening of brain tissue in the operative region and leads to neurological deficits such as dizziness, headache, epilepsy, incomplete paralysis and pero-anepia, as demonstrated in this study. Probably, it is difficult for impaired brain tissue to recover, although the source of the lesion has been removed.

The focal brain edema in the operative region includes not only original peritumoral brain edema but also that induced by surgical trauma. Since operation on meningiomas with conspicuous PTBE is much more difficult than that on meningiomas with obsolete PTBE, it requires much more severe drag and cauterization, leading to greater trauma to surrounding tissue.

Ischemia has been implicated as a major cause of secondary brain injury and death following severe brain injury [21-22]. During the early phase of injury, the metabolic needs of the injured brain tissue are increased, and cerebral blood flow (CBF) and delivery of oxygen in the substrate are decreased [23]. Oxygen ($0_2$) delivery to brain tissue is impaired not only by decreased CBF but by reduced 02 diffusion into cells, caused by vasogenic and cytotoxic edema. Inadequate $0_2$ supply to the traumatized brain results in the conversion of an aerobic metabolism to an anaerobic metabolism [24]. This induces acidosis, the loss of ionic homeostasis, abnormally high intracellular concentrations of calcium [25,26], the release of excitatory amino acids and the formation of highly reactive free radicals. The high levels of calcium and excitatory amino acids have been shown to impair the mitochondrial respiratory chain-linked oxidative phosphorylation, leading to further functional failure of aerobic metabolism [23,27-28]. Studies have shown that local brain tissue oxygen levels are significantly correlated with ischemia and outcome [29-30].

Hyperbaric oxygen (HBO2) therapy is defined as a treatment in which a patient intermittingly breathes 100% oxygen under a pressure that is greater than the pressure at sea level [a pressure greater than 1 atmosphere absolute (ATA)] [31]. Current and past studies all seem to agree that the administration of HBO2 is both a potent and viable means to reduce edema formation and improve neurological deficits [5-7].

Jadhav *et al.* reported that hyperbaric oxygen preconditioning could reduce postoperative brain edema and improve neurological outcomes after surgical brain injury in a mouse model of surgical brain injury [5]. In this study, hyperbaric oxygen therapy was applied to patients with conspicuous PTBE at the nonage after resection of meningiomas. After one course of treatment (half a month), compared with the Control Group (which received conventional therapy only), the focal brain edema in the operative region of the HBO2 Group (which received early HBO2 treatment in addition to conventional therapy) decreased significantly, and the KPS in the HBO2 Group increased definitely.

Six months after surgery, compared with the Control Group, the volume of abnormal density in the operative region of the HBO2 group was smaller, and the neurological deficits in the HBO2 Group were relieved more significantly. lt is thus clear that HBO2 therapy is effective on the reduction of edema formation and improvement of neurological deficits after Operation on meningiomas with conspicuous PTBE.

The mechanisms of HBO2 are not yet definite and can be summarized as follows [32]: Following episodes of ischemia, the resultant hypoxia leads to a decrease in energy metabolism. The alterations in energy metabolism can initiate a vicious cycle of events, including brain swelling and raised intracranial pressure, which can lead to secondary ischemia, ultimately leading to cell death. Inhalation of oxygen at increased atmospheric pressures might produce a marked elevation in arterial blood oxygen partial pressures [31] and combat this vicious cycle and facilitate cell survival through three simple mechanisms of action:

I) improve oxygenation to counter the hypoxia;
2) improve or restore energy metabolism; and
3) reduced raised ICP through the improvement in energy metabolism and the vasoconstriction of cerebral vessels [32].

## CONCLUSIONS

To our knowledge, this is the first study demonstrating the effect of $HBO_2$ therapy on the clinical outcome of patients after resection of meningiomas with conspicuous PTBE. As for meningiomas with conspicuous PTBE, the resection of tumor removes the source of brain edema, creating a favorable condition for functional recovery, and it is useful for early HBO2 therapy to reduce edema and

improve neurological function after surgery. HBO2 therapy can be applied as a conventional therapeutic method for this kind of disease.

REFERENCES


1. Bondy M, Ligon BL. Epidemiology and etiology of intracranial meningiomas: a review. J Neurooncol. 1996 Sep;29(3):197-205.

2. Johnson WD, Loredo LN, Slater JD. Surgery and radiotherapy: complementary tools in the management of benign intracranial tumors. Neurosurg Focus. 2008;24(5):E2.

3. Trippa F, Maranzano E, Costantini S, Giorni C. Hypofractionated stereotactic radiotherapy for intracranial meningiomas: preliminary results of a feasible trial. J Neurosurg Sci. 2009 Mar;53(1):7-11.

4. King WA BK. Peritumoral edema with meningiomas. In: HH S, editor. Meningiomas and their Surgical Management. Philadelphia: W.B.Saunders Company; 1991. p. 56-62.

5. Jadhav V, Ostrowski RP, Tong W, Matus B, Chang C, Zhang JH. Hyperbaric oxygen preconditioning reduces postoperative brain edema and improves neurological outcomes after surgical brain injury. Acta Neurochir Suppl. 2010;106:217-20.

6. Perez-Espejo MA, Garcia-Fernandez R, Tobarra-Gonzalez BM, Palma-Copete JD, Gonzalez-Lopez A, De la Fuente-Munoz 1, et al. [Usefulness of hyperbaric oxygen in the treatment of radionecrosis and symptomatic brain edema after LINAC radiosurgery]. Neurocirugia (Astur). 2009 Oct;20(5):449-53.

7. Veltkamp R, Siebing DA, Sun L, Heiland S, Bieber K, Marti HH, et al. Hyperbaric oxygen reduces blood-brain barrier damage and edema after transient focal cerebral ischemia. Stroke. 2005 Aug;36(8):1679-83.

8. Bradac GB, Ferszt R, Bender A, Schorner W. Peritumoral edema in meningiomas. A radiological and histological study. Neuroradiology. 1986;28(4):304-12.

9. Sigel RM, Messina AV. Computed tomography; the anatomic basis of the zone of diminished density surrounding meningiomas. AJR Am J Roentgenol. 1976 Jul;127(1):139-41.

10.Bitzer M, Klose U, Geist-Barth B, Nagele T, Schick F, Morgalla M, et al. Alterations in diffusion and perfusion in the pathogenesis of peritumoral brain edema in meningiomas. Eur Radiol. 2002 Aug;12(8):2062-76.

11.Tatagiba M, Mirzai S, Samii M. Peritumoral blood flow in intracranial meningiomas. Neurosurgery. 1991 Mar;28(3):400-4.

12.Stevens JM, Ruiz JS, Kendall BE. Observation on peritumoural oedema in meningioma. Part I: Distribution, spread and resolution of vasogenic oedema seen on computed tomography. Neuroradiology. 1983;25(2):71-80.

13.Hiyama H, Kubo 0, Tajika Y, Tohyama T, Takakura K. Meningiomas associated with peritumoural venous stasis: three types on cerebral angiogram. Acta Neurochir (Wien). 1994;129(1-2):31-8.

14.Bitzer M, Topka H, Morgalla M, Friese S, Wockel L, Voigt K. Tumor-related venous obstruction and development of peritumoral brain edema in meningiomas. Neurosurgery. 1998 Apr;42(4):730-7.

15.Philippon J, Foncin JF, Grob R, Srour A, Poisson M, Pertuiset BF. Cerebral edema associated with meningiomas: possible role of a secretory-excretory phenomenon. Neurosurgery. 1984 Mar;14(3):295-301.

16.Constantini S, Tamir J, Gomori MJ, Shohami E. Tumor prostaglandin levels correlate with edema around supratentorial meningiomas. Neurosurgery. 1993 Aug;33(2):204-10; discussion 11.

17.Brandis A, Mirzai S, Tatagiba M, Walter GF, Samii M, Ostertag H. Immunohistochemical detection of female sex hormone receptors in meningiomas: correlation with clinical and histological Features. Neurosurgery. 1993 Aug;33(2):212-7; discussion 7-8.

18.Kalkanis SN, Carroll RS, Zhang J, Zamani AA, Black PM. Correlation of vascular endothelial growth factor messenger RNA expression with peritumoral vasogenic cerebral ederna in meningiomas. J Neurosurg. 1996 Dec;85(6):1095-101.

19.Ito U, Tomita H, Tone 0, Masaoka H, Tominaga B. Peritumoral edema in meningioma: a contrast enhanced CT study. Acta Neurochir Suppl (Wien). 1994;60:361-4.

20.Bitzer M, Nagele T, Geist-Barth B, Klose Gronewaller E, Morgalla M, et ah Role of hydrodynamic processes in the pathogenesis of peritumoral brain edema in meningiomas. J Neurosurg. 2000 Oct;93(4):594-604.

21.Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg. 1992 Sep;77(3):360-8.

22.Siesjo BK, Siesjo P. Mechanisms of secondary brain injury. Eur J Anaesthesiol. 1996 May;13(3):247-68.

23.Menzel M, Doppenberg EM, Zauner A, Soukup J, Reinert MM, Bullock R. Increased inspired oxygen concentration as a factor in improved brain tissue oxygenation and tissue laetate levels after severe human head injury. J Neurosurg. 1999 Jul;91(1):1-10.

24.Krebs EG. Protein kinases. Curr Top Cell Regul. 1972; 5:99-133.

25.Siesjo BK. Basic mechanisms of traumatic brain damage. Ann Emerg Med. 1993 Jun;22(6):959-69.

26.Young W. Role of calcium in central nervous system injuries. J Neurotrauma. 1992 Mar;9 Suppl 1:S9-25.

27.Siesjo BK, Agardh CD, Bengtsson F. Free radicals and brain damage. Cerebrovasc Brain Metab Rev. 1989 Fall;1(3):165-211.

28. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL,
Xiong Y, Lee CP. Mitochondrial dysfunction after experimental and human brain injury and its possible reversal with a selective N-type calcium channel antagonist (SNX-111). Neurol Res. 1997 Jun;19(3):334-9.

29, Valadka AB, Goodman JC, Gopinath SP, Uzura M, Robertson CS. Comparison of brain tissue oxygen tension to microdialysis-based measures of cerebral ischemia in fatally head-injured humans. J Neurotrauma. 1998 Jul;15(7):509-19.

30. van den Brink WA, van Santbrink H, Steyerberg EW, Avezaat CJ, Suazo JA, Hogesteeger C, et al. Brain oxygen tension in severe head injury. Neurosurgery. 2000 Apr;46(4):868-76; discussion 76-8.

31. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mcchanisms of action and outcomes. QJM. 2004 Jul;97(7): 385-95.

32. Calvert JW, Cahill J, Zhang 111. Hyperbaric oxygen and cerebral physiology. Neurol Res. 2007 Mar;29(2):132-41.

# Effects of early hyperbaric oxygen therapy on clinical outcome in postoperative patients with intracranial aneurysm

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## ABSTRACT

**Objective:** To investigate the effects of hyperbaric oxygen (HBO2) in postoperative patients with intracranial aneurysm.

**Methods:** A total of 120 patients who underwent clipping of intracranial aneurysm of the anterior circulation were randomized into the HBO2 group (n=60) or the Control group (n=60). Compared with the Control group, patients in the HBO2 group received additional HBO2 therapy, which was initiated within one to three days as soon as they were deemed clinically stable, for at least 20 sessions (one session per day). Mean flow velocities of the middle cerebral artery (MCA) on the operative approach side were measured on Days 1, 3, 7, 14 and 21 after operation. CT scans were performed on Days 1, 7, 14 and 21 after surgery to determine the abnormal density volume in the operative area. Cases associated with symptomatic cerebral vasospasm (CVS) were assessed on Days 3, 7 as well as 14, and the functional state determined by Karnofsky Performance Scale (KPS) score was evaluated on Days 3 and 21 after operation. Finally, Glasgow Outcome Scale (GOS) scores were obtained at six months after surgery.

**Results:** There were no differences between groups in terms of the mean flow velocities of MCA on the operative approach side, the cases with symptomatic CVS, and the KPS scores within three days after surgery ($P>0.05$). Compared with those of the Control group, the mean flow velocities of MCA on the operative approach side were significantly lower in the HBO2 group on Days 7 and 14 ($P<0.05$ or $P<0.01$). On Days 7, 14 and 21, patients in the $HBO_2$ group had smaller HBO2 density volume in the operative region than those in the Control group ($P<0.05$). The $HBO_2$ group developed less cases of symptomatic CVS than the Control group did on Days 7 ($x^2=4.04$, $P<0.05$) and 14 ($x2=4.18$, $P<0.05$). The KPS scores were higher on Day 21 after surgery in the $HBO_2$ group ($P<0.05$). More patients in the $HBO_2$ group achieved GOS scores of 4 and 5 at six months after surgery ($x^2=6.032$, $P<0.05$).

**Conclusions:** Early $HBO_2$ appears to be beneficial as an adjunctive treatment of postoperative intracranial aneurysm. Attenuating postoperative CVS, brain edema, and cerebral ischemia contributes to the effectiveness of HBO2.

## INTRODUCTION

Surgical management of intracranial aneurysm has been gradually improving. Owing to the irreversible brain damage and the secondary brain injuries stemming from subarachnoid hemorrhage (SAH), brain retraction and postoperative cerebral vasospasm (CVS), a substantial fraction of such patients are still involved in a long recovery period with poor outcomes [1,2,3]. A wide variety of prophylactic and therapeutic neuroprotective strategies have been proposed to protect the brain from such insuits, but outcomes remain disappointing [4,5]. Clazosentan, a lad of endothelin receptor antagonist, showed marked prevention of angiographic vasospasm, yet little effect on neurological function and clinical outcome at three months were found [6]. Intraoperative hypothermia did not improve the neurologic outcome among good-grade patients with aneurysmal SAH [1]. Even the traditional "triple-H" therapy (treatment that induces hypertension, hypovolemia and hemodilution to help counteract vasoaspasm) has been challenged by a recent randomized trial, in which the postoperative prophylactic hypervolemic therapy exhibited no effect on the incidence of symptomatic CVS nor on clinical outcome at the time point of Day 14 and three months after surgery in patients with aneurysmal SAH [7].

Hyperbaric oxygen (HBO2) therapy has been used in multiple neurological diseases and has shown satisfying therapeutic effects [8-13]. Up to now, however, few

studies have focused on the effects of $HBO_2$ therapy in postoperative intracranial aneurysm patients. We therefore conducted the current randomized trial to investigate the influences of HBO2 in the patients with intracranial aneurysm of anterior circulation alter surgery.

## PATIENTS AND METHODS

### Study design and setting

Patients enrolled into this trial were those who underwent clipping of intracranial aneurysm of the anterior circulation at the Affiliated Hospital of North Sichuan Medical College from July 2002 to March 2009. The exclusion criteria were:

(i) intracranial hemorrhage after surgery;
(ii) history of severe hematological, respiratory, cardiovascular and central nervous diseases;
(iii) underwent operation again or died during the trial.

Eligible patients were randomly allocated to receive either early $HBO_2$ in addition to conventional therapy (HBO2 group) or conventional therapy alone (Control group). The study protocol was approved by the Medical Ethics Comrnittee of the hospital. Before the study, informed consent was obtained from all patients or their relatives.

Because no previous studies have identifiecl a correlation between clinical outcomes and $HBO_2$ in such patients, we estimated that a sample size of 100 patients would be sufficient for this study. Considering there would be 20-30% dropout after randomization according to local experiences and literature, we aimed to recruit 150 patients in total, and the random selection was based on a computer-generated list that assigned patients with a ratio of 1:1 to groups consecutively.

### Conventional therapy

All patients underwent surgical clipping of the aneurysm under highpower magnification from a surgical microscope via a pterional approach [14]. In addition, all patients received 20mg nimodipine administered intravenously (IV) once a day for seven to 10 days and 30mg papaverine given intramuscularly (IM) three times a day for three days after surgery. Triple-H treatments were provided for patients who exhibited symptomatic CVS on the basis of the guidelines proposed by the Stroke Council of the American Heart Association in 2009 [15].

### Hyperbaric oxygen therapy

A CT scan was performed within 24 hours after surgery, with vital signs closely monitored. $HBO_2$ therapy was initiated within one to three days as soon as the patients in the $H80_2$ group were deemed clinically stable The patients were placed in a monoplace HBO2 chamber that was pressurized to 2 ATA (atmospheres absolute) over a 20-minute period. The pressure was maintained for 20 minutes and then slowly depressurized over a 20-minute period. Each patient received at least 20 $HBO_2$ sessions, one session per day, unless severe complications occurred, illness condition worsened, surgery was reinitiated or the patient died during the treatment procedure.

### Outcome measurements

The primary endpoint was the Glasgow Outcome Scale (GOS) scores, and the secondary endpoints were mean ftow velocities of the middle cerebral artery (MCA), abnormal density volume in the operative region, cases associated with symptomatic CVS, and Karnofsky Performance Scale (KPS) scores.

The mean flow velocity on the operative approach side of MCA was measured by transcranial Doppler (TCD) on Days 1, 3, 7, 14 and 21 after surgery. An additional 10 gender- and age-matched healthy volunteers were selected to examine mean flow velocity of MCA as normal controls. CT scans were performed on Days 1, 7, 14 and 21 after surgery to determine the abnormal density volume — mainly including cerebral infarction or focal brain edema, in the operative region according to the Tada Formula [16]. Cases associated with symptomatic CVS were assessed on Days 3 and 7, as well as 14 days after surgery.

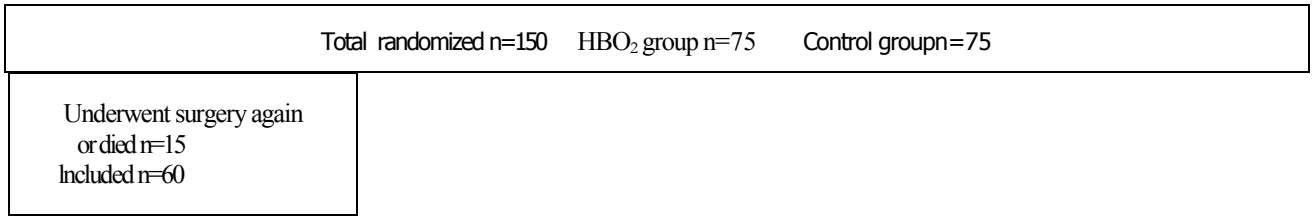
We diagnosed symptomatic CVS on the basis of a combination of:

1. the development of focal neurological signs or deterioration of the level of consciousness, or both, occurring between 3 and 14 days alter surgery; and
2. an increase in mean TCD velocities of 120 cm/second in the investigated territories [17].

We considered a 1-point Glasgow Coma Scale (GCS) decrease as a meaningful deterioration. The KPS scores, a well-known numerical scale designed to measure patients' status relative to the degree of independence in carrying out normal activities and self-care [18], were assessed on Days 3 and 21 after surgery. By interviewing or telephoning the patient or the patient's relatives, GOS scores [19] were obtained at six months after surgery to assess the clinical outcome. Good clinical outcome was defined as a GOS of 4 or 5 **[20].**

**FIGURE 1**

***CONSORT flow diagram of trial***




**Statistical analysis**

Data were statistically analyzed using SPSS 10.0 (SPSS Inc., Chicago, 111., USA). Values were expressed as mean ± SD. Descriptive statistics were calculated for the entire sample and for individual study groups. Group differences were tested with ANOVA, Student T-test, $\chi^2$ and the Mann-Whitney test for numeric and categorical variables, respectively. In all analysis, a *P*-value of <0.05 was deemed statistically significant.

## RESULTS

**Participant characteristics**

During the nearly seven years of the study period, 213 patients were assessed for eligibility. A total of 120 — 60 in each group — were included *(Figure I, above).* There were no significant differences between the two groups in terms of age, sex, aneurysm location or illness condition at the time of study entry *(Table 1, Page 496).*

Patients in the $HBO_2$ group received 20-50 HBO2 sessions; total number of $HBO_2$ treatments was 1,750 sessions. Duration of triple-H therapy patients received was seven to 10 days without differences between groups.

**Mean flow velocities of MCA**

As depicted in *Figure 2 (Page 497),* the mean flow velocities of MCA on the operative approach side were significantly higher in two groups, compared with the normal subjects on Days 1 and 3 after surgery (P<0.01), but there were no differences between groups (P>0.05). On Days 7 and 14 after surgery, the mean flow velocities of MCA in both groups were still higher than those of the normal subjects (P<0.05). However, $HBO_2$ group exhibited lower than did the Controls (P<0.05 or P<0.01). On Day 21 after surgery, the mean flow velocities of MCA of both groups decreased to the normal level and no differences were found between groups (P<0.05).

**TABLE 1**

*Summary of demographics and aneurysm characteristics*

| | HBO2 GROUP | CONTROL GROUP |
|---|---|---|
| **No. of patients** | 60 | 60 |
| **M:F ratio** | 32:28 | 30:30 |
| **Age** (years) | | |
| Average age | 47.6 | 48.3 |
| Range | 31-76 | 29-75 |
| **Blood pressures** (mmHg) | | |
| Systolic pressure | 135.1±14.9 | 134.7±15.5 |
| Diastolic pressure | 87.3±11.1 | 85.5±12.3 |
| **Hunt-Hess Grade** | | |
| | 4 | 6 |
| | 26 | 28 |
| Ili | 18 | 16 |
| IV | 12 | 10 |
| **Aneurysm location** | | |
| PCoA | 28 | 29 |
| ACoA | 16 | 15 |
| ICA-C1.C2 segment | 6 | 7 |
| MCA | 3 | 2 |
| ACA | 2 | 3 |
| Others | 5 | 4 |
| **Co-morbidities** | | |
| Hypertension | 20 | 17 |
| Coronary artery disease | 10 | 11 |
| Hepatitis | 12 | 14 |
| Diabetes mellitus | 7 | 6 |
| Others | 4 | 4 |
| **Total HBO2 sessions** (n) | 1750 | |
| **Duration of triple-H therapy** (d) | 8.1±1.1 | 8.3±1.2 |

**TABLE 1:** *PCoA:* posterior communicating artery; *ACoA:* anterior communicating artery; *ICA:* internal carotid artery; *MCA:* middle cerebral artery; *ACA:* anterior cerebral artery.

Data are *n* or mean±SD.

**TABLE 2**

| Group | D3 *(n)* | *D7 (n)* | D14 *(n)* |
|---|---|---|---|
| **HBO** | 41 | 26 | 5 |
| **Control** | 39 | 37 | 13 |
| **P** | >0.05 | <0.05 | <0.05 |

**TABLE 2:** Comparison of cases associated with symptomatic CVS at different times between groups

**Abnormal density volume in operative region**

On Day 1 after surgery, there was no significant cerebral infarction, brain edema or hemorrhage in any patients, while on Days 7, **14** and 21 alter surgery, 16 patients in the $HBO_2$ group and 18 in the Control group exhibited abnormal density lesions, cerebral infarction or brain edema without significant differences between two groups ($x^2$=0.164, P>0.05). However, on Days 7, 14 and 21 after surgery, patients in the $HBO_2$ group showed smaller abnormal density volumes than those in the Control group (P<0.05) *(Figure 3, facing page* and *Figure 4, Page 498).*

**Cases associated with symptomatic cerebral vasospasm**

There was no difference between groups on Day 3 after surgery as to the symptomatic CVS exhibited, with 41 patients in the $HBO_2$ group and 39 in the Control group ($x^2$=0.15, P>0.05). These values decreased to 26 and 37 on Day 7 after surgery, respectively, and a significant difference was found ($x^2$=4.04, P<0.05). At Day 14 after surgery, only five showed symptomatic CVS in the $HBO_2$ group while 13 displayed in the Control group, with significant differences ($x^2$=4.18, P<0.05) *(Table 2, below left).*

KPS and GOS score

As illustrated by *Figure 5 (Page 498),* the HBO2 group showed higher KPS scores than those of the Control group on Day 21 after surgery (t=3.942, P<0.05). As to the clinical outcome at six months alter surgery measured by GOS score, three patients in the $HBO_2$ group and two in the Control group failed to follow up. Among these patients, 54 (94.7%) in the $HBO_2$ group achieved GOS scores of 4 and 5 at six months after surgery, while only 46 (79.3%) in the control group did ($x^2$=6.032, P<0.05) *(Table 3, Page 499).*

## FIGURE 2

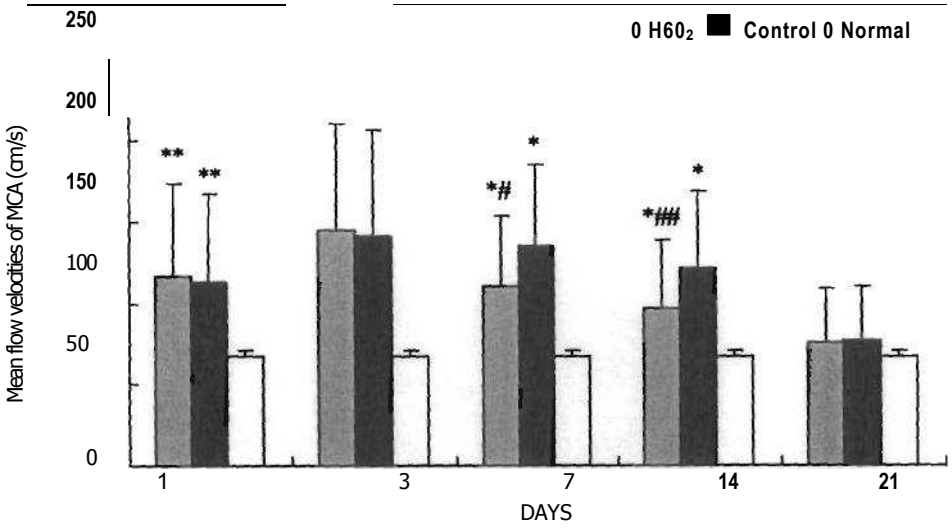
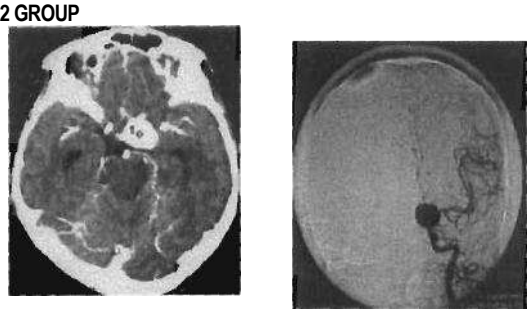



**FIGURE 2:** Comparison of mean flow velocities of MCA on the operative approach side at different times between groups. Data are mean±SD (cm/s). "*P*< 0.05 for HBO2 or Control *vs.* Normal values. "* *P* < 0.01 for HBO2 or Control *vs.* Normal values. # *P* < 0.05 for HBO2 *vs.* Control group. ## *P* < 0.01 for HBO2 *vs.* Control group.

## FIGURE 3

**11B02 GROUP**



**CONTROL GROUP**

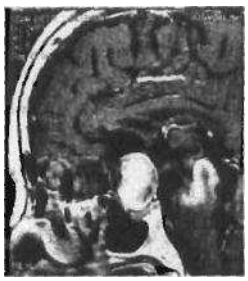


**FIGURE 3:** Comparison of CT scans of two representative cases between groups on Day 14 after surgery. The two patients were female and without differences in terms of the age, aneurysm size and location, surgical approach, and the illness condition at the time of study enlry. On Day 14 alter surgery, as indicated by the arrows in the above CT images, the patient who received $HBO_2$ therapy exhibited slightly abnormal density areas in the operative region with no midline shift and a normal cerebral ventricle system. However, the patient in the Control group showed marked *I* arger abnormal density areas, mild midline shift, and the narrowing of the cerebral ventricle system.

**FIGURE 4**

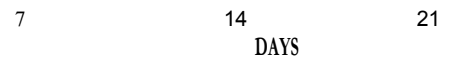



FIGURE 4: Comparison of abnormal density volume in operative region at different times between groups. Data are mean±SD (m1). *$P$< 0.05 for the Control group versus the $HB0_2$ group.

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DISCUSSION

Despite the present treatment strategies, the rate of related permanent disability in intracranial aneurysm patients is estimated as 30% [2]. In our study, 20.6% of the Control group exhibited GOS scores of 2 or 3 at six months after surgery as demonstrated in *Tuble 3 (facing*

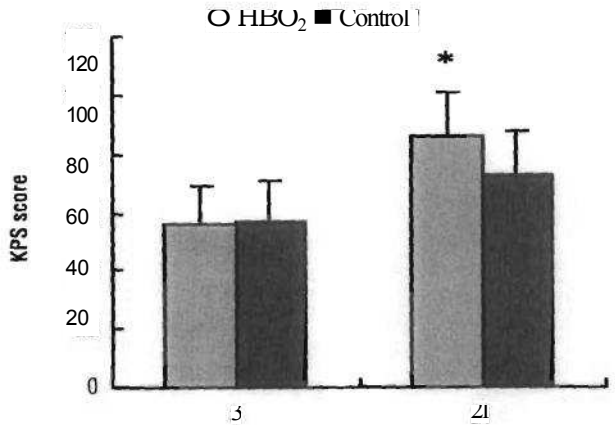


**FIGURE 5**

FIGURE 5: Comparison of KPS scores between groups. *P<0.05 for $HB0_2$ versus Control group

*page).* The excluded patients who underwent surgery a second time might partially contribute to the slightly declined rate. However, patients in the $HBO_2$ group had higher KPS scores an Day 21, and only 5.3% of the $HBO_2$ group showed GOS scores of 3 at six months after surgery, indicating that an early adjunctive HBO2 therapy could significantly improve clinical outcomes.

