

Hyperbaric Medicine Literature Update

The Year in Review

UHMS Annual Scientific Meeting
Maui, Hawaii

June 15, 2007

www.baromedical.com/scientific_literature.asp

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Newly Approved Medicare Indication

Arterial Insufficiency Ulcer

'Arterial insufficiency ulcers may be treated with HBO therapy if they are persistent after reconstruction surgery has resolved large vessel function'

LCD's L1315 & L6691 HBO Therapy
First Coast Service Options; Florida F.I. 2006

LCD L12834 HBO Therapy
National Government Services; Ohio F.I. 2006

'Newly' Approved Hyperbaric Use

Anthem BCBS

'Medically Necessary' Indication

Prophylactic pre and post-treatment for patients undergoing dental surgery in an irradiated jaw

Anthem Medical Policy *
MED. 00005 8/2006

Common Medicare F.I. Language
** merged with Wellpoint*

'HBO is not covered to prepare the patient for dental extractions in order to prevent development of osteoradionecrosis'

Newly Approved Hyperbaric Uses

Aetna Insurance Company

'Medically Necessary Indications'

- Ø Prophylactic pre and post-treatment for patients undergoing dental surgery within an irradiated jaw
- Ø Ideopathic sudden deafness, acoustic trauma or noise-induced hearing loss
- Ø Complications of *artificial* skin grafts
- Ø Pnematosis cystoides intestinalis

Aetna Insurance Comp.
Policy No. 0172; 2007

Evidence-based Medicine

Two key concepts frequently overlooked...

Lack of high level evidence does not mean lack of efficacy

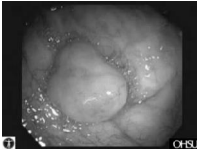
If no Level 1 evidence exists for a given condition one follows the trail to the next best level and works from there

Sackett DL, et al. 1996
BMJ; 312: 71-72

~ purchasers of health care are likely to view evidence somewhat differently than a clinician

Treatment of Pneumatosis Cystoides Intestinalis

Method	Number of Cases	Recovery Rate (%)
Observe	21	95%
Normobaric O2	30	92%
HBO therapy	11	100%
Ventrotomy		
i. Intestinal resection	38*	91%(2 died)
ii. Ventrotomy only	17**	85%(1 died)



* peritoneal signs present – 42%

** peritoneal signs present – 22%

20/55 (37%) surgeries probably unnecessary ... 5% mortality

Togawa S, et al. 2004
UHM;31(4):387-393

Treatment Recommendations by Etiology

i. Disrupted Mucosa:
Fragile membranes may rupture and allow gas entry into the intestinal wall in the setting of high intra-luminal pressures

Treat symptomatic cases with normobaric oxygen; use HBO in poorly, or non-responding, cases

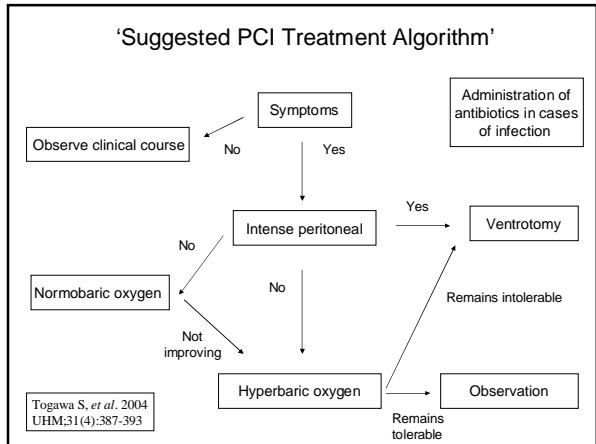
ii. Gas Dissection:
Leaking pulmonary gases dissect from the alveoli or bronchial structures

Treat symptomatic cases with normobaric O2; HBO for more symptomatic or non-responding cases, and use with caution

Treatment Recommendations by Etiology

iii. Gas Retention:
Gas forms in the intestinal wall secondary to infection process, involving gas-producing bacteria

Intestinal resection is likely to be the preferred option



Adjunctive HBO Therapy for Diabetic Foot Ulcers

An economic analysis

HBO more effective than standard care alone
Major LEA's decreased from 32% to 11%

HBO cost effective compared to standard care alone
... 19% reduction in overall health care costs *
... 'large' increase in Q-ALY's

* 12-year cost

Hailey D, Jacobs P, Perry DC, et al. 2007
Canadian Agency for Drugs and Technologies in Health;
Report No. 75 www.cadth.ca

Caveats

Most diabetic foot ulcers heal with standard care
~ *guidelines necessary for suitable hyperbaric candidates*

