Die Hyperbare Sauerstofftherapie

Adjuvant zur Behandlung von

Infektionen

in den Druckkammerzentren des

Verbandes Deutscher Druckkammerzentren e.V.

Verband Deutscher
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Zusammenstellung von Informationen
für Ärzte und Patienten

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Einführung

Durch seine direkte Wirkung auf Bakterien, Verbesserung der zellulären Abwehrmechanismen des Körpers und synergistische Effekte auf die Wirkung von Antibiotika ist die HBO in Kombination mit Chirurgie und Antibiotika als adjuvante Therapie extrem nützlich bei der Behandlung von Gewebsinfektionen sowohl mit anaeroben als auch aeroben Bakterien in hypoxischen Wunden und Geweben. Ihre Nützlichkeit wurde klar belegt mit einer großen Zahl von in vitro und in vivo experimenteller Forschung und im Weiteren bestätigt durch extensive klinische Serien. Der Vorteil, den die HBO im Breich infektiöser Erkrankungen bewirkt ist vor allem auf die adaequate Wiederherstellung normaler oder übernormaler Sauerstoffpartialdrücke in hypoxischen infizierten Geweben zurückzuführen (Mathieu 96).

Die Verabreichung von erhöhten Sauerstofffraktionen (normobar) bei der Anaesthesie zur Infektionsprophylaxe wird zunehmend in der Chirurgie, speziell der Bauchchirurgie eingesetzt.

Bereits 1961 berichteten Brummelkamp & Boerema über die erste erfolgreiche Behandlung eines Gasbrandes beim Menschen mit HBO als Adjuvans. Einige Jahre später erkannte man die chronische Osteomyelitis als Indikation für die HBO bei Infektionen an (Slack et al. 65). (Evidenzklasse II (1a beim diabetischen Fuß)). In den letzten Jahrzenten wurden sehr viele experimentelle und klinische Forschungsergebnisse über die Effekte von Sauerstoff im Überdruck auf Bakterien, die körpereigenen Infektabwehrmechanismen und die Heilungsprozesse veröffentlicht.

Hyperbarer Sauerstoff (HBO) wird weltweit bei einem Evidenzgrad 1a zur adjuvanten Behandlung des Gasbrandes eingesetzt. Auch der deutsche gemeinsame Bundesausschuss (g.BA) hat den hohen Evidenzgrad bestätigt und den Einsatz bei clostridialen Weichteilinfektionen zu Lasten der gesetzlichen Krankenkassen zugelassen.

Bei weiteren Infektionen wird die HBO weltweit auf Basis von Studien eingesetzt. Der Evidenzgrad der klinischen Studien ist dabei unterschiedlich und zum Teil schwach. Häufig sind Studien nicht möglich gewesen weil Rekrutierungsprobleme bestehen oder weil eine Randomisierung bei den oft kritisch Kranken nicht machbar war. Das Fehlen von Studien mit hohem Evidenzgrad bedeutet jedoch nicht, dass die HBO in diesem Einsatzgebiet „unwirksam“ ist. Es fehlt jedoch für einen Teil der Infektionen der belastbare Wirksamkeitsnachweis.

Die Rationale für den Einsatz der HBO bei ausgewählten infektiösen Prozessen ist durch zahlreiche in Vitro und experimentelle Studien sicher belegt. Damit rechtfertigt sich der adjuvante Einsatz der HBO insbesondere bei sonst therapieresistenten Infektionen.

Hemmende Sauerstoffenwirkung auf Bakterien:

fakultative Anaerobier: **strikt anaerobe Bakterien:**

Enterobakteriaceae
Enterococcus faecalis
Escherichia coli
Pseudonomas aeruginosa
Proteus vulgaris
Salmonella typhi, et murium
Staphylocokken, Staph. Albus

aerotolerante Anaerobier:
Enterocokken
Streptokokken

Weitere:
Klebsiella pneumoniae

***Bacteroides** fragilis, et oralis*
***Clostridien**: bifermentans; perfringens; haemolitycum haemolitycum; histolyticum novyi*; *septicum*; *tetani*
Fusobakterium, et necrophorum
Melaninogenica
Nucleatum
Peptostreptococcus
Peptokokkus Magnus
Prevotella

Wirksamkeitssteigerung von Antibiotika

Aminoglykside	**Fluoroquinolone**	
Amikacin	Ciprofloxacin	Nitrofurantoin
Gentamycin	Norfloxacin	Sulfisoxazol
Kanamycin	Ofloxacin	Sulfamethoxazol mit Trimethoprim
Tobramycin		Vancomycin

- Die Steigerung des Sauerstoffpartialdruckes in ischemischen Geweben verbessert die Wirkung von Antibiotika wie Aminoglykoside, einiger Sulfonamide, der Fluorquinolone, von Vancomycin und Trimethoprim,
- Die Hemmung einiger Reaktionen im Rahmen der bakteriellen Biosynthese wie die Verstärkung von Sulfonamiden und Verlängerung der postantibiotischen Effekte von Aminoglykosiden bei von Pseudomonas verursachten Infektionen.
- Die Veränderung des Redoxpotentials von Bakterien kombiniert mit einer Vermehrung von reaktiven Zwischenprodukten wie Nitrofurantoin und geminderter Wirkung von antimikrobiellen Stoffen wie Metronidazol das ein niedriges Redoxpotential braucht.

Effekte des gesteigerten Partialdruckes von Sauerstoff auf Bakterien

Nach: D, Mathieu F. Wattel: PHYSIOLOGIC EFFECTS OF HYPERBARIC OXYGEN ON MICROORGANISMS AND HOST DEFENCES AGAINST INFECTION Chapter 1.6, Mathieu Hrsg: Handbook on Hyperbaric Medicine Springer 2006 Übersetzt Ch.Heiden.

Empfindlichkeit von Bakterien gegenüber Sauerstoff

Bakterien können in Abhängigkeit ihrer Toleranz von Sauerstoff in folgende Gruppen eingeteilt werden (Avril et al. 92; Finegold et al. 77; Chavatte et al. 90; Finegold 95; Rimbault et al. 00):

1. ***strikt aerobe Bakterien***
   Ihr Wachstum ist absolut von Verfügbarkeit von molekularem Sauerstoff abhängig, weil dieser letztendlich den obligaten Elektronenrezeptor darstellt.

2. ***Mikroaerophile:***
   Sie können Sauerstoff verwerten, gedeihen aber am besten bei Sauerstoff-konzentrationen, die geringer sind als in Luft.

3. ***Aero-Anaerobier oder fakultativ Anaerobier:***
   Die mit und ohne Sauerstoff leben können weil sich ihr Stoffwechsel sowohl auf Atmung als auch auf Fermentationsprozesse stützen kann. *(Staphylocokken* und *Enterobakteriaceae)*

4. ***aerotolerante Anaerobier:***
   die sich auch in Gegenwart von molekularem Sauerstoffthose entwickeln können, sich aber besser ohne Sauerstoff vermehren. *(Streptocokken* und *Enterocokken)*

5. ***strikt anaerobe Bakterien mit anoxybiotischem Stoffwechsel:***
   für die molekularer Sauerstoff tödlich ist. Diese Bakterien nutzen Fermen-tationsprozesse zur Energiegewinnung (der finale Electronenen-Akzeptor ist organisch oder mineralisch aber nicht Sauerstoff). Die meisten von ihnen haben keines der üblichen Enzyme der Atmung wie z.B. Superoxid Dismutase, Katalase oder Peroxidase. Die toxischen Effekte des molekularen Sauerstoffs sind unterschiedlich:
   Einige Bakterien sind extrem empfindlich gegen Sauerstoff (EOS) und sterben nach kurzer Exposition. Sie tolerieren nur Sauerstoffkonzentrationen von weniger als 0,1%. EOS Bakterien, die beim Menschen untersucht wurden, leben symbiotisch im Verdauungstrakt und auf der Haut und scheinen keine pathogene Wirkung zu entfachen.
   Andere strikt anaerobe Bakterien können sich nicht bei Sauerstoffkonzen-trationen über 0,5% entwickeln. *(C. haemolyticum)*
   Die meisten der an Infektionen beteiligten anaeroben Bakterien sind moderat anaerob und tolerieren Sauerstoffkonzentrationen bis 5%. Dazu gehören *B. fragilis, C. novy, P. malaninogenika*, *Peptostreptococcus*, (Finegold 77 + 95, Lösche 69)
   Im Gegensatz dazu können sich andere Anaerobier auch in Luft, aber nur in kleinen

Kolonieen entwickeln. (Avril et al. 92; Rimbault et al. 2000)

Tabelle 1 In vitro Sauerstoffverträglichkeit strict anaerober Bakterien (Loesche 69)

Sauerstoffdruck in mmHg	0	1	2	3.5	5	8	15	20	30	45	60	75	90
Bakterium													
Clostridium haemolitycum	++	++	++	++	+	0	0						
Peptostreptococcus	++	++	++	++	++	++	+	0	0				
Clostridium novyi	++	++	++	++	++	++	+	0	0				
Bacteroides oralis	++	++	++	++	++	++	++	++	+,V	+,V	0	0	
Prevotella Melaninogenica	++	++	++	++	++	++	++	++, V	++ V	+,V	+ v	0	0
Fusobacterium Nucleatum	++	++	++	++	++	++	++	++	++	++	+,V	0	0
Bacteroides fragilis	++	++	++	++	++	++	++	++	++	++	+,V	0	0

++ : normale Entwicklung
+ : Entwicklung verlangsamt
V : Entwicklung variiert strain or incubation duration
0 : kein Wachstum

Effekte von erhöhtem Sauerstoffpartialdruck auf Entwicklung und Vitalität von Bakterien

Diese Effekte wurden in Vitro und in Vivo an experimentellen Bakterienmodellen studiert

In Vitro

Partialdrücke von Sauerstoff über 4 mmHg sind für strikte Anaerobier schnell letal. Der Sauerstoffpartialdruck in Luft bei Normaldruck (20% Sauerstoff, PO_2 bei 152 mmHg) ist für *Peptokokkus Magnus* nach 2 Stunden, für *Bakteroides fragilis* nach 5 Stunden und für *Clostridium perfringens* nach 10 Std. letal. (Walden et al. 75)

HBO hat bakteriostatische und auch bakteriozide Wirkung auf *Clostridien*. Der inhibierende oder letale Effekt hängt dabei vom Bakterienstamm, dem bakteriellen Reproduktionscyclus (Entwicklungsphase), Sauerstoffdruck, Expositionszeit und vom Kulturmedium ab. Ruhende Sporen von Clostridium perfringens sind nicht empfindlich für Sauerstofftoxicität. In vitro ist HBO baktericid auf *Clostridium perfringens, C. novyi, C. histolyticum* und *C. tetani*, wogegen *C. bifermentans* und *C. septicum* widerstandsfähiger sind (Hill et al 72). Blut und Gewebereste mindern die Wirksamkeit von Sauerstoff, weil die dort gebildete Katalase die autodestruktiven Peroxide zerstört, die in sauerstoffreicher Atmosphäre von Clostridien produziert werden. (Hill et al 72; Finegold 77; Kaye 67).

Einer der größten Vorzüge von HBO ist ihre Hemmung der Toxinbildung, die ab Sauerstoffpartialdrücken von 80 mmHg eintritt. (Fredette 65; van Unnike 65). Während HBO die Wirkung von einigen Toxinen stoppt, wie z.B. bei Theta Toxinen hat HBO jedoch keine Wirkung auf bereits produzierte alpha Toxine (Hill 72).

Fakultative Anaerobier und Aerobier überleben im hyperoxischen Milieu (P02 unter 760 mmHg). Eine 24stündige Exposition bei 3 ATA 100% 02 hat jedoch bactericide Wirkung auf *Pseudonomas aeruginosa, Proteus vulgaris* und *Salmonella typhi* (Bomside et al. 75)
Hohe Sauerstoffpartialdrücke können die Entwicklung fakultativer Anaerobier oder strikten Areobiern hindern oder fördern. Aerobier antworten auf die Steigerung des Sauerstoffpartialdruckes in 2 Phasen. Bis zu einem Druck von 1,5 ATA 100% 02, werden sie stimuliert und bei Drücken oberhalb inhibiert (Park et al. 92 + 99). Bei Drücken zwischen 1,5 und 3 ATA wurde ein bakteriostatischer Effekt auf *E. coli* (Mathis et al. 76 Muhvic 89), wie auch auf viele *Enterobacterien*, *Pseudonomas aeruginosa* and *Enterococcus faecalis* (Park 62) gesehen. Der bakteriostatische Effekt wurde bei kurzen Expositionen in achtstündigen Intervallen gesehen. (Brown et al 79)

.

