



# Hyperbaric Oxygen Therapy in Selected Infections

*A Summary of its Science,  
Evidence and Practice*

**HyperBaric Oxygen<sup>KC</sup>**  
Wound Healing Center of Mid America

To refer a patient or speak with a member  
of our staff, please call 816.943.4600.  
Normal business hours are Monday-Friday  
8:00 a.m. – 5:00 p.m.

## Introduction

An antibiotic effect of hyperbaric oxygen (HBO) therapy was first identified in the early 1960's. Hyperbaric doses of oxygen proved to be bactericidal or bacteriostatic (depending upon its dose) in anaerobic and facultative anaerobic infections. Mortality is, therefore, reduced when HBO therapy is added to standard care in Clostridial perfringens infections (gas gangrene). HBO therapy has helpful antimicrobial effects in aerobic infections. It serves to correct and enhance tissue oxygen tensions required for normal leukocyte and neutrophil killing activities.

The following are some examples in which the inclusion of HBO therapy will, or is likely to, improve morbidity and mortality.

## Chronic Refractory Osteomyelitis

As the title implies, refractory bone and bone marrow infections are difficult to cure. They are persistent, frequently severe and sometimes incapacitating. Surgical debridement represents mainstay treatment. It provides a clean platform for future healing and samples for microbiology to guide antibiotic therapy. Advances in surgical technique, including bone grafting, Ilizarov procedures and microvascular free flaps have improved cure rates, which now range between 70-80%.



Common appearance of long bone chronic osteomyelitis

In the balance of patients whose infections fail to resolve, additional interventions are warranted. HBO therapy is one such example. Its mechanistic basis centers around restoration of normal to elevated oxygen tensions in infected bone. Neutrophils require tissue oxygen tensions of 30-40mmHg to destroy bacteria. Leukocyte killing of aerobes is restored when low oxygen levels are increased to physiologic and supraphysiologic (hyperbaric oxygen-induced) levels. These HBO produced elevations have been observed.<sup>(1)</sup> Active transport of some antibiotics across bacterial cell walls is impaired when tissue oxygen tensions are below 30 mmHg. HBO, through provision of adequate tissue oxygen tensions, has been shown to be synergistic with aminoglycosides, quinolones, and cephalosporin classes of antibiotics.<sup>(2)</sup> HBO therapy enhances osteogenesis<sup>(3)</sup> and stimulates osteoclast activity.<sup>(4)</sup>

The Cierny-Mader classification system (Table) has proven an effective guide to determine who is likely to benefit from HBO therapy. It appears those patients with Stage 3 or 4 osteomyelitis complicated by adverse local or systemic risk factors benefit most.

Chronic refractory osteomyelitis is also a difficult condition to study, given its many variables, such as location, staging, bacteriology, and host issues. It is not surprising, therefore, that no high quality clinical studies have been reported for any of the currently employed surgical and medical options. In their absence, one must rely on the results of prospective and retrospective studies, in concert with supportive laboratory science. HBO's basic and clinical science has been recently and comprehensively summarized, in this regard.<sup>(5)</sup>

One aspect of HBO's clinical research is worthy of specific mention. Orthopedic surgeons from Taiwan prospectively studied patients who had failed at least three surgical debridements and concurrent parenteral antibiotics. In companion papers<sup>(6,7,8)</sup> they reported improved overall cure rates when HBO was *added* to standard care. All infections were located in long bones (tibia and femur). For tibia cases, 24 of 29 (83%) were cured, with a mean follow-up of 17 months. Cure rate for femur infections was 12 of 13 (92%), with a mean follow-up of 22 months.

In summary, HBO overcomes tissue hypoxia, improves neutrophil and leukocyte killing activities, increases antibiotic effectiveness, stimulates osteoclast activity and promotes osteogenesis. Clinical data, while limited, is suggestive of an encouragingly high cure rates in otherwise refractory cases.