As standard care evolves and better quality studies become available, HBO's comparative advantage may change

Hailey D, Jacobs P, Perry DC, *et al.* 2007
Canadian Agency for Drugs and Technologies in Health;
Report No. 75 - www.cadth.ca

Hyperbaric Oxygen for Diabetic Foot Wounds

Point:

- Ø Most 'non-healing' wounds heal with meticulous standard care
- Ø TcPO2 has a predictive capacity; can be used to follow treatment
- Ø Argues the CMS/Medicare position
- Ø HBO may lower overall health costs (major amps. and rehab)
- Ø Large high quality RCT's 'imperative'

Barnes RC, 2006
Clinical Infectious Diseases;43:188-192

Hyperbaric Oxygen for Diabetic Foot Wounds

Counterpoint:

- Ø Questions basic science assumptions; faith that overcorrecting hypoxia is beneficial has its roots in 19th century quackery
- Ø Argues present clinical science flawed; no blinding or placebo
- Ø High costs better spent elsewhere (prevention; better therapies)
- Ø Time for advocates to organize large RCT's

Berendt AR; 2006
Clinical Infectious Diseases;43:193-198

Reversal of DM Impaired EPC Mobilization and Homing by HBO and SDF-1 α

~ *murine model*

Wound and circulating EPC's levels decreased in DM

Homing of EPC's to diabetic wounds is diminished

HBO's NO activation role explored; along with SDF-1 α admin.

1. 2.4 ATA O2 x 90 increased BM NO and circulating ERC counts
2. Admin. of SDF-1 α reversed homing impairment
3. Both agents synergistically enhanced acute wound closure

Gallagher KA, *et al.* 2007
J Clinical Investigation;117(5)

Thoughts...

Excellent science; used the known HBO NO connection
Important advancement
These were acute wounds...and relevance to humans
Incorporate this sampling and analysis into RCT's
Other repair stimulating factors...working in sequence or in parallel?
This type of research impresses the academic skeptics

Guidelines for the Treatment of Diabetic Ulcers

EBM, employing the modern approach and representing the position of the Wound Healing Society

Systemic Agents

Guideline 7.3.1: Hyperbaric oxygen therapy may be of benefit in reducing amputation rates in patients with ischemic diabetic foot ulcers (Level 1 evidence *)

* *The highest of three levels allocated*

Stead DL, *et al.* 2006
Wound Repair and Regen.;14:680-692

Guidelines for the Treatment of Arterial Insufficiency Ulcers

EBM, employing the modern approach and representing the position of the Wound Healing Society

Systemic Agents

Guideline #6.B.1a: HBO an adjunct in non-reconstructable cases, or in those ulcers not healing despite revascul.

Selection criteria based upon reversible local hypoxia, per tcPO2
Level 11 B (this committee rated DFU's Level 1A)

Recommendations:

- A. Strongly recommended
- B. Recommended

Hopf, HW, et al. 2006
Wound Repair and Regen.;14:693710

Guidelines for the Treatment of Arterial Insufficiency Ulcers

Systemic Agents

Guideline #6.B.1b: HBO should be investigated in the treatment of I-R injury after revascularization in such patients

'The benefits of HBO therapy in the treatment of ischemia reperfusion in skin flaps are well known'

Hopf, HW, et al. 2006
Wound Repair and Regen.;14:693710

Hyperbaric Oxygen vs. Hypoxic Cerebral Preconditioning

Hypoxic stress induces significant neuro-protection in certain experimental settings

~ Clinically risky and impractical

Alternatives sought for high risk clinical conditions...cerebral and cardiovascular surgery

Freiberger JJ, et al. 2006
Brain Research;1075:213-222

Hyperbaric Oxygen vs. Hypoxic Cerebral Preconditioning

~ rat pup model

Insult: unilateral carotid cauterization then 90 mins. 8% O2 on postnatal day 7

HBO...high dose = 1 x 2.5 ATA for 150 mins. 24 hrs. pre-insult
low dose = 2 x 2.0 ATA for 60 mins. 48 hrs. pre-insult
or 3 x 2.0 ATA for 60 mins. 24 hrs. pre-insult

Hypoxic Preconditioning ...8% oxygen up to 150 mins.