In vivo

Der größte Teil der experimentellen Forschung zur Wirkung der HBO bei Infektionen bezieht sich auf Infekte mit Anaerobiern. Bereits 1972 wies Holland die Wirksamkeit der HBO in einer randomisierten Studie an einem Modell mit *Clostridieninfektion* bei Mäusen nach.(Holland et al. 75). Demello erreichte im Vergleich von chirurgischem Debridement, Antibiotika und HBO (100 % 02, 3 ATA über 2 Stunden am 1. Tag 3 Sitzungen, am 2. Tag 2x und 1x am dritten Tag) in einem Tiermodell für Gasbrand an Hunden (*Clostridium perfringens)* die besten Überlebensraten wenn alle drei Komponenten kombiniert wurden (Demello et al. 73). Hill & Osterhout haben die Wirksamkeit der HBO an zwei Modellen mit Mäusen nachgewiesen (implantierbare Scheiben, Injection von *Clostridium perfringens*) (Hill et al. 72). Spätere Studien zeigten, dass die Effektivität der HBO gesteigert wird, wenn der zeitliche Abstand zwischen Inokulierung und Anwendung der HBO verringert wird. HBO zeigte sich auch gegen intrahepatische Mikroabszesse bei Mäusen mit *Bacteroides fragilis* und *Fusobacterium necrophorum* wirksam. Letztere waren empfindlicher (Hill 76).

1986 zeigte Thom die Nützlichkeit der HBO bei Peritonitismodellen an Ratten, die durch Iokulierung von Kombinationen mit *E. coli, Enterocokken*, *Bacteriodes fragilis oder fetaler flora* erzeugt wurde (Thom et a. 86). An Inokulationen von *E. coli* und *Bacteriodes fragilis* am gleichen Peritonitismodell mit Ratten zeigten Muhvich et al.(88) die Effektivität der Kombination von HBO, Chirurgie und Antibiotika. In jüngerer Zeit bestätigten Stevens et al. (93) und Hirn et al. (92) den additiven Effekt der Dreierkombination HBO, Chirurgie und Antibiotika.

Wenn es auch keine kontrollierten Studien dafür gibt, wurde die Effektivität der adjuvanten HBO bei anaeroben Weichteilinfektionen in Kombination mit antibiotischer Behandlung und Chirurgie klinisch von einer großen Zahl von Forschungsgruppen in den letzten 30 Jahren bestätigt (Mathieu et al 94).

Bakteriocide Aktivität und Bakteriostasis: Mechanismen der Wirkung

Molekularer Sauerstoff ist relativ inert. Er kann aber mit organischen Mole-külen reagieren. Das kann zur Produktion von hochreaktiven Zwischen-produkten führen: freie Radikale oder ROS (reaktive Sauerstoff Species) (ROS) (Debry et al. 91; Fridovich 98). Die Entwicklung und Akkumulierung von freien Radikalen sind für die bakteriociden und bakteriostatischen Effekte bei steigendem Sauerstoffpartialdruck verantwortlich. Es ist allgemein anerkannt, dass Bakterien ohne Abwehrmechanismen gegen freie Radikale empfindlicher auf steigende Sauerstoffpartialdrücke reagieren (Chavatte et al.90; Park et al. 92)

.

Freie Radicale sind Moleküle mit einem oder mehreren freie Elektronen. Sauerstoffmoleküle haben 2 freie Elektronen auf zwei unterschiedlichen Orbitalen, die aber parallel kreisen. Um mit anderen Molekülen zu reagieren und Elektronen aufzunehmen (Oxidation), müssen diese gegenläufig kreisen – darum sind Sauerstoffmoleküle nicht besonders reaktionsfreudig. Wenn aber Sauerstoffmoleküle nur ein Elektron aufnehmen entseht ein Sauerstoffradikal (O_2') (Fridovich 98):

$$O_2 + e^- \quad O_2'$$

Superoxid Radikale werden meistens während Redox Reaktionen in Mitochondrien gebildet. Die produzierte Menge von O_2' steigt proportional mit der Konzentration von Sauerstoff. Im wässrigen Medium wandelt sich O_2' in Hydrogen-peroxid (H_2O_2) durch eine Dismutation-Reaktion:

$$2\ O_2' + 2\ H^+ \text{—>}\ H_2O_2 + O_2$$

Hydrogen-peroxid wird nicht als ein freies Radikal angesehehn, weil e skein freies Elektron hat. Hydrogen-peroxide passiert aber leicht Membranen währen Radikale wie O_2' aufgeladen warden und deshalb nicht passieren. Die zerstörerische Kraft des Hydrogen-peroxids beruht daher auf seiner hohen durchdringungsfähigkeit. Es wird reaktiv wenn es mit Metallionen wie Eisen oder Kupfer in Kontakt kommt. Diese Reaktion führt zu hoch reaktiven Hydroxylradikalen (OH') (Fenton's Reaktion):

$$Fe2+ + H_2O_2 \text{--->}\ Fe3+ + O2' + OH$$

Weder das Superoxid-Radikal Anion noch das Hydrogen-peroxid sind für sich speziell zytotoxische. Beide können aber Hydroxylradicale erzeugen die potentiell hochgefährlich sein können. Hydroxylradicale reagieren sehr schnellmit vielen Molekülen wie z.B. DNS, Proteinen, und Karbohydraten. Es zerstört daz Lipide in Membranen durch eine Kettenreaktion, der Lipidperoxydation. Freie Radikale können durch ihre Einwirkung auf Zellmembranen die Produktion von sekundären Botenstoffen fördern wie Diacylglycerol oder phosphatische Säure.

Empfindlichkeit von Bakterien auf Sauerstoff: Abwehrmechanismen

Die Sauerstofftoleranz von Bakterien hängt von deren Abwehrmöglichkeiten für freie Radikale ab: Superoxid-dismutase, Katalase, Glutathion-peroxidase und NADH-oxidase sind die hauptsächlich beteiligten Enzyme (Chavatte et al. 90; Fridovich 98).

Die Superoxid Dismutase (SOD) ist die wichtigste Abwehr von freien Radikalen der Bakterien. Dieses Enzym katalysiert die Dismutationereaktion die das Superoxid eliminiert and in Hydrogen peroxide umwandelt das weniger toxisch ist:

$$2\ O_2' + 2\ H^+ \dashrightarrow H_2O_2 + O_2$$

Alle SODs sind Proteine mit Metallen. MnSOD (Mangan - SOD) ist in den Mitochondrien zu finden, wogegen Cu & ZnSOD (Kupfer und Zink- SOD) im Zytoplasma vorkommt. Sie zerstören die in den Zellen produzierten freien Radikale weil Sauerstoff in der Regel biologische Membranen nicht passiert. Es gibt auch extracelluläre Formen von Cu & ZnSOD (Chavatte et al. 90; Fridovich 98). Hydrogenperoxid (H202) wird von den Enzamen Katalase und Glutathionperoxidase eliminiert. Glutathionperoxidase braucht reduziertes Glutathion und Selen. Sie induuieren die Auflösung von Hydrogenperoxid in Wasser und molekularen Sauerstoff, und vermeiden so die erneute Produktion von Sauerstoffradikalen:

$$2\ H_2O_2 \Rightarrow 2\ H_2O + O_2$$

Alle aeroben Organismen mit Zytochromsystemen besitzen Superoxidedismutase und Katalase. Strikte Anaerobier haben dagegen keine Superoxidedismutase und gewöhnlich keine Katalase. Aerotolerante Anaerobier haben keine Katalase aber haben SOD. Einige Autoren (Mc Cord et al 71) sehen in dem Mangel an SOD den Hauptgrund warum Anaeronier Luft nicht tolerieren können. Man hat jedoch enzymatische Aktivität in einer Anzahl von strikten Anaerobiern gesehen. In einer Studie an 22 Stämmen pathogener Anaerobier konnten Tally et al. 77 eine Korrelation zwischen Aerotoleranz und SOD-Spiegeln sehen. Diese können einen Faktor für Virulenz darstellen, weil er den Anaerobiern ermöglicht in oxygenierten Geweben zu überleben, bis für sie günstigere Bedingungen ihnen die weitere Entwicklung erlauben. (Chavatte et al. 90). Die meisten Bakteroides haben Superoxidedismutase die für deren Aerotoleranz verantwortlich ist.

Einige Bakterien, wie etwa *Lactobacillus plantarum* (Gregory et al. 74) haben jedoch keinerlei SOD, Katalase oder Peroxidase, und tolerieren dennoch Luft. Archibald & Fridovich haben zeigen können, wie intrazelluläres Magnesium das Superoxidradikalanion fangen kann und somit das Fehlen der Enzyme zur Entgiftung der Sauerstoffreduktionsderivate kompensiert. (Archibald et al 81). NADH-oxydase wandelt NADH in NAD. Mit Wasserstoff und Sauerstoff entsteht Wasser

$$4\ NADH + O_2 \Rightarrow 4\ NAD + H_2O$$

Effekte des Sauerstoffpartialdruckes auf Abwehrmechanismen des Wirtes

Konfrontiert mit einer Infektion antwortet der Körper abgesehen von den zuvor beschriebenen direkten Wirkungen des Sauerstoffs auf zwei Wegen: einer richtet sich spezifisch direkt gegen den angreifenden Mikroorganismus durch Aktivierung des Immunsystems. Der andere Weg basiert auf der Entzündungsreaktion und deren Folgen. HBO ermöglicht es durch die Wiederherstellung einer adäquaten Gewebeoxygeniereung den Abwehrmechanismen sich zu erholen und ihre Wirksamkeit wieder zu erlangen (Mathieu et al. 90). Das Eindringen von Bakterien in den Körper induziert eine Entzündungsreaktion mit Infektionsherden in denen zelluläre und humorale Reaktionen das infektiöse Agens beseitigen.

Phagozytose

Die Funktion der Phagozyten, speziell die der polymorphkernigen Leukozyten, und die der Makrophagen ist es die Mikroorganismen aufzunehmen, sie zu zerstören und zu verdauen. Zu Beginn werden die Akterien an die Phagozyten angeheftet. Die Phagozyten umfassen die Bakterien dann mit Pseudopoden und nehmen sie in sich auf durch Invagination mit einer Cytoplasmamembran. Es entwickelt sich eine Blase in der Zelle, die das Bakterium enthält: das Phagosom. Die Phagozytose steigert den Sauerstoffverbrauch der Phagozyten auf mehr als das dreißigfache des normalen Verbrauchs, was als Oxidative Burst bezeichnet wird. Die NAPDH Produktion durch den Hexose – Monophosphate -Shunt steigt sehr an. Die NADPH - Oxidase dringt in die Phagosome ein. NADPH - Oxidase reduziert in den Phagosomen moleculären Sauerstoff zu uperoxidradikalen. SOD wandelt diese Superoxidionen in hochgradig bacterizides H202 um, das wiederum von Catalase, Myeloperoxidase oder Glutathionperoxidase entgiftet wird. Das wichtigste System in Polymorphkernigen ist die Myeloperoxidase, die hochgradig bakterizides Hypochlorit produziert (ClO^-) (Allen 94; Klempner et al. 92). Mit erhöhtem Sauerstoffverbrauch (Oxidative burst), verschmelzen Phagolysosome und der Inhalt der Lysosome ergießt sich in die Phagosome. Die Verschmelzung beginnt mit den primären Granula, die große Mengen von Myeloperoxidase enthalten. Die sekundären Granula verschmelzen dann, um das Verdauungsstadium zu vervollständigen. Dabei werden die Bakterienbestandteile durch Exocytose eliminiert. Die Antigene der Bakterien warden dabei freigesetzt wodurch sie für die immunkompetenten Zellen des Immunsystems verfügbar werden (spezifishe Immunantwort) (Allen 94; Klempner et al. 92).

Hypoxie und Infektion

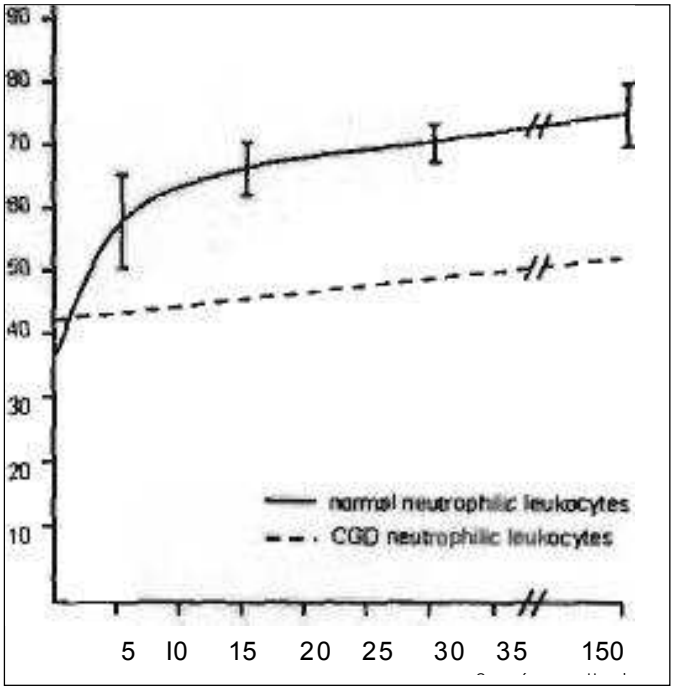
Es ist schon lange bekannt, dass ischemische Wunden Gewebe besonder anfällig für Infektionen sind. Die Abnahme der lokalen Perfusion und die damit reduzierte Sauerstoffzufuhr haben zur Folge, dass sich die Entzündungs-vorgänge mit Einwanderung von polymorphkernigen Leukozyten und den Mediatoren aus dem Plasma nicht normal entfalten können. Hypoxie ist der bedeutenste Faktor für die Unfähigkeit des Körpers Bakterien zu zerstören (Rabkin et al. 88). Seit den Arbeiten von Silver ist bekannt, dass der Sauerstoffdruck im Zentrum von Infektionsherden beträchtlich vermindert ist und auch nur 3 mmHg betragen kann. Diese Hypoxie resultiert sowohl aus der verminderten Sauerstoffzufuhr aufgrund der verminderten Perfusion als auch dem gesteigerten Sauerstoffverbrauch durch die Entzündungsvorgänge nach bakterieller Invasion (Silver 84).