### Table

Cierny-Mader Classification System			
Anatomic Type		Host	
Stage 1	Medullary	A	Normal
Stage 2	Superficial	B	Systemic or Local Compromise
Stage 3	Localized	C	Treatment Worse than Disease
Stage 4	Diffuse		

## Perioperative Neurosurgical Infections

Postoperative neurosurgical infections are particularly concerning, sometimes untreatable and associated with substantial morbidity and mortality. Despite modern antibiotics and prophylactic regimens, current rates of infection are little changed from the 1960's.

Conventional therapy involves use of antibiotics and removal of both infected bone flaps and fixation devices. Further complicating subsequent healing is the presence of malignant disease, radiation injury, chemotherapy, tissue

## Intracranial Abscess

The term 'intracranial abscess' can refer to either a cerebral abscess, a subdural empyema or an epidural empyema. Each of these conditions shares many etiologic, diagnostic and therapeutic similarities. Mortality, as high as 30% two decades ago, has decreased to slightly less than 20% secondary to more accurate diagnosis, minimally invasive surgery and better antibiotic selection.

This evolution has resulted in a trend to a more conservative therapeutic approach. However, a subset of patients continues to pose major therapeutic challenges. They include those with multiple abscesses, an abscess in a deep or dominant location, immune compromise and those who fail to respond or continue to deteriorate in spite of standard surgical and medical treatment.

Under these circumstances, HBO therapy may provide additional therapeutic benefit. High partial pressures of oxygen may inhibit flora found in these abscesses, most of which are anaerobic. HBO can also reduce swelling and has the potential to enhance host defense mechanisms. Preliminary evidence is encouraging. While retrospective in nature, a characteristic of essentially every other report addressing management of brain abscess, the addition of HBO therapy to standard care resulted in one fatality (1.5%) and shortened length of time on antibiotics in 66 patients.<sup>(5)</sup> Equally encouraging results were seen in children.<sup>(10)</sup> Patient selection criteria for HBO therapy centers around the finding of multiple abscesses, deep or dominant location, compromised host, poor surgical candidates and no response or deterioration with standard care.<sup>(5)</sup>



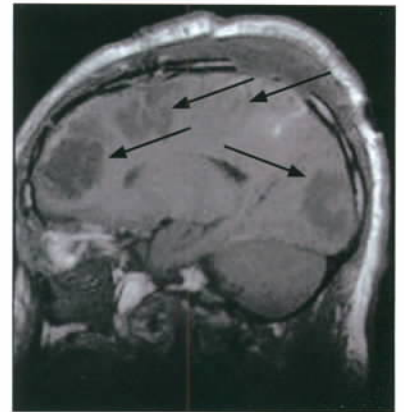
*Occipital medulloblastoma surgery resulted in suppurative wound infection, treated by removal of bone flap. Condition deteriorated after radiotherapy, leading to wound breakdown, exposed dura and necrotic cavities. MRSA was cultured. HBO allowed gradual healing and clearing of MRSA without antibiotics. Full wound contracture had occurred after 38 treatments.*



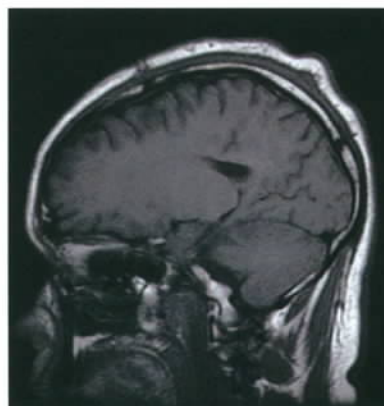
transplants and foreign material. HBO therapy has been applied in a variety of infected, hypo-perfused and hypoxic wounds. In 2002, a Journal of Neurosurgery paper written by a multidisciplinary team at Karolinska Hospital in Stockholm, Sweden, reported their experience with HBO therapy in 39 consecutive patients referred from the Department of Neurosurgery with post-operative infection.<sup>(9)</sup> Patients were those whose treatment would have otherwise been repeated surgery and removal of bone flaps or foreign material. Infection control and healing without removal of flaps or hardware was considered to represent hyperbaric treatment success.