Outcomes Measures:
~mortality and brain weight

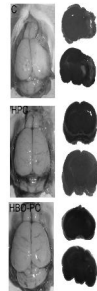
Freiberger JJ, et al. 2006
Brain Research;1075:213-222

Findings

Essentially identical brain weight improvement and survival between both preconditioned groups, compared to controls

Mortality: Controls 14.7%
H-PC 5.9%
H-HBO 5.7%
p = 0.04

Brain Weight Decrease: Controls 42%
H-PC 25%
H-HBO 26%
p = 0.001



Freiberger JJ, et al. 2006
Brain Research;1075:213-222

Thoughts

- Ø More excellence science; temperature control critical
- Ø Hypoxic preconditioning effective but impractical, particularly in likely target populations
- Ø Single hyperbaric treatment within 24 hours of insult has a largely identical protective effect to hypoxia, imminently more feasible and safer
- Ø Mechanisms of protection very different; will hopefully stimulate additional research
- Ø Other possible markers of injury/recovery?
- Ø Clinical relevance?

Hyperbaric Pre-conditioning Effect on Neuropsychometric Dysfunction & Systemic Inflammatory Response after CABG

~ a randomized controlled double-blind trial

64 patients randomized to HBO (2.4 ATA) or HBA (1.5 ATA) before on-pump CABG

~ 24, 12 and 4 hours pre-operatively

Both groups well matched for demographic and pre-operative factors

Alex J. et al. 2005
J Thoracic Cardiovasc Surg;130(6)

Comprehensive Screening Battery:

~ at 48 hours pre-op and 4 months post-op

16/31 (51%) controls with significant dysfunction, vs. 9/33 (27%) HBO

~ $p = 0.05$

Inflammatory Markers:

~ at pre-op, 2 hours post-op and 24 hours post-op

ANOVA found significant post-op increases in 3 (sE-selectin 0.05; CD18 0.001, HSP-70 0.007) of 8 markers in controls vs. HBO group

~ there were increases in other markers in both groups

Alex J. et al. 2005
J Thoracic Cardiovasc Surg;130(6)

What to take home from this one?

Clinical relevance!

Encouraging recruitment percentage (84%)

Controls received 30% O₂; what of 100% O₂ at 1.0 ATA?

None of the tested variables predictive of neuropsych. decline

HBO reduced inflammatory response amplitude

Mechanism?

Dental Implant Surgery in Irradiated Bone

The case for hyperbaric oxygen...

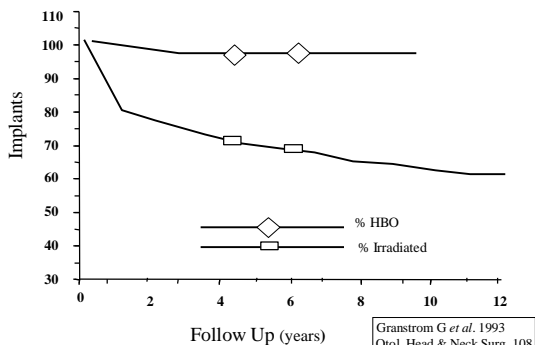
Gosta Granstrom; J Oral Maxillofacial Surg. 2006;64:812-818

The case against hyperbaric oxygen...

R Bruce Donoff; J Oral Maxillofacial Surg. 2006;64:819-822

It's the radiation portal!

Cumulative Implant Loss



Hyperbaric Oxygen in Support of Osseo-integration Implant Surgery

Hyper

No (lower failure risk) Yes (higher failure risk)

XRT pre/post tumor surgery?	no	yes
XRT pre O.I. surgery?	no	yes
Time(months) from surgery?	< 3	> 3
XRT dose (Gy), per implant site?	< 40	> 50
Adjuvant chemotherapy (at O.I.)?	no	yes
Implants into grafted bone?	yes	no
Implant length?	long	short (3-7mm)
Console® abutments?	no	yes
Coarse implant surfaces?	yes	no

Skin Flaps and Skin Grafts: An Evidence-Based Appraisal of HBO

AHA EBM Scheme

<p>Skin Flaps assessed by design:</p> <ol style="list-style-type: none"> 1. Local rotation <ol style="list-style-type: none"> i. random pedicle flaps ii. axial pedicle flaps 2. Distant 3. Free 	<p>Skin Grafts assessed as:</p> <ol style="list-style-type: none"> 1. Split thickness 2. Full thickness 3. Composite
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HBO assessed by:
Pre and/or post-op; timing; pressure; length; duration

And compared to other interventions that influence survival

Friedman HI, et al. 2006
Plastic and Reconstructive Surgery;117

Composite Skin Grafts

Animal data conclusions:

HBO improves partial flap survival of composite grafts if administered often enough and long for enough ... *AHA level VI*

If the flap is too large or too distant from its potential blood supply, a portion or all will die, regardless of HBO