Folgen der Hypoxie für die mikrobiocidale Aktivität von Polymorphkernigen

Experimentelle Untersuchungen in vitro und in vivo haben den schädigenden Effekt der Hypoxie auf die Phagozytose nachgewiesen. Bereits 1976 haben Hohn et al. die bakterizide Wirkung von Sauerstoffdrücken zwischen 0 und 150 mmHg auf Kulturen von Staphylococcus aureus zusammen mit normalen menschlichen polymorphkernigen Leukozyten. and und solchen von Kindern mit chron. granulomatöser Erkrankung (CGE) untersucht. Sie beobachteten, das der bakterizide Effekt auf normale polymorphkernige Leukozyten abnahm, wenn der Sauerstoffdruck unter 30 mmHg auf 50% abfiel .Bei Druck von ca 0 mmHg ereichte er Werte wie von CGE Leukozyten. (ABB. 1.6-1). Die Abnahme der bakteriziden Leistung der hypoxischen Leukozyten war mit der wiederherstellung normaler Oxygenationswerte reversible nicht aber die Leukozyten von CGE-Kranken. Hypoxie, die einem Substratmangel in Bezug auf das Oxydative Burst Phänomen entspricht, hat die gleiche Konsequenz für das NADPH-Oxidase Enzymedefizit (i.e. CGE Leidende) (Holm et al. 76). In einem hypoxischen Milieu haben andere Autoren die Abnahme der bakteriziden Leistung von Polymorphkernigen gegenüber einer Reihe von Bakterien gefunden, die üblicher Weise in Wunden und Abszessen vorkommen wie*: Proteus vulgaris, Salmonella typhi murium, Klebsiella pneumoniae, Staphylococcus albus, Pseudomonas aeruginosa, Escherichia coli, etc.* (Mc Ripley et al. 67; Mnadell 74; Selvaraj et al. 66). Danach ist die Bildung freier Radikale durch polymorphkernige Leukozyten im anaeroben Milieu m 90% reduziert. Anaerobe Bedingungen verhindern den oxidativen burst ***in vitro***.

In vivo wurde das Ausmaß der Abnahme der bakteriziden Potenz der polymorphkernigen Leukozyten unter hypoxischen Bedingungen an einem experimentellen Hundemodell gezeigt bei denen Haut- und Haut-Muskel-Lappen mit Staphylococcus aureus inokuliert wurden (Chang et al. 82; Gottrup et al. 83). Diese Arbeiten haben klar gezeigt, wie sich infektiöse Nekrosen in Bereichen mit weniger als 30 – 40 mmHg Sauerstoffdruck entwickelten. Radioaktive Markierung zeigte das die Leukozyten weiterhin wanderten. Ihre bakterizide Aktivität war aber gemindert. Hams hat gezeigt wie die bakterizide Aktivität gegen *Staphylococcus aureus, Escherichia coli und Klebsiella pneumoniae* in hypoxischen Mäuselungen abnahm (Hams et al. 77).

ABB. 1.6-1. Wirkung unterschiedlicher Sauerstoffdrücke auf Polymorphkernige gesunder Patienten und solcher von Patienten mit chronischer granulomatöser Erkrankung bei *Staphylococcen*



Effekte der HBO auf die Abwehrmechanismen des Körpers

Hamblen führte 1968 die erste Studie über die Wirkung von HBO bei Osteomyelitis bei Ratten durch. An einem Kaninchenmodell für Osteomyelitis zeigten Mader et al. 1980 wie HBO (100% O_2 bei 2 ATA) die Aktivität der Polymorphkernigen gegen *Staphylokokken* steigerte und wie intramedullär der PO2 von 20 mmHg bei Normoxie auf 104 mmHg bei 2 ATA anstieg. In einer in vitro Studie zur gleichen Zeit steigerte sich die Aktivität der Polymorphkernigen gegenüber Staphylococcus aureus bei Steigerung des Sauerstoffpartialdruckes von 45 auf 150 mmHg von 44% auf 71%. Der Sauerstoffpartialdruck im osteomyelitischen Knochen und in vitro vor HBO hatte den bakteriziden Effekt der Polymorphkernigen in größerem Umfang behindert als die Entwicklung der *Staphylococcus aureus* selber. Das zeigt den Einfluss der HBO auf die Abwehrmechanismen des Körpers sehr deutlich. Wir können daher daraus schließen, dass der bakterizide Effekt der HBO auf der Wiederherstellung des Sauerstoffdruckes zurückzuführen ist, wie er für den oxydativen Burst erforderlich ist.

Mit einem Kaninchenmodell mit subkutanen Infektionen zeigte Hunt (ABB. 1.6-2) dass die bakterizide Wirkung bei Tieren in hyperoxischem Milieu (40 – 45% O_2) größer ist als bei Tieren in Hypoxie (12 – 14% O_2) indem er die Bakterien-zahl im Wundexsudat bestimmte.(Rabkin et al. 88; Hunt et al. 75; Knighton et al. 84). In gleicher Weise konnte Knighton in einem Modell für Hautinfektionen bei Guinea Schweinen in unterschiedlichen Sauerstoffdrücken zeigen, dass nach 24 und 48 Stunden der Durchmesser der infektiösen Nekrosen bei Tieren in Hyperoxie im Vergleich zu

solchen in Hypoxie abnahm. (Hyperoxie: 45% O_2; Mormoxie: 21% O_2; Hypoxie: 12% O_2)(Knighton et al. 86).

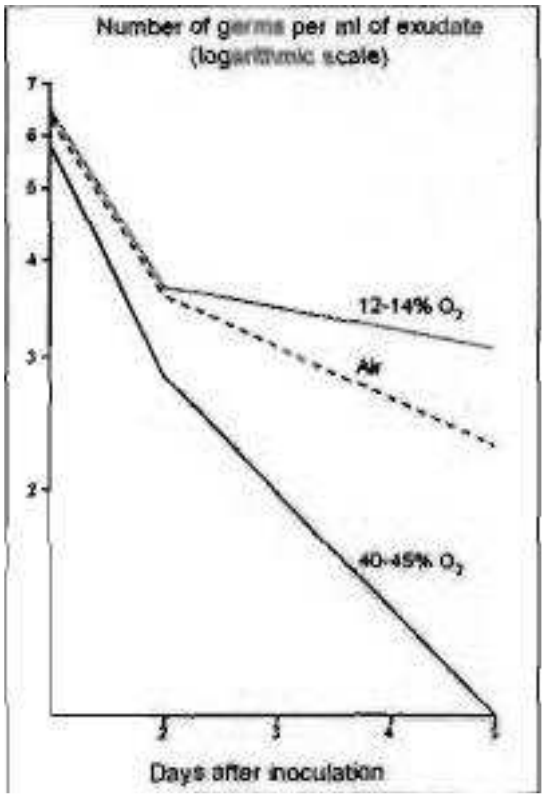


ABB 1.6-2. Wirkung von Sauerstoff auf die Anzahl von Bakterien im Wundexsudat experimenteller Wunden an Kaninchen (Muhvich et al. 89)

Im Gegensatz zu diesen Studien mit Nachweis der Nützlichkeit der HBO in der Bekämpfung von Infektionen in hypoxischen Geweben kann eine ausgedehnte Exposition in hohen Drücken von Sauerstoff auch schädigende Einwirkung auf die Funktion der Polymorphkernigen und Makrophagen zur Folge haben. Bei Guinea Schweinen führte die ausgedehnte Exposition in Hyperoxie (85 % O_2, 90 Stunden) eine Abnahme der Anheftung, Chemotaxis, Phagozytose und bakteriziden Aktivität der Polymorphkernigen Leukozyten (Rister 82). In einer jüngeren Studie mit 10 gesunden Probanden in HBO über 136 min. bei 1.8 ATA beobachtete Labrouche eine Änderung der Funktion der Polymorphkernigen mit einer Minderung der Chemotaxis und der Chemokinese bei einer Steigerung des oxidativen Bursts.und der Phagozytose (Labrouche et al. 99).

Effekt von Sauerstoff auf die Aktivität von Makrophagen

Anaerobiose reduziert die phagozytotische Aktivität peritonealer Makrophagen nicht. Verlängerte Exposition in vitro (über 24 Std.) in Hyperoxie oder in HBO induziert in Makrophagen eine Abnahme der Phagozytoseleistung, der bakteriziden Aktivität, der zellulären Mobilität und der DNS Synthese (Suttorp et al. 83). Diese Änderungen könnten auf Veränerung der Oxidierungsleistung beruhen, da die Aktivität der NADPH Oxidase und die Produktion von O_2' vermindert sind. Kurze Expositionen (2 Std.) HBO (100 % O_2, 2 bis 3 ATA) ändert die Phagozytenaktivität in Makrophagen der Milz von Mäusen nicht (Park 99).

Die Lebensfähigkeit der Phagozyten wird durch kurze HBO-Exposition nicht verändert. In vivo Studien haben den schädlichen Effekt verlängerter Hyperoxiephasen (85 % 02, 90 Std.) auf alveoläre Makrophagen mit verminderter Chemotaxis, Adhesion, Phagocytose und bakterizider Akivität bestätigt. Das gilt insbesondere für die große Zahl von Atemwegsinfekten bei Patienten in HBO Therapie (Rister 82).

Effekte von Sauerstoff auf die Lymphozytenfunktion

Lymphozyten überleben gut in Hypoxie, wie auch in Hyperoxie. In menschlichen mit Phytohemagglutinin stimulierten Lymphozyten *in vitro* nimmt die RNSsynthese während 48 stündiger Anoxie ab (3 bis 9 % O_2) und hört danach auf. Gleichermaßen hemmt Hyperoxie (70 bis 100 % O_2 für mehr als 48 Std.) die DNSsynthese bei Lymphozyten. Hyperoxie hemmt die Bildung von B und T Lymphozyten (Dosis- und Zeitabhängiger Effekt) (Warren et al. 78). Nach einer Latenzperiode ist der Effekt reversibel. Eine Anzahl von Studien haben in vivo nachgewiesen, dass Hyperoxie und HBO eine Abnahme der DNSsynthese in B und T Lymphozyten auslösen. In den meisten Fällen geht die *in vivo* immunsuppressive Aktivität der HBO mit einer Abnahme der verzögert auftretenden Sensibilisierungsreaktionen und einer Lymphozytenproliferation einher (Gadd et al. 90; Hansbrough 80).

Wirksamkeitssteigerung von Antibiotika

In vitro Studien für minimale Hemmkonzentrationen (MIC) und minimale bakterizide Konzentrationen (MBC) für eine Reihe von Antibiotika und Sauerstoffkonzentrationen haben bereits eindeutig nachgewiesen, dass die Wirksamkeit von Antibiotika im anaeroben Milieu abnimmt. Im anaeroben Bereich ist die MIC für Aminoglycoside (Amikacin, Gentamycin, Kanamycin, Tobramycin) signifikant größer für *E. coli, Enterobacter, Klebsiellen, Salmonellen, Staphylococcen and Streptococcen sp* (Park et al. 92; Park et al. 99). Die Abnahme der Wirksamkeit von Aminoglykosiden in Hypoxie beruht auf einer Abnahme der sauerstoffabhängigen Penetration der Antibiotika durch die zytoplasmatische Membran. Darauf beruht auch die Unempfindlichkeit der Anaerobier gegen Aminoglycosiden, weil sie nicht den aeroben Stoffwechsel haben, der für den Sauerstofftransport durch die zytoplasmatische Membran erforderlich ist. Einige fakultative Anaerobier sind auf Aminoglykoside empfindlich bei Normoxie. Ihre Empfindlichkeit nimmt aber in Hypoxie, Anoxie und Azidose ab. (Park et al. 92; Park et al. 99). Die Wirksamkeitssteigerung der Aminoglykoside in Hyperoxie scheint vom Antibiotikum und dem Bakterienstamm abzuhängen. Die Wirksamkeitsabnahme für

Aminoglykoside in Anaerobiose und deren Normaliserung in normoxischem Milieu ist ein uneingeschränktes Phänomen (Hansbrough et al. 80).
Auch bei einer ganzen Anzahl anderer Antibiotika ist deren Wirksamkeit unter anaerobiotischen Bedingungen vermindert, wenngleich die zugrundeliegenden Wirkprinzipien noch nicht verstanden werden. Der bakteriostatische Effekt von Sulfamethoxazol mit Trimethoprim bei *E. coli, Klebsiella sp, Proteus sp und Staphylococcus sp* ist anaerob sehr stark reduziert (Virtanen 74). Die MIC und MBC von Vancomycin gegen *Staphylococcus aureus* ist bei Anaerobiose vierfach höher als in Normoxie (Norden et al. 83). Die bakterizide Wirkung der Fluoroquinolone wie Ciprofloxacin, Ofloxacin und Norfloxacin gegen *E. coli* mindert sich im Anaeroben. Ciprofloxacin behält dann aber seine bakteriostatishe Wirkung.
Im Gegensatz dazu ist die MIC von Cefazolin, Cefalotin, Chloramphenicol, Clindamycin, Moxalactam und Piperacillin für eine Reihe von gram-positiven und -negativen Bakterien unter anaeroben Bedingungen nicht verändert (Park 99).