CVS often occurs between three and 12 days after aneurysmal SAH and remains the classic cause of delayed neurological deterioration in such patients, leading to cerebral ischemia and infarction, and thus to poor outcome and, occasionally, death [21]. In our study, we monitored symptomatic CVS though clinical signs of neurologic deterioration combined with the MCA mean flow velocities via TCD, which has a sensitivity that is similar to that of cerebral angiography for the detection of narrowed vessels, particularly in the middle cerebral and internal cerebral arteries [22], with the results of significantly increased mean flow velocities of MCA within 14 days after surgery and approximately 60% of the patients developing symptomatic CVS in this period. Mechanical stimulation to the vascular wall, intraoperative bleeding as well as SAH before surgical clipping are regarded as the causes of postoperative CVS [23]. The following increased levels of oxyhemoglobin, erythrocytes and hemolysates of erythrocytes, endothelin, oxygen-derived free radicals, arachidonic acid, serotonin. and cytokines, as well as the decreased levels of nitric

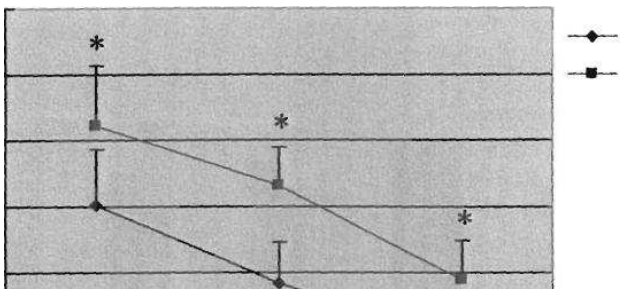

**TABLE 3**

| GOS | HBO | | Control | |
|---|---|---|---|---|
| | No. | Percentage | No. | Percentage |
| 5 | 44 | 77.1% | 36 | 62.1% |
| 4 | 10 | 17.5% | 10 | 17.2% |
| 3 | 3 | 5.2% | 10 | 17.2% |
| 2 | 0 | | 2 | 3.4% |
| Total | 57 | | 58 | |

*Comparison of GOS scores between groups*

oxide in the cerebrovascular microenvironment may be responsible for the development of CVS [24,25]. Studies have shown HBO7 could inhibit inflammation [26]; enhance superoxide dismutase [26]; reduce COX-2 mRNA and protein expression in ischemic hemispheres after MCA occlusion/reperfusion in rats [27]; downregulate prostaglandin-E in rabbits [28]; induce the release of caeruloplasmin [29], an antioxidant capable of catalyzing both the release of NO from RSNOs [30] and the formation of RSNOs [31]. An animal study showed that intracarotid infusion of NO in primate vasospastic arteries increased cerebral blood flow (CBF) and significantly reversed angiographic spasm [32]. The current study demonstrated evident therapeutic effect an symptomatic CVS with the application of $HBO_2$, which might be attributable to its ability to regulate the changed cerebrovascular microenvironment after SAH.

The endothelin receptor antagonist clazosentan showed obvious prevention of CVS, yet patients' outcome was not improved [6]. Rabinstein *et al.* [33] reported that patients with better clinical grades (World Federation of Neurosurgical Societies Grades I-11I) at hospital admission were less likely to suffer symptomatic vasospasm when treated by endovascular coil occlusion, compared with craniotomy and clip application. However, no significant differente as to the longest overall outcome, measured by GOS score, was found between the two treatment groups. Hence, it implies that CVS is not the only cause of poor outcome and that there are some other mechanisms responsible for the HBO2-induced effects.

A number of studies have shown that initial neurological condition of the patient and delayed cerebral ischemia were closely associated with poor outcome [5,34]. SAH can directly lead to increased intracranial pressure (ICP) and decreased cerebral perfusion pressure (CPP) with the consequence of brain ischemia [5].

Microthrombi were common in small cerebral blood vessels in patients who developed clinical or radiological delayed ischemia [35]. In addition, hypoxiainducible factor la (H1F-1 a) and caspase-3 are activated in response to SAH [36,37]. As a result, the neuronal apoptosis is triggered. Besides, HIF-la could activate vascular endothelial growth factor (VEGF) and further contribute to blood—brain barrier (BBB) dysfunction, leading to brain edema [36]. Animal studies have demonstrated that there are apoptotic neurons exhibited in 35% of rats seven days after SAH while in the absente of anterior cerebral artery vasospasm [38]. In our study, however, more patients exhibited vasospasm while fewer patients displayed abnormal density volume around the aneurysm region as reflected by CT scans. The reason for it might be that CT scan is ineffective to detect all brain infarctions or minor neuronal death. Stein *et al.* [39] also found in 29 SAH patients, clinical ischemia was documented in only 14 (48%) patients, but 27 (93%) exhibited pathological evidence of ischemia when the brains of these patients were examined after they died.

As illustrated by Figure 3 and Figure 4, patients in the HBO, group exhibited smaller abnormal density volumes than the Control group, indicating $HBO_2$ attenuates brain edema and cerebral ischemia. Its ability to increase tissue oxygen delivery directly, and consequently improve penumbral energy metabolism, decrease 1CP, improve CBF and CPP, stimulates angiogenesis and establish a new capillary blood supply may be the most evident underlying mechanisms [26,36]. In addition, HBO2 may inhibit the aggregation of platelet via NO to reduce the formation of microthrombi. What's more, recent studies have found that $HBO_2$ may directly affect gene expression related to apoptosis. Yin *et al.* [40] and Huang *et al.* [41] reported HBO2 decreased the expression of caspase-3 and HIF-la in focal cerebral ischemic rats. Ostrowski *et al.* [36] also found that $HBO_2$ reduced the expression of H1F-la and its target genes VEGF and $BNIP_3$ in SAH rats. Accordingly, BBB function was preserved and neuronal death was inhibited. Besides, several studies showed that $HBO_2$ was capable of activating neural stem cells existing in the brain lifelong, and promoting brain cell proliferation in cerebral ischemic rats [42,43].

The main limitation of this study was we did not adopt some measures, such as having the controls breathed air in a monoplace chamber to let patients not know the specific group they entered. However, a great number of patients participating in the study were unconscious

and those who detected and monitored the medical conditions were blind to the study design. Thus, this would not exert significant influence on the results of the study. The second limitation was that we did not measure some biomarkers related to putative underlying mechanisms. This will be done in our future study to help us better understand and interpret the effects of $H130_2$.

## CONCLUSIONS

Results from the current study elucidated that early HBO2 therapy as an adjunct treatment of postoperative intracranial aneurysm improved the postoperative CVS, brain edema, cerebral ischemia and neurologic function. The mechanisms of the actions of $HBO_2$ require further study.



## REFERENCES


1. Todd MM, Hindman BJ, Clarke WR, et al. Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005;352:135-145.

2. Van Gijn J, Rinkel GJE. Subarachnoid haemorrhage: Diagnosis, causes and management. Brain 2001;124:249-278.

3. Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. N Engl J Med 2006:354:387-396.

4. Frietsch T, Kirsch JR. Strategies of neuroprotection for intracranial aneurysms. Best Pract Res Clin Anaesthesiol 2004;18:595-630.

5. Macdonald RL, Pluta RM, Zhang JH. Cerebral vasospasm after subarachnoid hemorrhage: The emerging revolution. Nat Clin Pract Neurol 2007;3:256-263.

6. Macdonald RL, Kassell NF, Mayer S. et al. Clazosentan to overcome neurological ischemia and infaretion occurring after subarachnoid hemorrhage (conscious-1): Randomized, double-blind, placebo-controlled phase 2 dose-finding trial. Stroke 2008;39:3015-3021.

7. Capampangan DJ, Wellik KE, Aguilar MI, et al. Does prophylactic postoperative hypervolemic therapy prevent cerebral vasospasm and improve clinical outcome after aneurysmal subarachnoid hemorrhage? The Neurologist 2008;14:395-398.

8. Hardy P, Johnston KM, Beaumont LD, et al. Pilot case study of the therapeutic potential of hyperbaric oxygen therapy on chronic brain injury. J Neurol Sci 2007;253:94-105.

9. Chen S, Xiao N, Zhang X. Effect of combined therapy with ephedrine and hyperbaric oxygen on neonatal hypoxic-ischemic brain injury. Neurosci Lett 2009:465:171-176.

10.Topuz K, Kutlay A M, Simsek H, et al. Effect of hyperbaric oxygen therapy on the duration of treatment of spinal tuberculosis. J Clin Neurosci 2009;16:1572-1577.

11. Fischer BR, Speckmann EJ, Greiner C, et al. Hyperbaric oxygen in neurosurgery. Acta Neurochir (Wien) 2009;151:415-418.

12. Larsson A, Engstr m M, Uusijrvi J, et al. Hyperbaric oxygen treatment of postoperative neurosurgical infections. Neurosurgery 2008;62:562-571.

13. Rockswold SB, Rockswold GL, Zaun DA, et al. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. J Neurosurg 2010;112:1080-94.

14. Eguchi T. Our surgical tactics for cerebral aneurysms, especially modified pterional approach and transcondylar and fossa approach. International Congress Series 2004;1259:191-196.

15. Bederson JB, Connolly Jr ES, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 2009;40:994-1025.

16. Matteis M, Vernieri F, Troisi E, et al. Early cerebral hemodynamic changes during passive movements and motor recovery after stroke. J Neurol 2003;250:810-817.

17. Charpentier C, Audibert G, Guillemin F, et al. Multivariate analysis of predictors of cerebral vasospasm occurrence after aneurysmal subarachnoid hemorrhage. Stroke 1999;30:1402-8.

18. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Evaluation of Chemotherapeutic Agents. New York: Cotumbia University Press: 1949:191-205.

19. Jennett B, Bond M. Assessment of outcome after severe brain damage: A practical scale. Lancet 1975;305:480-484.

20. Hop JW, Rinkel GJE, Algra A, van Gijn J. Case-fatality rates and functional outcome after subarachnoid hemorrhage: a systematic review. Stroke 1997;28:660-664.

21. Brisman JL, Song JK, Newell DW. Cerebral aneurysms. N Engl J Med 2006;355:928-939.

22. Suarez JI, Qureshi AI, Yahia AB, et al. Symptomatic vasospasm diagnosis after subarachnoid hemorrhage: Evaluation of transcranial doppler ultrasound and cerebral angiography as related to compromised vascular distribution. Crit Care Med 2002;30:1348-1355.

23. Kitazawa K, Hongo K, Tanaka X, et al. Postoperative vasospasm of unruptured paraclinoid carotid aneurysms: Analysis of 30 cases. 1 Clin Neurosci 2005;12:150-155.

24. Khurana VG, Besser M. Pathophysiological basis of cerebral vasospasm following aneurysmal subarachnoid haemorrhage. J Clin Neurosci 1997;4:122-131.

25. Pluta RM. Delayed cerebral vasospasm and nitric oxide: Review, new hypothesis, and proposed treatment. Pharmactii Ther 2005;105:23-56.

26. Zhang JH, Lo T, Mychaskiw G, et al. Mechanisms of hyperbaric oxygen and neuroprotection in stroke. Pathophysiology 2005;12:63-77..

27. Yin W, Badr AE, Mychaskiw G, et al. Down regulation of cox-2 is involved in hyperbaric oxygen treatment in a rat transient focal cerebral ischemia model. Brain Res 2002;926:165171.

28. Niu K; Huang WT, Lin MT, et al. Hyperbaric oxygen causes both antfinflammation and antipyresis in rabbits. Eur J Pharmacol 2009;606:240-245.

29. Shaw FL, Winyard PG, Smerdon GR, et al. Hyperbaric oxygen treatment induces platelet aggregation and protein release, without altering expression of activation molecules. Clin Biochem 2009;42:467-476.

30. Crane MS, Rossi AG, Megson IL. A potential role for extracellular nitric Oxide generation in cgmp-independent inhibition of human platelet aggregation: Biochemica1 and pharmacological considerations. Br J Pharmacol 2005;144:849859.

31. Inoue K, Akaike T, Miyamoto Y, et al. Nitrosothiol Formation catalyzed by ceruloplasmin. J Biol Chem 1999;274:27069-27075.

32. Afshar JKB, Pluta RM, Boock RJ, et al. Effect of intracarotid nitric oxide on primate cerebral vasospasm after subarachnoid hemorrhage. J Neurosurg 1995;83:118-122.

33. Rabinstein AA, Pichelmann MA, Friedman JA, et al. Symptomatic vasospasm and outcomes following aneurysmal subarachnoid hemorrhage: A comparison between surgical repair and endovascular coil occlusion. J Neurosurg 2003;98:319-325.

34. Ducruet AF, Gigante PR, Hickman ZL, et al. Genetic determinants of cerebral vasospasm, delayed cerebral ischemia, and outcome after aneurysmal subarachnoid hemorrhage. J Cereb Blood Flow Metab Jan 13, 2010 online.

35. ichba FA, Mustafa G, Friedrich Jr V, et al. Acute microvascular platelet aggregation after subarachnoid hemorrhage. J Neurosurg 2005;102:1094-1100.

36. Ostrowski RP, Colohan ART, Zhang JH. Mechanisms of hyperbaric oxygen-induced neuroprotection in a rat model of subarachnoid hemorrhage. J Cereb Blood Flow Metab 2005;25:554-571.

37. Guo FY, Li ZH, Song LJ, et al. Increased apoptosis and cysteinyl aspartate specific protease-3 gene expression in human intracranial aneurysm. J Clin Neurosci 2007;14:550-555.

38. Prunell GF, Svendgaard NA, Alkass K, et al. Delayed cell death related to acute cerebral blood flow changes following subarachnoid hemorrhage in the rat brain. J Neurosurg 2005;102:1046-1054.

39. Stein SC, Browne KD, Chen XH, et al. Thromboembolism and delayed cerebral ischemia after subarachnoid hemorrhage: An autopsy study. Neurosurgery 2006;59:781-787.

40. Yin D, Zhou C, Kusaka I, et al. Inhibition of apoptosis by hyperbaric oxygen in a rat focal cerebral ischemic model. J Cereb Blood Flow Metab 2003;23:855-864.

41. Huang ZX, Kang ZM, Gu GJ, et al. Therapeutic effects of hyperbaric oxygen in a rat mode] of endothelin-1-induced focal cerebral ischemia. Brain Res 2007;1153:204-213.

42. Günther A, Köppers-Tiedt L, Schneider PM, et al. Reduced infarct volume and differential effects on glial cell activation after hyperbaric oxygen treatment in rat permanent focal cerebral ischemia. EurJ Neurosci 2005;21:3189-3194. 43, Wang XL, Zhao Y, Yang YJ, et al. Therapeutic window of hyperbaric oxygen therapy for hypoxic-ischemic brain damage in newborn rats. Brain Res 2008;1222:87-94.

# Supportive Tumortherapie mit HBO

**Abschlussbericht des**

# Ausschusses Krankenhaus nach §137c SGB V (g-BA)

## Methode:
## Hyperbare Sauerstofftherapie (HBO)
## Indikation:
## Neuroblastom im Stadium IV

Laut Bekanntmachung im
Bundesanzeiger Nr. 240, Seite 26 001 vom 23. Dezember 2003



### Hyperbare Sauerstofftherapie bei Neuroblastom im Stadium IV

Bei der Überprüfung des Neuroblastoms im Stadium IV kommt der Ausschuss zu einem zweiteiligen Ergebnis.

„Die hyperbare Sauerstofftherapie bei der Indikation Erstmanifestation eines Neuroblastom im Stadium IV erfüllt derzeit weder alleine noch in Kombination mit einer anderen Therapie die Kriterien des § 137 c SGB V (ausreichend, zweckmäßig, wirtschaftlich) und ist damit keine Leistung im Rahmen der gesetzlichen Krankenversicherung."

„Bei der Indikation Rezidiv eines Neuroblastoms im Stadium IV erfüllt derzeit die hyperbare Sauerstofftherapie als Kombinationstherapie mit 131I-MIBG die Kriterien des § 137 c SGB V und ist damit Leistung im Rahmen der gesetzlichen Krankenversicherung."

Bei der Beratung der relevanten Studien wurde festgestellt, dass für die Erstmanifestation des Neuroblastoms im Stadium IV keine Evidenz gefunden

werden konnte, die auf den Einsatz der hyperbaren Sauerstofftherapie hinweist. Aufgrund der Schwere der Erkrankung wurde in diesem Zusammenhang intensiv die besondere Bedeutung des Beschlusses für die betroffenen Patienten beraten. Hierbei zeigte sich, dass bereits heute ca. 90 % der an Neuroblastom erkrankten Kinder im Rahmen von klinischen Studien behandelt werden, so dass die Anwendung des Verfahrens als Ultima-ratio im Rahmen von klinischen Studien, welche bekanntermaßen in ihrer Durchführung von den Beschlüssen des Ausschuss Krankenhaus unberührt bleiben, fortgesetzt werden kann. Eine diesbezügliche Klärung der Evidenzlage wird von Seiten des Ausschusses empfohlen.

Zum Rezidiv bei Neuroblastom im Stadium IV konnte gezeigt werden, dass die hyperbare Sauerstofftherapie in Kombination mit der 131I-MIBG derzeit den Kriterien nach § 137 c SGB V entspricht. Grundlage ist eine entsprechende Studie, die zeigen konnte, dass durch die Therapie mit 131I-MIBG und HBO die Mortalität gesenkt und die kumulative Überlebenszeit verlängert werden konnte.

Beppu T, Kamada K, Nakamura R, Oikawa H, Takeda M, Fukuda T, Arai H, Ogasawara K, Ogawa A.: A phase II study of radiotherapy after hyperbaric oxygenation combined with interferon-beta and nimustine hydrochloride to treat supratentorial **malignant gliomas**. . J Neurooncol. 2003 Jan;61(2):161-70.

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Hypoxic cells play a key role in the radioresistance of malignant glioma. Interferon-beta, ACNU as nimustine hydrochloride and radiotherapy (IAR) is a common therapy for malignant glioma in Japan.

Since hyperbaric oxygenation (HBO) increases oxygen pressure in glioma tissue, we applied a modified IAR therapy, radiotherapy after HBO combined with interferon-beta and ACNU (HBO/IAR therapy), for supratentorial malignant gliomas. Daily radiation therapy was completed within 15 min after HBO. We assessed HBO/IAR with respect to toxicity, response rates and the time of tumor progression (TTP). We also examined the incidence of responses by some prognostic factors before HBO/IAR, namely, age, Karnofsky performance scale (KPS), histological type, tumor size, tumor site and operation type.

Of **39 patients** who participated in this study, 35 underwent a complete schedule of HBO/IAR therapy in which toxicity was permissible. Thirty patients (76.9%) either maintained or increased KPS during HBO/IAR with a mean duration of 68 +/- 14 days. The response rates (CR + PR%) for glioblastoma, anaplastic astrocytoma and overall were 50%, 30% and 43%, respectively. The incidence of therapeutic responses among all prognostic factors before HBO/IAR did not significantly differ. Median TTP for patients with glioblastoma, patients with anaplastic astrocytoma, and overall were 38, 56 and 43 weeks, respectively.

The present study suggested that HBO/IAR therapy could be applied to especially patients with poor prognostic factors, because of its short treatment period, its permissible toxicity and identical response to patients with good prognostic factors.PMID: 12622455 [PubMed – indexed)

Suzuki Y[1] Tanaka K', Yoshida Y[1], Shimizu Yamazaki W, Hashimoto: EFFICACY AND PHARMACOKINETIC PARAMETERS FOR MALIGNANT **GLIOMA** PATIENTS TREATED WITH **CARBOPLATIN IN COMBINATION WITH HYPERBARIC OXYGENAT**ION *UHM 2008, Vol. 35, No. 4 — Abstracts from UHMS ASM 2008.*

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**BACKGROUND:** We reported that high efficacy of an antineoplastic agent carboplatin was obtained in combination with hyper baric oxygenation (HBO) therapy on malignant glioma patients. The objective was to gain the insight into the relationship between malignant contractions observed by MRI and pharmacokinetic parameters of carboplatin modulated with HBO.

**METHODS:** Plasma ultra-filtrate samples (range 16 courses/patient) in 10 Japanese patients (27-66 y) between 2006 and 2007 alter intravenous administration of 400 mg carboplatin/m2 body surface area for 60 min were analyzed by a reverse-phase HPLC system using an NH2 column. HBO therapy (at 0.2 MPa for 60 min) for malignant or brain stern gliomas was conducted with a hyperbaric oxygen chamber (model 2500B, Sechrist, Anaheim, CA) in St. Marianna Hospital. Relationship between area under the curve (AUC) or mean residence time (MRT) for carboplation calculated by WinNonlin software and brain tumor reduction rates determined by MR1 were evaluated.

**RESULTS:** There were no differences among the AUC values for carboplatin in different clinical response or disease groups. In contrast, the mean MRT value for carboplation in the combined complete or partial response group (4.3+-1.7 h; mean+-SD, n = 6) was significantly higher than that in the stable or progressive disease group (2.4+-0.1 h, n=3) ($p < 0.05$). These results may efficiently suggest a possibility of modified pharmacokinetics of carboplatin caused by HBO therapy, although determinations in more cases would be necessary to confirm these findings.

**CONCLUSIONS:** A possibility of prolonged biological residence time of carboplatin might be relevant to the efficacy with HBO therapy. The present results suggest that the MRT value for carboplation in patients with HBO therapy could be useful for predicting clinical antitumor effects on malignant gliomas.

Ogawa K, Yoshii Y, Inoue O, Toita T, Saito A, Kakinohana Y, Adachi G, Iraha S, Tamaki W, Sugimoto K, Hyodo A, Murayama S.: Phase II trial of radiotherapy after **hyperbaric oxygenation with chemotherapy for high-grade gliomas**. Br J Cancer. 2006 Oct 9;95(7):862-8. Epub 2006 Sep 5.

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We conducted a **phase II trial** to evaluate the efficacy and toxicity of radiotherapy immediately after hyperbaric oxygenation (HBO) with chemotherapy in adults with high-grade gliomas. Patients with histologically confirmed high-grade gliomas were administered radiotherapy in daily 2 Gy fractions for 5 consecutive days per week up to a total dose of 60 Gy. Each fraction was administered immediately after HBO with the period of time from completion of decompression to irradiation being less than 15 min.
Chemotherapy consisted of procarbazine, nimustine (ACNU) and vincristine and was administered during and after radiotherapy.
A total of **41 patients** (31 patients with glioblastoma and 10 patients with grade 3 gliomas) were enrolled. All 41 patients were able to complete a total radiotherapy dose of 60 Gy immediately after HBO with one course of concurrent chemotherapy.

Of 30 assessable patients, 17 (57%) had an objective response including four CR and 13 PR. The median time to progression and the median survival time in glioblastoma patients were 12.3 months and 17.3 months, respectively. On univariate analysis, histologic grade (P=0.0001) and Karnofsky performance status (P=0.036) had a significant impact on survival, and on multivariate analysis, histologic grade alone was a significant prognostic factor for survival (P=0.001). Although grade 4 leukopenia and grade 4 thrombocytopenia occurred in 10 and 7% of all patients, respectively, these were transient with no patients developing neutropenic fever or intracranial haemorrhage. No serious nonhaematological or late toxicities were seen.

These results indicated that radiotherapy delivered immediately after HBO with chemotherapy was safe with virtually no late toxicity in patients with high-grade gliomas. Further studies are required to strictly evaluate the effectiveness of radiotherapy after HBO for these tumours.

PMCID: PMC2360529
PMID: 16953239 [PubMed - indexed for MEDLINE]

Kohshi K, Yamamoto H, Nakahara A, Katoh T, Takagi M.: Fractionated stereotactic radiotherapy using **gamma unit after hyperbaric oxygenation** on recurrent high-grade gliomas. J Neurooncol. 2007 May;82(3):297-303. Epub 2006 Nov 22.

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BACKGROUND: To reduce this complication and to enhance the radiation effect to hypoxic cells of high-grade gliomas, the authors performed noninvasive fractionated stereotactic radiotherapy (FSRT) using a Gamma unit combined with hyperbaric oxygen (HBO) therapy for the treatment of recurrent disease.

PATIENTS AND METHODS: Twenty-five consecutive patients who had previously received radiotherapy with chemotherapy for recurrent high-grade gliomas, including 14 patients with anaplastic astrocytoma (AA) and 11 with glioblastoma multiforme (GBM), underwent Gamma FSRT immediately after HBO therapy (2.5 atmospheres absolute for 60 min). The Gamma FSRT was repeatedly performed using a relocatable head cast. Median tumor volume was 8.7 cc (range, 1.7-159.3 cc), and the median total radiation dose was 22 Gy (range, 18-27 Gy) to the tumor margin in 8 fractions.

RESULTS: Actuarial median survival time after FSRT was 19 months for patients with AA and 11 months for patients with GBM, which was significantly different (P = 0.012, log-rank test). Two patients underwent subsequent second FSRT for regional or remote recurrence. Seven patients (28%) underwent subsequent craniotomies and resections at a mean of 8.4 months after FSRT treatment, and 4 of them had radiation effects without viable cells and remained alive for 50-78 months.

CONCLUSION: Gamma FSRT after HBO therapy appears to confer a survival benefit for patients with recurrent high-grade gliomas and warrants further investigation.

PMID: 17120158 [PubMed - indexed for MEDLINE]

# postoperative Infektionen

# Hyperbaric Oxygen Treatment of Postoperative Neurosurgical Infections

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**OBJECTIVE: To evaluate the clinical usefulness of hyperbaric oxygen (HBO) therapy for neurosurgical infections after craniotomy or laminectomy.**

**METHODS: The study involved review of medical records, office visits, and telephone contacts for 39 consecutive patients who were referred in 1996 to 2000. 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.**

**RESULTS: Successful results were achieved for 27 of 36 patients, with a mean follow-up period of 27 months (range, 6–58 mo). One patient discontinued HBO therapy because of claustrophobia, and two could not be evaluated because of death resulting from tumor recurrence. In Group 1 (uncomplicated cranial wound infections), 12 of 15 patients 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; three of four bone flaps and three of six acrylic cranioplasties could be retained. In Group 3 (spinal wound infections), all infections resolved, five of seven without removal of fixation systems. There were no major side effects of HBO treatment.**

**CONCLUSION: HBO treatment is an alternative to standard surgical removal of infected bone flaps and is particularly useful in complex situations. It can improve outcomes, reduce the need for reoperations, and allow infection control without mandatory removal of foreign material. HBO therapy is a safe, powerful treatment for postoperative cranial and spinal wound infections, it seems cost-effective, and it should be included in the neurosurgical armamentarium.** (Neurosurgery 50:287–296, 2002)

**Key words:** Artificial implant, Cranioplasty, Hyperbaric oxygenation, Osteomyelitis, Radiation injuries, Spinal infections

Infections remain a common complication of surgery. In neurosurgery, postoperative infections are particularly bothersome, sometimes virtually untreatable, and are associated with substantial morbidity and mortality rates (1). A 2.5% incidence of postoperative wound infections after craniotomies, including subdural empyemas and brain abscesses, was recently reported in a large, prospective, multicenter study (15). This rate of infection does not differ much from those observed in the 1950s and 1960s (3, 23), despite modern antibiotics and prophylactic regimens.

Conventional therapy involves the use of antibiotics, mandatory removal of the infected bone flap, and secondary reconstructive surgery with an acrylic implant (so-called delayed cranioplasty) (16). Such cranioplastic implants have hitherto required removal in cases of infection, leading to an even more complicated situation and often large cranial defects. Spinal infections represent another complex situation; the fixation material cannot be removed as easily, because of instability. The situation may be further complicated by factors such as malignant disease, radiation injury, chemotherapy, repeated surgery, tissue transplants, and foreign material. Such risk factors result in suboptimal conditions for healing, largely because of poor tissue quality and the presence of hypoperfused, hypoxic, infected wounds. Any treatment that could improve outcomes and reduce the need for reoperations would be of value.

Hyperbaric oxygen (HBO) therapy is used to treat a variety of infected, hypoperfused, and hypoxic wounds (11). Oxygen tensions play an important role in the outcomes of infections (21). The leukocyte bacteria-killing capacity is substantially

impaired at the low oxygen tensions often observed in wounds (2, 13, 17). HBO therapy increases the oxygen tension in infected tissues, including bone (17), resulting in direct bactericidal effects on some anaerobic organisms. The therapeutic effect of HBO treatment on aerobic organisms is attributable to significant improvements in phagocytic killing of bacteria such as *Staphylococcus aureus*, which is the most common pathogen observed in infected incisional neurosurgical wounds (1, 15, 23). HBO therapy improves host defenses and has proved adjunctive, with antibiotics and surgery, for the treatment of infectious wound complications after surgery in the irradiated head and neck (20), gas gangrene and other necrotizing soft-tissue infections (11), infected ischemic diabetic foot ulcers (7), and chronic refractory osteomyelitis (5). It has also been successfully used to reduce complications after crush injuries of the extremities (4). In radiation-injured tissues, HBO therapy induces the formation of new capillaries, thus improving tissue oxygen tensions and host defenses (18, 19) and improving osseointegration and reducing implant failure rates (10). This article reports the clinical usefulness of HBO therapy in the treatment of postoperative neurosurgical infectious complications among 39 consecutive patients who were referred for HBO therapy for the treatment of neurosurgical infections.

## PATIENTS AND METHODS

The ethics committee at the Karolinska Hospital approved this retrospective study. Between January 1, 1996, and December 31, 2000, 39 consecutive patients were referred by the Department of Neurosurgery for adjuvant HBO treatment at the Division of Hyperbaric Medicine at the Karolinska Hospital. All patients had received a clinical diagnosis of a postoperative infection, on the basis of local signs, suppuration, sepsis, laboratory findings, and/or radiologically detectable pathological features. Only patients for whom the alternative treatment would have been repeated surgery with removal of the bone flap or foreign material and patients whose infections had a poor prognosis of healing, because of previous irradiation or other risk factors, were referred.

All patients received antibiotics appropriate to their bacterial culture results. The most common bacteria cultured were *Staphylococcus epidermidis* and *S. aureus*. Infectious disease specialists initiated and modified the antibiotic treatment of the pathogenic organism(s) for in-patients. Antibiotic treatment varied between 2 and 27 weeks. Eight patients underwent surgical procedures for wound drainage and removal of devitalized tissues or foreign materials, according to the judgment of the managing surgeon. For three patients, a plastic surgeon assisted in the repair of soft-tissue defects and the covering of acrylic implant areas.

One 17-year-old patient, who had undergone repeated surgery because of shunt infection, refused HBO therapy after the first session because of claustrophobia and was excluded from further analysis. The structure of our patient series suggested three subgroups, i.e., Group 1, with uncomplicated cranial wound infections; Group 2, with complicated cranial wound infections; and Group 3, with spinal wound infections.

### Group 1

Group 1 included patients with osteomyelitis of a free cranial bone flap after craniotomy, without additional risk factors (n = 15). This group included 5 male and 10 female patients, with a median age of 55 years (range, 16–69 yr) (*Table 1*). Reasons for neurosurgery included meningiomas (n = 8), other benign tumors (n = 4), aneurysms (n = 2), and traumatic hemorrhage (n = 1). The mean interval between surgery and diagnosis of the wound infection was 9 weeks (range, 1–52 wk). The mean interval between surgery and initiation of HBO treatment was 15 weeks (range, 3–52 wk). The primary treatment goal was to avoid removal of the infected bone flap. *S. epidermidis* was cultured from seven patients and *S. aureus* from three patients. A variety of other microorganisms, such as *Propionibacterium* and *Streptococcus milleri*, were also observed.

### Group 2

Group 2 included patients with osteomyelitis, with or without remaining bone/acrylic flap, after craniotomy with additional risk factors, such as repeated surgery, foreign material, malignant disease, or previous radiotherapy (n = 16). This group included 6 male and 10 female patients, with a median age of 53 years (range, 27–69 yr) (*Table 2*). Reasons for neurosurgery included malignant tumors (n = 6), recurrent meningiomas (n = 6), basal cell carcinoma and hydrocephalus (n = 1), and trauma (n = 3). The mean interval between surgery and diagnosis of the infection was 6 weeks (range, 0–26 wk). The mean interval between surgery and HBO treatment was 12 weeks (range, 0.5–48 wk). All patients were hospitalized and received intravenous antibiotic treatment. *S. epidermidis* was cultured from three patients and *S. aureus* from five patients. A variety of other agents, such as *Propionibacterium*, *Klebsiella*, and *Corynebacterium*, were also observed.