Other modalities may potentiate graft survival

More information is needed on combining therapies

Friedman HI, et al. 2006
Plastic and Reconstructive Surgery;117

Composite Skin Grafts

Clinical data conclusions:

Much less data than animal studies, yet available data does suggest efficacy...AHA IV
in supporting 'take' of relatively large grafts

Important to emphasize the absence of any other clinical studies of other modalities, so Level IV is *best* evidence

Friedman HI, et al. 2006
Plastic and Reconstructive Surgery;117

Split and Full Thickness Skin Grafts

Animal and clinical data conclusions:

No clear laboratory or clinical data specifically demonstrating improved graft survival with pre-op HBO
...the same can be said for other suggested modalities

Rational conjecture...Level 8...suggests improved angiogenesis in otherwise compromised wounds with pre-op HBO
...argues for its application in certain clinical states

Providing HBO during graft take (post-op) period not usually necessary

Friedman HI, et al. 2006
Plastic and Reconstructive Surgery;117

Random Flaps

Animal data conclusions:

HBO therapy increases length of dorsal flap survival (18-25%) of total flap length...Level VI
...best results obtained with combination pentoxifylline

Similar results seen in epigastric flaps (20-30%)

Human data conclusions:

A paucity of controlled data; evidence does reaches Level IV

'By combining above data when applied immediately post-op and for an undetermined time, HBO may increase amount of surviving tissue. Can be calculated from animal work as likely sufficient to avoid repeat surgery'

Friedman HI, et al. 2006
Plastic and Reconstructive Surgery;117

Distant Flaps

Animal data conclusions: (no clinical data)

HBO therapy does provide some protection against I-R injury... Level VI...for free flaps with prolonged primary or secondary ischemia

Summary... *'there is enough animal evidence and observational data to warrant HBO in selective situations'*

- Ø to enhance skin graft take in compromised recipient beds
- Ø to support unusually large composite grafts
- Ø to aid in survival of compromised flaps

Friedman HI, et al. 2006
Plastic and Reconstructive Surgery;117

Decompression Illness and the Monoplace Chamber

Treatment using the Hart/Kindwall protocol
~ clinical outcomes

Cianci P, Slade JB, 2006
Aviat Space Environ Med;77(10):1003-8

Treatment using US Navy Table 6
~ the management process

Weaver L, 2006
Undersea Hyperbaric Med;33(2):85-88

Early HBO Life-saving in Severe Blunt Chest Trauma

~ 26 patients grouped by outcome

Hypothesis: Based upon the observation that such injuries often result in profound cardio-respiratory dysfunction...drastic decreases in O2 delivery and considered major predictor of fatal outcome

'HBO is the most potent anti-hypoxic strategy'

Group A: Conventional care, survived 4

Group B: Conventional care, died 14 (77% mortality)

Group C: Conventional care and HBO; all 8 survived

Rogatsky GG, Mayersky A, 2007
UHM;34(2):75-81

Thoughts...

Any survival advantage should be further researched

Study limitations...consecutive patients? HBO selection process? Historic or concurrent controls?

Modest and non-uniform hyperbaric oxygen dosing...1.6 to 2.0 ATA O2; 40-60 minutes; 4-15 txs.

Monoplace hyperbaric delivery system...25/26 had a pneumo. or hemo-pneumothorax

Lung Metastatic Load Limitation with HBO Therapy

Mouse mammary adenocarcinoma cell line

~ lung isolation and perfusion
~ followed by fluorescence microscopy

Group 1: (32) QD HBO 2.8 ATA x 45 mins. x 25

Group 2: (34) Controls; no HBO exposure

Abu TMY, et al. 2007
UHM;34(2):83-90

Lung Metastatic Load Limitation with HBO Therapy

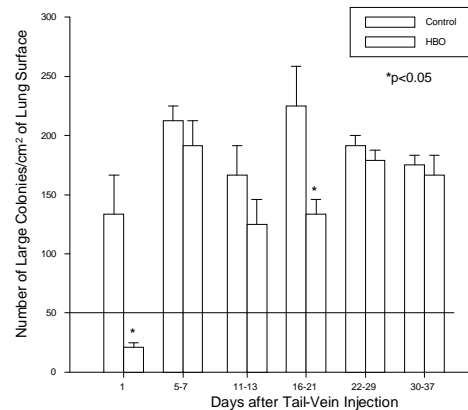
Results:

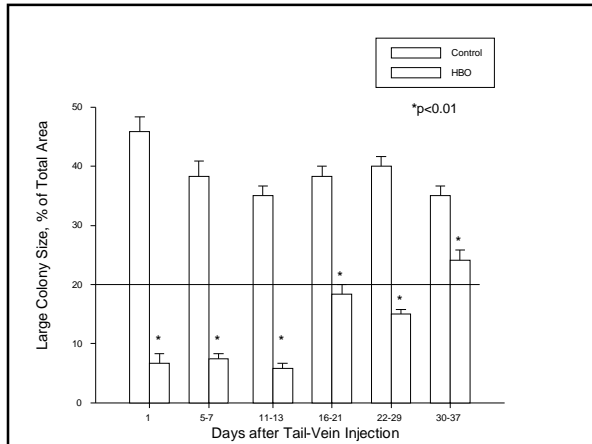
- Ø No increase in large or small tumor cells colonies
- Ø A significant reduction in number of large colonies
- Ø A significant decrease in large cell colony size

Conclusions:

- Ü HBO not pro-metastatic for breast cancer cells
- Ü HBO restricts growth of large tumor cell colonies

Abu TMY, et al. 2007
UHM;34(2):83-90





Interstitial Cystitis

A randomized, sham controlled, double-blind trial

2.4 ATA O₂ x 90 mins. for 30 treatments... 14 patients
 1.3 ATA air x 90 mins. for 30 treatments... 7 patients

Patient satisfaction upon unblinding

	3 mos		6 mos		12 mos	
	HBO	SC	HBO	SC	HBO	SC
No. pts:	14	7	12	7	12	7
Satisfaction:						
Poor	5	7	5	7	7	7
Fair	4	0	2	2	2	2
Good	4	0	4	4	2	2
Excellent	1	0	1	1	1	1

van Ophoven A *et al.* 2006
 Journal Urology:176:1442-1446

Take home messages

Disease of exclusion; symptomatic presentation which may disappear and return spontaneously

So, would have been helpful to also follow controls

No cure; no effective therapies as cause(s) unknown

No predictive capability for HBO response

Mechanism?

HBO compared to bladder manipulation and oral meds

Further study warranted

Mortality Protective Potential of HBO in Sepsis: Mechanism?

~ murine model

Is HBO protective in cecal ligation and puncture?

If so, is this process linked to macrophage production of interleukin-10?

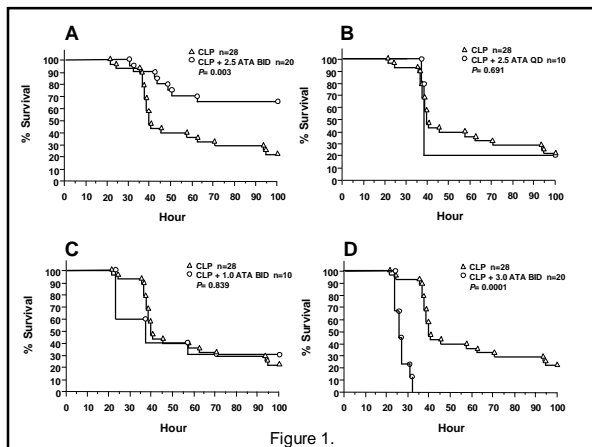
Is any such protective effect dose-dependent?

Outcomes

Survival comparison over 100 hrs

HBO's effect on bacterial load/clearance

Buras JA, *et al.* 2006
 Critical Care Med:34(10)



HBO may be protective in CLP sepsis, in a narrow dosing window

Significantly greater mortality at 3.0 vs. 2.5 ATA
~ direct effect of oxygen toxicity?

Mechanism appears linked to enhanced expression IL-10

Buras JA, *et al.* 2006
 Critical Care Med:34(10)

Ischemic Scleroderma and HBO Therapy

Two otherwise refractory cases treated successfully

Tissue oximetry confirmed hyperbaric candidacy

30 treatments; 2.4 ATA O₂ x 90 mins. X 30 treatments

Both remain healed at six months follow-up

Publication bias?

No better evidence... Level V ...with alternate therapies

Markus YM, *et al.* 2006
J Rheumatology;33:8

Transplantation

Renal transplant; rat model.

Solmazgul E, *et al.* 2006
Urologia Int.;78:82-85

Group	Histopathological Score	Neutrophil Infiltration
Control	0.0	1.1 +/- 0.1
I/R	3.2 +/- 0.3* **	15.2 +/- 2.3* **
I/R + HBO	1.4 +/- 0.2 *	6.4 +/- 1.3*

* p < 0.05 vs. control ** p < 0.05 vs. HBO

* * * * * * *

Liver transplant; case report

Post-liver transplantation hepatic artery thrombosis
~ re-canalized with heparin and HBO, after TPA failure

Grover L, *et al.* 2006
Pediatr Transplantation;10