Metronidazol wirkt am Besten in Anaerobiose und wirkt nicht in Aerobiose. Die Wirkung steigert sich mit Abnahme des Redoxpotentials.

Eine Serie von Studien haben bestätigt, dass Sauerstoffdrücke den postantibiotischen Effekt beeinflussen. Bayer et al. beobachteten 1989, dass bei einem PO_2 von 80mmHg anstelle von 40mm Hg, Amikacin einen besseren bakteriziden Effekt auf *Pseudonomas aeruginosa* hat und dessen postantibiotische Wirkung verdoppelt. Park et al. haben 1991 auch gezeigt, wie Hyperoxie den postantibiotischen Effekt von Tobramycin auf Pseudonomas aeruginosa verstärkt. HBO steigert die Bakteriostase von Sulfisoxazol bei *Pseudonomas aeruginosa* und steigert den bakteriostatischen Effekt von Sulfisoxazol und Trimethoprim auf *Corynebacterium diphteriae*. HBO verstärkt auch die Wirkung von Nitrofurantoin auf *E. coli* (Park et al. 92)

Diese *in vitro* ermittelten Daten wurden durch experimentelle Modelle *in vivo* bestätigt. In einem Kaninchenmodell für experimentelle Osteomyelitis zeigte sich die HBO (100 % 2 ATA 2 Std.-Sitzungen) in der Eliminierung von *Staphylococcus aureus* genau so wirksam wie Cefalotin (Mader et al. 89). Knighton et al. kamen 1986 zu ähnlichen Schlussfolgerungen: nach intradermaler Injektionvon *E. coli* nahmen die durch Infektion erzeugten Nekrosen bei Guinea Schweinen ab, wenn die Sauerstoffkonzentrationen von 12 auf 45% anstiegen. Sie beobachteten auch, dass Sauerstoff kombiniert mit Ampicillin besser wirkten als die Komponenten alleine (Knighton et al. 86).
(ABB 1.6-3).

Durchmesser der nekrotischen Läsionen in (in mm)

12% O2

.

12% O2 + Ampic

21% O2

.

21% O2 + Ampic

45% O2

45% O2 + Amic.

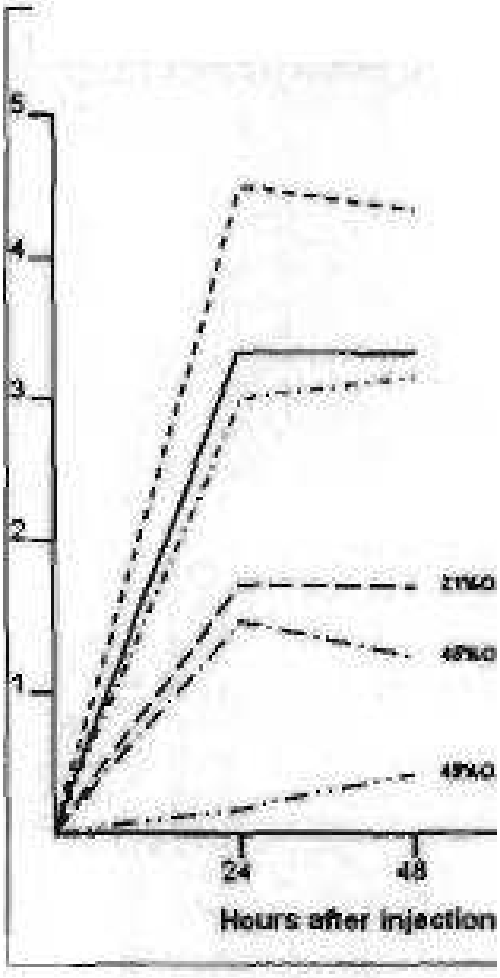


ABB 1.6-3.
Wirksamkeit von alleiniger Sauerstoffgabe oder kombiniert mit Ampicillin auf den Durchmesser nekrotisierender Läsionen nach intradermaler Infektion mit *Escherichia coli* bei Guinea Schweinen ((Knighton et al. 86)

In einer anderen Studie zeigten Mader et.al. dass HBO (100 %, 2.5 ATA, 1.6 Std., zweimal tgl.) kombiniert mit Tobramycin effektiver waren als HBO oder Tobramycin alleine (Mader et al. 89). Die Wirksamkeitssteigerung von Tobramycin mit HBO wurde mit der Erholung der Sauerstoffspiegel im infizierten Knochen erklärt, der sowohl den Aminoglycosiden die Wiederaufnahme ihrer Wirkung ermöglicht, als auch die bakterizide Wirkung der Polymorphkernigen steigert.

In einem Rattenmodell mit Mischinfektion studierten Marzella et al. 1996 den additiven Effekt von HBO und einigen Antibiotika. Sie konnten die Synergie anhand reduzierter Mortalität bestätigen. HBO steigerte die Wirkung von Piperacillin, Clindamycin und Vancomycin. Bei Metronidazol fand sich die Synergie nicht. Letztlich beobachteten sie,

dass der additive Effekt mit Vancomycin und Clindamycin zu einer verlängerten Überlebenszeit führte.

Mindestens drei Wirkungswege sind verantwortlich für die Rolle, die die HBO bei der Infektionsbekämpfung spielt (Park 99):

- Die Steigerung des Sauerstoffpartialdruckes in ischemischen Geweben verbessert die Wirkung von Antibiotika wie Aminoglykoside, einiger Sulfonamide, der Fluorquinolone, von Vancomycin und Trimethoprim,
- Die Hemmung einiger Reaktionen im Rahmen der bakteriellen Biosynthese wie die Verstärkung von Sulfonamiden und Verlängerung der postantibiotischen Effekte von Aminoglykosiden bei von Pseudomonas verursachten Infektionen.
- Die Veränderung des Redoxpotentials von Bakterien kombiniert mit einer Vermehrung von reaktiven Zwischenprodukten wie Nitrofurantoin und geminderter Wirkung von antimikrobiellen Stoffen wie Metronidazol das ein niedriges Redoxpotential braucht.

Schlussfolgerung:

Durch seine direkte Wirkung auf Bakterien, Verbesserung der zellulären Abwehrmechanismen des Körpers und synergistische Effekte auf die Wirkung von Antibiotika ist die HBO in Kombination mit Chirurgie und Antibiotika als adjuvante Therapie extrem nützlich bei der Behandlung von Gewebsinfektionen sowohl mit anaeroben als auch aeroben Bakterien in hypoxischen Wunden und Geweben. Ihre Nützlichkeit wurde klar belegt mit einer großen Zahl von in vitro und in vivo experimenteller Forschung und im Weiteren bestätigt durch extensive klinische Serien. Der Vorteil, den die HBO im Breich infektiöser Erkrankungen bewirkt ist vor allem auf die adaequate Wiederherstellung normaler oder übernormaler Sauerstoffpartialdrücke in hypoxischen infizierten Geweben zurückzuführen.

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 (B_S)
Stage 3	localized osteomyelitis		local compromise (B_L) both
Stage 4	diffuse osteomyelitis		compromises (B_{LS})
		C host	treatment worse than disease

TABLE II

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 (B_S), locally at the site of osteomyelitis (B_L) or both (B_{LS}). 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.

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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 ± 2.7 *vs.* 48.8 ± 10.5 days, $p<0.05$); shortened duration of mechanical ventilation (4 ± 1.5 *vs.* 34.8 ± 8.3 days, $p<0.05$) or positive pressure support (4 ± 1.9 *vs.* 22.3 ± 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

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C18

HYPERBARIC OXYGEN THERAPY FOR SUPPURATIVE OSTEOMYELITIS

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UHM 2010, VOL. 37, NO. 5 - 2010 ABSTRACTS: WOUND HEALING AND HBO2 TREATMENTS

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Introduction: Osteomyelitis patients have been treated with hyperbaric oxygen therapy (HBO2) in Kawashima Orthopaedic Hospital since 1981. We reported the results of the treatment sometimes in past, in 2004. This time we are going to report the updated data on treatment.

Methods: Before the surgical treatment, we took an X-ray, bone scintigraphy, MRI and sinogram to check the range of focus. All cases took antibiotics and HBO. for 30 times. If the case showed an improvement, patients took a week off from HBO2 therapy. After the pause, 30 HBO2 treatments were carried out again. If the treatment did not improve symptoms, closed irrigation suction therapy was carried out. After the irrigation therapy, 30 treatments of HBO2 is completed once again. From June 1981 to December 2009, **642 osteomyelitis patients** were treated. The criteria of results are as follows:

- good: no infiammation symptoms, normal blood sedimentation rate and no sequesters;
- improvement: improvement of symptoms;
- failure: obvious infiammation and necessitation of continuous treatment.

Results: When patients were treated by HBO2 alone, the results were as follows:

- good — 364 cases (84.1%);
- improvement — 40 cases (9.2%);
- failure — 29 cases (6.7%).

When patients were treated by 111302 and irrigation therapy, the results were as follows:

- good — 194 cases (92.8%);
- improvement — 12 cases (5.7%);
- failure — 3 cases (1.4%).

Conclusions: We concluded that HBO2 alone is an effective treatment for osteomyelitis. However, the combination therapy of HBO2 and irrigation and suction treatment is more effective.

Bundesärztekammer
Arbeitsgemeinschaft der deutschen Ärztekammern

Stellungnahme der Bundesärztekammer gem. § 91 Abs. 8a SGB V zur **Beschlussempfehlung "Hyperbare Sauerstofftherapie bei der Indikation Clostridiale Myonekrose"** des Unterausschusses "Methodenbewertung im stationären Bereich" (Bewertung von Untersuchungs- und Behandlungsmethoden im Krankenhaus gem. § 137c SGB V)

Die Bundesärztekammer nimmt zum Entwurf des Abschlussberichts des Gemeinsamen Bundesausschusses nach § 91 Abs. 7 SGB V "Krankenhausbehandlung", Methode: Hyperbare Sauerstofftherapie, Indikation: Clostridiale Myonekrose (Gasbrand), vom 04.10.2005 zur Sitzung des Unterausschusses "Methodenbewertung" am 22.11..2005 wie folgt Stellung:

Die systematische Literaturrecherche ergab sieben HTA-Berichte bzw. systematische Reviews und MDK-Gutachten aus den Jahren 1999 bis 2003, vier Publikationen zu retrospektiven Studien mit Vergleichsgruppen aus den Jahren 1973 bis 1992 sowie (nach Anwendung der Filterkriterien, wonach u.a. bei Fallserien Studien mit weniger als 50 Patienten ausgeschlossen wurden) sieben Veröffentlichungen zu retrospektiven Fallserien aus den Jahren 1977 bis 1996. Publikationen zu kontrollierten Vergleichsstudien — mit oder ohne Randomisierung —, in denen die hyperbare Sauerstofftherapie (HBO) prospektiv gegen eine Kontroll- oder Leerbedingung bei clostridialer Myonekrose verglichen worden wäre, wurden in der Literatursuche nicht gefunden.
HBO wurde in keiner der Studien als Mono-Therapie untersucht, sondern lediglich adjuvant in Kombination mit chirurgischen Maßnahmen und Antibiotika-Verabreichung, häufig unter intensivmedizinischen Bedingungen. Zu den retrospektiven Vergleichsstudien muss einschränkend angemerkt werden, dass es sich dabei nicht um parallele, sondern historische Vergleichsgruppen mit Datenerhebung in unterschiedlichen Zeiträumen handelte, was die Vergleichbarkeit von Patienten aus verschiedenen Studienkollektiven mindert und die Beurteilbarkeit der Studienergebnisse erschwert. Als einziger patientenrelevanter Endpunkt wurde aufgrund einer als problematisch eingeschätzten Vergleichbarkeit anderer Zielgrößen die Mortalität definiert.