Patient 2.7 had undergone extensive transcochlear surgical treatment of a widely growing petrous meningioma and underwent initial wound closure with fat but developed a cerebrospinal fluid leak and a deep wound infection. Patient 2.14 had a subdural empyema after repeated burr-hole drainage of a chronic subdural hematoma. Patient 2.10 underwent a second series of HBO treatments 17 months after the end of his first series, and his outcome results have been reported as 2.10a and 2.10b. Patient 2.15 developed an infection after a highly contaminated, traumatic open fracture of the forehead and face. Patients 2.8 and 2.11 had undergone previous vascularized, microsurgical, tissue transplants to allow healing of atrophic radiation-injured tissues. The treatment goals were to achieve infection control and wound healing in complex situations and, if possible, to avoid removing the bone flaps/foreign material.

### Group 3

Group 3 included patients with osteomyelitis and deep wound infections after spinal surgery with implantation of fixation material (n = 7). This group included four male and three female patients, with a median age of 37 years (range, 22–74 yr) (*Table 3*). Reasons for neurosurgery included cervi-

**TABLE 1. Patients (Group 1) Treated with Hyperbaric Oxygen for Osteomyelitis of a Free Bone Flap after Craniotomy, without Additional Risk Factors[a]**

| Patient No. | Age (yr)/ Sex | Diagnosis | Infection | No. of HBO Sessions | Follow-up Period (mo) | Result | HBO Cost (SEK) |
|---|---|---|---|---|---|---|---|
| 1.1 | 16/M | Epidural hematoma | Bone flap | 40 | 27 | Flap removed 2 mo after HBO | 72,000 |
| 1.2 | 57/F | Aneurysm | Bone flap | 40 | 57 | Resolved | 62,160 |
| 1.3 | 50/F | Aneurysm | Bone flap | 40 | 24 | Flap removed 2 mo after HBO | 75,800 |
| 1.4 | 58/F | Arteriovenous malformation | Bone flap | 16 | 28 | Resolved | 28,800 |
| 1.5 | 38/M | Foramen of Monro cyst | Bone flap | 40 | 58 | Resolved | 62,160 |
| 1.6 | 66/M | Foramen of Monro cyst | Bone flap | 40 | 31 | Resolved | 71,334 |
| 1.7 | 24/F | Cavernoma | Bone flap | 40 | 13 | Resolved | 76,800 |
| 1.8 | 57/F | Meningioma | Bone flap | 40 | 55 | Resolved | 62,160 |
| 1.9 | 40/F | Meningioma | Bone flap | 47 | 27 | Flap removed 9 mo after HBO | 95,400 |
| 1.10 | 55/F | Meningioma | Bone flap | 40 | 32 | Resolved | 103,770 |
| 1.11 | 43/F | Meningioma | Bone flap | 40 | 28 | Resolved | 72,000 |
| 1.12 | 67/F | Meningioma | Bone flap | 40 | 15 | Resolved | 72,000 |
| 1.13 | 51/M | Meningioma | Bone flap | 40 | 12 | Resolved | 88,000 |
| 1.14 | 69/F | Meningioma | Bone flap | 40 | 10 | Resolved | 88,000 |
| 1.15 | 59/M | Meningioma | Bone flap | 15 | 7 | Resolved | 33,000 |

[a] HBO, hyperbaric oxygen therapy; SEK, Swedish kroner (1 American dollar equals approximately 10 kroner).

cal trauma (n = 2), thoracic spinal fractures (n = 1), lumbar spinal fractures (n = 2), cervical spinal stenosis (n = 1), and cervical intramedullary ependymoma (n = 1). The mean interval between surgery and diagnosis of the infection was 3 weeks (range, 1–12 wk). The mean interval between surgery and HBO treatment was 6 weeks (range, 3–16 wk). *S. epidermidis* was cultured from three patients and *S. aureus* from three patients. Other agents, such as *Propionibacterium* and enterococci, were also observed. The primary treatment goal was to achieve infection control and healing without removal of fixation material.

### Follow-up monitoring

The patients were monitored through reviews of chart notes from clinic visits in the Department of Neurosurgery and the Division of Hyperbaric Medicine, as well as other clinics. Telephone interviews were conducted during February and March 2001, after examination of the Swedish National Register of deaths.

### HBO treatment

The Karolinska Hospital Division of Hyperbaric Medicine is staffed by anesthesiology and intensive care physicians and nurses trained in the medical, mechanical, and physical aspects of hyperbaric medicine. Because of the long distance from the neurosurgical intensive care unit to the hyperbaric chamber, no intubated patients were treated with HBO ther apy. All patients in this study were spontaneously breathing and were treated in either of our two acrylic monoplace chambers (model 2500B or 3200; Sechrist Industries, Inc., Anaheim, CA) pressurized with 100% oxygen, which allowed the patients to breathe without a mask or hood. Chamber passthroughs allowed continued intravenous therapy and monitoring.

Hyperbaric treatment was administered at a pressure of 2.5 to 2.8 bar (250–280 kPa), which is equivalent to a water depth of 15 to 18 m. The patients breathed pure oxygen for three 25-minute periods, which were interrupted by two 10-minute air breaks. The treatment protocol was chosen according to the clinical severity of the infection, as judged by the attending neurosurgeon and HBO specialist. Treatment was normally administered once daily for 5 days each week, with a schedule of up to 40 sessions. In cases of severe infections, threatened tissues, and/or life-threatening situations, initial treatments were administered at 2.8 bar, twice daily and on weekends.

## RESULTS

### Group 1

The infections resolved and the wounds healed for all patients with osteomyelitis after craniotomy (*Table 1*). For 12 of 15 patients, with a mean follow-up period of 29 months, healing occurred without removal of the bone flap.

**TABLE 2. Patients (Group 2) Treated with Hyperbaric Oxygen for Osteomyelitis, with or without Remaining Bone/Acrylic Flaps, after Craniotomy, with Additional Risk Factors such as Repeated Surgery, Foreign Material, Malignant Disease, or Previous Radiotherapy[a]**

| No. | Age/ Sex | Diagnosis | Therapy and Complications | Infected Tissue | Time to Infection (mo) | HBO Sessions | Result | Cost (SEK) |
|---|---|---|---|---|---|---|---|---|
| 2.1 | 29/M | Astrocytoma | Malignant tumor | Bone flap | 40 | 21 | Resolved | 72,000 |
| 2.2 | 36/M | Ependymoma | Radiotherapy, wound breakdown | Bone flap | 40 | 8 | Bone flaps removed 6 mo after HBO, wound healed | 88,000 |
| 2.3 | 55/F | Glioblastoma | Radiotherapy | Bone flap | 4 | <6 | Tumor recurrence, dead 3 mo after HBO | 16,800 |
| 2.4 | 40/F | Glioblastoma | Radiotherapy, repeated surgery for tumor recurrence | Bone flap | 38 | <6 | Tumor recurrence, dead 2 mo after HBO | 67,014 |
| 2.5 | 27/M | Medulloblastoma | Radiotherapy, flap infection, flap removed, wound breakdown, dura mater exposed, MRSA | Soft tissue and bone | 38 | 39 | Resolved (no vancomycin used) | 68,400 |
| 2.6 | 57/F | Urothelial metastasis | Malignant kidney tumor | Acrylic flap | 40 | 28 | Resolved, acrylic flap retained | 72,000 |
| 2.7 | 59/F | Meningioma | Large tumor, complicated surgery, soft-tissue transfer | Bone flap | 40 | 35 | Resolved | 124,800 |
| 2.8 | 40/F | Meningioma | Radiotherapy, repeated surgery for tumor recurrence, angioplasty and free tissue transfer | Acrylic flap | 40 | 29 | Resolved, acrylic flap retained | 72,000 |
| 2.9 | 63/F | Meningioma | Repeated surgery for tumor recurrence, infected bone and acrylic flaps and sinus frontalis fistulae, hemophilia | Acrylic flap | 38 | 27 | Acrylic flap removed 6 mo after HBO, wound healed | 68,400 |
| 2.10a | 69/M | Meningioma | Radiotherapy, repeated surgery for tumor recurrence and infected bone and acrylic flaps | Soft tissue and bone | 38 | 16 | Resolved, continued below | 68,400 |
| 2.10b | Meningioma, same patient as 2.10a | | Chemotherapy, 3 wk after 1st HBO series, tumor recurrence and reoperation with angioplasty, 2nd HBO series 17 mo after 1st | Acrylic flap | 37 | 7 | Acrylic flap removed after HBO Session 14, meningitis, cardiac infarction, wound healed after HBO Session 37, tumor recurrence, dead 7 mo after HBO | 67,000 |
| 2.11 | 53/F | Meningioma | Repeated radiotherapy, repeated surgery | Acrylic flap | 36 | 12 | Resolved, acrylic flap retained, tumor recurrence, dead 12 mo after HBO | 64,800 |
| 2.12 | 60/F | Meningioma | Repeated radiotherapy, repeated surgery, bone flap removed, wound breakdown, cranium exposed | Soft tissue and bone | 30 | 15 | Resolved | 88,242 |
| 2.13 | 66/F | Basal cell carcinoma | Radiotherapy, 40 yr repeated surgery for tumor recurrence, reconstructive surgery, postinfectious aqueductal stenosis with hydrocephalus, shunt infections, shunt exposed and removed, CSF drainage | Soft tissue and bone | 46 | 18 | Ventriculocisternostomy after HBO Session 6, persistent wound | 82,800 |
| 2.14 | 48/M | Subdural hematoma | Repeated surgery, subdural empyema | Empyema, bone flap | 7 | 41 | Resolved | 37,218 |
| 2.15 | 42/F | Cranial and facial fractures | Contaminated traumatic wound, fixation material | Soft tissue and bone | | 13 | 27 Resolved, fixation material left | 69,600 |
| 2.16 | 53/M | Cranial fracture, epidural hematoma | Hemicranectomy | Acrylic flap | 40 | 6 | Wound healed, epidural abscess, acrylic flap removed 5 mo after HBO | 88,000 |

[a] HBO, hyperbaric oxygen therapy; SEK, Swedish kroner; MRSA, methicillin-resistant *Staphylococcus aureus;* CSF, cerebrospinal fluid.

TABLE 3. Patients (Group 3) Treated with Hyperbaric Oxygen for Osteomyelitis and Deep Wound Infection after Spinal Surgery, with Implantation of Fixation Material

| Patient No. | Age (yr)/ Sex | Diagnosis | Surgery | Complications | Infection | No. of HBO Sessions | Additional Therapy | Follow-up Period (mo) | Result | HBO Cost (SEK) |
|---|---|---|---|---|---|---|---|---|---|---|
| 3.1 | 74/F | Fracture at C6—C7, quadraplegia, cervical spine luxation, central cord syndrome | Frontal discectomies and fusions at C5—C7 and corpectomy at C6 | Failure to dose esophageal fistula, infection, removal of loose fixation material, posterior fusion with Apofix | Soft tissue and bone mediastinitis (life-threatening) | 59 | Repeated surgery, including closure of ruptured esophagus and bone transplantation | 46 | Resolved, fixation material left, survived | 188,160 |
| 3.2 | 61/M | Fracture at C6—C7, epidural hematoma at C2—T6 | Anterior and posterior fusion | Abscess, CSF leakage | Soft tissue and bone | 40 | 36 | Resolved, fixation material left | | 135,792 |
| 3.3 | 37/M | Fractures at T12, paraplegia | Laminectomy at T12, posterior fusion, bone transplantation | Abscess, fistula, necrotizing fasciitis, myositis, revision | Soft tissue and bone | 40 | 17 | Resolved, fixation material left | | 72,000 |
| 3.4 | 29/M | Fracture at L1, paraplegia | Laminectomy, posterolateral fusion | Reoperation, removal of bone fragment, discectomy, fusion, bone transplantation, CSF leakage | Soft tissue and bone | 18 | Fixation material removed 4 mo after HBO because of dislocation threatening to penetrate the skin | 38 | Resolved, fixation material removed | 105,000 |
| 3.5 | 22/F | Fractures at L2 and calcaneus, paraplegia | Posterolateral fusion | Abscess, fistula | Soft tissue and bone | 24 | Fixation material removed 4 days after HBO, reoperation for fistula 6 mo later | 21 | Resolved, fixation material removed | 43,200 |
| 3.6 | 60/M | Cervical spinal stenosis | Corpectomy at C5, bone transplantation, fusion | Intraspinal abscess at C2—C4 | Soft tissue and bone | 18 | Two metal screws in danger of penetrating the esophagus removed surgically | 32 | Resolved, fixation material left | 71,400 |
| 3.7 | 34/F | Ependymoma at C2—T3 | Laminectomy at C2—T2, extirpation of tumor, fixation | Abscess, fistulae, radiotherapy postponed because of infection | Soft tissue and bone | 40 | One screw aborted | 23 | Resolved, fixation material left | 71,604 |

a HBO, hyperbaric oxygen therapy; SEK, Swedish kroner; CSF, cerebrospinal fluid.

### Group 2

Three of six acrylic cranioplasties and three of four free bone flaps could be retained (*Table 2*). The infections resolved and the wounds healed for 13 of 16 patients. Treatment was discontinued for Patient 2.3 after only four HBO sessions, because of rapid tumor progression and transfer to a hospice for terminal care. Patient 2.4 received a full course of HBO treatments, with good results. Both patients exhibited improvement of their wound infections but were classified as failures because wound healing could not be satisfactorily evaluated. The patients were treated for terminal disease in other institutions and died as a result of recurrent glioblastomas within 3 months. Patient 2.13 exhibited a persistent wound in follow-up examinations.

One patient (Patient 2.10) underwent two series of HBO treatments. The first series (denoted 2.10a) was to achieve infection control in an area that had been subjected to repeated surgery and radiotherapy, in which both bone and acrylic flaps had been removed before HBO treatment. Infection control made chemotherapy possible, and the patient underwent replacement of an acrylic flap 3 months after HBO treatment. The second HBO series (denoted 2.10b) was administered 17 months after the first series, because of a renewed postoperative infection after surgery to treat a recurrence. At that time, the acrylic flap needed to be removed to ensure wound healing. The patient died 7 months after the second HBO series, as a result of yet another tumor recurrence.

### Group 3

All infections resolved, and spinal fixation materials were retained for all except two patients (*Table 3*). Patient 3.5 exhibited a rapid favorable response, with infection control and wound contraction. The HBO series and medical and surgical therapies were discontinued after 24 HBO sessions by the patient, who left the hospital against medical advice. The fixation material was subsequently removed at another hospital. The remaining fistulae of the patient were surgically resolved 6 months later, with complete healing at the 21-month follow-up examination. Patient 3.4 received 18 HBO treatments, following our aggressive HBO treatment protocols, which led to rapid infection control and healing. The fixation material migrated 4 months after HBO treatment, threatened skin penetration, and was removed; the spine had become stable. Four months later, a recurrent wound infection was diagnosed and successfully treated with 6 months of antibiotic therapy based on bacteriological culture results.

Treatments were discontinued prematurely because of favorable responses and rapid healing for two patients (Patients 3.4 and 3.6). One elderly patient (Patient 3.1) had an epidural abscess, an esophageal fistula, and severe, life-threatening mediastinitis after surgery to treat a traumatic cervical dislocation. The patient recovered, despite a grim initial prognosis.

### Compliance and side effects

The rate of compliance with HBO treatments was high. Only one patient refused additional HBO treatments after her first session, because of claustrophobia. Patient 1.15 discontinued therapy after 15 sessions because of alcohol abuse. Patient 3.5, with a history of heavy drug abuse, discontinued her HBO series and medical and surgical therapies after 24 HBO sessions when she left the hospital to return to her previous lifestyle. Treatment was discontinued prematurely, after only 16 HBO sessions, for Patient 1.4 because of transient myopia. Treatment series were prolonged for three patients with complicated infections. The number of treatments for each patient ranged from 7 to 57.

The side effects of HBO treatment were minimal. Some minor problems with pressure equalization and serous otitis occurred. In our series, only Patient 1.9 experienced a significant change in refraction, resulting in myopia. Her original refractive state returned within 6 weeks after the discontinuation of therapy.

## DISCUSSION

Our previous clinical experience with neurosurgical infections indicates that the results achieved with HBO therapy are remarkable. HBO treatment allowed infection control and healing for 27 of 36 patients and became an alternative to standard treatment involving surgical removal of infected bone flaps, acrylic flaps, or foreign fixation material.

It is considered difficult to draw scientific conclusions from retrospective data for a series of selected patients. However, the selection used in our series would seem to have been biased against HBO therapy. Generally, patients with complications that were expected to be difficult to treat were referred for HBO therapy. Furthermore, conducting a randomized trial was not feasible, because the alternative treatment was removal of the bone flap or foreign material.

### Clinical results

Among patients with uncomplicated cranial wound infections (Group 1), successful resolution with a retained bone flap was achieved for 12 of 15 patients. Attempts have been made to retain the flap via continuous suction with topical antibiotic irrigation (6), but the usual treatment involves removal of the bone flap and extensive debridement, followed by primary closure and antibiotic treatment (1). This is followed by secondary cranioplasty 3 to 6 months later. This approach involves the risks and expense of two operations, additional hospital stays, repeated failure, spread of infection to the brain, and large cranial defects and disfigurement if ablative surgery becomes necessary. In our hospital setting, the cost of these two surgical procedures alone, during the study period of 1996 to 2000, was 130,000 to 210,000 Swedish kroner, whereas the actual cost of HBO therapy in our series averaged 71,000 kroner.

Among patients with complicated cranial wound infections (Group 2), HBO therapy allowed healing despite risk factors such as malignant disease, radiation injury, chemotherapy, repeated surgery, or foreign material. Traditional therapy would have necessitated removal of bone or acrylic flaps (sometimes covering more than one-half of the calvarium) or entailed very protracted healing, if any, of irradiated tissues.

Several patients with a previous history of a "bad meningioma," with multiple recurrences, radiation treatment, and extensive complex cranioplasties, were cured of their open purulent infections without removal of foreign material. Because of tumor recurrence, two patients (Patients 2.3 and 2.4) were monitored for insufficient periods to reach the minimal 6-month evaluation. Their responses to treatment seemed to be acceptable, but the practice of subjecting patients with limited expected survival times to a prolonged HBO regimen, instead of rapidly removing the bone flap, may be questionable. The average cost of HBO therapy in Group 2 was 71,000 Swedish kroner.

Dramatic beneficial effects of HBO therapy were also observed for patients with spinal wound infections (Group 3). In particular, Patient 3.1 was considered to be in immediate danger of death as a result of a combination of old age, a spinal epidural infection, an esophageal fistula, and mediastinitis. We achieved infection control and healing in complex settings with deep postoperative spinal wound infections, without removal of fixation material, for five of seven patients. The failures were not primarily attributable to poor responses to HBO treatment. Discontinued treatment because of drug addiction may have caused one "failure" (Patient 3.5). The other patient (Patient 3.4) was classified as experiencing 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. The costs of HBO therapy in Group 3 averaged 98,000 Swedish kroner.

## Mechanism of action and rationale for HBO treatment

Most nonhealing infected wounds are hypoxic (13) because of ischemia. Ischemia not only hinders oxygen delivery to tissues but also compromises antibiotic delivery. These marginally viable tissues are vulnerable to infection and exhibit poor infection control and wound healing despite meticulous wound care and antibiotic treatment. For many years, surgeons have used revascularization procedures or flaps to counteract the deleterious effects of ischemia and hypoxia on wound healing. Animal experiments using microelectrodes to measure oxygen partial pressures in normal, healing, and infected tissues and in tissues containing foreign bodies demonstrated marked hypoxia, especially if the foreign body was infected (22). Infections, and concurrent inflammation, increase oxygen consumption dramatically, because phagocytes consume more oxygen. In parallel with this, oxygen delivery is reduced because of tissue edema and ischemia. Wound tissue oxygenation and resistance to infection are thus further compromised.

HBO therapy has been used to treat a variety of infections and postoperative complications in bone and soft tissues (11, 20). Osteomyelitic bone exhibits decreased blood flow and a markedly reduced partial pressure of oxygen (17). The mode of action of HBO treatment is chiefly via stimulation of the bactericidal action of white blood cells. The leukocyte bacteria-killing capacity is impaired in hypoxic surroundings, improves with normoxia, and is further enhanced with hyperoxia (2, 14). HBO therapy restores intramedullary bone oxygen tension and phagocytic killing to normal or above-normal levels (17). The greatly increased tissue oxygen levels in ischemic tissues during HBO therapy also stimulate neovascularization (18), fibroplasia (12), and bone remodeling (9), making the tissues less ischemic and improving long-term wound healing. Treatment with 100% oxygen under normobaric conditions has no such effect.

Irradiated tissues may not heal, despite aggressive procedures, because of progressive vascular damage leading to secondary microvascular ischemia and hypoxia. Infections involving atrophic irradiated tissues with reduced regional blood supply are feared but exhibited successful healing in this series. HBO treatment is the only therapy known to reverse this vascular compromise, and it has become a widely accepted adjuvant therapy for the treatment and prevention of osteoradionecrosis of the mandible (19). HBO therapy exhibits dose-dependent angiogenic effects, causing an eight- to ninefold increase in the vascular density of tissues (18). A good example of this is Patient 2.5, who had a continuously deteriorating wound after surgery, attributable to a medulloblastoma, irradiation, cranial flap removal, and chronic infection with methicillin-resistant staphylococci (*Fig. 1*). The wound healed well with 6 weeks of HBO therapy, and the methicillin-resistant staphylococcal infection was cured by the patient's own host defenses, without the use of antibiotics.

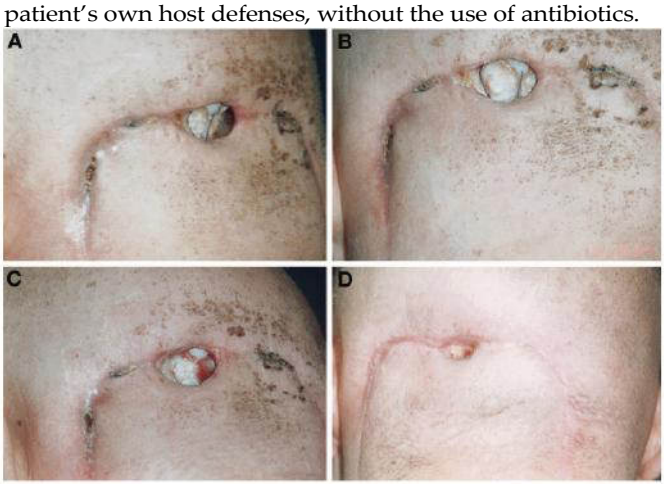


**FIGURE 1. Photographs demonstrating HBO treatment results. Surgery to treat an occipital medulloblastoma (Patient 2.5) caused a suppurative wound infection that was treated by traditional methods, with removal of the osteomyelitic bone flap. The condition worsened after radiotherapy, with wound breakdown, exposed dura mater, and necrotic suppurative cavities. Methicillin-resistant *S. aureus* was cultured from the wound. Continuous deterioration was observed until HBO treatment, which allowed gradual healing, with granulation tissue in the necrotic cavities, disappearance of methicillin-resistant *S. aureus* without antibiotic treatment, and contraction of the wound within 38 HBO sessions. *A* and *B*, immediately before the initiation of HBO treatment; *C*, after 11 HBO sessions; *D*, after 29 HBO sessions.**

### Side effects

The side effects of HBO treatment were minimal, with only one patient experiencing reversible myopia. There were no episodes of central nervous system toxicity. Oxygen seizures may occur, especially when therapy is administered at very high pressures to patients with fever or when hypercapnia attributable to hypoventilation is present. An incidence of 1/10,000 treatments is often cited. Seizures are self-limiting, and sequelae are uncommon. Contraindications to HBO therapy are few but include concurrent administration of certain chemotherapeutic agents, e.g., doxorubicin, bleomycin, mitomycin C, and cisplatin, because of interference with oxygen radical-scavenging mechanisms. Pneumothorax is another condition that can be deleterious during decompression if not treated. Malignancy is not a contraindication. According to the literature (8), HBO therapy has no cancer-causing effects and does not stimulate growth of residual tumor.

### Indications

The use of HBO therapy for the treatment of uncomplicated wound infections with osteomyelitis of a bone flap may be controversial. The standard treatment is not ineffective, and it does not require 40 sessions of HBO treatment. However, several of our patients preferred the prospect of HBO treatment in an attempt to avoid two additional operations. In addition, HBO therapy seems to be cost-effective (with a cost less than one-half that of surgery), with a moderate failure rate.

HBO therapy is particularly useful in complex settings. It has a good chance of helping to resolve complicated cranial and spinal wound infections for which no simple solution exists. Removal of foreign material is usually required even when potent parenteral antibiotics are administered.

On the basis of considerations similar to the rationale for the use of HBO therapy to treat gas gangrene and severe, necrotizing, soft-tissue infections, the treatment of intracranial abscesses with adjunctive HBO therapy has been approved by the Undersea and Hyperbaric Medical Society since 1996 (11). In our study, HBO therapy allowed discharge of a patient 4 days after surgical treatment of a subdural empyema. The beneficial effects of HBO therapy on complex infections, including the postoperative empyema, suggest that this treatment should be evaluated as an adjunctive treatment also for such primary, suppurative, central nervous system conditions.

### Dose and duration

The issues of the dose and duration of HBO therapy remain unsettled. To achieve infection control in the acute phase, higher treatment pressures (2.8 bar) were initially used, with more than one treatment session per day and HBO therapy on weekends. After a positive clinical response had been obtained, pressures were decreased (2.5 bar) and treatments were administered once daily, 5 days each week. The general principle was to treat patients until we judged that their host responses could sustain infection control and healing. When surgical treatment was required, we continued HBO treatment postoperatively.

With our protocol of 40 HBO sessions at 2.5 bar, we may have overtreated some patients. Patients 1.9 and 1.15 were successfully treated with 16 and 15 sessions of HBO treatment, respectively. HBO treatment was discontinued early for Patients 2.14 and 2.15 because of rapidly resolving infection. One patient (Patient 2.14) with a subdural empyema after burr hole evacuation of a chronic subdural hematoma recovered rapidly and could be discharged, with orally administered antibiotics, after only seven HBO treatments. For other patients (e.g., Patient 3.4), a longer treatment period might have been beneficial. Some of the patients who experienced failure (e.g., Patients 1.1 and 2.9, with large open defects) might have experienced better outcomes with a more aggressive reconstructive surgical approach.

Our clinical experience regarding HBO treatment dose and duration indicates that infection control and establishment of the healing process can be quite rapid and that many patients continue to exhibit improvement after cessation of HBO therapy. However, the bone-remodeling phase and long-term infection control may require a longer treatment protocol with up to or more than 40 HBO sessions. Our initial treatment schedule has been successful, but future refinements could certainly improve individual responses to treatment.

## CONCLUSION

We conclude 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. HBO therapy should be included in the neurosurgical armamentarium.

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## REFERENCES

1. Allen MB, Johnston KW: Preoperative evaluation: Complications, their prevention and treatment, in Youmans JR (ed): *Neurological Surgery*. Philadelphia, W.B. Saunders Co., 1990, ed 3, pp 833–900.
2. Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H, Chang M, Le AX, Hopf HW, Hunt TK: Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. **Arch Surg** 132:991–996, 1997.
3. Balch RE: Wound infections complicating neurosurgical procedures. **J Neurosurg** 26:41–45, 1966.
4. Bouachour G, Cronier P, Gouello JP, Toulemonde JL, Talha A, Alquier P: Hyperbaric oxygen therapy in the management of crush injuries: A randomised double-blind placebo-controlled clinical trial. **J Trauma** 41:333–339, 1996.
5. Davis JC, Heckman JD, DeLee JC, Buckwold FJ: Chronic nonhematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. **J Bone Joint Surg Am** 68A:1210–1217, 1986.
6. Erickson DL, Seljeskog EL, Chou SN: Suction-irrigation treatment of craniotomy infections: Technical note. **J Neurosurg** 41: 265–267, 1974.
7. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A: Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: A randomised study. **Diabetes Care** 19:1338–1343, 1996.
8. Feldmeier JJ, Heimbach RD, Davolt DA, Brakora MJ, Sheffield PJ, Porter AT: Does hyperbaric oxygen have a cancer-causing or -promoting effect? A review of the pertinent literature. **Undersea Hyperb Med** 4:467–475, 1994.
9. Granström G: Hyperbaric oxygen therapy as a stimulator of osseointegration, in Yanagita N, Nakashima T (eds): *Hyperbaric Oxygen Therapy in Otorhinolaryngology*. Basel, Karger, 1998, vol 54, pp 33–49.
10. Granström G, Tjellström A, Brånemark PI: Osseointegrated implants in irradiated bone: A case-controlled study using adjunctive hyperbaric oxygen therapy. **J Oral Maxillofac Surg** 57:493– 499, 1999.
11. Hampson NB: *Hyperbaric Oxygen Therapy: 1999 Committee Report*. Kensington, Undersea and Hyperbaric Medical Society, 1999, pp 1–82.
12. Hehenberger K, Brismar K, Lind F, Kratz G: Dose-dependent hyperbaric oxygen stimulation of human fibroblast proliferation. **Wound Repair Regen** 5:147–150, 1997.
13. Hunt TK, Hopf HW: Wound healing and wound infection: What surgeons and anesthesiologists can do. **Surg Clin North Am** 77:587–606, 1997.
14. Knighton DR, Halliday B, Hunt TK: Oxygen as an antibiotic: A comparison of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance. **Arch Surg** 121:191– 195, 1986.
15. Korinek AM: Risk factors for neurological site infections after craniotomy: A prospective multicenter study of 2944 patients— The French Study Group of Neurosurgical Infections, the SEHP, and the C-CLIN Paris-Nord Service Epidemiologie Hygiene et Prevention. **Neurosurgery** 41:1073–1081, 1997.

15a. Larsson A, Engström M, Uusijärvi J, Lind F, Mathiesen T: Hyperbaric oxygen (HBO) therapy in neurosurgical postoperative infections. **Undersea Hyperb Med** 27(Suppl):34, 2000 (abstr).

16. Leedom JM, Holtom PD: Infectious complications, in Apuzzo MLJ (ed): *Brain Surgery: Complication Avoidance and Management*. New York, Churchill Livingstone, 1993, pp 127–144.
17. Mader JT, Brown GL, Guckian JC, Wells CH, Reinarz JA: A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. **J Infect Dis** 142: 915–922, 1980.
18. Marx RE, Ehler WJ, Tayapongsak P: Relationship of oxygen dose to angiogenesis induction in irradiated tissue. **Am J Surg** 160: 519–524, 1990.
19. Marx RE, Johnson RP, Kline SN: Prevention of osteoradionecrosis: A randomized prospective clinical trial of hyperbaric oxygen versus penicillin. **J Am Dent Assoc** 111:49–54, 1985.
20. Neovius EB, Lind MG, Lind FG: Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck: A review of the literature and a report of 15 consecutive patients. **Head Neck** 19:315–322, 1997.
21. Park MK, Myers AM, Marzella L: Oxygen tensions and infections: Modulation of microbial growth, activity of antimicrobial agents, and immunological responses. **Clin Infect Dis** 14:720– 740, 1992.
22. Silver I: Tissue $PO_2$ changes in acute inflammation. **Adv Exp Med Biol** 94:769–774, 1978.
23. Wright RL: A survey of possible etiologic agents in postoperative craniotomy infections. **J Neurosurg** 25:125–132, 1966.