Success occurred in 27 of 36 (75%) patients, with a mean follow-up of 27 months. Twelve of 15 (80%) patients with uncomplicated cranial infections healed with bone flap retention. Seven of eight (87%) patients with complicated cranial wound infections healed, with retention of three of six acrylic cranioplasties. All of those with spinal wound infections healed, five of the seven without removal of fixation systems.

Invited commentary from the journal's editor produced several and consistently positive replies.<sup>(9)</sup> The paper's authors were commended on their successful outcomes and high degree of bone and hardware retention rates. It was felt that the choice of HBO therapy was logical, that results were superior to those whose infections are managed conventionally and that reported outcomes strongly supported a beneficial role of HBO therapy in postoperative neurosurgical infections.



*Multiple intracranial abscesses; left hemiplegia. No improvement following aggressive surgical (three craniotomies) and medical care. HBO considered as a 'last resort'.*



*Marked improvement apparent following 12 HBO treatments. Hemiplegia has resolved and patient now ambulatory. Mental status has returned to baseline.*

## Postoperative Sternal Surgical Site Infections

Postoperative sternal wound infections continue to complicate cardiac surgery involving midline sternotomies. These infections are potentially devastating (mortality reported as high as 15%) and involve all age groups. Myocutaneous flaps have represented a major management advance. In those patients who are not candidates for flap repair or continue to suffer infection after undergoing flap repair, additional interventions are warranted. HBO therapy can prove a valuable adjunct in this regard.

The sternal wound is, by its nature, ischemic and hypoxic. These conditions hinder neutrophil-mediated killing of bacteria and the subsequent healing cascade. As applied in other infections discussed within this document, HBO therapy can reverse hypoxia, reduce local edema, salvage marginally perfused tissue, augment host defenses, decrease bacterial proliferation and inhibit growth of anaerobic bacteria.<sup>(5)</sup> Published data describing the inclusion of HBO therapy to standard care is limited but positive.<sup>(11)</sup>

The most recent report describes the clinical course of 34 patients.<sup>(11)</sup> This prospective study involved offering HBO to standard care in all 34 patients. Fourteen accepted, the remaining 18 either declined or had hyperbaric contraindications. Both groups were well matched for clinical and operative characteristics, with staphylococcus the most common pathogen. Hospital length of stay, duration of antibiotic use and relapse rates were all significantly lower in the HBO group ( $p = 0.026$ ;  $p = 0.036$  and  $p = 0.024$ , respectively). No HBO-related adverse effects occurred. While additional data is clearly desirable, HBO appears to represent a valuable adjunct, in refractory cases. Its therapeutic benefits are multifactorial and its risk profile very acceptable.

## Invasive Rhinocerebral Fungal Infections

Invasive mucormycosis and aspergillosis infections are frequently lethal<sup>(12)</sup> in immunocompromised patients and a leading cause of early death in many transplant centers. Mortality is also high in non-immunocompromised patients. Oxygen levels are decreased in these infected tissues since fungi invade blood vessels, causing occlusion, thrombosis and hypoxia. This hypoxic environment results in tissue necrosis, diminished oxidative anti-fungal effects of amphotericin B, impaired oxidative killing capacity and reduced white cell phagocytosis. Standard care involves anti-fungal agents, surgical debridement and where possible, correction of the predisposing condition. Interestingly, debridement in neutropenic patients has actually increased mortality secondary to delayed post-operative hemorrhage.<sup>(13)</sup>

Given such a very poor overall prognosis it is imperative that other interventions are sought in order to maximize multimodal therapy. HBO therapy holds promise in this regard. It elevates oxygen levels in hypoxic tissue and has an additive fungicidal effect when combined with amphotericin B.<sup>(14)</sup>

A single center retrospective study of ten consecutive aspergillosis patients treated with HBO therapy reported a 60% response rate.<sup>(15)</sup> One of the non-survivors was free of infection at the time of death. A similar single center report of various fungal infections and anatomic sites noted a 55% response rate in rhinocerebral cases. These rates compare favorably with those reported where HBO therapy was not incorporated.