In den vier retrospektiven Vergleichsstudien lag die Mortalität bei den zusätzlich mit HBO behandelten Patienten (n = 184) mit 29% niedriger als bei den nicht mit HBO behandelten (n= 81) mit 59%. Ein statistisch signifikanter Unterschied zugunsten der HBO-Zusatzbehandlung ließ sich nur für die jüngste Studie aus dem Jahr 1992 mit dem größten Studienkollektiv nachweisen.. In den drei übrigen retrospektiven Vergleichsstudien aus den Jahren 1973 bis 1978 war dies nicht der Fall, wobei hier der Fehler II.. Art aufgrund der geringen Stichprobenumfänge berücksichtigt werden muss. Ein aggregierter, ggf. gewichteter Effektschätzer für das relative Mortalitätsrisiko über alle Vergleichsstudien hinweg wurde nicht berechnet, **doch kann offenbar das Sterberisiko bei clostridialer Myonekrose unter adjuvanter HBO halbiert werden**,. (Ein möglicher, bei retrospektiven Studien schwer ausschließbarer Selektionsbias bleibt hier unberücksichtigt.) Schließt man die Patientenbeobachtungen aus den sieben Fallserien zu HBO mit ein, ergibt sich für insgesamt 1192 Fälle unter HBO-Zusatztherapie eine Mortalitätsrate von 24% über Unterschiede zwischen den Patientenkollektiven, prognostischen Faktoren und Therapieschemata hinweg. Schwerwiegende Nebenwirkungen wurden nicht berichet.

In den ausgewerteten HTA-Berichten, systematischen Reviews und MDK-Gutachten wird überwiegend ein therapeutischer Nutzen einer HBO-Zusatztherapie angenommen bzw. HBO wird — so von Seiten des MDK — als fester Bestandteil der etablierten Verfahrensweisen angesehen. Der HTA-Bericht des Bundesausschusses der Ärzte und Krankenkassen aus dem Jahr 2000 zu HBO im Rahmen der vertragsärztlichen Versorgung kommt zu der Einschätzung, dass eine Aussage zum medizinischen Nutzen der HBO aufgrund des Mangels kontrollierter Vergleichsstudien nicht möglich sei.

Nach der Neufassung der Verfahrensordnung des G-BA vom 20.09.2005 würden die in der Literaturrecherche detektierten Therapiestudien mit den Evidenz-stufen III und IV klassifiziert. Allerdings wären Studien höherer Evidenzstufen, insbesondere prospektive randomisierte kontrollierte Studien, wegen der Seltenheit einer clostridialen Myonekrose, ihres foudroyanten Verlaufs und angesichts der immer noch hohen Letalität schwerlich durchführbar und würden in den nächsten Jahren noch nicht zu verwertbaren Ergebnissen führen; sie wären daher kaum als obligate Entscheidungsgrundlage zu fordern. Eine alternative Bewertungsfindung nach dem "All or none"-Schema (Evidenzstufe Ic nach nach den Oxford Centre for Evidence-based Medicine Levels of Evidence aus dem Jahr 2001) ist in der Verfahrensordnung des G-BA nicht vorgesehen. Eine Bewertung der HBO muss daher jetzt aufgrund der besten, derzeit verfügbaren Evidenz erfolgen. Nach den vorliegenden Studien-

ergebnissen ist eine Reduktion des durch eine clostridiale Myonekrose bedingten Mortalitätsrisikos durch eine HBO-Zusatzbehandlung und damit ein therapeutischer Nutzen wahrscheinlich.

Die Bundesärztekammer schließt sich der Position des Berichtsentwurfs mit Stand vom 4..10.2005 an, wonach eine hyperbare Sauerstofftherapie in Kombination mit einer Antibiotikatherapie und chirurgischer Therapie — nicht aber eine alleinige hyperbare Sauerstofftherapie — bei der Indikation einer clostridialen Myonekrose als Leistung im Rahmen der gesetzlichen Krankenversicherung anerkannt wird.

Berlin, den 04.11. 2005

gez.

Dr. med. Regina Klakow-Franck, M.A.
Dezernentin

Escobar SJ, Slade JB Jr, Hunt TK, Cianci P.: Adjuvant hyperbaric oxygen therapy (HBO2)for treatment of necrotizing fasciitis reduces mortality and amputation rate. Undersea Hyperb Med. 2005 Nov-Dec;32(6):437-43

Department of Hyperbaric Medicine, Doctors Medical Center, San Pablo, CA, USA.

OBJECTIVE: A retrospective analysis of **42 patients** with necrotizing soft tissue infections treated with adjunctive HBO2 to ascertain efficacy and safety. Overall mortality was 11.9% and morbidity 5%.´

SUMMARY BACKGROUND DATA: Necrotizing soft tissue infections have historically high rates of mortality and morbidity, including amputation. Common misconceptions that prevent widespread use of adjunctive HBO2 for this diagnosis include delays to surgery, increased morbidity, and significant complications.

METHODS: Forty-two consecutive patients (average age 56.1) with necrotizing fasciitis presenting to a major referral center were treated with adjunctive HBO2 as part of an aggressive program of surgery, antibiotics, and critical care. Involved areas included the lower abdomen (15 patients), thigh and perineum (9 patients), flank (4 patients), lower leg (3 patients), and arm, shoulder, and axilla (2 patients). Co-morbidities included diabetes mellitus, chronic renal failure, intravenous drug abuse, peripheral vascular disease, and malignancy.

RESULTS: Mortality was 11.9% (5 patients). Both amputations (a finger and a penis), occurred prior to transport to our facility. The average number of surgical debridements was 2.8 per patient; 1.25 performed prior to the start of HBO. The infectious process was controlled after an average of 7 HBO2 treatments were administered to ensure successful wound closure. Complications consisted of only mild ear barotrauma in 3 patients (7%), and confinement anxiety in 17 (41%) but did not prevent treatment.

CONCLUSION: Compared to national reports of outcomes with "standard" regimens for necrotizing fasciitis, our experience with HBO2, adjunctive to comprehensive and aggressive management, demonstrates **reduced mortality (34% v. 11.9%),** and **morbidity (amputations 50% v. 0%).** The treatments were safe and no delays to surgery or interference with standard therapy could be attributed to HBO2.

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Barclay, Laurie: Hyperbaric Oxygen May Improve Outcome in Necrotizing Soft Tissue Infection
Archives of Surgery. 2004; 139:1339-1345

Hyperbaric oxygen improves survival and limb salvage in necrotizing soft tissue infection (NSTI), according to the results of a retrospective cohort study published in the December issue of the *Archives of Surgery*.

"Necrotizing soft tissue infection (NSTI) refers to a spectrum of infective diseases characterized by necrosis of the deep soft tissues," write David Wilkinson, FANZCA, from the Royal Adelaide Hospital and The University of Adelaide in Australia, and colleagues. "Features of manifestation and medical management have been analyzed for association with outcome. The use of hyperbaric oxygen (HBO_2) therapy has been recommended as an adjunctive treatment but remains controversial."

Records of all patients admitted with a diagnosis of NSTI to a major tertiary hospital during a five-year period were analyzed for the association of various clinical features with survival to hospital discharge, and for the association of HBO_2 therapy with long-term survival. The primary outcome measure was survival to hospital discharge, and secondary outcome measures were limb salvage and long-term survival after hospital discharge.

Of **44 patients** whose records were reviewed, six (14%) died. Factors associated with mortality were increased age, renal dysfunction, unknown etiology of infection, and lack of HBO_2 therapy. Based on logistic regression, the best predictor of survival was the use of HBO_2 therapy (P = .02), which **increased survival nearly nine-fold** (odds ratio, 8.9; 95% confidence interval, 1.3-58.0; number needed to treat, 3).

When NSTI involved an extremity, HBO_2 treatment reduced the incidence of amputation (P = .05). Survival analysis revealed that the HBO_2 group had an improved long-term outcome (P = .002).

"Hyperbaric oxygen therapy was associated with improved survival and limb salvage and should be considered in the setting of NSTI," the authors write. "Hyperbaric oxygen therapy can be provided safely to patients who are intubated and require intensive care. The incidence of ear barotrauma in this study (eight of 29 patients) suggests prophylactic myringotomy should be routinely considered prior to initiating HBO_2 therapy."

Medscape

Reviewed by Gary D. Vogin, MD

HBO AND SEPSIS - A SHORT OVERVIEW

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Introduction:

Roughly 10 years ago the high ranking scientific journal *Critical Care Medicine* has titled an editorial with *"HBO* — not just a movie channel anymore" [Slotman 1998]. This editorial referred to a paper that was published in the same issue, dealing with a topic that nobody would have seen to be related to the therapeutical application of hyperbaric oxygen. The subject of this study was experimental sepsis and thus far away from any traditional approach an where hyperbaric oxygen may be a useful adjunct to therapy. Today, almost 10 years later, a couple of papers have been published in this field from different groups, showing that hyperbaric oxygen may play a role in the therapy of septic states, although clinical studies still are lacking. In addition, these studies are suited to show non-hyperbarics that HBO definitely is not Voodoo, as it is sometimes stated. Physicians that work in the field of hyperbaric medicine the same papers can show that there is much more behind it, than it was believed until now. Therefore, another editorial, published in *Intensive Care Medicine* has to be cited:"HBO *and sepsis: time to recognize!"* [Muth et al 2005]

Background: a short summary of the pathophysiology of sepsis and SIRS

Sepsis is a serious problem that presents a management challenge to those who care for patients at intensive care units. Generally, sepsis is considered to comprise a confusing spectrum of disorders that result from infection by microorganisms with massive invasion into the bloodstream, or the toxic products of these microorganisms. The Basis of sepsis therefore is the presence of such an infection and the subsequent physiologic alterations in response to that infection, namely the activation of the inflammatory cascade [Cohen 2002]. The spectrum of sepsis ranges early signs of circulatory compromise, including tachycardia, tachypnea, peripheral vasodilation, and fever, to circulatory collapse with multiorgan system failure. These manifestations are part of the so-called systemic inflammatory response syndrome (SIRS), which also is used with sepsis to signify any of these manifestations and which results from an insult and the host response that follows. The outcome mainly depends an the interplay of upregulating and downregulating cytokines and inflammatory cells and the direct effects of the insult itself.

When it comes to a SIRS, the inflammatory cascade is triggered [Weigand et al 2004]. This inflammatory cascade is a complex process that involves numerous humoral and cellular responses, complement and cytokine cascades. In a first step local cytokines are produced with the goal of inciting an inflammatory response, thereby promoting wound repair and recruitment of the reticular endothelial system. Then, small quantities of local cytokines are released into circulation to improve the local response, leading to growth factor stimulation and the recruitment of macrophages and platelets. This acute phase response is normally well controlled by a decrease in the proinflammatory mediators and by the release of endogenous antagonists. The goal is homeostasis. But if homeostasis is not restored,

a significant systemic reaction occurs. The cytokine release then is not protective anymore but leads to destruction, resulting in the activation of numerous humoral cascades and the activation of the reticular endothelial system with subsequent loss of circulatory integrity and, at the end, in end-organ dysfunction.
When SIRS is mediated by infection, the inflammatory cascade is often initiated by endotoxin or exotoxin. Tissue macrophages, monocytes, mast cells, platelets, and endothelial cells are able to produce a multitude of cytokines. The cytokines tissue necrosis factor-a (TNF-a) and interleukin (IL)-1 are released first and initiate several cascades. The release of IL-1 and TNF-a (or the presence of endotoxin or exotoxin) leads to cleavage of the nuclear factor-KB (NF-KB) inhibitor. Once the inhibitor is removed, NF-KB is able to initiate the production of mRNA, which induces the production other proinflammatory cytokines [Cohen 2002, Weigand et al 2004]. IL-6, IL-8, and interferon gamma are the primary proinflammatory mediators induced by NF-KB. In vitro research suggests that glucocorticoids may function by inhibiting NF-KB. TNF-a and IL-1 have been shown to be released early in large quantities and have both local and systemic effects. Other cytokines, especially IL-6, stimulate the release of acute-phase reactants such as C-reactive protein (CRP). The proinflammatory interleukins either function directly an tissue or work via secondary mediators to activate the coagulation cascade, complement cascade, and the release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes. Numerous proinflammatory polypeptides are found within the complement cascade. Protein complements C3a and C5a have been the most studied and are feit to contribute directly to the release of additional cytokines and to cause vasodilatation and increasing vascular permeability. Prostaglandins and leukotrienes incite endothelial damage, leading to multiorgan failure.
The correlation between inflammation and coagulation is crucial for the understanding the potential progression of SIRS [Opal 2004]. Endothelial surfaces are directly affected by IL-1 and TNF-a, leading to the expression of tissue factor. Tissue factor initiates the production of thrombin, what promotes coagulation, and is proinflammatory itself. The production of plasminogen activator inhibitor-1 by IL-1 and TNF-a will impair Fibrinolysis. Proinflammatory cytokines disrupt the anti-inflammatory mediators antithrombin and activated protein-C (APC). This coagulation cascade leads to complications of microvascular thrombosis, with subsequent organ dysfunction.