## COMMENTS

The authors report their significant experience with hyperbaric oxygen (HBO) treatment of neurosurgical infections. The results obtained are commendable for this patient population. A search of the literature on neurosurgery and HBO treatment did not yield any other articles on this subject, and it is difficult to identify historical control subjects with whom to compare such patients. The traditional neurosurgical approach, as the authors discuss, is to remove the bone or prosthesis in the presence of infection. The use of HBO therapy to avoid such removal might be preferable, with the main limitation being the scarcity of such units in medical centers.

**R. Loch Macdonald** *Chicago, Illinois*

In this retrospective study, Larsson et al. report their results of using HBO therapy to treat neurosurgical wounds. It seems most logical that HBO therapy would be effective in treating the Group 2 patients described by Larsson et al., for whom wound healing might be compromised by ischemia and poor wound oxygenation. HBO therapy has been routinely used to treat anaerobic wound infections and devascularized wounds throughout the body. In the presence of wound infections, HBO therapy can potentially have two positive effects, i.e., the killing of anaerobic bacteria and the potentiation of white blood cell function. It is not clear whether HBO treatment afforded superior results, compared with surgical therapy, for any other than Group 2 patients. Patients with spinal wound infections after instrumented fusion seem to respond to surgical therapy. A review of the literature indicates that spinal instrumentation can usually be left in place in infected spinal wounds treated with one or more surgical debridements (2, 3).

Similarly, the treatment of acute cranial infections, as observed for Group 1 in this study,

seems to be evolving. I have had the opportunity to observe acute postoperative wound infections successfully treated with surgical debridement replacing the bone flap or with suction irrigation, as described by Erickson et al. (1). Unfortunately, I do not know of a series of patients reported in the literature for comparison with the patients treated with HBO therapy.

This study documents the effectiveness of HBO therapy in treating neurosurgical wounds. The relative effectiveness of HBO treatment and the indications defining when HBO treatment is superior to other modes of therapy will need to be defined in future reports.

*h Carolina*


1. Erickson DL, Seljeskog EL, Chou SN: Suction-irrigation treatment of craniotomy infections. **J Neurosurg** 41:265–267, 1974.
2. Picada R, Winter RB, Lonstein JE, Denis F, Pinto MR, Smith MD, Perra JH: Postoperative deep wound infection in adults after posterior lumbosacral spine fusion with instrumentation: Incidence and management. **J Spinal Disord** 13:42–45, 2000.
3. Weinstein MA, McCabe JP, Cammisa FP Jr: Postoperative spinal wound infection: A review of 2391 consecutive index procedures. **J Spinal Disord** 13:422–426, 2000.


Larsson et al. retrospectively analyzed the effects of HBO therapy for patients with a variety of intracranial and intraspinal infections and/or foreign bodies. Although there is no comparison group and some of the follow-up periods are relatively short, the rate of successful treatment was generally better than might be expected. I disagree with the authors' contention that a randomized trial is not practical or ethical; if HBO therapy is to be considered an adjunctive treatment for neurosurgical infections, then it must be tested using valid scientific methods.

**Marc R. Mayberg** *Cleveland, Ohio*

HBO therapy has been successfully used to treat carbon monoxide poisoning and decompression sickness. The use of HBO therapy to treat other disease processes, such as acute ischemic stroke and cerebral air embolism, is of unproved benefit. With respect to infected tissues, HBO therapy has been used to treat gas gangrene, diabetic foot ulcers, necrotizing soft-tissue infections, and chronic refractory osteomyelitis. In neurosurgery, HBO treatment has been used to assist in the healing of scalp infections among patients with malignant brain tumors that have been treated with radiotherapy. This study represents the first large series of cases in which HBO therapy was used to treat cranial osteomyelitis, complex cranial infections in the presence of implants, and spinal infections. As anticipated, the success rate for bone flap or implant preservation was highest for less complicated cases without cranioplasties. The excellent

**A l l a n H . F r i e d m a n**

*D u r h a m , N o r t*

# STEREOTACTIC ASPIRATION AND ANTIBIOTIC TREATMENT COMBINED WITH HYPERBARIC OXYGEN THERAPY IN THE MANAGEMENT OF BACTERIAL BRAIN ABSCESSES

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**OBJECTIVE:** Despite advances in surgical techniques in the management of the brain abscess, long-term antibiotics are as crucial to cure as the initial surgical procedure itself. This study was designed to evaluate the effect of adjuvant hyperbaric oxygen (HBO) therapy on the duration of antibiotic treatment.

**METHODS:** Between 1999 and 2004, 13 patients with bacterial brain abscesses treated with stereotactic aspiration combined with HBO and systemic antibiotic therapy. Patients younger than 18 years of age were excluded from this study. Post-operatively, all patients were given a 4-week course of intravenous antibiotics. Additionally, patients received hyperbaric oxygen (HBO, 100% $O_2$ at 2.5 ATA for 60 min) twice daily for five consecutive days, and an additional treatment (100% $O_2$ at 2.5 ATA for 60 min daily) was given for 25 days.

**RESULTS:** There were eight male and five female patients. Their ages ranged between 18 and 71 years, with a mean of 43.9 years. The average duration of follow-up was 9.5 months (range, 8–13 mo). This treatment modality allowed infection control and healing for all 13 patients with 0% recurrence rate. HBO treatment was tolerated well, and there were no adverse effects of pressurization. At the end of the follow-up period, 12 patients had a good outcome: nine are without sequelae, and three have a mild hemiparesis but are capable of self-care. One patient has a moderate hemiparesis.
**CONCLUSION:** Although the number of patients is small, this series represents the largest reported group of brain abscess patients treated with stereotactic aspiration combined with antibiotic and HBO therapy. Our preliminary results indicate that the length of time on antibiotics can be shortened with the use of HBO as an adjunctive treatment.

**KEY WORDS:** Brain abscess, Hyperbaric oxygen therapy, Stereotactic aspiration

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Although the diagnosis and treatment of many neurosurgical conditions have improved as a result of technological advances, the management of brain abscesses still presents a challenging problem (12, 22, 28, 37). Despite the reported success with nonoperative as well as various forms of surgical therapy, there is no consensus as to what constitutes optimum management of these lesions. In recent years, there is increasing tendency to use stereotactic surgery as the first modality that has proved to be a relatively simple and safe method of aspirating abscesses (2, 3, 10, 19, 28, 29, 33, 41, 47). However, as it is well known, long-term antibiotic therapy is still required in these patients, regardless of the preferred method of treatment.

On the other hand, hyperbaric oxygen (HBO) has become a recognized treatment for a number of disorders such as gas gangrene, severe, necrotizing, soft-tissue infections, skin transplants, radiation-induced necroses, skin-muscle flaps, neural tissue transplants, crush syndrome, necrotic wound infections, compartment syndrome, and burns (5, 8, 11, 14, 23, 27, 31, 34, 36). On the basis of this observation, we think that it may be worthwhile to try a combination of HBO and stereotactic aspiration in the management of brain abscesses. Both have been tried individually bu

not been combined so far. In this article, we report our 5 years' experience in treating brain abscesses using stereotactic aspiration combined with antibiotic and HBO therapy.

## PATIENTS AND METHODS

Between March 1999 and June 2004, 13 patients with brain abscesses were treated by stereotactic aspiration combined with HBO and systemic antibiotic therapy. There were eight male and five female patients. Their ages ranged between 18 and 71 years, with a mean of 43.9 years. Patients younger than 18 years of age and patients with fungal, parasitic, or protozoal abscesses were excluded from this study. The initial work-up consisted of routine laboratory evaluation with complete blood count, coagulation profile, serum chemical testing, erythrocyte sedimentation rate (ESR), and urinalysis. In all cases, chest, cranium, sinus, and dental films were also obtained. Blood, urine and sputum cultures were obtained when appropriate. In all patients, a search was made for predisposing factors. One patient was an alcoholic. One patient had endocarditis, resulting from an infected prosthetic aortic valve, no causes were identified in the remaining eleven. Pretreatment neurological states were graded as alert, no deficits (Grade 0), alert, slight deficits (Grade I), lethargic, moderate deficits (Grade II), and obtunded, marked deficits (Grade III).

### Surgery

We used the Leksell Model 'G' Stereotactic system (AB Elekta Instruments, Stockholm, Sweden) for all of our procedures. We obtained computed tomographic (CT) scans both preoperatively for treatment planning and immediately postoperatively to detect complications and to assess the adequacy of treatment. After the coordinate frame is attached to the patient's head using local anesthesia, intravenous contrast-enhanced CT scanning was obtained using a 3- to 5-mm slice thickness to determine the target coordinates. The patient was then transported to the operating room where the stereotactic procedure was performed under local anesthesia. For small lesions (> 4 cm in diameter) gentle aspiration was performed. To drain lesions larger than 4 cm in greatest dimension we inserted an external drainage catheter (in three cases). Catheters generally were left in place for 2 to 4 days. In four patients with multiple abscesses, the abscesses bigger than 3 cm in diameter were drained in a single setting. In three of these patients, two different targets were entered, and three abscesses were aspirated in the remaining one. After completion of the procedure, the patient was closely observed by the nursing staff in the postanesthetic care unit for an additional 2 hours of observation. The aspirates obtained from patients were smeared immediately as well as sent for pathological examination. They were also cultured for aerobic and anaerobic bacteria, mycobacteria, and fungi. We began administrating an antimicrobial therapy in the operating room after learning the results of the Gram stain or the histopathologic diagnosis. Initial treatment for abscesses consisted of a combination of cafotaxime and metronidazole. Antibiotics were changed according to the results of culture and sensitivity studies. All patients were continued on a 4-week course of intravenous antibiotics. Patients in whom all cultures were negative continued to receive the initial antibiotics. The steroid dose was tapered on an individual basis depending on the extent of mass effect and edema seen on follow-up CT scans. Antiepileptics were continued for one to two years after which they are tapered providing EEG shows no epileptogenic activity.

### HBO treatment protocol

In accordance with our protocol, patients received HBO (100% $O_2$ at 2.5 ATA for 60 min) twice daily for 5 consecutive days, and then an additional treatment (100% $O_2$ at 2.5 ATA for 90 min daily) was given for 25 days (*Fig. 1*). Regular neuroradiological studies were performed every 3 days for the first 2 weeks. Later, providing there was evidence of clinical improvement, CT scans were obtained weekly for the duration of therapy. Following discontinuation of treatment, regular neuroradiologic studies were also performed at 4-week intervals until there was complete resolution of the abscess. After this evaluation, the last neurological and radiological controls were done six months later.

## RESULTS

During a 5-year period, there were 13 patients with bacterial brain abscesses treated with this treatment modality. Characteristics of these 13 patients are summarized in *Table 1*. The initial CT scans showed a total of 21 abscesses. In seven instances, the abscesses were cortical in location, nine were deep within the white matter, and five were within the thalamus or caudate nucleus. Four of these 13 patients had multiple abscesses. In this group, two patients had two abscesses each, one had three, and

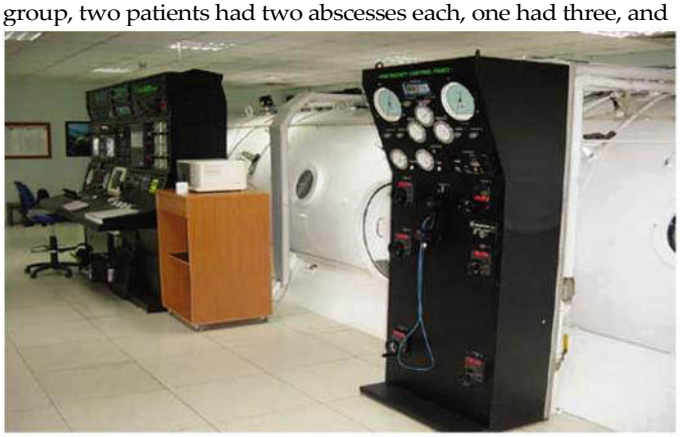

**FIGURE 1.** *Multiplace hyperbaric chamber; 100% oxygen given by hood at 2.5 ATA.*

**TABLE 1. Details of 13 patients with bacterial brain abscess**

| Characteristics | No. of patients |
|---|---|
| Total patients | 13 |
| *Male* | 8 |
| *Female* | 5 |
| Age (yr) | |
| *Mean* | 43.9 |
| *Range* | 18–71 |
| Etiology | |
| *Contiguous infection* | |
| *Middle ear infection* | 2 |
| *Frontoethmoidal sinusitis* | 1 |
| Hematogenous spread | |
| *Chronic pulmonary infection* | 2 |
| *Endocarditis* | 1 |
| *Skin pustules* | 1 |
| *Osteomyelitis* | 1 |
| *Neurosurgical procedure* | 1 |
| *Unknown* | 4 |
| *Location of abscess*[a] | |
| *Deep white matter* | 9 |
| *Cortical* | 7 |
| *Basal ganglia* | 3 |
| *Thalamic* | 2 |
| Neurological state at admission[b] | |
| *Grade 0* | 3 |
| *Grade I* | 6 |
| *Grade II* | 4 |
| *Grade III* | — |
| Isolated microorganisms[c] | |
| *Aerobes* | |
| *Streptococcus species* | 3 |
| *Pseudomonas species* | 3 |
| *Staphylococcus aureus* | 1 |
| *Anaerobes* | |
| *Peptostreptococcus species* | 3 |
| *Bacteroides fragilis* | 2 |
| *Negative culture* | 3 |
| Outcome | |
| *Grade 0* | 9 |
| *Grade I* | 3 |
| *Grade II* | 1 |
| *Grade III* | — |

[a] Four patients had multiple abscesses.
[b] Grade 0 alert, no deficits; Grade I alert, slight deficits; Grade II lethargic, moderate deficits; Grade III obtunded, marked deficits.
[c] Two patients had mixed infection.

one had a total of five abscesses. The majority of these patients (n = 9, 69.2%) were either alert without any neurological deficits (Grade 0, n = 3, 23%), or were alert and had slight neurological deficits (Grade I, n = 6, 46%). The remaining patients were lethargic and had moderate deficits (Grade II, n = 4, 30.7%).

A total of 20 aspirations were performed. There were no complications associated with the stereotactic procedure. HBO treatment was tolerated well. There were no cases of baro-

trauma, treatment-induced seizure, or other major side effects of HBO treatment. Each patient received a total of 4 weeks of intravenous antibiotic therapy. In the 10 patients (76.9%) in whom organisms were identified by culturing aspirate of abscesses, the antibiotics used were specific for those organisms. Two patients had mixed infection, they had both aerobic and anaerobic bacteria. The aerobic bacteria were *Streptococcus* species in three patients, *Pseudomonas* species in three, and *Staphylococcus* species in one. The anaerobic bacteria were *Peptostreptococcus* species in three patients and *Bacteroides Fragilis* in two patients. In three patients (23%), the causative organisms could not be identified. In patients with negative cultures, brain abscess was diagnosed according to the classic clinical and neuroradiologic findings and good therapeutic response to therapy. We were able to identify the source of infection in nine of these patients (69.2%). Hematogenous spread from a remote focus was the most common source of infection, occurring for six patients (66.6%). About 33.3% of brain abscesses were caused by spread of adjacent paranasal sinus, or middle ear infections.

The immediate postoperative CT examination showed a reduction of the targeted abscess diameter in all patients, but follow-up monitoring revealed that two abscesses recollected in the first 2 weeks. In these patients, we performed a second aspiration. The rate of abscess recurrence after initial surgery was 15.3%. The time course of abscess resolution on CT scans varied. A decrease in size was noticeable in the first 2 weeks after surgery, whereas complete resolution of the abscess cavity occurred 2 to 7 months (mean, 3.5 mo). The follow-up period was at least 8 months. The average duration of follow-up was 9.5 months (range, 8–13 mo). There have been no recurrences in this follow-up period (*Fig. 2, A* and *B*).

At the end of their follow-up period, 12 patients were in a good condition: nine (69.2%) are without sequelae and three (23%) have

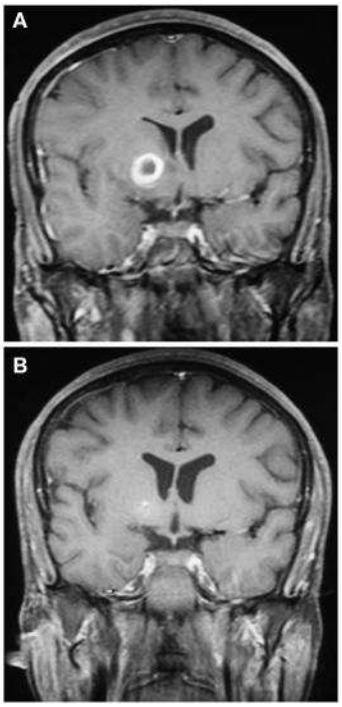


**FIGURE 2.** A, *gadolinium-enhanced coronal T1-weighted MRi scan showing the characteristic appearances of an abscess with peripheral rim enhancement in the* right *basal ganglia.* B, *gadolinium-enhanced coronal T1-weighted MRI scan obtained 9 months after stereotactic aspiration revealing complete resolution of the abscess.*

a mild hemiparesis, but are capable of self-care. One (7.6%) patient has a moderate hemiparesis.

## DISCUSSION

Despite advances in methods of radiological diagnosis, advances in surgical techniques, improved microbiological identification, and more effective antibiotic regimens, bacterial brain abscess continues to constitute one of the most important neurosurgical diseases. Throughout the history of the management of intracranial abscess there has been continuous controversy over the different methods employed (22, 43). Despite some evidence that brain abscesses can be adequately managed with antibiotics alone (41–43), various surgical procedures have been advocated for the treatment of brain abscesses, including drainage, aspiration, and excision (4, 7, 43). Although, as it is well known, the choice of one procedure over another may be influenced by the age and neurological condition of the patient, location and stage of the abscess, the type of abscess, and whether multiple lesions are present, modern-day therapy of brain abscesses generally includes a combined surgical and medical approach (22, 28, 32). Even though surgical management has been revolutionized by the development of image-guided stereotaxy that has proven to be a relatively simple and safe method, antibiotics continue to be an integral part of the treatment of these lesions (2, 3, 6, 9, 10, 19, 28, 29, 33, 41, 42, 47). However, the duration of treatment with antibiotics is a matter of some debate. Systemic antibiotics are generally given for six to eight weeks (3, 10, 12, 18, 28, 33, 40, 43), even in those instances where no organism can be identified (32, 40). Some centers now prescribe two weeks of intravenous antibiotics followed by up to four weeks of oral therapy (33, 43). Brain abscesses are at significant risk of recurrence despite what is considered adequate therapy. In the literature, rates of recurrence are reported to be between 5% and 50%, and most such events become apparent in the first 8 weeks after initiation of therapy (4, 7, 40, 44). In our study, parenteral antibiotics and HBO therapy were administered for a total of four weeks, even in patients without bacteriological diagnosis. Overall, initial surgery failed in two patients (15.3%). Two abscesses that recurred were again aspirated six and nine days after the first procedure. However, long-term radiological evaluation has failed to show recurrence of abscesses in any of the cases after an average follow-up period of 9.5 months. The main difference between our study and those reported in the literature is the reduced duration of antibiotic therapy. We think that this might be attributable to some beneficial effects of HBO therapy. It has been shown that HBO has been used in the management of a variety of infected, hypoperfused, and hypoxic wounds as a supplement to medical treatment, particularly where the latter has not been successful (5, 8, 11, 14, 27, 31, 34, 36). On the basis of considerations similar to the rationale for the use of HBO therapy to treat these disorders, the treatment of intracranial abscesses with adjunctive HBO therapy has been approved by the Undersea and Hyperbaric Medical Society since 1996 (14). In several studies, clinical experience with neurosurgical infections indicates that the results achieved with HBO therapy are remarkable (24–27).

One of the most important effects of HBO treatment is stimulation of the bactericidal action of white blood cells (15, 26, 27). Most infected tissues are hypoxic because of ischemia (45). It has been reported that the leukocyte bacteria-killing capacity is substantially impaired in hypoxic surroundings (1, 30). HBO therapy increases the oxygen tension in infected tissues, resulting in improvements in phagocytic killing of bacteria direct bactericidal effects on some microorganisms (21, 27, 30, 35). Additionally, improved tissue oxygen tensions in ischemic tissues during HBO therapy inhibits the growth of aerobic and facultative anaerobic bacteria by inducing a variety of metabolic effects involved with the synthesis of proteins, nucleic acids and essential cofactors of metabolic reactions. These effects of this treatment are mediated in large part by oxygen-based free radicals that oxidize proteins and membrane lipids, damage DNA, and inhibit metabolic functions essential for growth (17, 38). HBO can also affect the outcome of infections indirectly by influencing tissue repair and regeneration responses in infected necrotic tissues (20, 21, 38). It has also been shown that HBO therapy induces the formation of new capillaries, making the tissues less ischemic and improving long-term wound healing (23, 27, 34). However, the issues of the dose and duration of HBO therapy remain unsettled. With our protocol of 35 sessions at 2.5 ATA, we may have overtreated some patients. We believe that time will tell whether or not 2.5 ATA/35 sessions is the optimal treatment pressure for these patients, and future refinements could certainly improve individual responses to treatment. In the entire series of 13 patients managed with this protocol, no signs of cerebral oxygen toxicity were observed nor were other adverse effects of pressurization seen.

Brain abscesses displace the brain tissue to a marked degree, but often little brain tissue is actually destroyed. Many of the focal deficits produced by abscesses can be ascribed to a significant amount of perilesional edema, and they are reversible (22). The expansive growth of an intracranial abscess and the formation of its perifocal edema may result in secondary lesions in surrounding brain tissue. The other beneficial effect of HBO on increased ICP has been clearly documented (24, 26, 39, 46). Elevated arterial oxygen tension results in a vasoconstriction leading to a decrease in cerebral blood flow, and consequently, to a reduction in intracranial pressure (16, 26). We think that the therapeutic impact of these physiological effects of HBO may be of major importance in the prevention or treatment of secondary brain damage. Additionally, we have performed stereotactic surgery. It has been proven that stereotactic aspiration not only does it minimize iatrogenic brain damage caused by brain retraction and dissection, it also minimizes operation time and hospital stay (2, 6, 9, 10, 13, 19, 28, 29, 33, 47).

Difficulty in the treatment of multiple abscesses is well known. They have been associated with high recurrence rates

(12, 33, 41, 43). In this group, long-term antibiotics are as crucial to cure as the initial surgical procedure itself. Moreover, according to some authors' opinions, patients with multiple brain abscesses, with or without bacteriological diagnosis, will usually require three months of systemic antibiotic therapy which may be a high dose initially followed by a tapered maintenance dosage (28). Although surgical treatment of these lesions, particularly with bilateral and/or deep-seated lesions presents a challenging problem, they can easily be treated in a single setting utilizing local anesthesia with stereotaxy. This usually can be done with local anesthesia and a single pass to reach each lesion (6, 10, 28). In our series there were four patients with multiple abscesses. Any difficulties in targeting abscesses were never encountered in the patients with stereotactic aspiration where only one pass was made for each abscess. Although systemic antibiotics and HBO therapy were given for only four weeks, there were no recurrences in the long-term follow-up period in this group.

In our study, the overall mortality rate was 0%. However, as has been reported before, the most important determinant of the morbidity and mortality rate is the neurological condition of the patient at the time of diagnosis (7, 28, 33, 37, 44). Most of our patients were in good neurological status (Grades 0 and I), which has resulted in patients being treated while in better neurological condition. It is clear that the success of treatment of intracranial abscess still depends on early clinical and radiological diagnosis, awareness in the medical community and prompt referral for neurosurgical management.

## CONCLUSION

Although the overall numbers are too small to make any definite conclusions, this series represents the largest reported group of brain abscess patients treated with stereotactic aspiration combined with antibiotic and HBO therapy. This treatment modality allowed infection control and healing for all 13 patients with a 0% recurrence rate. These preliminary results indicate that adjunctive HBO therapy can reduce the need for re-operations (repeated aspiration), the duration of antibiotic therapy, and also reduce overall costs.

Despite advances in surgical techniques in the management of the brain abscess, long-term antibiotics are as crucial to cure as the initial surgical procedure itself. On the other hand, HBO has been shown to have a beneficial effect in the management of a variety of infected, hypoperfused, and hypoxic wounds. This study was sought to evaluate the effect of HBO therapy on the duration of antibiotic treatment. After surgery, all patients received a total of 4 weeks of antibiotic therapy specific for a cultured organism in 8 of 11 patients. Additionally, patients received HBO ( 100% $O_2$ at 2.5 ATA for 60 min) twice daily for 5 consecutive days, and an additional treatment (100% $O_2$ at 2.5 ATA for 90 min daily) was given for 25 days. The average duration of follow-up was 9.5 months (range, 8–13 mo). This treatment modality allowed infection control and healing for all 13 patients with 0% recurrence rate. HBO treatment was tolerated well, and there were no adverse effects of pressurization. Although the overall numbers are too small to make any definite conclusions, it would appear that adjunctive HBO therapy can reduce the length of time on antibiotics.

## REFERENCES


1. Allen DB, Maguire JJ, Mahdavian M, Wicke C, Macocci L, Scheuenstuhl H, Chang M, Le AX, Hopf HW, Hunt TK: Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. **Arch Surg** 132:991–996, 1997.
2. Apuzzo MLJ, Chandrosoma PT, Cohen D, Zee C, Zelman V: Computed imaging stereotaxy: Experience and perspective related to 500 procedures applied to brain masses. **Neurosurgery** 20:930–937, 1987.
3. Barlas O, Sencer A, Erkan K, Eraksoy H, Sencer S, Bayındır C. : Stereotactic surgery in the management of brain abscess. **Surg Neurol** 52:404–410, 1999.
4. Beller AJ, Sahar A, Praiss I: Brain abscess: Review of 89 cases over a period of 30 years. **J Neurol Neurosurg Psychiatry** 36: 757–768, 1973.
5. Bouachour G, Cronier P, Gouello JP, Toulemonde JL, Talha A, Alquier P: Hyperbaric oxygen therapy in the management of crush injuries. A randomized double-blind placebo-controlled clinical trial. **J Trauma** 41:333–339, 1996.
6. Brith RH: Brain abscess, in Wilkins RH, Rengachary SS (eds): *Neurosurgery.* New York, McGraw-Hill, 1985, pp 1928–1956.
7. Carey ME, Chou SN, French LA: Experience with brain abscesses. **J Neurosurg** 36:1–9, 1972.
8. Davis JC, Gates GA, Lerner C, Davis MG Jr, Mader JT, Dinesman A: Adjuvant hyperbaric oxygen in malignant external otitis. **Arch Otolaryngol Head Neck Surg** 118:89–93, 1992.
9. Duma CM, Kondziolka D, Lunsford LD: Image-guided stereotactic management of non-AIDS-related cerebral infection. **Neurosurg Clin N Am** 3:291–302, 1992.
10. Dyste GN, Hitchon PW, Menezes AH, Vangilder JC, Greene GM: Stereotaxic surgery in the treatment of multiple brain abscesses. **J Neurosurg** 69:188–194, 1988.
11. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A: Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: A randomised study. **Diabetes Care** 19:1338–1343, 1996.
12. Haines SS, Mampalam T, Rosenblum ML, Nagrib MG: Cranial and intracranial bacterial infections, in Youmans JR (ed): *Neurological Surgery.* W.B. Saunders Co., Philadelphia, 1990, pp 3707–3735.
13. Hall WA: The safety and efficacy of stereotactic biopsy for intracranial lesions. **Cancer** 82: 1749–1755.
14. Hampson NB:*Hyperbaric Oxygen Therapy:1999 Committe Report.* Kensington, Undersea and Hyperbaric Medical Society, 1999, pp 1–82.
15. Hohn DC: Oxygen and leukocyte microbiol killing, in Davis JC, Hunt TK (eds): *Hyperbaric Oxygen Therapy.* Bethesda, Undersea Medical Society, 1977, pp 101–110.
16. Holbach KH, Wassmann H, Hohelüchter KL, Jain KK: Differentiation between reversible and irreversible post-stroke changes in brain tissue: Its relevance for cerebrovascular surgery. **Surg Neurol** 7:325–331, 1977.
17. Jamieson D, Chance B, Cadenas E, Boveris A: The relation of free radical production to hyperoxia. **Ann Rev Physiol** 48:703–719, 1986.
18. Juneau P, Black P: Intra-axial cerebral infectious processes, in Apuzzo MLJ (ed): *Brain Surgery. Complication Avoidance and Management.* New York, Churchill Livingston Inc., 1993, pp 1411–1417.
19. Kelly P, Kall BA, Goerss S, Cascino TL: Results of computer-assisted stereotactic laser resection of deep-seated intracranial lesions. **Mayo Clin Proc** 61:20–27, 1986.
20. Kivisaari J, Niinikoski J: Effects of hyperbaric oxygenation and prolonged hypoxia on the healing of open wounds. **Acta Chir Scand** 141:14–19, 1975.

