

REFRACTORY OSTEOMYELITIS

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Rationale

Refractory osteomyelitis is a chronic osteomyelitis that persists or recurs after appropriate interventions have been performed or where an acute osteomyelitis does not respond to accepted management techniques. (1) Patients with refractory osteomyelitis frequently suffer from coexisting local and systemic factors that compromise their responsiveness to infection. Hyperbaric oxygen (HBO2), when combined with appropriate antibiotics, nutritional support, surgical debridement and reconstruction, provides a useful clinical adjunct in the management of refractory bone infections. Overall, the addition of HBO2 therapy to the clinical management of previously refractory osteomyelitis produces infection arrest rates in approximately 80% of cases.

Initial evidence for this therapeutic benefit stemmed from reports collected during the 1960s, in which difficult cases of osteomyelitis were successfully treated by the addition of HBO2 therapy. (2-5) A series of controlled animal studies subsequently confirmed the perceived clinical benefit of HBO2. (6-9) More recently, **in vitro** and **in vivo** studies have revealed specific mechanisms of action that explain the benefits seen with HBO2 treatment of refractory osteomyelitis. Common to each mechanism is the generation of normal to elevated tissue oxygen tensions in infected bone. Mader and Niinikoski demonstrated that the decreased oxygen tensions typically associated with infected bone can be elevated to normal or above normal while breathing 100% oxygen in a hyperbaric chamber. (5, 10) Such elevations have important consequences for the hypoxic milieu of osteomyelitic tissues.

First, neutrophils require tissue oxygen tensions of 30-40 mmHg to destroy bacteria by oxidative killing mechanisms. (11) Leukocyte mediated killing of aerobic Gram-positive organisms including **Staphylococcus aureus** and aerobic Gram-negative organisms is returned to normal or above normal levels when osteomyelitic bone's low oxygen tension is increased to physiologic or suprphysiologic levels. (10) Indeed, HBO2 has been proven effective as adjunctive therapy in animal models of chronic **S. aureus** and **Pseudomonas aeruginosa** osteomyelitis. (6-8, 12) HBO2 also has a direct suppressive effect on anaerobic organisms. (2, 13) This effect can be clinically important, as anaerobes make up approximately 15% of the isolates in chronic non-hematogenous osteomyelitis.

Secondly, aminoglycoside (gentamicin, tobramycin, amikacin) transport across the bacterial cell wall is oxygen-dependent and is inhibited in conditions of a hypoxic environment. Active transport of antibiotics across bacterial cell walls does not occur if tissue oxygen tensions are below 20 to 30 mmHg. (14) Therefore, HBO2 therapy may enhance transport and augment the antibiotic efficacy. (12,14) This synergistic effect has also been shown for the cephalosporin class of antibiotics, where the combination of cefazolin and HBO2 therapy produced a 100-fold greater reduction in bacterial counts than either antibiotic or HBO2 therapies alone. (15) In this setting, regional blood flow measurements and wound oxygen tensions have been suggested as potential objective criteria for guiding the use of adjunctive HBO2. (16-18) Regardless, antibiotic therapy should be chosen on the basis of bone culture results and macro- or microdilution sensitivity testing. (19)

Third, there is evidence that HBO2 may enhance osteogenesis. (20-24) The osteoclast function of removing necrotic bone (microscopic surgical debridement) is an oxygen-dependent function. The osteoclast is very active metabolically, perhaps 100 times more active than the osteocyte. However, without adequate oxygen tensions, the osteoclast cannot remove dead, infected bone. HBO2 provides the optimum environment for this host factor function. This stimulatory effect of HBO2 on osteoclast function has been observed in multiple animal models. (25, 26) Ultimately, because demarcation between healthy and involved bone is not always clear at the time of surgery, enhancement of osteoclast activity improves the overall quality of debridement and reduces the chances that local infection will recur.

Finally, the pathophysiology of chronic osteomyelitis is characterized by both acute and chronic

sources of ischemia. HBO2 therapy has been shown to be acutely effective in reducing tissue edema, lowering intra-compartmental pressures and ameliorating the detrimental effects of inflammatory reactions. (27-30). Over the longer term, HBO2 can be used to promote new collagen formation and capillary angiogenesis in the hypoxic bone and surrounding tissues. (31-34). This neovascularization works to counter the less easily reversible consequences of osteomyelitis, such as repeated surgical trauma, tissue scarring and nutrient blood vessel occlusion. Further, by providing sustained improvements in the arterial perfusion of previously hypoxic bone and surrounding soft tissue, HBO2 reduces the susceptibility of these tissues to recurrent infection and subsequent tissue breakdown.