Back to HBO — the current literature

A major problem in understanding the underlying mechanisms of hyperbaric oxygen was that it was believed over the time that HBO-T does nothing more than diminishing a lack of oxygen delivery, either locally or systemically. Newer findings suggest that this is only one aspect of its action, but oxygen administered at supranormal pressures may also act as a signal transducer [Davidson JD, Mustoe TA (2001)], and thus may trigger the expression of antioxidative enzymes as well as alter the expression of growth factors and cytokines. These findings opened new windows in the research of for instance carbon monoxide poisoning or reperfusion injury — and may have encouraged to look at systemic inflammation as well.
In 1998 Luongo and co-workers [Luongo et al 1998] published a study on the effects of HBO therapy on a Zymosan-induced experimental shock model in rats. Zymosan, a cell wall component of Saccharomyces cerevisiae, induces acute peritonitis, severe hypotension, and signs of systemic illness, thus inflammation by causing the production of various cytokines and pro-inflammatory mediators. Zymosan-induced shock is very similar to septic shock, as it is believed to be mediated by

overproduction of nitric oxide and serves as an experimental model of septic shock. In this study, rats were exposed to either HBO at 2 ata, or or to intraperitoneally administered Zymosan and HBO at 2 ata. In both groups peritoneal exudate, plasma, and peritoneal nitric oxide metabolites (NOx) and Zymosan determined a time-dependent increase in peritoneal and plasma NOx concentrations, and peritoneal leukocytes were determined and the clinical symptomatology in the rats were observed. The authors observed that the administration of Zymosan indeed caused the appearance of a severe illness in the rats with acute peritonitis and the production of turbid exudate. Furthermore, Zymosan determined an increase in peritoneal as well as plasma NOx, and TNF-a concentrations. Treatment with HBO lead to an attenuated morbidity of the Zymosan shocked rats, associated with a significant reduction either of peritoneal leukocytes and exudate, or plasma and peritoneal NOx concentrations. Moreover, TNF-alpha levels were significantly reduced in animals shocked by Zymosan and treated with HBO.
These were the first results on the effects of hyperbaric oxygen exposure on such an experimental shock model that were published. However, this Zymosan —induced shock model is artificial and therefore not identical to any clinically observed insult. Nevertheless it produces a highly reproducible generalized systemic inflammation, which is consistent with consensus definitions of the host inflammatory response. In 2000 the same group evaluated the effects of HBO-T on multiple organ failure induced by Zymosan in the same animal model [Cuzzocrea S et al (2000)]. In this study, administration of Zymosan in the rat induced neutrophil infiltration in the lung, liver, and intestine as evaluated by increase in myeloperoxidase (MPO) activity. Therefore, lipid peroxidation was significantly increased in Zymosan-treated rats. This inflammatory process coincided with the damage of lung, liver, and small intestine. Immunohistochemical examination demonstrated a marked increase in the immunoreactivity to nitrotyrosine in the lung, liver, and small intestine of Zymosanshocked rats. Again, HBO exposure to 2 ata attenuated the increase in the tissue levels of MPO and malondialdehyde (MDA) caused by Zymosan in the lung, liver, and intestine. In addition, HBO was effective in preventing the development of injuries in these organs. The authors concludet that these results showed that HBO may be an efficacious treatment in multiple organ failure induced by Zymosan.
Later, in 2004 Imperatore and co-workers focussed on the vascular derangement during a Zymosan-induced multiple organ failure syndrome and the effects of HBO-T in this set-up [Imperatore et al (2004)]. Again the well established animal model on Zymosan-induced inflammatory response was used, in which alter induction of a systemic inflammatory response (SIR) in the treatment groups a HBO-T was performed in one of the treatment groups and in one control group. Later then, ex vivo vascular reactivity was evaluated alter preparation of the descending aorta and tyrosine nitration and iNOS expression were determined by immunohistochemistry. As a marker for lipid peroxidation malondialdehyde (MDA) was determined as well. The fmdings were that HBO attenuated the degree of Zymosan-induced cardiovascular derangement in the rat, as MDA-levels were lower, staining of nitrotyrosine and iNOS were reduced and contractility of aortic rings were increased in the HBO-treated animals of the Zymosan group.These findings correlate to the previous findings with this animal model, suggesting that HBO can substantially attenuate systemic inflammatory response, at least in an animal model like this
The next step was a study on the effects of hyperbaric oxygen (HBO) therapy on the coagulation cascade using this well established animal model of Zymosan induced shock [Imperatore et al 2006]. As in previous studies, symptomatology was induces by intraperitoneal application of Zymosan in rats, and HBO treatment was performed with 2 ata. The Zymosan administration caused a multi organ failure by affecting the coagulation cascade with a significant increase in plasma levels of fibrinogen,

tissue plasminogen activator, inhibitor of tissue plasminogen activator of type 1, and plasma levels of fibrin degradation products. Furthermore, a significant increase in von Willebrand antigen plasma levels were observed, as well as a significant fall in mean arterial blood pressure and alteration in blood gas values in all Zymosan treated animals, while HBO therapy significantly reduced the derangements of coagulation cascade, the fall in mean blood pressure and alteration in blood gas induced by Zymosan administration. The authors conclusion was that hypercoagulability, which could lead to multi organ failure, was significantly influenced by the application of HBO therapy, which significantly prevented the alteration in the coagulation cascade and arterial blood gases in this experimental setting.

These studies showed that HBO exposure may have beneficial effects experimental models of systemic inflammation. Even though the described interventions lead to a highly reproducible, generalized systemic inflammation, which is consistent with consensus definitions of the host inflammatory response, the Zymosan—induced shock cannot mirror all aspects of human bacterial sepsis and, hence, may be referred to as artificial and therefore not identical enough to any clinically observed insult. In 2005, Öter et al have investigated an animal model of systemic bacterial sepsis as a result of localized infection, which, furthermore, integrated standard clinical care using antibiotics [Öter et al 2005]. In this study, the authors report on the effect of HBO -alone or in combination with an antibiotic - on liver function and morphology in rats rendered septic by intraperitoneal injection of an *E. coli* suspension. The main findings of this study are that a) sepsis *per se* resulted in a pronounced increase of markers of tissue oxidative stress increased while the activities of the antioxidant enzymes decreased, associated with b) a rise in blood transaminase activity documenting hepatocyte injury and c) marked neutrophil infiltration and cell "degeneration" in the liver. Antibiotic treatment and HBO alone resulted in both reduced plasma transaminase activities and attenuated tissue oxidative stress, but combining HBO and antibiotics was most efficient. Furthermore, the combined treatment only allowed to achieve virtually normal histologic findings. Finally, the HBO-treated animals even presented with increased antioxidant enzyme acitivities in the liver. The authors concluded that HBO may be a useful adjuvant to improve the efficacy of the treatment of sepsis.

The next step was a study by Buras et al [Buras et al 2006], where again sepsis was induced in mice by a mechanism that is dose to the clinical situation: cecal ligation and puncture (CLP). The study was performed to determine whether hyperbaric oxygen therapy with different time intervals and therapeutical pressures is protective in such a CLP-induced sepsis and if protection is dependent on oxygen dosing. Furthermore, another goal was to determine whether HBO affected bacterial clearance or altered macrophage production of interleukin (IL)-10 in this setting and whether the mechanism of protection in sepsis is related to IL-10 production. The fmdings were that HBO significantly improved survival when administered at 2.5 atmospheres absolute every 12 hrs. Other treatment schedules were not protective, and treatment at 3.0 atmospheres absolute significantly worsened survival outcome. Bacterial load was significantly reduced in splenic homogenates but not peritoneal fluid at 24 hrs. Macrophages isolated from HBO treated mice demonstrated enhanced IL-10 secretion in response to lipopolysaccharide as compared with controls, while IL-10 deficient mice were not protected from CLP-induced mortality by HBO treatment. Buras and co-workers therefore concluded that HBO may be protective in this model of sepsis within a certain rate of oxygen dosing. The mechanism of HBO protection appears to be linked in part to expression of IL-10, as peritoneal macrophages

demonstrated enhanced IL-10 expression and IL-10 deficient mice were not protected by HBO treatment.

Discussion

HBO therapy is still perceived by many physicians only as a tool for augmentation of oxygen delivery. A steadily growing body of evidence provides a much broader scientific basis for understanding mechanisms of the effects of hyperoxia in relevant clinical conditions. The effects of hyperoxia on the microvascular/inflammatory response have already been studied in a considerable number of experimental models. Most of the attention focused on mechanisms of the effects of hyperoxia in models of ischemia and reperfusion (I/R) which in many cases provoke local and systemic responses that frequently culminate in systemic inflammatory response (SIR) and multiple organ failure. The commonly accepted paradigm of I/R injury emphasizes a central role for oxygen derived free radicals formation in activation of the inflammatory cascade, what initially evoked a concern that hyperoxia could exacerbate the injury by adding extra oxygen to the system thus increasing free radical formation. In contrast, evidence from biochemical and in vitro studies and from animal models supports a protective role of hyperoxia in UR , as it appears to exert a simultaneous effect an a number of steps in the proinflammatory cascades in this pathophysiology. It has also been shown that prolonged hyperoxia enhances eNOS activity and may thus improve microvascular perfusion and ameliorate tissue hypoxia [North et al 1996]. These effects have been shown in the various settings of the Zymosan-induced septic shock model as well. The main weakness of this model lies in the fact that Zymosan induced systemic inflammatory response and shock does not have a straightforward clinical correlate and does not mimic a specific disease state. However, this model is a strong generator of SIRS and circulatory shock, both being common consequences of many pathologies that are encountered with in the intensive care unit. Hence, the findings of the present study add significant new information that provides further support and mechanistic hints about the beneficial effects of hyperoxia in severe systemic inflammatory response and shock [Bitterman et al. 2004].

Nevertheless, these previous fmdings get their confirmation in the study by Öter et al., which also has the merit of investigating an animal model of systemic bacterial sepsis as a result of localized infection, which is dose to reality and integrates standard clinical care using antibiotics. In this context, the crucial role of HBO-induced improvement of host defense may have assumed particularly importance for the authors' findings: it is well-established in humans that HBO exposure increases both the respiratory burst and phagocytic capacity, while interestingly, chemotaxis is reduced [Labrouche et al 1999]. Several further mechanisms established in models of ischemia-reperfusion injury and already mentioned above may help to explain the data reported here. Furthermore, Öter et al. demonstrated that HBO even beneficially influenced oxidative stress in their model. This observation seems to be paradoxical, since due to the enhanced formation of oxygen free radicals is directly related to the 02 partial pressure [McCord 2000], and, in fact, it is well-known that exposure to HBO may promote oxidative stress [Benedetti et al 2004]. It is noteworthy, however, that HBO was affiliated with increased local endothelial surface superoxide dismutase (SOD) activity, and may induce efficient adaptive mechanisms of protection against subsequent oxidative stress, at least in healthy volunteers [Speit et al 2002].

The effect of the 11130 related increase in tissue oxygen transport must not be underestimated, but the signal transduction properties of HBO with its modulation of nitric oxide release and the expression of cytokines, heat shock proteins, or antioxidative enzymes seem to contribute at least as much to its therapeutic effects in sepsis as both increased tissue oxygen availability and bactericidal potency [Calzia et al 2006]. The report from Buras and colleagues add another piece to the puzzle of understanding the potential therapeutic value of HBO in sepsis, using a well-established murine model of cecal ligation and puncture—induced polymicrobial sepsis. Buras and colleagues themselves [Buras et al 2006] correctly emphasize that these findings "should not be extrapolated directly to the human clinical scenario," a conclusion that is also imposed by the marked species differences with respect to tissue antioxidant capacity and susceptibility to oxidative stress. Nevertheless, the findings are of particular importance because it is the first report describing a U-shaped dose response for HBO under conditions of hyperinflammation. Furthermore, taking into account both the evidence of increased oxidative and nitrosative stress in human sepsis [Alonso de Vega et al 2002] and the fact that the oxygen partial pressure is referred to directly determine reactive oxygen species formation, their findings confirm the "friend and foe" character of these molecules [Magder 2006]. Using IL-10 strains, Buras and co-workers could demonstrate that the protective effect of HBO was dependent an the animals' capacity to produce this anti-inflammatory cytokine. This conclusion was confirmed by the IL-10 secretion in adherent CD11b cells stimulated *ex vivo* with lipopolysaccharide: in peritoneal macrophages isolated from HBO treated mice with sepsis, the lipopolysaccharide-induced IL-10 release was nearly twice as high as in cells from animals with cecal ligation and puncture alone. Furthermore, although the HBO treatment in this study did not affect the bacterial load measured directly in the peritoneal fluid, it resulted in a three-fold lower number of colony-forming units in the spieen, which suggested that inhibition of bacterial dissemination rather than a direct bactericidal effect was responsible for the HBO-related improved survival.