21. Knighton DR, Halliday B, Hunt TK: Oxygen as an antibiotic. A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance. **Arch Surg** 121:191–195, 1986.
22. Kole KM, Rosenblum ML: Management of multiple brain abscesses, in Batjer HH, Loftus CM (eds): *Textbook of Neurological Surgery. Principles and Practice.* Philadelphia, Lippincott Williams and Wilkins, 2003, pp 3151–3157.
23. Kutlay M, C¸ olak A, Demircan N, Akın ON, Kıbıcı K, Dündar K, Yıldırım S: Effect of hyperbaric oxygen therapy on fetal spinal grafts: an experimental study. **Undersea Hyper Med** 27:205–213, 2000.
24. Lampl LA, Frey G, Dietze T, Trauschel M: Hyperbaric oxygen in intracranial abscesses. **J Hyperbaric Med** 4:111–126, 1989.
25. Lampl LA, Frey G, Bock KH: Hyperbaric oxygen in intracranial abscesses-update of a series of 13 patients. **Undersea Biomed Res** 19[Suppl]:83, 1992 (abstr).
26. Lampl LA, Frey G: Hyperbaric oxygen in intracranial abscess, in Kindwall EP (ed): *Hyperbaric Medicine Practise.* Arizona, Best Publishing Co., 1995, pp 661–670.
27. Larsson A, Engström M, Uusijarvi J, Kihlström L, Lind F, Mathiesen T: Hyperbaric oxygen treatment of postoperative neurosurgical infections. **Neurosurgery** 50:287–296, 2002.
28. Loftus CM, Osenbach RK, Biller J: Diagnosis and management of brain abscess, in Wilkins RH, Rengachary SS (eds): *Neurosurgery.* New York, McGraw-Hill, 1996, pp 3285–3298.
29. Lunsford LD: Stereotactic drainage of brain abscesses. **Neurol Res** 9:270–274, 1987.
30. Mader JT, Brown GL, Guckian JC, Wells CH, Reinarz JA: A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. **J Infect Dis** 142:915–922, 1980.
31. Mader JT, Adams KR, Wallace WR, Calhoun JH: Hyperbaric oxygen as adjunctive therapy for osteomyelitis. **Infect Dis Clin N Am** 4:433–440, 1990.
32. Mamelak AN, Mampalam TJ, Obana WG, Rosenblum ML: Improvement of management of multiple brain abscesses: a combined surgical and medical approach. **Neurosurgery** 36:76–85, 1995.
33. Mampalam TJ, Rosenblum ML: Trends in the management of bacterial brain abscesses: A review of 102 cases over 17 years. **Neurosurgery** 23:451–458, 1988.
34. Marx RE, Ehler WJ, Tayapongsak P, Pierce LW: Relationship of oxygen dose to angiogenesis induction in irradiated tissue. **Am J Surg** 160:519–524, 1990.
35. Muhvich KH, Park MK, Myers RA, Marsella L: Hyperoxia and the antimicrobial susceptibility of Escherichia coli and Pseudomonas aeruginosa. **Antimicrob Agents Chemother** 33:1526–1530, 1989.
36. Neovius EB, Lind MG, Lind FG: Hyperbaric oxygen therapy for wound complications after surgery in the irradiated head and neck: A review of the literature and a report of 15 consecutive patients. **Head Neck** 19:315–322, 1997.
37. Osenbach RK, Loftus CM: Diagnosis and management of brain abscess. **Neurosurg Clin N Am** 3:403–420, 1992.
38. Park MK, Muhvich KH, Myers RA, Marzella L: Effects of hyperbaric oxygen in infectious disease: Basic mechanism, in Kindwall EP (ed): *Hyperbaric Medicine Practise.* Arizona, Best Publishing Co., 1995, pp 141–172.
39. Pence EC, Jacobson JH: Cerebral edema, in Davis JC, Hunt TK (eds): *Hyperbaric Oxygen Therapy.* Bethesda, MD, Undersea Medical Society, 1977, pp 287–301.
40. Poffenbarger GJ, Khajavi K: Management of solitary intracranial abscess, in Batjer HH, Loftus CM (eds): *Textbook of Neurological Surgery. Principles and Practice.* Philadelphia, Lippincott Williams and Wilkins, 2003, pp 3142–3150.
41. Rosenblum ML, Hoff JT, Norman D, Weinstein PR, Pitts L: Decreased mortality from brain abscesses since advent of computerized tomography. **J Neurosurg** 49:658–668, 1978.
42. Rosenblum ML, Hoff JT, Norman D, Edwards M, Berg B; Nonoperative treatment of brain abscesses in selected high-risk patients. **J Neurosurg** 52:217–225, 1980.
43. Rosenblum ML, Mampalam TJ, Pons VG: Controversies in the management of brain abscesses. **Clin Neurosurg** 33:603–632, 1986.
44. Samson DS, Clark K: A current review of brain abscess. **Am J Med** 54(2): 201–210, 1973.
45. Silver I: Tissue $PO_2$ changes in acute inflammation. **Adv Exp Med Biol** 94:769–774, 1978.
46. Sukoff MH, Ragartz RE: Hyperbaric oxygen for the treatment of acute cerebral edema. **Neurosurg** 10:29–38, 1982.
47. Wise BL, Gleason CA: CT-directed stereotactic surgery in the management of brain abscess. **Ann Neurol** 6:457, 1979.

## COMMENTS

The authors present a series of 13 consecutive patients with brain abscesses who were treated with stereotactic aspiration and four weeks of intravenous antibiotics in conjunction with hyperbaric oxygen therapy. Four of these patients had multiple abscesses. They report good results with no mortality or treatment-related morbidity and complete response to treatment in all patients, although two of the abscesses recurred early in treatment, requiring repeat aspiration. Although the number of patients treated in this series is relatively small, these results compare favorably against previously reported rates of recurrence, especially in light of the relatively short duration of antibiotic therapy.

The efficacy of hyperbaric oxygen therapy in the treatment of bacterial infections has been well documented. It is not surprising, therefore, that its beneficial effects would extend to the treatment of intracranial infections. The authors point out the relatively higher rate of recurrence among patients with multiple abscesses and the associated need for prolonged antibiotic therapy. We feel that in centers where hyperbaric oxygen therapy is available, its use should be considered as a potentially valuable treatment option in cases where the probability of failure of treatment is deemed to be high.

At this point, however, any potential reduction in treatment costs related to decreased duration of antibiotic therapy and possibly lower rates of recurrence has not been demonstrated. Additionally, while the use of stereotactic surgery has become fairly widespread, the capability of treating patients with hyperbaric oxygen remains relatively scarce. Given the lack of availability and the cost associated with this treatment, and in light of the excellent results that are obtained without the use of hyperbaric oxygen, we do not feel that it should be considered first-line therapy in the treatment of uncomplicated cases of brain abscess at this time.

**Erik C. Parker**
**Patrick J. Kelly**
*New York, New York*

The authors have written a clear and scholarly approach to the management of brain abscesses. They appropriately used stereotactic aspiration, catheter placement for larger lesions, and specific antibiotic therapy. In addition, they used a regimen of hyperbaric oxygen (HBO). Although they discuss the science behind HBO, its value in this setting is unclear. Because a randomized trial would be almost impossible to perform in this disease, a matched cohort study to patients managed without HBO would have been of interest. I continue to advocate all of the elements of care they propose, but this study will not lead me to use HBO as a routine.

**Douglas Kondziolka**
*Pittsburgh, Pennsylvania*

The authors report on 13 patients with brain abscesses who were treated with aspiration, 4 weeks of antibiotics, and 30 days of hyperbaric oxygen (HBO) at 2.5 ATA. In all patients, they observed resolution of the abscesses and no recurrence.

The organisms isolated were both aerobic and anaerobic. In three cases, cultures were negative. The authors provide a good discussion

of hypothesis about the antibacterial effect of HBO. As they indicate, the numbers of cases are too small to draw definite conclusions, but the potential for this treatment should be kept in mind.

**Robert G. Grossman** *Houston, Texas*

This paper is a small series of patients in which stereotactic aspiration of cerebral abscesses was performed followed by an abbreviated course (4 weeks) of intravenous (IV) antibiotics combined with hyperbaric oxygen therapy. The authors' conclusion that the abbreviated IV course is only made possible by the adjunctive hyperbaric oxygen treatment is interesting, but certainly not definitive. The suggestion that there were no recurrences is not entirely accurate because two patients required repeat aspirations. This implies a 15.3% early recurrence after the initial aspiration during treatment; it is true that there were no recurrences after completion of treatment during the period of follow-up. An important addition to future papers evaluating this combined therapy would be a cost analysis compared to other treatment paradigms. Overall, this contribution offers a baseline experience of a combination of IV antibiotics and hyperbaric oxygen therapy from which other more definitive studies can be performed.

**James M. Ecklund** *Washington, D.C.*

## *Clostridium perfringens* brain infection following a penetration wound of the orbit.

Sir: We present the first reported case whereby the response of clostridial cerebritis to antibiotics and hyperbaric oxygen was monitored using computed tomography. The mechanism of infection illustrates the danger of concealed penetrating injury and its possible consequences.

A 47 year old company director presented at his local hospital having tripped and fallen into a rose bush. A branch had pierced the inner aspect of his right eye. He had lacerations of the bulbar conjunctiva and the lower lid. The globe was intact. Tetanus toxoid was administered and he was admitted for repair of his injuries. An epistaxis that night and haematemesis the next day caused postponement of surgery. On the third day following injury he developed marked lid oedema and chemosis, with a pus-like discharge. The wound was explored and multiple fragments of wood were found together with pus. After irrigation and repair of the lid laceration, treatment with metronidazole, erythromycin and chloramphenicol was commenced. After Operation the eye was stable, but he developed pyrexia. On the sixth day following injury, he became aphasic with a right hemiparesis. Culture of pus from the wound showed a pure growth of *Clostridium perfringens.* He was then referred to Atkinson Morley's Hospital.

On admission, he was conscious, but aphasic and obeying only simple commands. His right eye had lid swelling and chemosis. There was a right hemiparesis: Grade IV of the arm, Grade 0 of the leg. Radiography revealed bony injury to the supero-medial aspect of the right orbit and the upper and lower walls of the right frontal sinus, which was opaque. There was a small gas loculus in the right frontal pole. Computed tomography showed oedematous changes in the medial aspect of both frontal lobes, more extensive on the right, where a gas bubble was present in the frontal pole (fig). Treatment was started with intravenous penicillin, metronidazole and chloramphenicol. Later that day hyperbaric oxygen therapy was commenced; three treatments over three days at 250 KPa (2 1/2 atm.) pressure for three hours was given.

Thereafter steady, uneventful improvement took place. Following review by an ENT surgeon the right fronto-ethmoidal sinus was explored. A fracture of the orbital roof was found, the frontal sinus containing

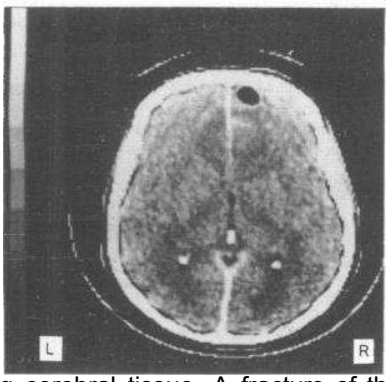


Fig *Computed tomography of the brain showing a gas bubble in the right frontal pole and oedematous changes in the medial aspect of both frontal lobes.*



pus and herniating cerebral tissue. A fracture of the superomedial aspect of the orbit was displaced into the ethmoid from which were removed two pieces of foreign material, one measuring 12 cm x 4 mm. The pus was sterile and biopsy of the brain hernia demonstrated only necrosis. Eighteen days following his injury the dysphasia and hemiparesis had resolved considerably. He was discharged for convalescence on antibiotics. On review a month later, speech was normal, although there was a flatness of affect. The right eye was normal and there was no limb weakness. A CT scan showed resolution of the intracranial gas, but with some residual frontal lobe oedema. Full recovery subsequently occurred.

Although potentially fatal, intracranial infection with *Clostridium perfringens* can be successfully treated following proinpt aspiration, where indicated, and antibiotic therapy.[1] The mortality rate from cerebral abscess due to clostridial infection has been assessed at 24%.[2]

In this case, only computed tomography made possible the diagnosis of "clostridial cerebritis" (with potential for abscess formation). Intensive therapy was clearly indicated and the patient's condition improved markedly during the use of hyperbaric oxygen in conjunction with antibiotics, although Keogh[3] has suggested that there is no place for the former. We would emphasise the importance of investigating the possibility of retained foreign material within penetrating wounds around the orbit, which may act as a source of infection.

We thank Dr J Ambrose and Dr G Hart of the Neuroradiology Department, Atkinson Morley's Hospital; Mr David Whittam, Consultant ENT Surgeon, St George's Hospital; The RAF Mobile Hyperbaric Oxygen Unit, Swindon; and our secretary Miss S Rostron for typing the manuscript.

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**References**

Cairns **H, Calvert** CA, Danial P. Complications of head wounds, with especial reference to infection. *Br J Sur (War Surgery Suppl)* 1947;1:198-211.

**2** Russell JA, Taylor JC. Circumscribed gasgangrene abscess of the brain. Case report together with an account of the literature. *Br J Surg* 1963;50:434-7.

Keogh Al. Clostridial brain abscess and hyperbaric oxygen. *Postgrad Med J 1973;49:64-6.*

*Hofmann VM[1], Liedtke H[2], Bloching M[1:]* Möglichkeiten und Grenzen der HBO-Therapie bei lebensbedrohlichen **craniofazialen Infektionen** HNO Informationen 2004 Thema: 7 Infektiologie 7.3

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Die **nekrotisierende Fasziitis** und die **invasive cerebrale Aspergillose** sind Infektionen, die in 70–95% der Fälle letal verlaufen. Neben ausgedehnter lokaler Destruktion ist häufig eine sich anschließende Sepsis dafür ursächlich. Die im Gesichtsbereich vorkommende Fasziitis stellt für den HNO-Arzt eine Herausforderung dar, die eine rasche Entscheidung über das notfallmäßige therapeutische Vorgehen verlangt. Je nach Ausdehnung der Entzündung und Geschwindigkeit des Fortschreitens kann im Gegensatz zum derzeit gültigen Goldstandard -der operativen Infektsanierung- in Einzelfällen eine notfallmäßige HBO-Therapie als Therapiealternative eingesetzt werden. Anhand von Fallbeispielen soll das unterschiedliche Vorgehen beschrieben werden. Auch bei der invasiven cerebralen Aspergillose im Bereich der Schädelbasis ist je nach Situation neben der primär chirurgischen Infektsanierung die HBO-Therapie als Therapiealternative oder als Ergänzung anzusehen. Auch hier soll anhand von Fallbeispielen das individuelle Vorgehen erläutert werden.

Neben Antibiose und chirurgischer Sanierung kann sowohl bei der nekrotisierenden Fasziitis, als auch bei der invasiven cerebralen Aspergillose, die HBO-Theapie als probate Methode zur Infektbehandlung angewandt werden. Möglichkeiten und Grenzen der Anwendung sollen aufgezeigt werden.

Keywords: HBO-Therapie, invasive cerebrale Aspergillose, nekrotisierende Fasziitis

Kurschel S, A Mohia, V Weigl, HG Eder; Hyperbaric oxygen therapy for the treatment of brain abscess in children. Childs Nerv Syst. 006; 22: 38-42 Epub 2005-5-5

Department of Neurosurgery, Medical University, Auenbruggerplatz 29, 8036 Graz, Austria.

INTRODUCTION: The treatment of brain abscess remains a challenging topic usually involving a multimodal concept.

METHODS: We report our experience with hyperbaric oxygen (HBO) therapy in five children presenting with brain abscesses between 1995 and 2002 at the Department of Neurosurgery, Graz. Mean age was 14.8 (range 11-17 years). All abscesses were located supratentorially. One child had a single abscess and one had multilocated abscesses. Two other patients presented with both subdural empyema and brain abscess, one of them showing an epidural empyema as well. In another child, the brain abscess was associated with meningoencephalitis and subdural empyema. In all of them the underlying condition was spread of infection from the paranasal sinuses, except for one, who was immunocompromised due to cytotoxic chemotherapy for acute lymphocytic leukaemia.

RESULTS: One single brain abscess and one of the multiple abscesses were drained. All subdural/epidural empyemas were treated surgically. Antibiotics were administered intravenously for 13 to 22 days (mean 22 days). All patients underwent HBO therapy; the number of treatments ranged from 26 to 45 "dives" (mean 30). Treatments were given once daily at 2.2 atmosphere absolutes for 60 min at 12 m. During the hospital stay all improved their clinical condition, with continued regression of abnormalities on magnetic resonance imaging (MRI). In the following weeks, other interventions were performed to treat the origin of the infections. At 6 months follow-up they were all in good clinical condition, either symptom free or with minor residual symptoms. MRI at this time showed no evidence of disease in three, a residual dural enhancement in one and a residual shrunken collection in the child with multilocated abscesses. No recurrence was observed during a mean follow-up of 21 months (range from 7 to 72 months).

CONCLUSION: HBO therapy in children with brain abscesses seems to be safe and effective, even when they are associated with subdural or epidural empyemas. It provides a helpful adjuvant tool in the usual multimodal treatment of cerebral infections and may reduce the intravenous course of antibiotics and, consequently, the duration of hospitalization. Multidisciplinary management is recommended to optimize care for these critically ill children.

Lampl L, Frey G, Fischer D, Fischer S.: [Hyperbaric oxygenation: utility in intensive therapy - part 2]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2009 Oct;44(10):652-8. Epub 2009

[Article in German]
Anästhesiologie und Intensivmedizin am Bundeswehrkrankenhaus Ulm.

Gangrene, non-clostridial myonecroses and **intracranial abscesses** are clinical entities for which hyperbaric oxygenation can be used therapeutically. Mortality and invalidity can be reduced by this means. Except for gangrene, HBO is used merely as an adjuvant for these diseases when conventional surgical, antibiotic and intensive therapy measures are not sufficient. The action of HBO is based on several points of attack: it reduces the formation of oedema, inhibits the production of alpha-toxins of the Clostridia, has a bacteriotoxic action, increases the effectivity of antibiotics and improves the immune defense system.

An early start is decisive for the success of HBO therapy.

Georg Thieme Verlag Stuttgart * New York.

PMID: 19834829 [PubMed - indexed for MEDLINE]

Pilgramm M, L Lampl, G Frey, U Wörner: [Hyperbaric oxygen therapy of anaerobic brain abscesses following tonsillectomy] HNO 1985;33:84-6

[Article in German]

This study describes the clinical course of a 31 year old woman who developed multiple anaerobic brain abscesses six days after tonsillectomy, followed by hemiparesis and dysarthria. In spite of craniotomy, repeated punctures and drainage of pus and high dose local and systemic antibiotics, there was an obvious deterioration in the patient's condition.

Hyperbaric oxygen therapy was tried as a last resort. The patient improved quickly, and six months after the tonsillectomy seems to be neurologically symptomfree.

# INTRACRANIAL ABSCESS

**UHMS.org (Undersea and Hyperbaric Medicune Society - USA)**

The term "intracranial abscess" (ICA) includes the following disorders: cerebral abscess, subdural empyema and epidural empyema. These disorders share many diagnostic and therapeutic similarities and, frequently, very similar etiologies.

The overall mortality described in six case series of ICA from different countries during the years 1981-1986 ranged from 10 to 36%, with a summed death rate of 22% (142 deaths in 636 patients).[1-6] Fifteen subsequent studies during the years 1987-1993 suggest that the mortality may have decreased slightly, with a combined death rate of 18% (115 in 634 patients).[7-21] Summing these 21 studies, the average mortality from ICA was 20%. This was confirmed in the neurosurgical literature in the late 1990's.[22]

Factors possibly responsible for a decrease in mortality include: (a) earlier and more accurate diagnosis through expanded use of computed tomography (CT), (b) advances in minimally invasive surgery, e.g. CT-guided fine needle aspiration, and (c) improved understanding of the bacteriology of ICA, leading to more appropriate antibiotic therapy.

Because of improving mortality, there is a general trend toward a more conservative therapeutic approach in the management of ICA patients. This is reflected in the current international literature. However, patients with certain conditions and complications continue to pose major therapeutic problems. These include patients with: (a) multiple abscesses, (b) abscess in a deep or dominant location, (c) immune compromise, and (d) no response or further deterioration in spite of standard surgical and antibiotic treatment.

Under these circumstances, adjunctive hyperbaric oxygen ($HBO_2$) therapy may confer additional therapeutic benefit. A number of mechanisms can be postulated by which $HBO_2$ could provide benefit in ICA. First, high partial pressures of oxygen may inhibit the flora found in ICA, the predominance of which are anaerobic.[1-4,23-40] Second, $HBO_2$ can cause a reduction in perifocal brain swelling.[41-47] Third, $HBO_2$ has the potential to enhance host defense mechanisms.[48,49] Finally, $HBO_2$ has been reported to be of benefit in cases of concomitant skull osteomyelitis.[40,50]

Preliminary experience using adjunctive $HBO_2$ to treat patients with ICA has been favorable. To date, 66 such patients have been reported with 1 death (1.5% mortality). These include 16 consecutive patients reported in a series from Germany,[39,51-54] 18 patients treated in Austria,[55] 8 patients treated in France (4 with brain abscess; 4 with subdural and epidural empyema),[56] 13 patients treated in Turkey (all with brain abscess and treated with stereotactic aspiration),[57] 5 pediatric patients treated in Austria (1 with single brain abscess, 1 with multiloculated brain abscesses, 2 with brain abscess and subdural empyema , 1 with brain abscess, subdural empyema, and epidural empyema)[58]

and an additional 6 patients treated in several centers in the United States (personal reports collected by Eric Kindwall). A patient with cervical epidural abscess treated in Japan has also been reported.[59] The single death to date occurred in a patient with epidural empyema who had suffered hemispheric venous infarction from superior longitudinal sinus thrombosis prior to referral for hyperbaric oxygen therapy.[56]

## Patient Selection Criteria

Adjunct $HBO_2$ should be considered under the following conditions:

1) Multiple abscesses

2) Abscesses in a deep or dominant location

3) Compromised host

4) In situations where surgery is contraindicated or where the patient is a poor surgical risk

5) No response or further deterioration in spite of standard surgical (e.g. 1-2 needle aspirates) and antibiotic treatment.

## Clinical Management

Hyperbaric oxygen treatment is administered at a pressure of 2.0 to 2.5 atmospheres absolute, with oxygen administration from 60 to 90 minutes per treatment. $HBO_2$ treatment may be one or two sessions per day depending on the condition of the individual patient. In the initial phase, twice daily treatment may be considered. The optimal number of $HBO_2$ treatments for ICA is unknown. In the largest series of ICA patients treated with $HBO_2$, the average number of $HBO_2$ sessions was 13 in the absence of osteomyelitis. Duration of the $HBO_2$ course must be individualized, based upon the patient's clinical response as well as radiological findings.

# Osteomyelitis (Refractory)
# With literature review supplement

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## CRITICAL SYNOPSIS

Osteomyelitis is an infection of bone or bone marrow, usually caused by pyogenic bacteria or mycobacteria. Refractory osteomyelitis is defined as a chronic osteomyelitis that persists or recurs after appropriate interventions have been performed or where acute osteomyelitis has not responded to accepted management techniques [1].

To date, no randomized clinical trials examining the effects of hyperbaric oxygen ($HBO_2$) therapy on refractory osteomyelitis exist. However, the substantial majority of available animal data, human case series and non-randomized prospective trials suggest that the addition of $HBO_2$ therapy to routine surgical and antibiotic management in *previously refractory* osteomyelitis is safe and improves the ultimate rate of infection resolution. Consequently, $HBO_2$ therapy should be considered an American Heart Association (AHA) Class II recommendation in the management of refractory osteomyelitis. More specifically, in uncomplicated extremity osteomyelitis or cases where signifycant patient morbidity or mortality is not likely to occur, $HBO_2$ therapy can be considered an AHA Class IIb treatment. For patients with more severe Cierny-Mader Class 3B or 4B disease, adjunctive $HBO_2$ therapy should be considered an AHA Class IIa intervention.

Additional consideration must also be given to patients with osteomyelitis involving the spine, skull, sternum or other bony structures associated with a risk for high morbidity or mortality. In these patients, $HBO_2$ therapy may be considered an AHA Class IIa intervention *prior* to undergoing extensive surgical debridement. Finally, for osteomyelitis in the subset of patients with associated Wagner Grade 3 or 4 diabetic ulcers, adjunctive $HBO_2$ should be rgarded as an AHA Class I intervention.

In most cases, the best clinical results are obtained when $HBO_2$ therapy is administered in conjunction with culture-directed antibiotics and scheduled to begin soon after thorough surgical debridement. $HBO_2$ therapy is ordinarily delivered on a daily basis for 90-120 minutes using 2.0-3.0 atmospheres of absolute pressure (ATA). Recommendation of a specific treatment pressure is not supported by data. Where clinical improvement is seen, the present regimen of antibiotic and $HBO_2$ therapy should be continued for approximately four to six weeks.

Typically, 20-40 postoperative $HBO_2$ sessions will be required to achieve sustained therapeutic benefit. In cases where extensive surgical debridement or removal of fixation hardware may be relatively contraindicated (*e.g.*, cranial, spinal, sternal or pediatric osteomyelitis), a trial of limited debridement, culture-directed antibiotics and $HBO_2$ therapy prior to more radical surgical intervention provides a reasonable chance for osteomyelitis cure.

Again, a course of four to six weeks of combined $HBO_2$ and antibiotic therapy should be sufficient to achieve the desired clinical results. In contrast, if prompt clinical response is not noted or osteomyelitis recurs after this initial treatment period, then continuation of the existing antibiotic and $HBO_2$ treatment regimen is unlikely to be effective. Instead, clinical management strategies should be reassessed and additional surgical debridement and/or modification of antibiotic therapy implemented without delay. Subsequently, reinstitution of $HBO_2$ therapy will help maximize the overall chances for treatment success.

**Rationale**

Initial evidence for a beneficial therapeutic effect of hyperbaric oxygen therpay ($HBO_2$) in managing osteomyelitis stemmed from reports collected during the 1960s [2-5]. *In vitro* and *in vivo* studies have subsequently uncovered specific mechanisms of action. Common to each of these mechanisms is the restoration of normal to elevated oxygen tensions in the infected bone. Mader and Niinikoski demonstrated that the decreased oxygen tensions typically associated with bony infections can be returned to normal or above normal levels while breathing 100% oxygen in a hyperbaric chamber [6, 7]. Achieving such elevations has important consequences for the hypoxic milieu of osteomyelitic tissues [8].

Neutrophils require tissue oxygen tensions of 30-40 mm Hg to destroy bacteria by oxidative killing mechanisms [9, 10]. Leukocyte-mediated killing of aerobic Gram-negative and Gram-positive organisms, including *Staphylococcus aureus*, is restored when the low oxygen tensions intrinsic to osteomyelitic bone are increased to physiologic or supraphysiologic levels. Mader *et al.* confirmed this finding in an animal model of *S. aureus* osteomyelitis, demonstrating that phagocytic killing markedly decreased at a $pO_2$ of 23 mm Hg, improved at 45 and 109 mm Hg, but was most effective at 150 mm Hg [7]. In this study, animals exposed to air achieved a mean $pO_2$ of 21 mm Hg and 45 mm Hg in infected and uninfected bone, respectively. When the same animals were exposed to 100% oxygen at 2 atmospheres absolute, mean $pO_2$ levels of 104 and 321 mm Hg in infected and non-infected bone were respectively achieved.

Subsequent animal studies by Esterhai confirmed these infection and $pO_2$-dependent results, measureing mean oxygen tensions in infected bone of 16±3.8 mm Hg in sea level air, 17.5±2.7 mm Hg in sea level oxygen, 198.4±19.7 mm Hg in 2 atm abs oxygen and 234.1±116.3 mm Hg at 3 atm abs oxygen, respectively. Corresponding values for non-infected bone were 31±4.6 mm Hg in sea level air, 98.8±22.0 mm Hg in sea-level oxygen, 191.5±47.9 mm Hg in 2 atm abs oxygen and 309.3±29.6 mm Hg at 3 atm abs oxygen [11].

Additionally, $HBO_2$ therapy has been noted to exert a direct suppressive effect on anaerobic infections [3, 8]. This effect can be clinically important, as anaerobes make up approximately 15% of the isolates in chronic, non-hematogenous osteomyelitis.

In addition to enhanced leukocyte activity, $HBO_2$ helps to augment the transport of certain antibiotics across bacterial cell walls. Aminoglycoside transport across the bacterial cell wall is both oxygen-dependent and impaired in a hypoxic environment. More specifically, active transport of antibiotics (*e.g,*. gentamicin, tobramycin, amikacin) across bacterial cell walls does not occur if tissue oxygen tensions are below 20 to 30 mm Hg [12]. Therefore, $HBO_2$ exposures can enhance the transport and augment the efficacy of antibiotic action [12-14]. This synergistic effect has also been shown for the cephalosporin class of antibiotics, where the combination of cefazolin and $HBO_2$ therapy produced a 100-fold greater reduction in bacterial counts than either antibiotics or $HBO_2$ therapy alone [15, 16].

Comparable effects are also seen with $HBO_2$ in mitigating localized soft tissue infections. Sugihara *et al.* demonstrated a 46% reduction in infection resolution time from a mean of 13 to only six days when $HBO_2$ therapy was added to antibiotics in the management of soft tissue infections [17]. As infected soft tissues often act as conduits for initiating and sustaining cortical bone infections, $HBO_2$ therapy's parallel benefit in ameliorating soft tissue infections may be critical to its overall efficacy in refractory osteomyelitis [18].

There is evidence that $HBO_2$ enhances osteogenesis [19-23]. Animal data suggest that bone mineralization and healing can be accelerated by intermittent exposure to $HBO_2$ [24, 25]. Remodeling of bone by osteoclasts is an oxygen-dependent function. Consequently, inadequate oxygen tensions inhibit microscopic debridement of dead, infected bone by osteoclasts. As previously noted, $HBO_2$ can restore physiologic or provide supraphysiologic oxygen tension in hypoxic bone environments, thus osteoclast function in infected bone can be improved. $HBO_2$ therapy's stimulatory effect on osteoclasts has been confirmed in animal models [26, 27]. Furthermore, as demarcation between healthy and necrotic bone is not always clear at the time of surgery, osteoclast enhancement may improve the overall quality of bony debridement and reduce the chances that local infections will recur [28].

The pathophysiology of chronic osteomyelitis is characterized by both acute and chronic sources of ischemia. $HBO_2$ therapy has been shown to be effective in acutely reducing tissue edema, lowering intracompartmental pressures and ameliorating the detrimental effects of inflammatory reactions [29-32]. Over the longer term, $HBO_2$ can be used to promote new collagen formation and capillary angiogenesis in both hypoxic bone and surrounding tissues [33-36]. This neovascularization works to counter the less easily reversible consequences of osteomyelitis, such as surgical trauma, tissue scarring and nutrient blood vessel occlusion. By creating a sustained

increase in the arterial perfusion of previously hypoxic bone and soft tissues, $HBO_2$ can reduce the susceptibility of these tissues to recurrent infection and necrosis.

***Patient selection criteria***

**Failure of standard therapy**

Depending upon the timing of patient presentation, source of infection, identified organism, degree of bony involvement and overall status of the host, osteomyelitis can be considered either a primarily medical or surgical disease [37-39]. Initial patient management efforts typically center on starting culture-directed antimicrobial therapy. Where present, infected sinus tracts, sclerotic bone and sequestra should be debrided [16, 40]. Various authors also suggest removal of internal fixation hardware and other foreign materials that do not directly contribute to the osseous stability of the site [41-47]. Others, particularly in complex spinal cases, have suggested that hardware removal is not necessarily required [46,48-52]. Advances in surgical technique, such as microvascular free muscle grafts and Ilizarov procedures, have decreased the incidence of postoperative infection in long bone fractures. However, these procedures often entail long durations of surgical therapy and significant expense [28, 53-55].

Resolution rates for primary osteomyelitis treated with surgery and antibiotics range between 35-100% [38, 56-72]. Despite the wide range of reported results, it can be estimated that an overall cure rate of 70-80% can be achieved using routine surgical and antibiotic management techniques [40, 59, 73-76]. This finding is in agreement with estimates for long-term osteomyelitis recurrence, which correspondingly range between 20 and 30% [77, 78].