Mechanistically, HBO has several benefits to offer. Clinical experience is limited to a number of small cases series and single case reports. Given the relative infrequency of this infection, however, it is, while highly desirable, unlikely that larger trials and higher evidence levels will be generated. Given the devastating nature of invasive fungal infections, and its potential value, HBO therapy should be viewed as a reasonably substantiated safe adjuvant therapy,<sup>(16)</sup> particularly given its low risk.

### References: (Available upon request)

1. Mader J, Brown GL, Gucklan JC. A Mechanism for the Amelioration by Hyperbaric Oxygen of Experimental Staphylococcal Osteomyelitis in Rabbits. *The Journal of Infectious Diseases* 1980; 142(6).
2. Mendel V, Reichert B, Simanowski HJ, et al. Therapy with Hyperbaric Oxygen and Cefazolin for Experimental Osteomyelitis Due to Staphylococcus Aureus in Rats. *Undersea & Hyperbaric Medicine* 1999; 26(3).
3. Steed DL. Enhancement of Osteogenesis with Hyperbaric Oxygen Therapy. *J. Dental Res* 1982; 61(A).
4. Jones JP. The Effect of Hyperbaric Oxygen on Osteonecrosis. *Orthopaedic Research Society* 1991.
5. Gesell LB. Hyperbaric Oxygen Therapy Indications 12th Edition 2008. Undersea & Hyperbaric Medical Society. Durham, NC.
6. Chen CY, Lee SS, Chan YS. Chronic Refractory Tibia Osteomyelitis Treated with Adjuvant Hyperbaric Oxygen: A Preliminary Report. *Chang Gung Med J* 1998; 21.
7. Chen CE, Shih ST, Fu TH, et al. Hyperbaric Oxygen Therapy in the Treatment of Chronic Refractory Osteomyelitis: A Preliminary Report. *Chang Gung Med J* 2003; 26(2).
8. Chen CE, Ko JY, Fu TH, et al. Results of Chronic Osteomyelitis of the Femur Treated with Hyperbaric Oxygen: A Preliminary Report. *Chang Gung Med J* 2004; 27(2).
9. Larsson A, Engstrom M, Uusijarvi J, et al. Hyperbaric Oxygen Treatment of Postoperative Neurosurgical Infections. *Neurosurgery* 2002; 50(2).
10. Kurschel S, Mohia A, Weigl V, et al. Hyperbaric Oxygen Therapy for the Treatment of Brain Abscess in Children. *Childs Nerv Syst* 2006; 22.
11. Barili E, Polvani G, Topkara VK, et al. Role of Hyperbaric Oxygen Therapy in the Treatment of Postoperative Organ/Space Sternal Surgical Site Infections. *World J Surg* 2007; 31.
12. Vandewoude KH, et al. Invasive Aspergillosis in Critically Ill Patients. *J. Hospital Infect.* 2004.
13. Denning DW, Stephens DA. Antifungal and Surgical Treatment of Invasive Aspergillosis: Review of 2,121 Published Cases. *Rev Infect Dis* 1996; 23.
14. Gudewicz TM, Mader JT, Davis CP. Combined Effects of Hyperbaric Oxygen and Antifungal Agents on the Growth of Candida Albicans. *Aviation, Space, and Environmental Medicine* 1987; 58.
15. Garcia-Covarrubias L, Barratt DM, Bartlett R, et al. Invasive Aspergillosis Treated with Adjunctive Hyperbaric Oxygenation. A Retrospective Clinical Series at a Single Institution. *SO MED J* 2002; 95(4).
16. Bitterman H. Hyperbaric Oxygen for Invasive Fungal Infections (Editorial). *IMAJ* 2007; 9.