Clinical Experience

The complex nature of refractory osteomyelitis makes the direct comparison of clinical management strategies difficult. Individual variations in the extent and location of bone involvement, presence of coexisting disease, identified infective organisms and total requirements for surgical debridement, render the development of generic prospective trials impractical. Regardless, the majority of published clinical series that have utilized adjunctive HBO2 therapy, while adhering to strict criteria for disease designation as chronic refractory osteomyelitis, confirmed the previously discussed animal data. In patients who remained infected after a primary course of parenteral antibiotics and aggressive surgical debridement, HBO2 assisted arrest of previously refractory osteomyelitis ranged from 60% to 85%. (35-39)

In a retrospective analysis of 28 patients, Esterhai et al. reportedly showed no value in adjunctive HBO2 therapy. (40, 41) However, on further inspection, all of the treatment failures in this study were related to the patient's refusal to have additional surgery, rather than a reflection on the effectiveness of HBO2. Additionally, with a baseline arrest rate of over 90% in the non-HBO2 group, the question is raised as to whether the patients in this study met specific criteria for refractory osteomyelitis. Indeed, as a co-author on a subsequent manuscript, Esterhai published a non-HBO2 arrest rate of 62%. (42) Thus, while Esterhai's paper was a welcome attempt at evaluating adjunctive HBO2 for osteomyelitis, it falls short of being clinically valuable.

More recently, three clinical papers have reported long term success rates with HBO2 treatment of previously refractory osteomyelitis. Chen et al. achieved an 86% cure rate in 15 patients followed for an average of 17.2 months post completion of HBO2 treatment. (43) Aitasalo demonstrated sustained resolution of refractory mandibular infections after a median of 34 months follow-up in 26 of 33 patients (79%) treated with secondary debridement and HBO2 therapy. (44) Of the seven treatment failures in that series, five went on to demonstrate a marked reduction in their symptomatology. Finally, Maynor et al. showed sustained resolution of symptoms in patients for whom HBO2 treatment was not initiated until after a median 12.5 months from initial diagnosis. (45) When combined with indicated surgical treatment, sustained resolution of wound drainage was achieved in 21 of 26 (86%), 12 of 15 (80%) and 5 of 8 (63%) patients on follow up at 24, 60 and 84 months, respectively.

HBO2 therapy has also been suggested as a useful adjunct in the pre-debridement phases of refractory osteomyelitis management. In a process analogous to necrotizing soft tissue infections, two weeks of HBO2 therapy given prior to subsequent surgical debridement helps demarcate infected bone from the surrounding healthy bone margins. (46,47) This seems especially true for cases of diffuse sclerosing osteomyelitis, where because of the extensive cortical involvement, demarcation is particularly ill defined.

Additional Clinical Indications

While the above information applies primarily to the consideration of extremity infections, successful HBO2 treatment of refractory osteomyelitis cases involving more central sites have also been identified. Larsson et al. recently reported their experience with the use of HBO2 treatment in postoperative neurosurgical infections. (48) In a series of patients with a mean follow up period of 27 months, infection control and healing was achieved in 27 of 36 patients presenting for cranial graft and spinal infections. Interestingly, these successes were obtained without the need for removal of the cranial grafts, implants or spinal instrumentation in the majority of cases.

Jarril et al. reported their experience with irradiated patients presenting for refractory osteomyelitis of the mandible. When adjunctive HBO2 therapy was added to their treatment regimen, complete resolution or clinical improvement was achieved in 14 of 16 patients.(49) Clinical experience has also shown HBO2 to be effective in the management of refractory sternal wound infections.(50)