It is when appropriate surgical and antibiotic interventions fail and osteomyelitis progresses, recurs or presents a high probability for excess morbidity or mortality that $HBO_2$ should be considered for inclusion in the therapeutic regimen.

**Defining refractory osteomylitis**

Clinical opinion differs as to what constitutes "appropriate interventions" and "accepted management techniques;" therefore defining specific time frames for the terms "chronic" or "refractory" osteomyelitis is not straightforward. Classically, chronic osteomyelitis differs from acute or subacute osteomyelitis by exceeding an arbitrary time limit of four to six weeks of clinical duration [39, 79, 80]. Similarly, osteomyelitis is considered refractory when it has failed to respond to definitive surgical debridement and a period of four to six weeks of appropriate antibiotic therapy [81]. Mechanistically, this treatment period was selected to ensure that antibiotic coverage is continued throughout the time necessary for surgically debrided bone to undergo revascularization [82]. While some authors have advocated longer courses of antibiotic treatment, others argue that a failure to achieve resolution after six weeks of culture-directed therapy is primarily due to inadequate surgical debridement, rather than an income-plete course of antibiotics [40, 75, 81, 82].

Further, the traditional mandate that parenteral antibiotics need be administered throughout this four- to six-week period has been questioned. A number of authors report equivalent success with converting from intravenous to oral antibiotic agents after one to two weeks [56, 83-87]. Comparable results have also been reported in children, although these studies focused principally on the treatment of acute *vs.* chronic osteomyelitis [88-90]. Regardless, it appears that, as long as adequate antibiotic serum and bone concentrations are maintained throughout the four- to six-week period, antibiotic specificity and compliance with the prescribed treatment regimen are more important than the route of administration [42, 81].

Some additional factors that need be considered when deeming a case of osteomyelitis "refractory" include the site of involvement and the medical status of the host [40]. Indeed, osteomyelitis has been considered refractory before c of the traditional antibiotic period if the infection is not promptly responding and the sternum, vertebrae, base of the skull or other sites critical to function and survival are involved [71, 91- 93]. This caveat is particularly apropos when the overall health of the patient is compromised by coexisting disease [18, 37].

**Patient classification**

The Cierny-Mader classification of osteomyelitis can be used as a guide to determine which patients will most likely benefit from adjunctive $HBO_2$ therapy [16]. Although alternative classification strategies have been proposed, Cierny-Mader staging functionally incorporates related elements of infectious etiology, anatomic location and host physiology into a single system that is valuable in guiding clinical treatment [82, 94-100].

Using Cierny-Mader staging, osteomyelitis is anatomically segregated into four distinct groups based on whether the infection involves the bone's intramedullary surfaces; superficial cortical aspects and adjacent soft tissues; full-thickness, but localized, segments of the cortex; or diffuse, through and through portions of the

**Table I**

| Anatomic Type | | Physiologic Class | |
|---|---|---|---|
| Stage 1 | medullary osteomyelitis | A host | normal host |
| Stage 2 | superficial osteomyelitis | B host | systemic compromise (BS) |
| Stage 3 | localized osteomyelitis | | local compromise (BL) both |
| Stage 4 | diffuse osteomyelitis | | compromises (BLS) |
| | | C host | treatment worse than disease |

**TABLE IIı**

| Systemic BS | Local (BL) |
|---|---|
| malnutrition | chronic lymphedema |
| renal failure | venous stasis |
| diabetes mellitus | major vessel compromise |
| chronic hypoxia | arteritis |
| immune deficiency | extensive scarring |
| malignancy | radiation fibrosis |
| extremes of age | small vessel disease |
| immunosuppression | complete loss of local sensation |
| tobacco abuse | |

bone [101, 102]. These anatomic distinctions are respectively termed "medullary," "superficial," "localized" and "diffuse" osteomyelitis and are correspondingly designated as Stages 1, 2, 3 and 4. Cierny-Mader's anatomic staging is summarized in Table I *(above)*. As also reflected in this table, patients are further classified by their host status as an "A host" (normal), "B host" (compromised) or "C host" (those for whom the treatment of the disease is worse than the disease). B hosts are subdivided according to whether they are compromised systemically (BS), locally at the site of osteomyelitis (BL) or both (BLS). Examples of systemic and local factors that can compromise the host are listed in Table II *(above)*.

Using the Cierny-Mader classification, Stage 1 disease is primarily managed with antibiotics alone. Similarly, Stage 2 disease generally responds well to appropriate antibiotics and superficial debridement of the affected bone and soft tissues. It is those patients with Stage 3 or 4 osteomyelitis, complicated by adverse local or systemic risk factors, who are most likely to benefit from $HBO_2$ therapy as an adjunct to continued antibiotics and repeat surgical debridement [16].

**Special indications**

As alluded to previously, certain cases of refractory osteomyelitis deserve special consideration due to their anatomic location and significant propensity for generating life-threatening infections. Specific areas of concern include the sternum, vertebrae, cranium and other central bony structures.

Sternal osteomyelitis after median sternotomy is an uncommon (0.4%-8.4%) but often fatal condition. Despite extensive surgical debridement and complex grafting procedures, recurrence ranges between 3-8% [103, 104]. More aggressive methods, though capable of eradicating sternal infection, are associated with high rates of mortality (20-35%) [105, 106]. The consequences of vertebral osteomyelitis are equally concerning. Fully 25% of individuals treated non-surgically for vertebral infections experience medical failure [107]. For the majority of these cases, extensive surgical

debridement and removal of retained fixation material has been described as necessary to eradicate the disease [92]. Postoperative morbidity and mortality from vertebral osteomyelitis has been reported to be 29% and 12%, respectively [52]. Cranial osteomyelitis, comprising about 1.5% of all osteomyelitis cases, occurs in approximately 2-9% of patients after craniotomy [92, 108-111]. Direct surgical morbidity and mortality are approximately 13% and 7%, respectively [112]. However, secondary mortality from complications of these cranial bone infections have been reported to be as high as 20-40% [108].

Malignant external otitis represents a special subcategory of cranial infections. In these otitis-associated skull base infections, Lucente contends that "renaming may be appropriate, for it is clear that even so ominous an adjective as 'malignant' is insufficient to convey the lethal import of this disease" [113]. As with other central bone infections, the standard methods of treatment have involved the use of antibiotics, local treatments and, where necessary, surgical excision of necrotic tissue [114]. Despite advances in antibiotic therapy, these approaches do not always provide a complete cure, and overall mortality remains in the 10-20% range [115].

What is clear in these cases of central-structure osteomyelitis is that aggressive clinical management is vital to limiting associated morbidity and mortality [116]. Consequently, these "special indications" have each earned independent consideration in the subsection entitled "Human Study Data."

**Evidence-based review**

***Review methodology***

All studies identified through online searches using the terms "hyperbaric oxygen" and "osteomyelitis" were abstracted. This search methodology returned a total of 201 articles, spanning the period from 1965 through the present. Of the accumulated English language studies, 79 studies contained original data on $HBO_2$ treatment of osteomyelitis in human [71] or animal [8] subjects; the balance consisted of literature reviews, foreign language articles, previously reported data or papers not directly addressing the effects of systemic $HBO_2$ therapy on the disease. Similarly, studies that co-mingled osteomyelitis and non-osteomyelitis patient treatment data or lacked distinction between non-$HBO_2$- and $HBO_2$-treated patients were also excluded. For the purposes of this review, studies having fewer than three patients were considered case reports and excluded from further analysis. This left a total of 34 studies (8 animal and 26 human) that could be evaluated in accordance with American Heart Association guidelines for this evidence-based review.

***Animal studies – Quality***

Eight prospective animal studies examining the effects of $HBO_2$ on experimentally induced bone infection were reviewed. The overall quality of the studies was considered "good", with two studies found to be "excellent" in terms of their methodological design and control. None of the studies included concurrent bony debridement as part of their overall management. This is unfortunate, as bony debridement is frequently considered an essential part of refractory osteomyelitis management, and an important parallel with clinical management was missed. Nevertheless, the results and import of these studies are presented in the following section.

***Animal studies – Data***

From the mechanistic standpoint, the ability of $HBO_2$ to increase intramedullary oxygen tensions was demonstrated by Esterhai [11]. Specifically, he showed that oxygen tensions could be elevated to levels at or above that required for normal phagocytic function. As previously discussed in the section entitled "Rationale," Esterhai's study provided early objective evidence for one of $HBO_2$ therapy's primary physiologic effects in osteomyelitis [7].

Two early studies evaluating osteomyelitis in animal models reported increases in bone healing after exposure to $HBO_2$ [4 117]. Specifically, Hamblin showed 70% primary healing in the $HBO_2$-treated group vs. 26% in controls. Similarly, Triplet demonstrated improved fracture stability in 75% of $HBO_2$-treated animals *vs.* 12.5% of controls. However, as neither author included antibiotic therapy or surgical debridement in their treatment models, these studies demonstrated a neutral effect of $HBO_2$ on bacterial colony counts.

In contrast, the effect of $HBO_2$ on bacterial growth when combined with antibiotics was prospectively evaluated in five separate studies [13, 15, 118-120]. Relative to non-treated controls, each study reported a statistically significant benefit in terms of improved wound healing or decreased bacterial colony counts after treatment with either $HBO_2$ or antibiotics therapy. Further, the two most recent studies demonstrated a significant synergy between $HBO_2$ and antibiotics relative to either agent being used alone [15, 118]. Specifically, combination therapy reduced colony counts relative to controls by a factor of 102-104 after two weeks and 103-106 after four weeks of continuous therapy,

respectively. Perhaps most importantly, Mendel showed that, when $HBO_2$ therapy was combined with antibiotics and debridement of overlying infected soft tissues, complete eradication of osteomyelitis could be achieved [118].

***Animal studies – Conclusions***

It can be concluded from these controlled animal trials that, while neither antibiotics nor $HBO_2$ alone reliably impede bacterial growth in infected bone, the synergy between these two agents does produce significant reductions in bacterial colony counts. However, it is when $HBO_2$ and antibiotics are combined with surgical debridement that the most efficacious results are achieved. Thus, the sum of animal data suggests that a management triad of culture-directed antibiotics, thorough surgical debridement and concurrent $HBO_2$ therapy would be the strategy most likely to effect clinical cure in refractory osteomyelitis.

***Human studies – Quality***

The significant majority of the available human study data included in this review was derived from clinical case series. Consequently, 23 of 26 reports were classified as AHA Level 5 evidence. Three studies made use of either a non-randomized cohort [1] or control group [2], therefore achieving AHA Level 4 and Level 3 classifications, respectively. The overall quality of the studies was judged to be intermediate between the AHA descriptors of "fair" and "good." Whereas five studies were considered "excellent" and eight studies "good" in their design and result documentation, the remaining 10 studies were judged to be less well designed. If only the 18 studies specifically reporting refractory osteomyelitis were considered, the median quality of the studies was assessed to be "good." Unfortunately, variations in the extent and location of involved bone, identified infective organisms, coexisting diseases, and strategies for antibiotic and surgical intervention made the direct comparison of clinical management strategies difficult. Further, conceptual differences existed in the application of terms such as "cure," "arrest." "improvement" and "failure," clouding interpretation of eventual clinical outcomes [14].

It must be stated, however, that the above caveats were not limited to HBO2 studies alone. Indeed, they were common to all treatment modalities applied to the management of osteomyelitis [71]. By way of example, Lazzarini *et al.* attempted to determine the most appropriate approach to antibiotic therapy in osteomyelitis [42]. After completing a retrospective analysis of 93 clinical trials, his group concluded that available literature on the treatment of osteomyelitis was inadequate to determine the best agent(s), route or duration of antibiotic therapy.

If one considers that the majority of clinical series evaluating the effects of $HBO_2$ therapy on osteomyelitis are conducted in patients who have previously failed one or more courses of antibiotics and/or surgery alone to control infection, the relative benefit of combining $HBO_2$ therapy with these standards of care therapies is more readily perceived.

***Human studies – Cohort and controlled trials***

In a large non-randomized series of 689 osteomyelitis patients, Kawashima reported differential outcomes for patients treated with antibiotics, debridement and closed irrigation *vs.* treatment with adjunctive $HBO_2$ therapy. For the cohort of 256 patients receiving no $HBO_2$ therapy, the results of treatment were 88.3% "good," 2.7% "fair" and 9% "poor" responders. In contrast, the cohort of 433 patients treated with $HBO_2$ was reported as having 91.9% "good," 2.3% "fair" and 5.8% "poor" responders. The difference between these two groups was noted to be statistically significant ($p<0.01$).

Unfortunately, it is not possible to determine from the data presented whether or not the term "good" represents complete healing. Additionally, there is no information provided regarding statistical uniformity of the two cohorts. Thus, although significant differences in outcome were reported between the two groups, the power of this study to determine a differential treatment effect is low.

In a non-randomized analysis of 28 patients, Esterhai *et al.* reported no benefit from the use of adjunctive $HBO_2$ therapy [121]. In this study, a total of four patients from both the control and experimental groups, all with tibial infections, failed to clear their disease. These failures occurred, in the author's opinion, "because of the inability to remove sufficient necrotic, infected bone."

Given this procedural complication and the fact that Esterhai experienced only four total treatment failures (three in the $HBO_2$-treated group and one in the non-treated group), the power of the study to statistically distinguish outcomes between the two groups was limited. Further, with an osteomyelitis arrest rate of more than 90% in the non-treated control group, questions are raised as to whether patients in this study met criteria for refractory osteomyelitis. Indeed, as an author and co-author on two subsequent manuscripts, Esterhai reported control group infection arrest rates of only 62% [122, 123]. Thus, while Esterhai's attempt at a controlled trial

evaluating the effect of $HBO_2$ in refractory Osteomyelitis was welcomed, it fell short of being clinically valuable.

Barili *et al.* conducted a prospective trial in 32 patients designed to evaluate the effect of $HBO_2$ therapy on postoperative sternal infections after median sternotomy [124]. Group 1 ($n$=14) included patients who accepted and were able to undergo $HBO_2$ therapy; Group 2 ($n$=18) included 16 patients who refused $HBO_2$ therapy secondary to claustrophobia and two patients originally assigned to the $HBO_2$ treatment group who were excluded by persistent medical contraindications (*i.e.*, postoperative pneumothorax).

From anatomic descriptions provided by the primary author, all patients were considered to have the equivalent of Cierny-Mader Class 4 infection. Though not strictly randomized, the two groups were well matched in terms of preoperative clinical characteristics, operative factors, duration and quality of their chronic sternal infection.

Upon completion of the treatment period, Barili found that infection relapse rates were significantly lower in the $HBO_2$-treated group relative to non-treated controls (0% *vs.* 33.3%, $p$=0.024). Moreover, the duration of intravenous antibiotic use (47.8+/-7.4 *vs.* 67.6+/-25.1 days, $p$=0.036) and total hospital stay (52.6+/-9.1 *vs.* 73.6+/-24.5 days, $p$=0.026) were both signifycantly shorter in the $HBO_2$-treated group.

As this prospective study's design was uncomplicated by variability in infection site, disease severity and surgical approach, the power of the trial to delineate an $HBO_2$ treatment effect is superior to all other studies considered in this review. Thus, Barili's study provides the most rigorous evidence to date of the curative benefits attainable when $HBO_2$ is added to "standard of care" osteomyelitis treatment.

### *Human study data*
### *Long Bone and Miscellaneous sites*

The earliest reports of $HBO_2$ therapy being applied to patients with chronic osteomyelitis were presented by Slack *et al.* [3]. In this series of five patients treated with antibiotics and $HBO_2$, 80% responded with clearance of infection. However, these cases were a mix of patients with both chronic and refractory disease and varied in terms of types of concurrent treatment.

Similarly, Welsh *et al.* reported the outcomes of five patients treated with $HBO_2$ for osteomyelitis. After an average of 34 treatments, the application of $HBO_2$ in concert with antibiotics resulted in four of five (80%) assorted site infections being healed [125]. However, as osteomyelitis was not the prime focus of Welsh's retrospective study, specifics regarding the refractory nature and concurrent management of the osteomyelitis cases were not defined.

In contrast, a number of authors reported experience with treating refractory cases of osteomyelitis. Specifically, Perrins *et al.* were the first to describe using $HBO_2$ to treat patients who had previously failed to heal with conservative antibiotic and/or surgical management [2]. Combining an average 20 days of $HBO_2$ treatment with antibiotics and occasional sequestrectomy, Perrins was able to stimulate complete healing in 19/24 (79%), improvement in two (8.3%) and failure in three (12.5%) of his patients. Four cases relapsed, yielding an overall cure rate of 62%. It must be noted, however, that concurrent debridement was not uniformly provided, and the osteomyelitis cases involved a variety of bony sites.

Demonstrating further variability in osteomyelitis sites amenable to $HBO_2$ treatment, Eltorai *et al.* described results in managing 44 spinal cord injured patients with osteomyelitis secondary to pressure sores [126]. While the distribution of infection was primarily centered on the hip (28), pelvis (6), sacrum (3) and lumbar spine (5), a few cases involved the extremities (8). In keeping with the overall cure rate found by Perrins, infection resolution was achieved in 30 of 44 (68%) of patients. None of these patients underwent surgical debridement in conjunction with their course of $HBO_2$ therapy. Regardless, the majority of treatment failures were attributed to concomitant vascular disease, presumeably due to generating suboptimal elevations in bone oxygen tensions during $HBO_2$ therapy. As a side note, all five cases of spinal osteomyelitis did clear without the need for surgical debridement.

Bingham and Hart addressed potential differences in $HBO_2$ treatment response depending upon the specifically involved osteomyelitis site [69]. In their series of 70 patients with a mix of refractory cranial, torsal, upper and lower extremity bone infections, an overall osteomyelitis clearance rate of 61% was achieved. Whereas infections in all patients were noted to have been "arrested" or "improved," significant differences in relative response by infection location were found. For tibial infections, the respective arrest and improvement rates were 73% and 27%. In the femur, arrest and improvement rates were reversed (40% and 60%), as they were for hip (38% and 62%). Consistent with the series by both Perrins and Eltorai, all patients received concurrent antibiotic therapy. However, it is unclear whether individuals underwent concurrent surgical debridement.

Reporting more definitive data on concurrent surgical management, Morrey *et al.* detailed the effects of $HBO_2$ in 40 patients with surgery and antibiotic refractory long bone osteomyelitis [72]. Prior to $HBO_2$ initiation, all patients were treated with three or more surgical debridements and concomitant antibiotics over an average period of 30 months. Coincident with the initiation of $HBO_2$ treatment, all patients received a new course of parenteral antibiotics and surgical debridement. An average of 42 $HBO_2$ sessions were provided and, after 23 months' average follow-up, 34 of 40 (85%) patients remained disease-free. Re-evaluation at the seven- to 10-year point demonstrated continued symptom resolution in 75% [71].

In a subsequent series of 38 patients, Davis *et al.* reported $HBO_2$ treatment outcomes in patients presenting with refractory, non-hematogenous osteomyelitis of the long bones [71]. All patients had failed at least one or more previous attempts at sterilization with combined surgery and antibiotics. An average of 45 $HBO_2$ treatments were provided in conjunction with debridement and antibiotics. After nearly three years of mean follow-up, 34 of 38 (89%) remained infection-free. For completeness, Esterhai's non-randomized analysis of 28 patients is reiterated at this point [121]. Although Esterhai reported no benefit from the adjunctive use of $HBO_2$ therapy, the power of his study was severely limited by the patients' refusal to undergo further surgical debridement. Thus, the study conclusions were rendered non-significant.

Combining $HBO_2$ treatment with autogenous microsurgical muscle transplantation, Maynor *et al.* reported long-term success in patients with refractory osteomyelitis of the tibia [127]. The median delay from diagnosis to initiation of $HBO_2$ therapy was 12.5 months. Additionally, all subjects had previously received treatment with parenteral antibiotics and an average of 8.3 failed surgical procedures.

Prior to commencing $HBO_2$ therapy, all patients resumed culture-directed antibiotics and underwent one additional open debridement. Twenty patients (59%) were given vascularized muscle flaps as part of their overall treatment. An average of 35 $HBO_2$ sessions was provided. After three months of follow-up, 28 of 34 (82%) patients were drainage-free. At 24 and 60 months respectively, 21 of 24 (81%) and 12 of 15 (80%) of the patients available for follow-up were still without drainage. At 84 months the previously stable rate of resolution dropped to 63%. It is unclear, however, whether this late fall in sustained resolution represents actual delayed recurrences or bias secondary to calculations involving only a small proportion of the original study group (*i.e.*, $\leq 22\%$).

Using a well-defined set of inclusion criteria, orthopedic surgeons from the Chang Gung Memorial Hospital, Taiwan, reported $HBO_2$ treatment effects in three separate prospective trials involving refractory long bone osteomyelitis [128-130]. Specifically, each study required eligible patients to: have had their infection for at least six months; failed at least three previous surgical procedures designed to eliminate the infection; and received concurrent treatment with parenteral antibiotics on each attempt. Additionally, all patients were expressly categorized as having Cierrny-Mader Stage III or IV infections.

In the first study by Chao-Yu Chen *et al.*, 13 of 15 (86%) patients with refractory tibial osteomyelitis were successfully treated with surgical debridement, parenteral antibiotics and an average of 26 $HBO_2$ treatments [128]. No recurrences among treatment responders were noted after a mean follow-up of 17 months. In a follow-on study using the same methodology, Chin-En Chen *et al.* demonstrated resolution of tibial infection in 11 of 14 (79%) previously refractory osteomyelitis patients [129]. Finally, Chin-En Chen's group used this paradigm to treat 13 patients with refractory osteomyelitis of the femur [130]. After an average of 50 $HBO_2$ treatments and a mean follow-up period of 22 months, 12 of 13 (92%) of the patients remained infection-free.

Although these three prospective trials were not strictly controlled, the specificity of the inclusion criteria and the fact that all patients previously failed three or more combined surgical and antibiotic intervenetions by the same surgeons strongly support a beneficial effect of $HBO_2$ in refractory osteomyelitis.

In summary, for refractory osteomyelitis involving the long bones and non-specified sites, $HBO_2$ therapy combined with antibiotics appears to provide cures in approximately 60-70% of cases. Unfortunately, in the absence of concurrent surgical debridement, $HBO_2$ does not confer a selective advantage over the 70-80% cure rates anticipated using standard of care management. Consequently, for the majority of osteomyelitis cases involving the long bones and miscellaneous sites, $HBO_2$ alone or in combination with antibiotics warrants only an AHA Class IIb recommendation and is not a preferred alternative to repeat surgical debridement and appropriate antibiotics.

In contrast, when $HBO_2$ is combined with appropriate antibiotics and concurrent surgical debridement, overall cure rates in refractory osteomyelitis of the long bones and miscellaneous sites range between 80-90%. This meets or exceeds outcomes expected for standard of care therapy. Thus, $HBO_2$ should be considered an AHA Class IIa intervention when combined with proximate surgical debridement and appropriate antibiotic treatment. Similarly, in refractory patients facing the potential for extremity amputation or debilitating surgery, a trial of adjunctive $HBO_2$ may be considered an AHA Class IIa supplement to limited surgical debridement and continued, culture-directed antibiotics prior to imposing radical surgical resection.

***Human studies***

***Mandibular Osteomyelitis***

A review of the available literature concerning the treatment of mandibular osteomyelitis yields as much variation in applied protocols as it does in response to the prescribed interventions. Overall cure rates of 30% to 100% have been reported [131].

In terms of $HBO_2$ therapy for mandibular osteomyelitis, Jamil reported results in 16 patients with treatment-resistant infections. $HBO_2$ therapy alone induced lasting resolution in only six of 16 (37%) patients [132]. This low response rate is in concurrence with that previously discussed for refractory long-bone osteomyelitis treated only with $HBO_2$. Similarly, Handschel attempted to manage a mix of primary and refractory osteomyelitis cases using $HBO_2$ alone [133]. In patients with no history of pretreatment, seven of 13 (54%) patients were relapse-free after receiving 40 $HBO_2$ treatments. In patients previously refractory to antibiotics and surgical debridement, only four of nine (44%) patients were rendered relapse-free after completing a course of $HBO_2$ treatment.

It is interesting to note, however, that superior results were achieved in younger patients. In this subset of osteomyelitis patients relapsing after receiving antibiotics alone, three of four (75%) experienced sustained resolution of their infection. Lentrodt's recent experience with refractory mandibular osteomyelitis in three other children tends to confirm this differential response in younger patients [134]. Despite the recurrent nature of each child's disease, the combination of $HBO_2$ and antibiotic therapy was effective in clearing three of three (100%) of these refractory infections.

Control of mandibular osteomyelitis by combined debridement, antibiotics and $HBO_2$ was reported by Mainous *et al.* [135]. Although distinctions between primary and refractory osteomyelitis were not reported, osteomyelitis resolution was achieved in 23 of 24 (96%) patients. The use of this tri-modality approach to mandibular osteomyelitis management was further supported by Van Merkesteyn [136]. In his series of 16 patients, only one of nine (11%) patients improved after bi-modality therapy with $HBO_2$ and antibiotics. In contrast, seven of seven (100%) patients treated concurrently with décortication, antibiotics and $HBO_2$ therapy were cured. The authors concluded that in patients with refractory osteomyelitis, the coordinated use of $HBO_2$, antibiotics and surgery tended to provide the best overall chance for cure.

In an interesting departure from the majority of osteomyelitis studies utilizing mainly postoperative $HBO_2$ treatment, Aitasalo used a series of 10 preoperative and five to seven post-operative $HBO_2$ treatments along with antibiotics to induce osteomyelitis resolution in 26 of 33 (79%) [137]. Despite the fact that these patients were previously refractory to "conservative" therapy with antibiotics alone, the author concluded that coordinated $HBO_2$ therapy allowed for a reduction in overall treatment duration. One might hypothesize, however, that Aitasalo's 79% treatment success may have been further improved if the total number of post-operative treatments were increased to more closely align with typical $HBO_2$ protocol totals. Nonetheless, Aitasalo's study provided additional support for a tri-modal approach to osteomyelitis treatment. Further, he highlighted the potential benefit of scheduling surgical debridement proximate to antibiotic and $HBO_2$ therapy.

Based on the results of these published series, $HBO_2$ cannot be recommended as a solitary treatment modality in the management of mandibular osteomyelitis (*i.e.*, AHA Class III). When combined with antibiotics in the treatment of adult primary or refractory mandibular osteomyelitis, $HBO_2$ therapy can be elevated to an AHA Class IIb intervention. In child and adolescent subpopulations, where the potential risk for disfigurement and impaired bone growth is high, a trial of $HBO_2$ and antibiotics prior to major debridement surgery may be considered an AHA Class IIa management. In adults, treatment of mandibular osteomyelitis with the combination of antibiotics, surgical debridement and $HBO_2$ appears to maximize the potential for infection clearance, particularly in recurrent or refractory cases.

While the wide variability in reported cure rates inhibits statistical comparison, the lack of viable clinical alternatives to this tri-modal treatment approach earns $HBO_2$ therapy an AHA Class IIa designation in the management of refractory mandibular osteomyelitis.

***Human studies***
***Spinal Osteomyelitis***

In a study of 44 patients evaluating the efficacy of antibiotic monotherapy in vertebral osteomyelitis, 27% of patients failed to respond to this conservative approach [138]. Extending antibiotic coverage to an average of 142 days, Priest was able to achieve a higher rate of infection cure, clearing hematogenous vertebral infections in 24 of 29 (83%). However, a full 50% of Priest's treated population still suffered infection-related sequelae [75].

While Kovalenko was able to further increase the resolution rate of hematogenous osteomyelitis, his 91% primary cure success required radical reconstructive surgery and was still associated with 6% recurrence and 2% perioperative mortality [139].

In technically more complex cases involving spinal fusion, Talmi could achieve infection resolution in only four of six (66%) patients. These results persisted despite treatment with one or more drainage procedures and the removal of hardware in two of six (33%) [51].

Chen also reported refractory deep space infections in a series of 36 patients after undergoing thoracic and lumbar instrumentation [46]. Despite extensive debridement, antibiotics and a course of continuous irrigation treatment, recurrence was noted in 11% of patients.

In contrast to these non-HBO treated patientsEltorai et al. reported success in using HBO and antibiotics lto eradicate osteomyelitis in five of five (100%) cases of adult lumbar osteomyelitis [126].

Similarly, Larsson reported benefit from combined $HBO_2$ and antibiotic therapy in patients suffering from osteomyelitis subsequent to spinal surgery and implanttation of fixation material [92]. After an average of 30 $HBO_2$ treatments, seven of seven (100%) of his patients' infections resolved. Of note, spinal fixation material was maintained *in situ* for five of seven (71%) patients. The success of this non-operative treatment compares favorably with other methods achieving osteomyelitis eradication in patients with retained spinal instrumentation. However, with no infection recurrence after treatment with adjunctive $HBO_2$ therapy (*vs.* 11% for antibiotics alone), Larsson's non-surgical success exceeds the outcomes experienced by Chen.

When combined with antibiotics, the ability of $HBO_2$ to eliminate spinal osteomyelitis and obviate hardware removal in the majority of patients warrants a trial of $HBO_2$ therapy prior to patients being scheduled for extensive surgical debridement. Thus, the addition of $HBO_2$ therapy to antibiotic therapy and, where indicated, limited surgical debridement should be considered an AHA Class IIa recommendation in patients with spinal osteomyelitis.

***Human studies***
***Cranial Osteomyelitis***

Following craniotomy, the bone flap generated is devascularized and devitalized, increasing its susceptibility to infection [92]. This increase in infection risk applies equally to retained prosthetics. Overall, a 5-9% postoperative infection rate can be anticipated [109-111]. Cures can subsequently be effected, but antibiotics, surgical debridement and, frequently, removal of the infected bone flaps or prostheses are required [140-143].

On the contrary, Larsson reported primary success with $HBO_2$ in a series of patients previously failing to resolve cranial osteomyelitis with antibiotic therapy [92]. Prior to initiation of $HBO_2$, none of his patients had undergone attempts at surgical debridement. Based on the presence or absence of confounding risk factors, Larsson divided the patients into two groups. "Group 1" patients had uncomplicated osteomyelitis of their free cranial bone flap and no known risk factors for delayed healing. "Group 2" patients presented with additional risk factors, such as repeated surgical procedures, retained foreign material, malignant disease or previous radiotherapy.

Of the patients in Group 1, 12 of 15 (80%) resolved their bone flap infection without a need for surgical intervention; 20 % recurred. In Group 2, after disregarding two patients' secondary early tumor death, 10 of 16 (62%) refractory infections were resolved non-surgically. Furthermore, three of four (75%) and three of six (50%) of bone and acrylic flaps were retained, respectively. If cures achieved subsequent to removal of the bone and acrylic sequestra are included, 15/16 (94%) of Group 2 patients resolved their infections.