A temporary conclusion

Taken together, specific research in the past 10 years provided new insight into the controversial issue of HBO treatment in septic shock, leading to changes in viewing this therapy from *"a therapy in search of diseases"* [Gabb et a11987] over a tool for augmentation of oxygen delivery to a mechanism for modulation of the immune response [Calzia et al 2006]. Nevertheless, many additional questions remain open and human studies an 11130 in sepsis still are lacking.

Future studies, preferably including a detailed analysis of the subtle balance between antioxidative capacity, reactive oxygen species formation, and oxidative stress, should reveal the complex balance between the "friend and foe" properties of HBO in inflammatory states and thus should ultimately help to develop a more effective and rational use of this potentially interesting therapeutic strategy [Calzia et al 2006].

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The aim of this **retrospective study** was to investigate the effect of adjuvant hyperbaric oxygen (HBO) therapy on the duration of antibiotic treatment and rate of radiological improvement in the management of spinal tuberculosis.

We reviewed a total of **51 patients** with tuberculous spondylitis of the spine who were treated by percutaneous abscess drainage or radical surgical debridement with chemotherapy, and of whom **16 randomly selected** patients also received adjuvant HBO therapy and 35 did not. Serological markers were monitored in the course of treatment. Percutaneous needle biopsy was performed on each patient before treatment. Spine and chest radiographs, CT scans and MRI were performed.

Infection control was achieved in all patients and no recurrence occured. To our knowledge this is the first reported series of patients with spinal tuberculosis treated with HBO therapy as an adjunct to antituberculous chemotherapy. **This combination provided earlier clinical and radiologic improvement than chemotherapy alone.**

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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 therapy. 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 pass-throughs 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 liyperbaric 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 Radiotherapya

No.	Age/ Sex	Diagnosis	Therapy and Complications	Material	HBO Sessions	Follow-up (mo)	HBO 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	Urinary 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 aqueduct stenosis with hydrocephalus, shunt infections, shunt exposed and removed, CSF drainage	Soft tissue and bone	46	18	Ventriculocisternotomy 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.

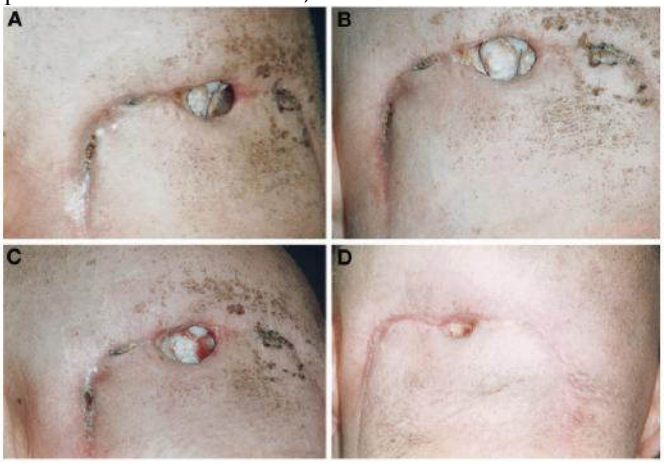

FIGURE 1. Photographs demonstrating HBO treatment results. Surgery to treat an occipital medulloblastoma (Patient 2.5) caused a suppurative wound infection that was treated by traditional methods, with removal of the osteomyelitic bone flap. The condition worsened after radiotherapy, with wound breakdown, 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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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.

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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 recovery results demonstrated in this report strongly suggest that HBO therapy is beneficial in the management of postoperative neurosurgical infections. However, it is not clear what the ideal treatment regimen for these patients should be and whether it is dependent on which microbes are responsible for the infection. The mechanism by which HBO treatment works probably involves a direct bactericidal effect on anaerobic organisms. *Propionibacterium acnes*, an anaerobic Gram-positive bacillus that is well known to cause focal intracranial infections after neurosurgery (1), was observed to be the causative infectious organism for several of the patients reported in this series. This fact makes it imperative for clinicians to identify the offending bacteria before initiating treatment. One concern associated with this form of therapy is that some patients (e.g., those with end-stage glioblastoma multiforme) may be too medically frail to tolerate a series of HBO treatments. Another unfortunate feature of this therapeutic modality is that it is not available to most neurosurgeons for the treatment of patients with severe postoperative infections.

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Call for Concepts and Innovations Contributions

The *Concepts and Innovations* section has been conceived to establish a new dimension i journalistic presentation. Because of individual variations in the creative mind and th ability to effectively carry ideas through to fruition, many concepts or novel ideas ar left "on the shelf" or are unheard because, for one reason or another, individuals do no have the capability to see them through to absolute or practically developed completion

This section of the *Journal* will offer a forum for all those who wish to present new concept or ideas related to neurosurgery and neuroscience, as applied to neurological disorders, an will offer the opportunity for the logical and substantive presentation of ideas and nove issues without absolute confirmation within clinical or laboratory sectors.

New concepts with potential application to all foci of practice will be welcomed.

ANAEROBIC PLEUROPULMONARY INFECTIONS--A POTENTIAL INDICATION FOR ADJUNCTIVE HYPERBARIC OXYGEN THERAPY IN SELECTED CASES

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Anaerobic bacteria are now generally considered as relatively common pulmonary pathogens and involved especially often in aspiration pneumonia and its suppurative complications : lung abscess and empyema. Although most patients respond well to antibiotic treatment associated to adequate drainage, 5 to 10 p.cent may experience persistent features of infection : smoldering fever, weight loss, fetid purulent sputum. This leads to reassess the initial treatment (antibiotics, closed chest drainage) and in some cases, to consider surgery. In few patients, despite multiple antibiotic regimens and drainage procedures, infection still persists and leads to respiratory failure, cachexia and death [1,2].

In these selected cases, we propose to consider Hyperbaric Oxygen (HBO) based an our experience in 13 patients.

I) ANAEROBIC PLEUROPULMONARY INFECTIONS

1) Incidence

The true incidence of anaerobic pulmonary infections is difficult to assess since specialized techniques are required for the collection of uncontaminated specimen from the upper airways, where anaerobes represent the dominant component of the flora. Complicating this situation are the need to obtain these specimens before antibiotic treatment and the necessity for laboratory expertise in the cultivation of anaerobic bacteria.

Most published reports deal with the role of anaerobic bacteria in aspiration pneumonia or lung abscess, where recovery rates range from 58 % to 100 % [3-8). The usual specimen sources in these studies are transtracheal and transthoracic aspiration. The most definitive study is that by Beerens and Tahon-Castel [3], who used transthoracic needle aspiration into lung abscesses and recovered anaerobic bacteria, usually in pure cultulre, in 22 (85 %) of 26 cases. More recently, Gudiol et al. [8] used a similar technique and found anaerobic bacteria in 37 (90 %) of 41 cases.

Empyema is obviously more easily studied than pulmonary abscess because of the relative ease of obtaining pleural fluid for anaerobic culture. Recent studies have shown a sharp decline in the frequency of empyema in general and a marked change in the

remaining cases. S. pneumoniae now accounts for only 5 % - 10 % of cases, while anaerobes account for 25 % - 40 % [3, 9-11].

There are relatively few studies of the frequency of anaerobic bacteria among unselected cases of community-acquired pneumonia. The best available information comes from the study by Ries et al. [121, who attempted trans tracheal aspiration for anaerobic culture in all patients admitted to a Philadelphia hospital with a diagnosis of pneumonia. Anaerobic bacteria were recovered from 29 (33 %) of 89 such patients. In an analogous study by Pollock et al.[13], fiberoptic bronchoscopy with a protected catheter was combined with quantitative cultures ; this approach led to the recovery of anaerobes from 16 (22 %) of 74 patients. These two reports suggest that anaerobic bacteria are relatively common among patients with community-acquired pneumonia, which is now commonlylabeled « atypical pneumonia » and often ascribed to organisms such as Mycoplasma pneumoniae, Chlamydia pneumoniae, or Legionella [1].

2) Pathophysiology

The usual source of bacteria in anaerobic lung infections is the oral cavity - presumably the gingival crevice, where anaerobic bacteria are found in concentrations up to 1012/g [25, 261.

A predisposition to aspiration as a result of compromised consciousness or dysphagia (e.g., in alcoholism, general anesthesia, seizure disorder, drug abuse, esophageal lesions, and neurological disorders) is commonly associated with these infections. The basal segments of the lower lobes of the lung are favored by gravitational flow in the upright position. Aspiration in the recumbent position favors the posterior segments of the upper lobes or the superior segments of the lower lobes [6, 14].

Additional conditions that appear to predispose to anaerobic lung infections include infarction, pulmonary obstruction due to a neoplasm or foreign body, and bronchiectasis. Each of these conditions is associated with stasis or necrosis of tissue, which presumably accounts for the predisposition.

A striking feature of anaerobic lung infections is the tendency toward necrosis of tissue, resulting in abscess formation and/or a bronchopleural fistula with an empyema. If numerous micro-organisms may cause pneumonia, anaerobic bacteria are clearly the most frequent germs associated with pulmonary necrosis and abscess formation.

Long ago, Smith showed that, following aspiration, the natural history of the infection consisted of pneumonia followed by abscess formation about 7 days alter bacterial challenge. He also demonstrated the importance of bacterial synergy in the pathological process [15, 16). Other virulence factors of anaerobic bacteria that appear to promote abscess formation are the polysaccharide capsule found in some strains of Bacteroides species [17, 18] and the short-chain volatile fatty acids that cause acid pH-dependent inhibition of phagocytic killing [19, 21].

3) Bacteriology

The bacteriology of anaerobic pulmonary infections has come about over the years with improved lower tract sampling techniques and constant revision of taxonometric classification. Anaerobes were first discovered to be involved in aspiration syndromes in large autopsy studies in the late ninetheenth and early twentieth centuries [6, 22]. Anaerobic flora at that time were classified as fusospirochetes.

In the recent studies [5, 6, 23, 24], the major anaerobic isolates in patients with aspiration syndromes are: Fusobacterium nucleatum, Peptostreptococcus, Prevotella rnelaninogenica and Pr. intermedia. An assortment of other anaerobic species occurs in these settings, however, at lesser frequency (Table I).

Aerobic bacteria associated with aspiration pneumonia tend to be those usually found in the setting in which the aspiration occurs. Hence, the primary aerobic isolates in the community setting are aerobic or microaerophilic streptococci. In half the cases, gram-negative flora are the predominant organisms in nosocomial-acquired illness, with Klebsiella and Escherichia coli the most common gram-negative isolates (23 and 14 per cent), whereas Pseudomonas can be expected in fewer than 10 per cent. Pneumococcus and Staphylococcus aureus can be expected to be cultured as often as 31 per cent and 26 per cent of the cases, respectively [25].

4) Clinical presentation and management.

The clinical presentation in patients with anaerobic pulmonary infection can be acute, subacute or chronic.

Patients with aspiration pneumonia generally present with an acute illness. Clinical features are often indistinguishable from those of community-aquired pneumonia, although initial presentation is often delayed compared to pneumococcal pneumonia. Response to adequate antibiotic treatment is usually prompt, with rapid clinical improvement and early defeverescence. An average of 50 p. cent of patients have strict anaerobic infection where as up to 80 p. cent have mixed anaerobic infection. The mortality rate of simple aspiration pneumonia is less than 5 p. cent [2].

Patients with necrotizing pneumonia tend to present acutely ill with high fever, leucocytosis, putrid sputum and weight loss. Median length of time to presentation is longer than in patients with aspiration pneumonia (15 vs 3 - 4 days), in spite of the severity of the illness. Chest x-ray shows extended pulmonary infiltration with multiple small cavitations (< 1 cm). Empyema is frequently associated. Antimicrobial therapy in these patients is identical to protocols used for aspiration pneumonia. Chest tube drainage is required if empyema is associated. Supportive measures as supplemental oxygen therapy or mechanical ventilation may be required. Complications are frequent and total resolution in often not achieved for at least 4 to 5 weeks. Mortality rate is dose to 20 p. cent [26].

Patients with lung abscess generally present with a sub acute illness. Fever, weight loss, cough, fetid sputum are the most frequent clinical features. Chest x-ray shows a cavitary lesion in a gravity - dependent section of the lung often surrounded by a infiltrate. Presence of an air-fluid level indicates that a bronchopulmonary fistula exists and drain the abscess. Less frequently, empyema may be associated. Treatment is based an prolonged antibiotic therapy adapted to the mixed anaerobic-aerobic bacterial flora. Adjunctive measures include abscess drainage, postural or bronchoscopic and closed chest tube drainage if empyema is present. Response to treatment is usually good, but in 10 to 15 p. cent of patients, this treatment fails and surgical intervention (intra-cavity tube drainage, decortication, lung and/or rib resection) has to be considered. Indicans for surgery are massive hemoptysis, failure to respond to chest tube thoracostomy in the presence of empyema, abscess drainage that fails with postural or bronchoscopic drainage and a diagnosis of carcinoma. The overall prognosis for survival is good (mortality between 5 to 10 p. cent). Poor prognosis is associated with large abscess

formation (> 6cm) severe underlying disease, extreme age, empyema, sepsis and prolonged time prior to presentation and treatment. Mortality associated with these risk factors may be as high as 75 p. cent [2].