A unique form of refractory osteomyelitis, "malignant otitis externa" is a progressive and potentially fatal *Pseudomonas aeruginosa* osteomyelitis of the ear canal and skull base. (51) Most patients with this disease are elderly diabetics. (51,52) Due to the critical location of this infection, HBO2 is a useful adjunct to culture directed parenteral antibiotic therapy and, when feasible, surgical debridement. (53,54) While the infection usually arises in the external auditory canal, *P. aeruginosa* is invariably isolated from cultures of infected tissues. Malignant otitis externa progresses through three characteristic stages, with involvement of superficial tissues, basilar skull and intracranial structures being the hallmark of each stage, respectively. (55) Previously, there have been no survivors whenever intracranial extension of the disease has occurred. (56) Between 1981 and 1984, Davis et al. studied seventeen patients with malignant otitis externa who received treatment with adjunctive HBO2. (54) Of nine patients with advanced infections (stages II and III), each had undergone prior surgical debridement and treatment with parenteral antibiotics without resolution of their infection. When adjunctive HBO2 was added to the treatment regimen, all patients had their downhill clinical course promptly reversed. Further, all seventeen patients recovered as defined by 90% or greater return of cranial nerve function and freedom from signs and symptoms of infection for one year or longer. These clinical results justify the conclusion that HBO2 should not be denied for patients with advanced malignant otitis externa in recurrent cases and in cases where the process has become refractory to appropriate antibiotic treatment.

HBO2 Treatment Indications / Selection Criteria

The Cierny-Mader classification of osteomyelitis can be used as a guide to determine which types of osteomyelitis may be benefited by adjunctive HBO2. The anatomic classification is summarized in Table 1 as medullary osteomyelitis, superficial osteomyelitis, localized osteomyelitis, and diffuse osteomyelitis. (57,58) Patients with diffuse osteomyelitis include those who have through-and-through osteomyelitis and those who have structurally unstable bone(s) either before or after surgical debridement.

Table 1; Cierny-Mader Classification System

Anatomic Type	
Stage 1	Medullary osteomyelitis
Stage 2	Superficial osteomyelitis
Stage 3	Localized osteomyelitis
Stage 4	Diffuse osteomyelitis
Physiologic Class	
A Host	Normal host
B Host	Systemic compromise (B_s)
	Local compromise (B_L)
CHost	Treatment worse than disease

Patients with osteomyelitis may also be physiologically classified as an "A host" (normal), "B host" (compromised) or "C host" (those in whom the treatment of the disease is worse than the disease). B hosts (Table

2) may be subdivided according to whether they are compromised systemically (Bs) or locally at the site of osteomyelitis (BL).

Table 2: Systemic or Local Factors that Affect Immune Surveillance, Metabolism, and Local Vascularity

Systemic (Bs)	Local (Bl)
Malnutrition	Chronic lumphedema
Renal liver failure	Venous stasis
Diabetes mellitis	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
Tabacco abuse	

In the Cierny-Mader classification, adjunctive HBO2 is used to treat the most difficult stages of refractory osteomyelitis, i.e. localized and especially diffuse osteomyelitis in the B host. It is recommended that HBO2 be used for patients with stage 3B and 4B osteomyelitis when the criteria for refractory osteomyelitis are met. Traditionally, these criteria include failure to respond to surgical debridement and a 4-6 week course of parenteral antibiotics.(19) Others have suggested that HBO2 application be expanded to include any patient in which osteomyelitis recurs after appropriate surgical and medical management.(47) This may be particularly true for cases where ablative procedures are being considered. As time from initial diagnosis appears to have little effect on the clinical outcome in refractory osteomyelitis, the decision to use HBO2 should also be made independently of the duration of refractory infection.(43,45,47) Thus, each case must be considered as if it were presenting de novo, by optimizing host status, tailoring antibiotic therapy to specific culture results, adequately debriding residual non-viable bone and applying pre- and postoperative HBO2 therapy as clinically indicated.

Utilization Review

The initial treatment depends on the severity of the patient's clinical disease. The HBO2 treatments are at a pressure of 2.0-2.5 ATA and last for 90-120 min. Following major debridement surgery, the patients should be treated daily if possible. Utilization review is recommended after 40 HBO2 treatments.

Based on American Heart Association 1999 Guidelines, Strauss reports that HBO2 receives a Class-II (Probably useful and effective with a favorable risk/benefit ratio) Evidence Based Indication for the treatment of chronic refractory osteomyelitis. (59) The author also contends it is the absence of randomized controlled trials that keeps HBO2 from receiving a Class-I indication.

Cost Impact

When used within the above guidelines, HBO2 is not only clinically effective but also significantly cost effective. Of patients who have failed to respond to years of costly repetitive surgery and antibiotic care, 60-85% have had infections successfully arrested when HBO2 was used in conjunction

with intensive surgical and antibiotic therapy. For other patients, especially those with infections involving the base of the skull, HBO2 has proved lifesaving. In a limited review, cost-effectiveness was 5-fold in favor of using HBO2 for refractory osteomyelitis. (60)

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