If overall success criteria are defined as clearance of infection *vs.* avoidance of surgery, Larsson was able to achieve a cure in 97% of his patients with refractory osteomyelitis. Interestingly, data regarding $HBO_2$-associated treatment costs were also provided, with primary cures using $HBO_2$ therapy conferring a 48-66% savings over repeat craniotomy.

Given the potential for a non-surgical cure rate approaching 71% and the conferred ability to minimize the risks and costs associated with repeat craniotomy, a trial of $HBO_2$ therapy prior to undergoing major cranial debridement should be considered. In the setting of antibiotic refractory cranial osteomyelitis, $HBO_2$ can be recommended as AHA Class IIa therapy.

***Human studies***

***Malignant External Otitis***

Malignant external otitis is an invasive form of osteomyelitis with a tendency to extend beyond the external auditory canal, potentially producing lethal results [113]. In an early series, Lucente reported mortality rates in antibiotic-treated patients of over 30%. Fortunately, advances in antibiotic therapy have increased projected survival rates to approximately 80-90% [115, 144-146]. However, in these later series, the extent of bony versus merely soft tissue involvement and the number of cases requiring surgical debridement was not clear. Thus, it is anticipated that the majority of these successes occurred in patients with less severe disease.

Addressing this potential for variation in infection severity, Tisch employed a classification system similar to Cierny-Mader's to stratify his patients into four categories [114]. Specifically, patients with superficial cortical disease only; local invasion without cranial nerve involvement; local invasion with zygomatic bone or cranial nerve involvement; and diffuse involvement of the cranium with meningitis or sepsis were classified as being Stage I, II, III and IV patients, respectively. Using this classification system, reported mortality after treatment with antibiotics and surgery was 14% for Stage I-II, 50% for Stage III and 70% for Stage IV disease.

$HBO_2$ therapy has been reported as a useful adjunct in managing refractory cases of malignant external otitis. In a series of 22 cases, Martel achieved 95% resolution of osteomyelitis without the need for surgery by combining $HBO_2$ with antibiotics [147]. These cases were not, however, reported as being previously refractory to antibiotics.

Narozny demonstrated resolution of infection in seven of eight (87.5%) antibiotic refractory patients using $HBO_2$ [148]. Only one patient required concurrent surgical debridement, and his single treatment failure was associated with a fungal etiology. Davis treated 16 cases, including six advanced cases, that were previously refractory to multiple courses of antibiotics [149]. After completing a 30-day course of $HBO_2$ combined with antibiotic therapy, all patients experienced resolution of their infection. This curative success persisted without recurrence throughout his one- to four-year year follow-up period. Similarly, Tisch was able to achieve cures in 21 of 22 (95%) antibiotic refractory malignant external otitis patients after adding $HBO_2$ to his overall management strategy. Although this resolution rate is comparable to that reported for quinolone antibiotic therapy in nonstratified cases, Tisch's success is remarkable given that 59% of his patients had either Stage III or IV involvement.

It is concluded that while malignant external otitis generally responds well to primary management with antibiotics and minimal surgical debridement, $HBO_2$ appears to be effective in cases refractory to standard therapy. This appears particularly true for more extensive Stage III and IV disease, where extensive debridement and historically high mortality rates can potentially be avoided. Thus, for Stage I and Stage II cases of malignant external otitis, $HBO_2$ should be considered AHA Class IIb therapy. In refractory cases, $HBO_2$ can be recommended as an AHA Class IIa intervention.

***Human studies***

***Sternal Osteomyelitis***

In a large series of patients undergoing coronary artery bypass grafting, the incidence of sternal osteomyelitis was reported to be 2.1%. Of these cases, 89% required surgical intervention to obtain control of the infection. Even so, 30% still failed primary surgical debridement and required secondary, more extensive procedures to eradicate the infection [150]/

In a small series of patients undergoing lung transplantation, four patients with sternal osteomyelitis were treated with $HBO_2$ therapy [91]. Despite the immunosuppressed status of these patients, two of four patients healed completely without the need for any surgical intervention. Additionally, one patient's infection was cleared, but required skin grafting to close a residual soft tissue defect. The fourth patient, who declined participation in further $HBO_2$ therapy after three uncomplicated sessions, subsequently died from complications of sepsis. Thus, of three patients completing a course of $HBO_2$ therapy, all were able to clear their infection without needing surgical debridement.

The previously discussed prospective study by Barili provides even stronger support for the use of $HBO_2$ in controlling sternal infections [124]. In his trial involving 32 baseline health and infection matched patients, the addition of $HBO_2$ therapy to his overall treatment regimen resulted in significantly lower infection relapse rates (0% *vs.* 33.3%, $p$=0.024), shortened antibiotic therapy

durations (47.8 +/- 7.4 *vs.* 67.6 +/- 25.1 days, $p$=0.036) and reduced hospital stay lengths (52.6 +/- 9.1 *vs.* 73.6 +/- 24.5 days, $p$=0.026) relative to controls managed only with antibiotics and surgical debridement.

Though few in number, these series demonstrate that $HBO_2$ is effective in reducing the need for sternal debridement and/or extensive surgical interventions. Consequently, $HBO_2$ therapy should be considered an AHA Class IIa adjunct in the management of sternal osteomyelitis.

***Human studies***
***Diabetic Patients***

Although covered extensively in another chapter of the Committee Report, it should be noted that the majority of patients requiring treatment for refractory osteomyelitis are those presenting with diabetic foot wounds [28]. Indeed, several authors contend that concurrent osteomyelitis can be assumed in virtually all diabetic patients presenting with plantar foot ulcers [18, 151, 152].

It is from the body of literature evaluating management strategies for Wagner Grade 3 and 4 diabetic ulcers that $HBO_2$ therapy derives its highest level of support for use in refractory osteomyelitis. Citing five randomized controlled trials involving patients with diabetic ulcers (118 patients), Roeckl-Wiedmann concluded from pooled data that adjunctive $HBO_2$ treatment confers a significant reduction in the risk of major amputation (RR: 0.31; c.i. 0.13 to 0.71) [153]. Further, others have noted in randomized prospective trials that $HBO_2$ can improve the mean rate of healing in diabetic foot ulcers [154-156]. Consequently, $HBO_2$ is both recommended and accepted as an AHA Class I therapy for refractory osteomyelitis associated with diabetic foot ulcers [157].

***Human studies***
***Safety Considerations***

While $HBO_2$ therapy is generally safe and well tolerated, exposures have been associated with adverse side effects. A description of these side effects, expected incidence rates and associated risk factors are discussed in detail elsewhere in the Committee Report. However, in the setting of refractory osteomyelitis, reports of adverse, $HBO_2$-related sequelae have been rare. The most common events reported were middle ear and sinus barotrauma.

Typically, these pressure-related events were both mild and self-limiting. In fact, no patient being treated for osteomyelitis discontinued $HBO_2$ therapy secondary to barotrauma. A few authors did report the need for tympanostomy tube placement in a few cases to help facilitate continuation of $HBO_2$ therapy.

In considering potential side effects associated with repeated exposure to elevated oxygen partial pressures, only transient myopia was reported to occur. As is characteristic for this clinical phenomenon, all cases of myopia resolved spontaneously after completion of $HBO_2$ therapy. More permanent visual changes, such as cataract formation, were not reported in this patient population. Similarly, no reports of CNS or pulmonary oxygen toxicity could be found.

***Human studies***
***Conclusions***

The bulk of available human data on refractory osteomyelitis was abstracted from retrospective clinical case series, thus constituting primarily AHA Level 5 quality evidence. Three studies did make use of either a control or cohort group, providing the literature's only AHA Level 3 and Level 4 reports addressing $HBO_2$ treatment of osteomyelitis. That said, the overwhelming majority of available studies supported the use of $HBO_2$ as a beneficial adjunct in the management of refractory osteomyelitis. Specifically, the highest-reported osteomyelitis cure rates were obtained when $HBO_2$ therapy was combined with culture-directed antibiotics and concurrent surgical debridement.

As these treatment success rates generally exceeded that found in the literature for "standard of care" therapy using antibiotics and surgical debridement alone, $HBO_2$ therapy can be generally recommended as an AHA Class IIa intervention in refractory osteomyelitis. In certain clinical settings, such as osteomyelitis involving children or bony structures adjacent to the central nervous system or other vital organs, a favorable risk-benefit balance appears to support $HBO_2$ and antibiotics as an AHA Class IIa therapy prior to attempting extensive surgical debridement.

For patients with refractory diabetic ulcers, adjunctive $HBO_2$ therapy can be definitively regarded as an AHA Class I intervention. In contrast, the combination of $HBO_2$ and antibiotics in most other forms of uncomplicated primary, extremity or miscellaneous site osteomyelitis typically garners only AHA Class IIb support. This variability in $HBO_2$ treatment recommendations is to be expected, however, given similar location-dependent irregularity in treatment success with standard of care therapies.

Finally, while one study did report a neutral benefit from the use of adjunctive HBO2 treatment, no study reported significant negative treatment effects from adding $HBO_2$ to standard of care therapies. Furthermore, as the addition of $HBO_2$ to osteomyelitis treatment regimens was not associated with reports of significant adverse side effects, the use of $HBO_2$ therapy to treat refractory osteomyelitis should be considered a safe, well-tolerated intervention.

**Clinical management**

As noted in the above section on Patient Selection Criteria, the initial treatment of osteomyelitis depends on the classification of the patient's clinical disease. Generally, patients with Cierny-Mader Stage 1 and 2 disease may be primarily managed with antibiotics and limited surgical debridement. In contrast, patients with refractory, Stage 3B and 4B osteomyelitis should be considered candidates for adjunctive $HBO_2$ therapy. In situations where alternative clinical classification systems more effectively apply (*i.e.*, Wagner classification of diabetic foot ulcers or Tisch classification of malignant external otitis), these systems may be used to guide decisions to include $HBO_2$ therapy.

If not already begun, culture-directed antibiotic therapy should be restarted. For most cases of extremity or miscellaneous site osteomyelitis, initiation of $HBO_2$ therapy should coincide as closely as possible with plans for pre-$HBO_2$ surgical debridement. In certain clinical settings, such as osteomyelitis affecting children or bony structures adjacent to the central nervous system or other vital organs, a trial of combined $HBO_2$ and antibiotic therapy should be considered prior to patients undergoing extensive surgical debridement or permanently debilitating procedures. A summary of AHA Class recommendations for $HBO_2$ treatment of osteomyelitis relative to specific anatomic site and clinical setting is provided in this section *(Table III, Page 764)*.

In determining an ideal treatment pressure, the primary goal is to restore oxygen tensions to normal or above-normal levels in the infected bone. Based on Mader's previously reviewed work, a target oxygen tension of ≥150 mm Hg is recommended [7]. Animal models suggest that a minimum of 2 ATA is necessary to achieve this goal [7, 11]. Given that mean bone oxygen tensions in Mader's model reached only 104 mm Hg while exposed to oxygen at 2.0 atm abs, treatment pressures greater than 2.0 atm abs may be required to achieve the desired clinical effects. When considering the practical range of osteomyelitis treatment pressures, all of the clinical studies included in this review reported $HBO_2$ treatment at pressures between 2.0-3.0 atm abs. However, the majority of successful treatment responses were associated with studies employing chamber pressures between 2.4-2.5 atm abs. Thus, in the absence of non-invasive clinical methods that can effectively guide bone $pO_2$ titration, initial $HBO_2$ treatment of refractory osteomyelitis at 2.4-2.5 atm abs may provide physicians with the best theoretical balance between clinical efficacy and oxygen toxicity risk.

Variability in $HBO_2$ treatment session duration and frequency also exists. Each $HBO_2$ treatment is generally delivered over a period of 90-120 minutes. Most clinicians provide $HBO_2$ therapy on a once-daily basis, five to seven times per week. However, some advocate twice-daily treatment during the first two to three post-operative days, the goal being to aggressively prevent bacterial recolonization and maximize other associated benefits of postoperative $HBO_2$ therapy (*i.e.*, mitigation of ischemia, edema, inflammation and reperfusion injury, mechanisms that are discussed in detail elsewhere in the Committee Report). This more aggressive initial treatment has also been suggested in cases of osteomyelitis involving the central nervous system and other structures where significant morbidity or mortality would be incurred if the infection were to progress. However, the osteomyelitis treatment data gleaned from this review does not explicitly support this intuitive clinical approach.

Similarly, the total number of required treatments varies with the severity and location of the patient's infection, the presence or absence of coexisting diseases and the patient's individual responsiveness to treatment. In the studies available for review, treatments ranged from 14 to over 100 total sessions, with the significant majority of studies reporting between 20 and 50 total sessions. As would be expected from the preceding discussions, variability in clinical presentations and concurrent management strategies render specific treatment number recommendations impractical. Instead, it is recommended that clinicians carefully consider each patient's disease severity, clinical responsiveness and risk for osteomyelitis recurrence in guiding such determinations.

Where initial treatment with indicated surgical debridement, appropriate antibiotics and concurrent $HBO_2$ is met with prompt clinical improvement, the regimen of antibiotic and $HBO_2$ therapy should be continued until the surgically debrided bone becomes adequately revascularized [81, 82]. As noted previously, this regenerative period usually corresponds to approximately four to six weeks. Depending upon the prescribed frequency of

**TABLE III – Summary of AHA Class Recommendations for $HBO_2$ Treatment of Osteomyelitis**

| | Patient Descriptors | Treatment Method Combination | AHA Class Recommendation |
|---|---|---|---|
| **LONG BONE / NON-SPECIFIED** | Adult | $HBO_2$, antibiotics & debridement | Class IIa |
| | Adult | $HBO_2$ & antibiotics | Class IIb |
| | Adult | $HBO_2$ alone | Class III |
| | Before debilitating surgery / amputation | $HBO_2$, antibiotics & *limited* debridement | Class IIa |
| **MANDIBuLAR** | Adult | $HBO_2$, antibiotics & debridement | Class IIa |
| | Adult | $HBO_2$ & antibiotics | Class IIb |
| | Adult | $HBO_2$ alone | Class III |
| | Child | $HBO_2$, antibiotics & *limited* debridement | Class IIa |
| | Child | $HBO_2$ & antibiotics | Class IIa |
| **SPINAL** | Before debridement surgery / hardware removal | $HBO_2$ & antibiotics | Class IIa |
| | All patients | $HBO_2$, antibiotics & *limited* debridement | Class IIa |
| **CRANIAL** | Before debridement surgery / hardware removal | $HBO_2$ & antibiotics | Class IIa |
| | All patients | $HBO_2$, antibiotics & *limited* debridement | Class IIa |
| **MALIGNANT OTITIS EXTERNAL** | Tisch Stage III or IV | $HBO_2$, antibiotics & debridement | Class IIa |
| | Tisch Stage I or II | $HBO_2$, antibiotics & debridement | Class IIb |
| **STERNAL** | All patients | $HBO_2$, antibiotics & *limited* debridement | Class IIa |
| **DIABETIC uLCERS** | Wagner Grade 3 or 4 | $HBO_2$, antibiotics & *limited* debridement | Class I |

$HBO_2$ treatment, a total of 20-40 postoperative $HBO_2$ sessions will typically have been delivered during this interval. After this point, as long as no occult nidus for reinfection exists (*i.e.*, retained sequestra or unsterile fixation hardware), the bony milieu should be sufficiently recovered to prevent infection recurrence. In cases where removal of fixation hardware or extensive surgical debridement may be relatively contraindicated (*e.g.*, cranial, spinal, sternal or pediatric osteomyelitis), a trial of limited debridement, culture-directed antibiotics and $HBO_2$ therapy prior to more radical surgical intervention provides a reasonable chance for osteomyelitis cure. Again, a course of four to six weeks of combined therapy should be sufficient to achieve the desired clinical results. Although co-existing local and systemic processes, such as Cierny-Mader "B" factors, may slow the expected rate

of infection resolution, extension of $HBO_2$ and antibiotic treatment beyond one to two more weeks is unlikely to provide definitive benefit. Indeed, if osteomyelitis fails to resolve or recurs after a total of six to eight weeks of continuous culture-directed antibiotics and $HBO_2$ treatment (*i.e.*, 30-40 sessions), then additional surgical debridement will likely be required to eradicate residual infection.

**Utilization review**

As discussed in the preceding section, no specific recommendations can be made for the total number of $HBO_2$ treatments required. Consequently, the duration of $HBO_2$ therapy must be judged on the basis of each patient's clinical response. If a patient responds to initial management with appropriate antibiotics, indicated surgical debridement and $HBO_2$, then antibiotics and $HBO_2$ therapy should be considered and AHA Class II intervention continued for a period of approximately four to six weeks. Although mitigating clinical circumstances do exist, utilization review is indicated after completion of 30-40 $HBO_2$ treatment sessions.

In contrast, if a patient does not respond with prompt clinical improvement, then the existing antibiotic and $HBO_2$ regimen is unlikely to be clinically effective, and continuation without modification should be considered an AHA Class III intervention. Instead, clinical management strategies should be reassessed and additional surgical debridement and/or adjustment of antibiotic therapy implemented without delay. Subsequent to initiation of appropriate treatment modifications, reinstitution of $HBO_2$ therapy will still help maximize the overall chances for clinical treatment success.

**Cost impact**

When used within the above guidelines, adjunctive $HBO_2$ can decrease overall healthcare costs in patients with refractory osteomyelitis. Analyzing a series of complicated osteomyelitis cases, Strauss reported an average expenditure of $204,000 on hospitalization and treatment prior to the initiation of $HBO_2$ therapy [1] (*n.b.*: all U.S. dollar values in these examples have been normalized to present-day equivalents).

Once $HBO_2$ was combined with surgery and antibiotic therapy for control of the infection, expenditures on these previously refractory cases were limited to an additional $35,500 per patient. While this did represent a one-time, 17% increase in total cost, it was projected that these patients would have experienced equal or greater costs in association with continued "standard of care" interventions. Consequently, cost-effectiveness was calculated as being five-fold in favor of adjunctive $HBO_2$ therapy in refractory osteomyelitis [158]. These results were seconded in a series of patients with infected cranial bone flaps, where Larsson demonstrated that treatment with $HBO_2$ therapy was effective in resolving cranial infection and preventing the need for revision cranioplasty [92].

Citing per-case surgical costs of 130,000-210,000 SEK versus an average 71,000 SEK for $HBO_2$ therapy, the adjunctive use of $HBO_2$ resulted in a two- to three-fold savings over standard of care surgical treatment (monetary figures are reported in Swedish *kroner*, as the exchange rate at the time of the study is unknown). In a separate cost analysis, patients undergoing $HBO_2$ treatment for sternal wound infections realized a relative reduction in hospital length of stay and pharmacy costs [159]. Calculated savings of $11,154 per case or approximately 12% were reported. Although not specifically reporting cost figures, *per se*, Barili's prospective, controlled trial noted that patients receiving $HBO_2$ therapy as part of their overall management of sternal osteomyelitis required shorter courses antibiotic therapy (47.8 +/- 7.4 *vs.* 67.6 +/- 25.1 days, $p$=0.036) and reduced hospital stay lengths (52.6 +/- 9.1 *vs.* 73.6 +/- 24.5 days, $p$=0.026) relative to non-$HBO_2$-treated controls.

Finally, in his Canadian technology assessment, Sheps noted that while overall management costs for chronic osteomyelitis are high (ranging from $144,000-360,000), the subset of costs associated with $HBO_2$ account for only 5% of the total cost per case [40, 73]. In sum, while $HBO_2$ therapy is costly, its addition to the management of patients with refractory osteomyelitis appears to reduce the total need for surgical procedures, required courses of antibiotic therapy and hence, overall health care expenditures.

**Review conclusions**

Animal studies have demonstrated basic mechanisms by which $HBO_2$ enhances the body's ability to inhibit bacterial growth. Specifically, $HBO_2$ therapy elevates oxygen tensions in infected bone to normal or supranormal levels. Elimination of hypoxia restores bacterial phagocytosis and oxidative killing by neutrophils. Further, active transport of aminioglycoside and cephalosporin antibiotics across bacterial cell walls is improved. When combined, antibiotic and $HBO_2$ therapy can produce a 100-fold reduction in bacterial cell counts relative to the use of either agent alone.

In clinical practice, this antibacterial synergy has resulted in numerous human case reports and clinical

series describing effective control of osteomyelitis in previously refractory patients. In the last four to five years, these results have also been confirmed by well-designed prospective trials. While variations in host status, bony involvement, pathogenic organisms, antibiotic regimens and surgical techniques still complicate the analysis of $HBO_2$ therapy's effectiveness; infection arrest rates remain superior to "standard of care" interventions alone. Thus, the evidence accumulated in this review supports $HBO_2$ therapy as an AHA Class II adjunct to routine surgical and antibiotic management of refractory osteomyelitis. In particular, for patients with Cierny-Mader Class 3B or 4B disease, adjunctive $HBO_2$ therapy should be considered an AHA Class IIa intervention. For the subset of patients with Wagner Grade 3 or 4 diabetic ulcers, adjunctive $HBO_2$ should definitively be regarded as an AHA Class I intervention. When refractory osteomyelitis involves children or bony structures adjacent to the CNS or other vital organs, a favorable risk-benefit balance earns AHA Class IIa support for combined $HBO_2$ and antibiotic therapy prior to extensive surgical debridement. In contrast, in the absence of adequate surgical debridement, such combined therapy for the management of uncomplicated primary, extremity or miscellaneous site osteomyelitis typically garners only an AHA Class IIb recommendation.

In terms of dosing, $HBO_2$ therapy is usually applied on a once-daily basis, five to seven times per week, and timed to begin just after the most recent surgical debridement. However, some clinicians advocate twice-daily treatment during the first two to three postoperative days to more aggressively prophylax against bacterial recolonization and maximize the secondary benefits of postoperative $HBO_2$ therapy. Further, individual $HBO_2$ treatment sessions are most frequently delivered over a period of 90-120 minutes. Although treatment pressures ranging from 2.0-3.0 atm abs are clinically appropriate, initial treatment at 2.4-2.5 atm abs may provide the best theoretical balance between clinical efficacy and oxygen toxicity risk.

Where prompt clinical improvement is seen, the present antibiotic and $HBO_2$ treatment regimen should be continued for approximately four to six weeks. Depending upon the frequency of prescribed $HBO_2$ treatment, a total of 20-40 postoperative $HBO_2$ sessions will be required to attain the desired clinical results. After this point, the bony milieu should be sufficiently revascularized to prevent infection recurrence. In those cases where removal of fixation hardware or extensive surgical debridement is relatively contraindicated (*e.g.*, cranial, spinal, sternal or pediatric osteomyelitis), a trial of limited debridement, culture-directed antibiotics and $HBO_2$ prior to radical surgical intervention will provide a reasonable chance for osteomyelitis cure. Again, a course of four to six weeks of combined therapy is indicated. Although co-existing diseases may slow the rate of infection resolution, extension of this treatment regimen beyond one to two additional weeks does not appear to provide definitive benefit.

Indeed, if osteomyelitis fails to resolve or recurs after a total of six to eight weeks of continuous culture-directed antibiotics and $HBO_2$ treatment (*i.e.*, 30-40 sessions), then a nidus of reinfection, such as an occult sequestra or fixation hardware refractory to sterilization, should be suspected. Therefore, further surgical debridement or removal of fixation hardware will likely be required to eradicate any residual infection.

Similarly, if initial antibiotic and $HBO_2$ treatment do not result in clinical improvement, then continuation of the regimen should be considered an AHA Class III intervention. Instead, patient management strategies should be reassessed and additional surgical debridement and/or adjustment of antibiotic therapy implemented without delay. Subsequent to these interventions, the reinstitution of $HBO_2$ will help maximize overall chances for treatment success. Regardless of the clinical presentation, utilization review is generally recommended after a total of 30-40 treatments.

In conclusion, while no randomized clinical trials exist, the overwhelming majority of published animal data, human case series and prospective trials support $HBO_2$ therapy as a safe and effective adjunct to the management of refractory osteomyelitis. Further, when used appropriately, $HBO_2$ therapy appears to reduce the total need for surgical procedures, required antibiotic therapy and, consequently, overall healthcare expenditures.

**REFERENCES**


1. Strauss, M.B. Refractory Osteomyelitis. J Hyperbaric Med, 1987. 2: p.147-159.

2. Perrins, D.J.D. et al. OHP in the management of chronic osteomyelitis. in Third international conference on hyperbaric medicine. 1966. Washington D.C.: National Academy of Sciences - National Research Council.

3. Slack, W.K., D.A. Thomas, and D. Perrins. Hyperbaric oxygenation chronic osteomyelitis. Lancet, 1965. 14: p.1093-4.

4. Hamblen, D.L. Hyperbaric oxygenation. Its effect on experimental staphylococcal osteomyelitis in rats. J Bone Joint Surg Am, 1968. 50(6): p.1129-41.

5. Sippel, H.W., C.D. Nyberg, and H.J. Alvis. Hyperbaric oxygen as an adjunct to the treatment of chronic osteomyelitis of the mandible: report of case. J Oral Surg, 1969. 27(9): p.739-41.

6. Niinikoski, J. and T.K. Hunt, Oxygen tensions in healing bone. Surg Gynecol Obstet, 1972. 134(5): p.746-50.

7. Mader, J.T. et al. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis, 1980. 142(6): p.915-22.

8. Park, M.K., R.A. Myers, and L. Marzella. Oxygen tensions and infections: modulation of microbial growth, activity of antimicrobial agents, and immunologic responses. Clin Infect Dis, 1992. 14(3): p.720-40.

9. Hohn, D.C. Oxygen and leukocyte microbial killing, in hyperbaric oxygen therapy, J.C. Davis and T.K. Hunt, Editors. 1977, Undersea Medical Society: Bethesda. p.101-10.

10. Kindwall, E.P., Uses of hyperbaric oxygen therapy in the 1990s. Cleve Clin J Med, 1992. 59(5): p.517-28.

11. Esterhai, J.L., Jr. et al. Effect of hyperbaric oxygen exposure on oxygen tension within the medullary canal in the rabbit tibial osteomyelitis model. J Orthop Res, 1986. 4(3): p.330-6.

12. Verklin, R.M., Jr. and G.L. Mandell. Alteration of effectiveness of antibiotics by anaerobiosis. J Lab Clin Med, 1977. 89(1): p.65-71.

13. Mader, J.T., K.R. Adams, and L.A. Couch. Potentiation of tobramycin by hyperbaric oxygen in experimental Pseudomonas aeruginosa osteomyelitis. in 27th Interscience Conference on Antimicrobial Agents and Chemotherapy. 1987. New York.

14. Mader, J.T. et al. Hyperbaric oxygen as adjunctive therapy for osteomyelitis. Infect Dis Clin North Am, 1990. 4(3): p.433-40.

15. Mendel, V. et al. Thera p.with hyperbaric oxygen and cefazolin for experimental osteomyelitis due to Staphylococcus aureus in rats. Undersea Hyperb Med, 1999. 26(3): p.169-74.

16. Mader, J., M. Shirtliff, and J.H. Calhoun. The use of hyperbaric oxygen in the treatment of osteomyelitis, in Hyperbaric medicine practice, E.P. Kindwall and H.T. Whelan, Editors. 1999, Best Publishing Company: Flagstaff. p.603-616.

17. Sugihara, A. et al. The effect of hyperbaric oxygen therapy on the bout of treatment for soft tissue infections. J Infect, 2004. 48(4): p.330-3.

18. Mader, J.T., M. Ortiz, and J.H. Calhoun. Update on the diagnosis and management of osteomyelitis. Clin Podiatr Med Surg, 1996. 13(4): p.701-24.

19. Coulson, D.B., A.B. Ferguson, Jr., and R.C. Diehl, Jr. Effect of hyperbaric oxygen on the healing femur of the rat. Surg Forum, 1966. 17: p.449-50.

20. Niinikoski, J., R. Penttinen, and E. Kulonen. Effect of hyperbaric oxygenation on fracture healing in the rat: a biochemical study. Calcif Tissue Res, 1970: p.Suppl:115-6.

21. Penttinen, R. Biochemical studies on fracture healing in the rat, with special reference to the oxygen supply. Acta Chir Scand Suppl, 1972. 432: p.1-32.

22. Yablon, I.G. and R.L. Cruess. The effect of hyperbaric oxygen on fracture healing in rats. J Trauma, 1968. 8(2): p.186-202.

23. Steed, D.L. Enhancement of osteogenesis with hyperbaric oxygen therapy. A clinical study. J Dent Res, 1982. 61A: p.288.

24. Ueng, S.W. et al. Bone healing of tibial lengthening is enhanced by hyperbaric oxygen therapy: a study of bone mineral density and torsional strength on rabbits. J Trauma, 1998. 44(4): p.676-81.

25. Sawai, T. et al. Histologic study of the effect of hyperbaric oxygen therapy on autogenous free bone grafts. J Oral Maxillofac Surg, 1996. 54(8): p.975-81.

26. Jones, J.P., Jr. The effect of hyperbaric oxygen on osteonecrosis. in Orthopaedic Research Society. 1991. Anaheim, CA.

27. Strauss, M.B. Effect of hyperbaric oxygen on bone resorption in rabbits. in Seventh Annual Conference on the Clinical Applications of Hyperbaric Oxygen. 1982. Anaheim, CA.

28. Strauss, M.B. and B. Bryant. Hyperbaric oxygen. Orthopedics, 2002. 25(3): p.303-10.

29. Skyhar, M.J. et al. Hyperbaric oxygen reduces edema and necrosis of skeletal muscle in compartment syndromes associated with hemorrhagic hypotension. J Bone Joint Surg Am 1986. 68(8): p.1218-24.

30. Strauss, M.B. et al. Reduction of skeletal muscle necrosis using intermittent hyperbaric oxygen in a model compartment syndrome. J Bone Joint Surg Am, 1983. 65(5): p.656-62.

31. Zamboni, W.A. et al. Morphologic analysis of the microcirculation during reperfusion of ischemic skeletal muscle and the effect of hyperbaric oxygen. Plast Reconstr Surg, 1993. 91(6): p.1110-23.

32. Nylander, G. et al. Reduction of postischemic edema with hyperbaric oxygen. Plast Reconstr Surg, 1985. 76(4): p.596-603.

33. Hunt, T.K., B. Halliday, and D.R. Knighton. Impairment of microbicidal function in wounds: Correction with oxygenation, in Soft and Hard Tissue Repair, T.K. Hunt, R.B. Heppenstall, and E. Pines, Editors. 1984, Praeger: New York. p.455-68.

34. Hohn, D.C. et al. Effect of O2 tension on microbicidal function of leukocytes in wounds and in vitro. Surg Forum, 1976. 27(62): p.18-20.

35. Hunt, T.K. and M.P. Pai. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. Surg Gynecol Obstet, 1972. 135(4): p.561-7.

36. Connolly, W.B. et al. Influence of distant trauma on local wound infection. Surg Gynecol Obstet, 1969. 128: p.713-8.

37. Wald, E.R. Risk factors for osteomyelitis. Am J Med, 1985. 78(6B): p.206-12.

38. Le Saux, N. et al. Shorter courses of parenteral antibiotic therapy do not appear to influence response rates for children with acute hematogenous osteomyelitis: a systematic review. BMC Infect Dis, 2002. 2: p.16.