II) RATIONALE FOR HYPERBARIC OXYGEN THERAPY

Although anaerobic pleuropulmonary infections carry a relatively low mortality rate under adequate treatment (5 to 10 p. cent), treatment failure may happen. Surgical intervention is reserved to selected indications. In spite of these therapeutic measures, some patients experience a long disease course with persisting septic state, parenchymal destruction and secondary infection localisation

In 1984, based on the beneficial action of HBO in anaerobic soft tissue infections, we were asked by our colleagues from the Pulmonary Medicine Department to consider HBO in a patient with an 3 month long history of lung abscess not responding to adequate and prolonged courses of antibiotic therapy and 2 surgical interventions. As this case turns to be a success, we began to accept for adjunctive HBO, patients with anaerobic pleuropulmonary infection (lung abscess or necrotizing pneumonia) if a 3 week long course of adequate antibiotic treatment and drainage has failed [27]. Considering the well known effect of HBO in anaerobic soft tissue infections and our experience in 13 patients, we propose that some highly selected cases of anaerobic pleuropulmonary infection may be accepted as an indication for adjunctive HBO.

1) Effects of HBO in anaerobic infections :

Beneficial effects of HBO in anaerobic infections have been extensively reviewed and are well known in the hyperbaric medical community (28). Therefore, they do not need to be described here in detail.

In brief: HBO
inhibits toxin production by anaerobes.
is bacteriostatic and bactericidal for strict and facultative anaerobes.
increases the host defences against bacteria in increasing the oxygen dependent microbicidal capability of polymorphonuclears by restoring normal P02 in ischemic infected tissues.
potentiates the activity of selected antimicrobial agents.

Beneficial effects have been found in several models of experimental bacterial infection: Clostridium perfringens gas gangrene, S. pyogenes myositis, Weinstein model of peritonitis, S. aureus Osteomyelitis

2) Literature review

When first asked to consider adjunctive HBO for anaerobic pleuropulmonary infection, we undertook a literature review. We did not find any study published in the French, English or German medical literature. On the other hand, we found 2 papers in the Russian language medical literature claiming HBO efficacy in suppurative and destructive lung and pleural diseases [29, 30]. A recent literature search found 4 more russian references [31-34]. However, differences in reporting data between Western and Eastern countries leads to difficulties in understanding and interpreting these papers and precludes any definite conclusion.

3) our experience

13 patients with anaerobic pleuropulmonary infection have been treated at our Critical Care Unit by adjunctive HBO since 1984. They were 11 males, 2 females. Mean age 45 ± 12 years [34 - 63 y]. Predisposing condition for anaerobic pleuropulmonary infections existed in all except one patients : aspiration in 5 cases, bronchial obstruction in 5, bronchiectasis in 1, chest trauma in 1.

Clinical presentation when referred to our HBO center consisted in fever over 38.5°C in 7 patients, leucocytosis over 12 000 / mm3 in 10, elevated C reactive protein in 7, large quantity of fetid sputum (over 30 mm3) in 8. Chest X-Ray showed lung abscess in 7 patients, necrotizing pneumonia with multiple small cavities in 6. Empyema was associated in 9 patients (lung abscess : 3, necrotizing pneumonia : 5).

Bacteriological study was negative in 3 patients, probably because of the antibiotic therapy received before the sarnpling. In the 10 others patients, 27 germs were isolated, 15 anaerobes, 12 aerobes. Within the anaerobes, Prevotella, Fusobacterium and Peptostreptococcus predominated as in the aerobes, Pseudomonas aeruginosa was the most frequent micro-organism.

Reason to consider adjunctive HBO was the persistence of the lung infection process despite adequate antibiotic therapy and drainage. Mean duration of the standard treatment before HBO was 31 ± 23 days.

HBO was just added to the current treatment. HBO was given in repeated session at 2.5 Ata, 90 minutes pure oxygen, twice a day. Mean HBO session number was 23 ± 11 Clinical response to HBO was impressive. Apyrexia, decrease in sputum volume occurs in 2 to 3 days in all patients. Roentgenographic improvement took about 10 days. Every patients except one, survived and were discharged from the hospital after the end of the HBO treatment. One patient died from a disseminated Candidosis, 3 weeks after the end of the HBO treatment, her lung abscess healed.

4) Risk of HBO in patients with air-filled lung or pleural cavity.

Pneumothorax, air-filled parenchymal bulla and emphysema are well known contra indications to HBO. Patients with anaerobic pleuropulmonary infections have often air-filled lung or pleural cavity and the risk of barotrauma is real if these cavities are not properly drained and put in contact with ambient pressure. If an air-fluid level signs a bronchopulmonary fistula which drains the cavity, any doubt about drainage efficacy must lead to directly drain the cavity by a tube.

HBO session has to be performed in a multiplace chamber, equipped for performing Critical Care and under the dose supervision of a physician trained in pulmonary / Critical Care Medicine and able to immediately perform an additional drainage.

In our 13 patients, we did not experience any complication during HBO session.

CONCLUSION

The well-known beneficial effect of hyperbaric oxygen therapy an anaerobic infections and our experience in 13 highly selected patients lead us to recommend adjunctive HBO to be considered in patients with anaerobic pleuropulmonary infections when a sufficiently long course of adequate antibiotic therapy and drainage has failed. However, in these patients at high risk of barotrauma, HBO may only be performed in a HBO facility located in the immediate proximity of a Critical Care Department and using a multiplace hyperbaric chamber under the permanent supervision of a trained pulmonary and/or critical care physician.

Table 1
Anaerobic Organisms Associated with Aspiration Syndromes (adapted from Finegold et al [24]}

Most Common Isolates:

Fusobacterium nucleatum
Prevotella melaninogenica
Prevotella intermedia
Bacteroides ureolyticus
Bacteroides fragilis
Peptostreptococcus

Less Common Organisms

Eubacterium	Clostridium
Lactobacillus	Proprionibacterium
Actinomyces	

Table 2
Clinical and bacteriological features

No	Age	Sex	Predisposing conditions	Diagnosis	Bacterial isolate
1	36	M	Aspiration due to neurologic disorder	Lung abscess Lung *abscess*	Pr. melaninogenica F. nucleatum Peptostreptococcus Pseudomonas aeruginosa
2	62	M	Obstruction due to bronchogenic carcinoma	Lung abscess	B. oralis P. aeruginosa
3	45	M	Brochiecstasis	Lung abscess	P. aeruginosa
4	39	F	Seizure, Splenectomy, Hodgkin disease		Pr. intermedia Acinetobacter baumanii
5	43	M	Aspiration due to neurologic disorder	Lung abscess	Pr. loeschii Peptostreptococcus as acharolyticus Clostridium sp. P. aeruginosa Enterococcus faecalis Streptococcus sp.
6	53	M	Obstruction due to bronchogenic carcinoma	Lung abscess	
7	50	M		Lung *abscess*	Bacteroides sp. Proteus mirabilis
8	51	M	Obstruction due to bronchogenic carcinoma	Necrotizing Pneumonia	Prevotella sp. Fusobacterium nucleatum Streptococcus anginosus
9	48	M	Coma from toxic origin	Necrotizing Pneumonia	Streptococcus milleni
10	34	F	Chest truama	Necrotizing Pneumonia	Fusobacterium nucleatum Pr. melaninogenica Streptococcus anginosus
11	36	M	Obstruction due to bronchogenic carcinoma	Necrotizing Pneumonia	Peptostreptococcus Peptococcus Staphylococcus aureus
12	63	M	Obstruction due to bronchogenic carcinoma	Necrotizing Pneumonia	
13	18	M	Tracheo-esophageal fistula	Necrotizing Pneumonia	

Table 3
Treatment and outcome

Antibiotic treament	Duration before HBO start (days)	Number of HBO sessions	Hospital stay alter HBO stop (days)	Outcome
Piperacillin Metronidazole	90	30	15	Cured
Ampicillin/ Sulbactam Metronidazole Ofloxacin	45	36	8	Cured
Piperacillin/ Tazobactam Amikacin	16	13	4	Cured
Ticarcillin/ Sulbactam Amikacin Metronidazole	45	12 Lung abscess	21	L cured Died from disseminated Candidosis
Piperacillin Metronidazole	21	15	4	Cured
Piperacillin Metronidazole Amikacin	21	15	4	Cured
Piperacillin Metronidazole Amikacin	30	40	1	Cured
Piperacillin Metronidazole	20	10	3	Cured
Piperacillin Metronidazole Cifloxacine	45	20	1	Cured
Piperacillin/ Tazobactam Amikacin	30	20	1	Cured
Ampicillin Metronidazole Amikacin	28	20	1	Cured
Piperacillin Metronidazole Amikacin	30	30	15	Cured
Piperacillin Metronidazole Amikacin	60	36	21	Cured

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STERNAL WOUND INFECTION MANAGEMENT WITH A COMBINATION OF HYPERBARIC OXYGEN THERAPY (HBO2) AND VACUUM-ASSISTED CLOSURE (VAC)

Sudarsky L', Fischer E[1], Al-Wali N[2], Butler G[3:] UHM 2010, VOL. 37, NO. 5 - 2010
ABSTRACTS: WOUND HEALING AND HBO2 TREATMENTS C17

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Introduction: Deep sternal wound infections are a major and often persistent complication following cardiac surgery. Despite accepted treatment modalities, the cost and mortality associated with this complication remain high with significant post operative hospitalizations cornmon. Hyperbaric oxygen (HBO2) and vacuum-assisted closure (VAC) are widely used for treatment of chronic wound infections and non-healing wounds but have not been reported in combination for sternal wound management. We report four patients with sternal wound infections, two treated with a combination of VAC and HBO2.

Materials and methods: Four patients were included in this study. Two patients were treated with a combination of HBO2, VAC, wound care and antibiotics. Two patients were treated conventionally with antibiotics, wound care and flap reconstruction. All patients had osteomyelitis, with positive Wood cultures, and received six weeks of IV antibiotics according to their organism (except Patient 4 ,who expired at three weeks). HBO2 treatment included 2.5 atmospheres absolute for 110 minutes, four to five sessions each week

Results: The average age was 73 years old, three males, one female, with all patients having multiple comorbidites. Two patients treated with conventional management expired from sepsis and multi-system failure. The two patients treated with HBO2 and VAC are alive and well. Follow-up is nine months-one year.

Conclusions: Results demonstrate that a combination of VAC, HBO2, antibiotics and minimal surgery helped resolve infections and accelerate sternal wound healing. This protocol of HBO2, VAC, and antibiotics, can minimize or even eliminate the extensive surgical debridements and reduces recovery time as compared to the traditional management of deep sternal infections

Segal E; Menhusen MJ; Shawn S**: Hyperbaric oxygen in the treatment of invasive fungal infections: a single-center experience.** The Israel Medical Association journal : IMAJ; VOL: 9 (5); p. 355-7 /2007

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NOTE:
Comment in: Isr Med Assoc J. 2007 May;9(5):387-8; Ref.PMID: 17591380 AB:

BACKGROUND: Invasive fungal infections by Mucorales or Aspergillus spp. are lethal infections in immune compromised patients. For these infections a multimodal approach is required. One potential tool for treating these infections is hyperbaric oxygen.

OBJECTIVES: To evaluate the clinical course and utility of hyperbaric oxygen in patients with invasive fungal infections by Mucorales or Aspergillus spp.

METHODS: We conducted a **retrospective chart review** of **14 patients** treated with HBO as part of their multimodal therapy over a 12 year period.

RESULTS: Most patients had significant immune suppression due to either drug treatment or their underlying disorder. Thirteen of the 14 underwent surgery as part of the treatment and all were receiving antifungal therapy while treated with the hyperbaric oxygen. The number of HBO sessions ranged between 1 and 44. Seven of the patients survived the infection. No patient developed complications due to HBO therapy.

CONCLUSIONS: HBO is a potentially significant adjunct in the treatment of invasive fungal infections. Evidence on its usefulness as a standard of care in these infections is still lacking. Since it will be difficult to generate conclusive data regarding the importance of HBO in these infections, the value of HBO in these patients should be considered on an individual basis.

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Das komplette Verzeichnis unserer bisherigen Literaturrecherchen unselektiert mit für HBO positiven und negativen Artikeln als Angebot für Ihre weitere Information. Sollten Sie Artikel besitzen die hier nicht mit " + " gekennzeichnet sind, wären wir für eine Kopie sehr dankbar.

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