39. Lew, D.P. and F.A. Waldvogel. Osteomyelitis. Lancet, 2004. 364(9431): p.369-79.

40. Davis, J.C. and J.D. Heckman. Refractory osteomyelitis, in problem tounds: the role of oxygen. J.C. Davis and T.K. Hunt, Editors. 1988, Elsevier Science Publishing Co., Inc.: New York. p.125-142.

41. Attinger, C. and P. Cooper. Soft tissue reconstruction for calcaneal fractures or osteomyelitis. Orthop Clin North Am, 2001. 32(1): p.135-70.

42. Lazzarini, L., B.A. Lipsky, and J.T. Mader. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? Int J Infect Dis, 2005. 9(3): p.127-38.

43. Zalavras, C.G., A. Singh, and M.J. Patzakis. Novel technique for medullary canal debridement in tibia and femur osteomyelitis. Clin Orthop Relat Res, 2007. 461: p.31-4.

44. Thonse, R. and J. Conway. Antibiotic cement-coated interlocking nail for the treatment of infected nonunions and segmental bone defects. J Orthop Trauma, 2007. 21(4): p.258-68.

45. Kocaoglu, M. et al. Reconstruction of segmental bone defects due to chronic osteomyelitis with use of an external fixator and an intramedullary nail. J Bone Joint Surg Am, 2006. 88(10): p.2137-45.

46. Chen, F. et al. [The treatment of deep wound infection after posterior thoracic and lumbar instrumentation]. Zhonghua Wai Ke Za Zhi, 2005. 43(20): p.1325-7.

47. Varzos, P.N. et al. Chronic osteomyelitis associated with monofilament wire fixation. J Foot Surg, 1983. 22(3): p.212-7.

48. Chang, W.C. et al. Successful treatment of extended epidural abscess and long segment osteomyelitis: a case report and review of the literature. Surg Neurol, 2007.

49. Barbarossa, V. et al. Treatment of osteomyelitis and infected non-union of the fmur by a modified Ilizarov technique: follow-up study. Croat Med J, 2001. 42(6): p.634-41.

50. Pappou, I.P. et al. Postoperative infections in interbody fusion for degenerative spinal disease. Clin Orthop Relat Res, 2006. 444: p.120-8.

51. Talmi, Y.P. et al. Postsurgical prevertebral abscess of the cervical spine. Laryngoscope, 2000. 110(7): p.1137-41.

52. Przybylski, G.J. and A.D. Sharan. Single-stage autogenous bone grafting and internal fixation in the surgical management of pyogenic discitis and vertebral osteomyelitis. J Neurosurg, 2001. 94(1 Suppl): p.1-7.

53. May, J.W., Jr., G.G. Gallico, 3rd, and F.N. Lukash. Microvascular transfer of free tissue for closure of bone wounds of the distal lower extremity. N Engl J Med, 1982. 306(5): p.253-7.

54. Steinlechner, C.W. and N.C. Mkandawire. Non-vascularised fibular transfer in the management of defects of long bones after sequestrectomy in children. J Bone Joint Surg Br, 2005. 87(9): p.1259-63.

55. Simard, S., M. Marchant, and G. Mencio. The Ilizarov procedure: limb lengthening and its implications. Phys Ther, 1992. 72(1): p.25-34.

56. Daver, N.G. et al. Oral step-down therapy is comparable to intravenous therapy for Staphylococcus aureus osteomyelitis. J Infect, 2007. 54(6): p.539-44.

57. Aneziokoro, C.O. et al. The effectiveness and safety of oral linezolid for the primary and secondary treatment of osteomyelitis. J Chemother, 2005. 17(6): p.643-50.

58. Cole, W.G., R.E. Dalziel, and S. Leitl. Treatment of acute osteomyelitis in childhood. J Bone Joint Surg Br, 1982. 64(2): p.218-23.

59. Gentry, L.O. Overview of osteomyelitis. Orthop Rev, 1987. 16(4): p.255-8.

60. Ketterl, R. et al. Use of ofloxacin in open fractures and in the treatment of post-traumatic osteomyelitis. J Antimicrob Chemother, 1988. 22 Sup p.C: p.159-66.

61. Lamp, K.C. et al. Clinical experience with daptomycin for the treatment of patients with osteomyelitis. Am J Med, 2007. 120(10 Sup p.1): p.S13-20.

62. Miller, D.J. and G.C. Mejicano, Vertebral osteomyelitis due to Candida species: case report and literature review. Clin Infect Dis, 2001. 33(4): p.523-30.

63. Petersen, S. et al. Acute haematogenous osteomyelitis and septic arthritis in childhood. A 10-year review and follow-up. Acta Orthop Scand, 1980. 51(3): p.451-7.

64. Powers, T. and D.H. Bingham. Clinical and economic effect of ciprofloxacin as an alternative to injectable antimicrobial therapy. Am J Hosp Pharm, 1990. 47(8): p.1781-4.

65. Rayner, C.R. et al. Linezolid in the treatment of osteomyelitis: results of compassionate use experience. Infection, 2004. 32(1): p.8-14.

66. Schurman, D.J. and M. Dillingham, Clinical evaluation of cefoxitin in treatment of infections in 47 orthopedic patients. Rev Infect Dis, 1979. 1(1): p.206-9.

67. Stefanovski, N. and L.P. Van Voris. Pyogenic vertebral osteomyelitis: report of a series of 23 patients. Contemp Ortho p.1995. 31(3): p.159-64.

68. Stratov, I., T.M. Korman, and P.D. Johnson. Management of Aspergillus osteomyelitis: report of failure of liposomal amphotericin B and response to voriconazole in an immunocompetent host and literature review. Eur J Clin Microbiol Infect Dis, 2003. 22(5): p.277-83.

69. Bingham, E.L. and G.B. Hart. Hyperbaric oxygen treatment of refractory osteomyelitis. Postgrad Med, 1977. 61(6): p.70-6.

70. Depenbusch, F.L., R.E. Thompson and G.B. Hart. Use of hyperbaric oxygen in the treatment of refractory osteomyelitis: a preliminary report. J Trauma, 1972. 12(9): p.807-12.

71. Davis, J.C. et al. Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. J Bone Joint Surg Am, 1986. 68(8): p.1210-7.

72. Morrey, B.F. et al. Hyperbaric oxygen and chronic osteomyelitis. Clin Orthop Relat Res, 1979(144): p.121-7.

73. Sheps, S.B., Hyperbaric oxygen for osteomyelitis and osteoradionecrosis. 1992, University of British Columbia: Vancouver. p.1-21.

74. Senneville, E. et al. Effectiveness and tolerability of prolonged linezolid treatment for chronic osteomyelitis: a retrospective study. Clin Ther, 2006. 28(8): p.1155-63.

75. Priest, D.H. and J.E. Peacock, Jr. Hematogenous vertebral osteomyelitis due to Staphylococcus aureus in the adult: clinical features and therapeutic outcomes. South Med J, 2005. 98(9): p.854-62.

76. Gomez, J. et al. [Orthopedic implant infection: prognostic factors and influence of long-term antibiotic treatment on evolution. Prospective study, 1992-1999]. Enferm Infecc Microbiol Clin, 2003. 21(5): p.232-6.

77. Eckardt, J.J., P.Z. Wirganowicz, and T. Mar. An aggressive surgical approach to the management of chronic osteomyelitis. Clin Orthop Relat Res, 1994(298): p.229-39.

78. Hall, B.B., R.H. Fitzgerald, Jr., and J.E. Rosenblatt. Anaerobic osteomyelitis. J Bone Joint Surg Am, 1983. 65(1): p.30-5.

79. Marx, R.E. Chronic osteomyelitis of the jaws. Oral Maxillofac Surg Clin North Am, 1991. 3: p.367-81.

80. Mercuri, L.G. Acute osteomyelitis of the jaws. Oral Maxillofac Surg Clin North Am, 1991. 3: p.355-65.

81. Mader, J.T. et al. Antimicrobial treatment of chronic osteomyelitis. Clin Orthop Relat Res, 1999(360): p.47-65.

82. Waldvogel, F.A., G. Medoff, and M.N. Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects (second of three parts). N Engl J Med, 1970. 282(5): p.260-6.

83. Gomis, M. et al. Oral ofloxacin versus parenteral imipenem-cilastatin in the treatment of osteomyelitis. Rev Esp Quimioter, 1999. 12(3): p.244-9.

84. Mader, J.T., J.S. Cantrell, and J. Calhoun. Oral ciprofloxacin compared with standard parenteral antibiotic therapy for chronic osteomyelitis in adults. J Bone Joint Surg Am, 1990. 72(1): p.104-10.

85. Gentry, L.O. and G. Rodriguez-Gomez. Ofloxacin versus parenteral therapy for chronic osteomyelitis. Antimicrob Agents Chemother, 1991. 35(3): p.538-41.

86. Jauregui, L.E., G. Hageage, and M. Martin. Oral enoxacin versus conventional intravenous antimicrobial therapy for chronic osteomyelitis. J Chemother, 1989. 1(4 Suppl): p.735-6.

87. Swiontkowski, M.F. et al. A comparison of short- and long-term intravenous antibiotic therapy in the postoperative management of adult osteomyelitis. J Bone Joint Surg Br, 1999. 81(6): p.1046-50.

88. Spencer, C.H. Bone and joint infections in children. Curr Opin Rheumatol, 1998. 10(5): p.494-7.

89. Tetzlaff, T.R., G.H. McCracken, Jr., and J.D. Nelson. Oral antibiotic therapy for skeletal infections of children. II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr, 1978. 92(3): p.485-90.

90. Wall, E.J. Childhood osteomyelitis and septic arthritis. Curr Opin Pediatr, 1998. 10(1): p.73-6.

91. Higuchi, T. et al. Preliminary report of the safety and efficacy of hyperbaric oxygen therapy for specific complications of lung transplantation. J Heart Lung Transplant, 2006. 25(11): p.1302-9.

92. Larsson, A. et al. Hyperbaric oxygen treatment of postoperative neurosurgical infections. Neurosurgery, 2002. 50(2): p.287-95; discussion 295-6.

93. Lucente, F.E., S.C. Parisier, and P.M. Som. Complications of the treatment of malignant external otitis. Laryngoscope, 1983. 93(3): p.279-81.

94. Waldvogel, F.A., G. Medoff, and M.N. Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med, 1970. 282(4): p.198-206.

95. Waldvogel, F.A., G. Medoff, and M.N. Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. 3. Osteomyelitis associated with vascular insufficiency. N Engl J Med, 1970. 282(6): p.316-22.

96. Ger, R. Muscle transposition for treatment and prevention of chronic post-traumatic osteomyelitis of the tibia. J Bone Joint Surg Am, 1977. 59(6): p.784-91.

97. Gordon, L. and E.J. Chiu. Treatment of infected nonunions and segmental defects of the tibia with staged microvascular muscle transplantation and bone-grafting. J Bone Joint Surg Am, 1988. 70(3): p.377-86.

98. Kelly, P.J. Infected nonunion of the femur and tibia. Orthop Clin North Am, 1984. 15(3): p.481-90.

99. May, J.W., Jr. et al. Clinical classification of post-traumatic tibial osteomyelitis. J Bone Joint Surg Am, 1989. 71(9): p.1422-8.

100. Weiland, A.J., J.R. Moore, and R.K. Daniel. The efficacy of free tissue transfer in the treatment of osteomyelitis. J Bone Joint Surg Am, 1984. 66(2): p.181-93.

101. Mader, J.T., M. Shirtliff, and J.H. Calhoun. Staging and staging application in osteomyelitis. Clin Infect Dis, 1997. 25(6): p.1303-9.

102. Cierny, G., 3rd, J.T. Mader, and J.J. Penninck. A clinical staging system for adult osteomyelitis. Clin Orthop Relat Res, 2003(414): p.7-24.

103. Fanning, W.J., J.S. Vasko, and J.W. Kilman. Delayed sternal closure after cardiac surgery. Ann Thorac Surg, 1987. 44(2): p.169-72.

104. Clarkson, J.H. et al. Our experience using the vertical rectus abdominis muscle flap for reconstruction in 12 patients with dehiscence of a median sternotomy wound and mediastinitis. Scand J Plast Reconstr Surg Hand Surg, 2003. 37(5): p.266-71.

105. Farinas, M.C. et al. Suppurative mediastinitis after open-heart surgery: a case-control study covering a seven-year period in Santander, Spain. Clin Infect Dis, 1995. 20(2): p.272-9.

106. Athanassiadi, K. et al. Omental transposition: the final solution for major sternal wound infection. Asian Cardiovasc Thorac Ann, 2007. 15(3): p.200-3.

107. Rezai, A.R. et al. Contemporary management of spinal osteomyelitis. Neurosurgery, 1999. 44(5): p.1018-25; discussion 1025-6.

108. Osei-Yeboah, C. et al. Osteomyelitis of the frontal bone. Ghana Med J, 2007. 41(2): p.88-90.

109. Blomstedt, G.C. Craniotomy infections. Neurosurg Clin N Am, 1992. 3(2): p.375-85.

110. Malone, D.G. et al. Osteomyelitis of the skull base. Neurosurgery, 1992. 30(3): p.426-31.

111. Stieg, P.E. and J.B. Mulliken. Neurosurgical complications in craniofacial surgery. Neurosurg Clin N Am, 1991. 2(3): p.703-8.

112. Gallagher, R.M., C.W. Gross, and C.D. Phillips. Suppurative intracranial complications of sinusitis. Laryngoscope, 1998. 108(11 Pt 1): p.1635-42.

113. Lucente, F.E. et al. Malignant external otitis: a dangerous misnomer? Otolaryngol Head Neck Surg, 1982. 90(2): p.266-9.

114. Tisch, M. and H. Maier. [Malignant external otitis]. Laryngorhinootologie, 2006. 85(10): p.763-9; quiz 770-3.

115. Bhandary, S., P. Karki, and B.K. Sinha. Malignant otitis externa: a review. Pac Health Dialog, 2002. 9(1): p.64-7.

116. Slattery, W.H., 3rd and D.E. Brackmann. Skull base osteomyelitis. Malignant external otitis. Otolaryngol Clin North Am, 1996. 29(5): p.795-806.

117. Triplett, R.G. et al. Experimental mandibular osteomyelitis: therapeutic trials with hyperbaric oxygen. J Oral Maxillofac Surg, 1982. 40(10): p.640-6.

118. Mendel, V., H.J. Simanowski, and H. Scholz. Synergy of HBO2 and a local antibiotic carrier for experimental osteomyelitis due to Staphylococcus aureus in rats. Undersea Hyperb Med, 2004. 31(4): p.407-16.

119. Mader, J.T. et al. Therapy with hyperbaric oxygen for experimental osteomyelitis due to Staphylococcus aureus in rabbits. J Infect Dis, 1978. 138(3): p.312-8.

120. Triplett, R.G. and G.B. Branham. Treatment of experimental mandibular osteomyelitis with hyperbaric oxygen and antibiotics. Int J Oral Surg, 1981. 10(Sup p.1): p.178-82.

121. Esterhai, J.L., Jr. et al. Adjunctive hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis. J Trauma, 1987. 27(7): p.763-8.

122. Esterhai, J.L., Jr. et al. Treatment of chronic osteomyelitis complicating nonunion and segmental defects of the tibia with open cancellous bone graft, posterolateral bone graft, and soft-tissue transfer. J Trauma, 1990. 30(1): p.49-54.

123. MacGregor, R.R., A.L. Graziani, and J.L. Esterhai. Oral ciprofloxacin for osteomyelitis. Orthopedics, 1990. 13(1): p.55-60.

124. Barili, F. et al. Role of hyperbaric oxygen therapy in the treatment of postoperative organ/space sternal surgical site infections. World J Surg, 2007. 31(8): p.1702-6.

125. Welsh, F.M.L., L.U. Matos, and T.P. deTreville. Medical hyperbaric oxygen therapy: 22 cases. Aviat Space Environ Med, 1980. 51(6): p.611-4.

126. Eltorai, I., G.B. Hart, and M.B. Strauss, Osteomyelitis in the spinal cord injured: a review and a preliminary report on the use of hyperbaric oxygen therapy. Paraplegia, 1984. 22(1): p.17-24.

127. Maynor, M.L. et al. Chronic osteomyelitis of the tibia: treatment with hyperbaric oxygen and autogenous microsurgical muscle transplantation. J South Orthop Assoc, 1998. 7(1): p.43-57.

128. Chen, C.Y. et al. Chronic refractory tibia osteomyelitis treated with adjuvent hyperbaric oxygen: a preliminary report. Changgeng Yi Xue Za Zhi, 1998. 21(2): p.165-71.

129. Chen, C.E. et al. Hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis: a preliminary report. Chang Gung Med J, 2003. 26(2): p.114-21.

130. Chen, C.E. et al. Results of chronic osteomyelitis of the femur treated with hyperbaric oxygen: a preliminary report. Chang Gung Med J, 2004. 27(2): p.91-7.

131. Calhoun, K.H. et al. Osteomyelitis of the mandible. Arch Otolaryngol Head Neck Surg, 1988. 114(10): p.1157-62.

132. Jamil, M.U., A. Eckardt, and W. Franko. [Hyperbaric oxygen therapy. Clinical use in treatment of osteomyelitis, osteoradionecrosis and reconstructive surgery of the irradiated mandible]. Mund Kiefer Gesichtschir, 2000. 4(5): p.320-3.

133. Handschel, J. et al. Evaluation of hyperbaric oxygen therapy in treatment of patients with osteomyelitis of the mandible. Mund Kiefer Gesichtschir, 2007.

134. Lentrodt, S. et al. Hyperbaric oxygen for adjuvant therapy for chronically recurrent mandibular osteomyelitis in childhood and adolescence. J Oral Maxillofac Surg, 2007. 65(2): p.186-91.

135. Mainous, E.G. Hyperbaric oxygen in maxillofacial osteomyelitis, osteoradionecrosis, and osteogenesis enhancement, in Hyperbaric oxygen therapy, J.C. Davis and T.K. Hunt, Editors. 1977, Undersea Medical Society: Bethesda. p.191-203.

136. Van Merkesteyn, J.P. et al. Hyperbaric oxygen treatment of chronic osteomyelitis of the jaws. Int J Oral Surg, 1984. 13(5): p.386-95.

137. Aitasalo, K. et al. A modified protocol for early treatment of osteomyelitis and osteoradionecrosis of the mandible. Head Neck, 1998. 20(5): p.411-7.

138. Carragee, E.J. et al. The clinical use of erythrocyte sedimentation rate in pyogenic vertebral osteomyelitis. Spine, 1997. 22(18): p.2089-93.

139. Kovalenko, D.G., A.V. Savchenko, and E.M. Milovanova. [Osteoplasty in surgical treatment of hematogenic osteomyelitis of the spine]. Vestn Khir Im I I Grek, 1978. 120(3): p.89-93.

140. Ibarra, S. et al. [Osteomyelitis of the frontal bone (Pott's puffy tumor). A report of 5 patients]. Enferm Infecc Microbiol Clin, 1999. 17(10): p.489-92.

141. Balm, A.J., R.M. Tiwari, and T.B. de Rijcke. Osteomyelitis in the head and neck. J Laryngol Otol, 1985. 99(10): p.1059-65.

142. Boeckx, W.D. et al. The role of free flaps in the treatment of persistent scalp osteomyelitis. Neurosurgery, 2006. 59 (1 Sup p.1): p.ONS64-7; discussion ONS64-7.

143. Marshall, A.H. and N.S. Jones. Osteomyelitis of the frontal bone secondary to frontal sinusitis. J Laryngol Otol, 2000. 114(12): p.944-6.

144. Levy, R. et al. Oral ofloxacin as treatment of malignant external otitis: a study of 17 cases. Laryngoscope, 1990. 100(5): p.548-51.

145. Lang, R. et al. Successful treatment of malignant external otitis with oral ciprofloxacin: report of experience with 23 patients. J Infect Dis, 1990. 161(3): p.537-40.

146. Gehanno, P. Ciprofloxacin in the treatment of malignant-external otitis. Chemotherapy, 1994. 40 Sup p.1: p.35-40.

147. Martel, J. et al. [Malignant or necrotizing otitis externa: experience in 22 cases]. Ann Otolaryngol Chir Cervicofac, 2000. 117(5): p.291.

148. Narozny, W. et al. Value of hyperbaric oxygen in bacterial and fungal malignant external otitis treatment. Eur Arch Otorhinolaryngol, 2006. 263(7): p.680-4.

149. Davis, J.C. et al. Adjuvant hyperbaric oxygen in malignant external otitis. Arch Otolaryngol Head Neck Surg, 1992. 118(1): p.89-93.

150. Strecker, T. et al. Sternal wound infections following cardiac surgery: risk factor analysis and interdisciplinary treatment. Heart Surg Forum, 2007. 10(5): p.E366-71.

151. Newman, L.G. et al. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. Jama, 1991. 266(9): p.1246-51.

152. Grayson, M.L. et al. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. Jama, 1995. 273(9): p.721-3.

153. Roeckl-Wiedmann, I., M. Bennett, and P. Kranke. Systematic review of hyperbaric oxygen in the management of chronic wounds. Br J Surg, 2005. 92(1): p.24-32.

154. Zamboni, W.A. et al. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. Undersea Hyperb Med, 1997. 24(3): p.175-9.

155. Abidia, A. et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg, 2003. 25(6): p.513-8.

156. Kessler, L. et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care, 2003. 26(8): p.2378-82.

157. Warriner, R.A., 3rd and H.W. Hopf. Enhancement of healing in selected problem wounds, in Hyperbaric oxygen 2003: Indications and Results: The Hyperbaric Oxygen Therapy Committee Report, J.J. Feldmeier, Editor. 2003, Undersea and Hyperbaric Medical Society: Kensington. p.41-55.

158. Strauss, M.B. Economic considerations in chronic refractory osteomyelitis. in Fifth Annual Conference on Clinical Applications of Hyperbaric Oxygen. 1980. Long Beach, CA.

159. Riddick, M. Sternal wound infections, dehiscence, and sternal osteomyelitis: the role of hyperbaric oxygen therapy, in Hyperbaric medicine practice, E.P. Kindwall and H.T. Whelan, Editors. 1999, Best Publishing Company: Flagstaff. p.617-39.

# Refractory osteomyelitis – Literature review supplement

Subsequent to the 2008 publication of the Refractory Osteomyelitis chapter in the UHMS book *Hyperbaric Oxygen Therapy Indications*, 12th Edition, 26 additional studies were published examining hyperbaric oxygen ($HBO_2$) treatment of osteomyelitis [1]. This supplement integrates the relevant findings of these recent studies into the overall context of the previous comprehensive review. In doing so, the chapter's original inclusion criteria were preserved. More specifically, literature reviews (nine papers), case reports including fewer than three patients (10 papers), and articles co-mingling $HBO_2$ treatment outcome data for osteomyelitis and non-osteomyelitis affected patients (one paper) were excluded from analysis in this addendum. Consequently, one trial reporting prospective data from an osteomyelitis animal model and five articles addressing osteomyelitis in humans are considered.

**Animal data**

In 2012, Shandley *et al.* reported results from a prospective murine trial evaluating $HBO_2$ as a stand-alone treatment for implant-associated long bone osteomyelitis [2]. After establishing acute tibial osteomyelitis with transcortically placed, bacteria-coated pins, the mice were exposed to daily $HBO_2$ treatment at 2.4 atm abs for 80 minutes for either 12 or 19 days.

Subsequent comparisons between $HBO_2$-treated and untreated mice demonstrated no significant differences in resultant bacterial colony counts. Given that Hamblen *et al.* previously demonstrated $HBO_2$ therapy was ineffective as a stand-alone agent (*i.e.*, without concurrent antibiotic treatment) in an uninstrumented rat model of tibial osteomyelitis, Shandley's results are not surprising [3]. In contrast, previous prospective animal models have shown that, relative to either agent alone, $HBO_2$ acts synergistically with antibiotics to decrease bacterial colony counts and improve wound healing [4, 5]

**Human data**

Not previously considered in the UHMS *Hyperbaric Oxygen Therapy Indications* chapter on Refractory Osteomyelitis are five retrospective studies describing osteomyelitis treatment of patients in an equal number of distinct clinical settings. Accordingly, each study warrants further consideration and is, therefore, discussed in the order of publication.

In 2008, Chen and colleagues used adjunctive $HBO_2$ in an attempt to eradicate diffuse tibial/humeral bone infections in a series of 10 hemodialysis-dependent patients [6]. Importantly, each patient met criteria for refractory osteomyelitis, in that the infection had persisted for at least one month, failed a minimum of one surgical debridement and endured despite concomitant treatment with a course of parenteral antibiotics. Employing a combination of surgical debridement, antibiotics and 20 $HBO_2$ treatment sessions, the multimodal therapy promoted osteomyelitis resolution in 80% of these systemically compromised patients, with only two of 10 ultimately requiring limb amputations to control their disease.

Roje *et al.* reported their combat-related experience in a series of 388 patients sustaining Gustilo type III A, B and C war wounds to the upper and lower extremities (*i.e.*, fractures involving extensive damage to the soft tissues, including muscle, skin and neurovascular structures) [7]. In this 2008 retrospective analysis, osteomyelitis developed in 74% of patients who received only "standard of care" treatment in accordance with North Atlantic Treaty Organization (NATO) surgical strategies *vs.* 63% of patients who additionally received $HBO_2$ treatment ($p$= 0.030). Although the study more accurately reflects the use of $HBO_2$ therapy to prophylax against osteomyelitis rather than treat it, the results of this study of complex long bone infections remain noteworthy.

Ahmed *et al.*, in a 2009 study, described using $HBO_2$ therapy to treat six patients with complicated spinal osteomyelitis [8]. In four patients, the osteomyelitis developed subsequent to spinal surgery, whereas two cases derived from hematogenous seeding. In each case, the infections were noted to be either refractory or progressive despite appropriate antibiotic treatment. Using $HBO_2$ therapy in conjunction with continued antibiotics and, in two cases, removal/revision of previously placed spinal instrumentation, osteomyelitis resolution was achieved in five of six cases. Ahmed noted no recurrence of infection during an average follow-up period of 1.6 years (range five months – three years).

In another 2009 study, Sandler *et al.* examined the effects of adjunctive $HBO_2$ in managing 10 patients with refractory, skull base osteomyelitis [9]. By combining antibiotics and surgical debridement with $HBO_2$ therapy, Sandler was able to achieve infection clearance in 80% of

these previously refractory patients. The two patients who failed to clear their refractory skull base infections (after receiving only two and five $HBO_2$ treatments, respectively) were notable for having refused further therapy and ultimately succumbed to their disease.

In the most recent of these retrospective series, Yu *et al.* compared treatment outcomes in 12 patients: six $HBO_2$-treated and six case-matched controls, all of whom developed sternal osteomyelitis after undergoing median sternotomy for cardiothoracic procedures [10]. While all of the patients received primary treatment with antibiotics and indicated surgical debridement, six patients additionally received $HBO_2$ treatment. Although total debridements required and hospital length of stay did not differ between groups, the six patients who additionally received $HBO_2$ therapy logged significant decreases in length of ICU stay ($8.7 \pm 2.7$ *vs.* $48.8 \pm 10.5$ days, $p<0.05$); shortened duration of mechanical ventilation ($4 \pm 1.5$ *vs.* $34.8 \pm 8.3$ days, $p<0.05$) or positive pressure support ($4 \pm 1.9$ *vs.* $22.3 \pm 6.2$ days, $p<0.05$); and overall reduced mortality (0 *vs.* 3 cases, $p<0.05$).

**Addendum summary**

This supplemental review of osteomyelitis literature not previously incorporated into the UHMS *Hyperbaric Oxygen Therapy Indications*, 12th Edition, Refractory Osteomyelitis chapter serves to bolster that chapter's previous American Heart Association (AHA) class recommendations for $HBO_2$ treatment of osteomyelitis. More specifically, while no new prospective human trials examining osteomyelitis were identified, a recent animal study helps confirm that $HBO_2$ therapy should be considered an AHA Class III intervention (*i.e.*, not recommended) when used without concurrent antibiotic and indicated surgical treatment to manage long bone osteomyelitis (see Table III, Page 764).

In contrast, two added retrospective human studies substantiate $HBO_2$ therapy's benefit as an adjunct to antibiotics and surgical debridement in treating refractory osteomyelitis of the long bones (*i.e.*, an AHA IIa intervention): a finding that is similarly congruous with the prior chapter's Table III recommendations.

Finally, the three retrospective series addressing refractory osteomyelitis of the central neuraxis and/or sternum each lend support to the chapter's prior recommendation that adjunctive $HBO_2$ therapy should be considered an AHA IIa intervention in treating patients at high risk for significant osteomyelitis-related morbidity and mortality

## REFERENCES

**REFERENCES**

1. Gesell, L.B., ed. Hyperbaric Oxygen Therapy Indications. 12th ed. The Hyperbaric Oxygen Therapy Committee Report. 2008, Undersea and Hyperbaric Medical Society: Durham. 220.

2. Shandley, S., et al. Hyperbaric oxygen therapy in a mouse model of implant-associated osteomyelitis. J Orthop Res, 2012. 30(2): p.203-8.

3. Hamblen, D.L. Hyperbaric oxygenation. Its effect on experimental staphylococcal osteomyelitis in rats. J Bone Joint Surg Am, 1968. 50(6): p.1129-41.

4. Mader, J.T., et al. Hyperbaric oxygen as adjunctive therapy for osteomyelitis. Infect Dis Clin North Am, 1990. 4(3): p.433-40.

5. Mendel, V., H.J. Simanowski, and H. Scholz. Synergy of HBO2 and a local antibiotic carrier for experimental osteomyelitis due to Staphylococcus aureus in rats. Undersea Hyperb Med, 2004. 31(4): p.407-16.

6. Chen, C.Y., et al. Adjuvant hyperbaric oxygen therapy in the treatment of hemodialysis patients with chronic osteomyelitis. Ren Fail, 2008. 30(2): p.233-7.

7. Roje, Z., et al. Influence of adjuvant hyperbaric oxygen therapy on short-term complications during surgical reconstruction of upper and lower extremity war injuries: retrospective cohort study. Croat Med J, 2008. 49(2): p.224-32.

8. Ahmed, R., M.A. Severson, and V.C. Traynelis. Role of hyperbaric oxygen therapy in the treatment of bacterial spinal osteomyelitis. J Neurosurg Spine, 2009. 10(1): p.16-20.

9. Sandner, A., et al. [Value of hyperbaric oxygen in the treatment of advanced skull base osteomyelitis]. Laryngorhinootologie, 2009. 88(10): p.641-6.

10. Yu, W.K., et al. Hyperbaric oxygen therapy as an adjunctive treatment for sternal infection and osteomyelitis after sternotomy and cardiothoracic surgery. J Cardiothorac Surg, 2011. 6: p.141.