

## Results of Chronic Osteomyelitis of the Femur Treated with Hyperbaric Oxygen: A Preliminary Report

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**Background:** Although only a few studies have shown the effectiveness, hyperbaric oxygen (HBO) therapy has been used as an adjunct in the management of chronic osteomyelitis in many hospitals in Taiwan. This retrospective study investigated the clinical results of HBO therapy for chronic refractory osteomyelitis of the femur.

**Methods:** From December 1999 through May 2002, 13 patients with chronic refractory osteomyelitis of the femur were treated with adjunctive HBO. The most common infecting microorganism was *Staphylococcus aureus*. All cases were classified as type III or IV osteomyelitis according to the Cierny-Mader classification. Adequate surgical debridement and parenteral antibiotic treatment were performed. The average number of operations before HBO therapy was 4.6 times. HBO therapy at 2.5 atmospheres absolute for 120 minutes was administered for 5 days per week in all patients for an average of 50 days. The average number of HBO treatments was 32.2 times. The average follow-up period was 22 months, ranging from 12 to 42 months.

**Results:** Complete eradication of infection with no recurrence of infection was noted in 12 of the 13 patients. One patient failed to respond to the treatment. The success rate of the treatment regimen was 92%. There were no HBO therapy related complications.

**Conclusion:** Hyperbaric oxygen therapy is an effective and safe adjunctive therapy for the management of chronic refractory osteomyelitis of the femur provided that patients had received adequate surgical debridement and appropriate antibiotic treatment.

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**Key words:** hyperbaric oxygen, chronic refractory osteomyelitis, atmosphere absolute.

The goals of treatment for chronic osteomyelitis are to eradicate the infection and maintain optimum physiologic function of the affected area. This imposes a challenge to orthopedic surgeons because of the high recurrence rate, expensive medical costs, and prolonged disability. Adequate surgical debridement, antibiotic treatment, and soft tissue reconstruction are the mainstay for treatment.<sup>(1,2)</sup> However,

optimal results are not always achievable. The recurrence rate was reported as high as 20 to 30% even with aggressive medical and surgical treatment.<sup>(2,3)</sup> One study from Mayo Clinic in 1983, reported an extraordinarily high recurrence of 61.5% with mixed aerobic and anaerobic osteomyelitis.<sup>(3)</sup>

Hyperbaric oxygen (HBO) therapy has been used for chronic refractory osteomyelitis since

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1965.<sup>(4)</sup> Its therapeutic effects have been reported in many in vitro and in vivo studies.<sup>(3,5-8)</sup> Although chronic refractory osteomyelitis is one of the indications which have been approved by the Undersea and Hyperbaric Medical Society (UHMS), only a few reports have confirmed the beneficial effects using results of controlled studies.<sup>(6,9)</sup> The purpose of this study was to evaluate the efficacy of HBO therapy in

the treatment of chronic refractory osteomyelitis of the femur.

## METHODS

From December 1999 through May 2002, 13 patients with chronic refractory osteomyelitis of the femur were treated with HBO (Table 1). There were

**Table 1.** Data for Patients

Case	Age/ Gender (years)	Lesion site	Ciorny- Mader Classification	Duration of infection (months)	Surgery (times)	Bacteria	Antibiotic beads	Antibiotic	HBO (times)	Follow-up (months)	Result	Complication and treatment
1	27/M	L distal	IVB	22	11	ORSA Pseudomonas aeruginosa	Vancomycin Gentamicin	Vancomycin Gentamicin	30	42	f	Persisted infection
2	35/M	R distal	IIIA	24	4	OSSA	Vancomycin	Cefamezine	42	40	H	N
3	54/M	L distal	IVB	6	4	Klebsiella pneumonia Pseudomonas aeruginosa Morganella morgannii	Vancomycin Pipril	Vancomycin Pipril	19	31	H	Knee stiffness
4	61/M	R distal	IVA	20	4	OSSA	Cefamezine	Cefamezine	30	31	H	Knee stiffness
5	46/M	L distal	IVA	32	7	Pseudomonas aeruginosa	Gentamicin	Fortum	30	30	H	Knee stiffness →quadricep- splasty
6	55/M	R distal	IVA	6	3	OSSA	Vancomycin	Cefamezine	75	28	H	Knee stiffness, LLD> 2 cm →knee fusion
7	21/M	L middle	IVA	6	4	ORSA	Vancomycin	Vancomycin	24	22	H	N
8	54/M	R distal	IVA	16	7	ORSA	Vancomycin	Vancomycin	30	21	H	Limited ROM of knee
9	48/M	R upper	IVA	7	5	OSSA Enterobacter cloacae	Vancomycin	Cefamezine	18	17	H	N
10	24/F	L middle	IVA	6	3	Enterococcus Citrobacter freundii	Vancomycin	Ampicillin Amikin	30	15	H	N
11	24/M	R middle	IVA	7	3	ORSA	Vancomycin	Vancomycin	30	13	H	Limited ROM
12	48/M	R middle	IVA	8	3	ORSA	Vancomycin	Vancomycin	30	12	H	N
13	20/M	R distal	IIIA	24	3	ORSA Escherichia coli	Vancomycin	Vancomycin Amikin	30	12	H	N

**Abbreviations:** M: Male; F: Female; R: Right; L: Left; f: failed to heal; H: Healed; N: none; LLD: leg length discrepancy; ROM: range of motion; OSSA: oxacillin-sensitive Staphylococcus aureus; ORSA: oxacillin-resistant Staphylococcus aureus.

12 males and one female with an average age of 40 years (range, 20 to 61 years).

The initial evaluation included a complete medical history, laboratory data, culture, antibiotic treatment, and operative history. Image studies included x-ray, bone scans or Gallium scans, and computerized tomograms as indicated. Chronic refractory osteomyelitis was defined as bone infections that persisted beyond 6 months, in those cases where aggressive, adequate surgical debridement and antibiotic treatment had failed.<sup>(10,11)</sup> All patients enrolled in this study had met the following criteria: (1) infection for at least 6 months, (2) underwent more than three surgical procedures to eradicate the infection, (3) treatment with parenteral antibiotics.

Chronic osteomyelitis was classified using the Cierny-Mader classification system.<sup>(4)</sup> All patients belonged to osteomyelitis anatomic type III or IV. Seven cases resulted from open fractures, and six from closed fractures. The involvement was upper-third in one case, middle-third in four cases, and distal-third in eight cases. Three patients with distal femoral fractures had received free tissue transfer for reconstruction of the soft tissue defect. Two patients with segmental bone defect had received free vascularized fibular grafting. Eleven patients with type IV osteomyelitis had received plating in two, nailing in two, and external fixation in seven for fracture stabilization. The duration of infection before HBO therapy averaged 14 months (range, 6 to 32 months). The average number of surgical procedures before entering the treatment protocol ranged from 3 to 11 times (average, 4.6 times).

All patients received adequate surgical debridement to eradicate the infection before HBO therapy. During the course of HBO therapy, additional debridement was performed when necessary. Eleven cases also received cancellous bone grafting to promote bone healing. The most common microorganism causing infection was *Staphylococcus aureus*. Mixed infection was noted in six cases (Table 1). The choice of antibiotics was determined according to the results of culture and sensitivity tests. Erythrocyte sedimentation rate and C-reactive protein were measured every other week to monitor the infection control. The duration of parenteral anti-

biotic treatment after operation was usually 2 weeks; followed by 2 to 4 weeks of oral antibiotics.

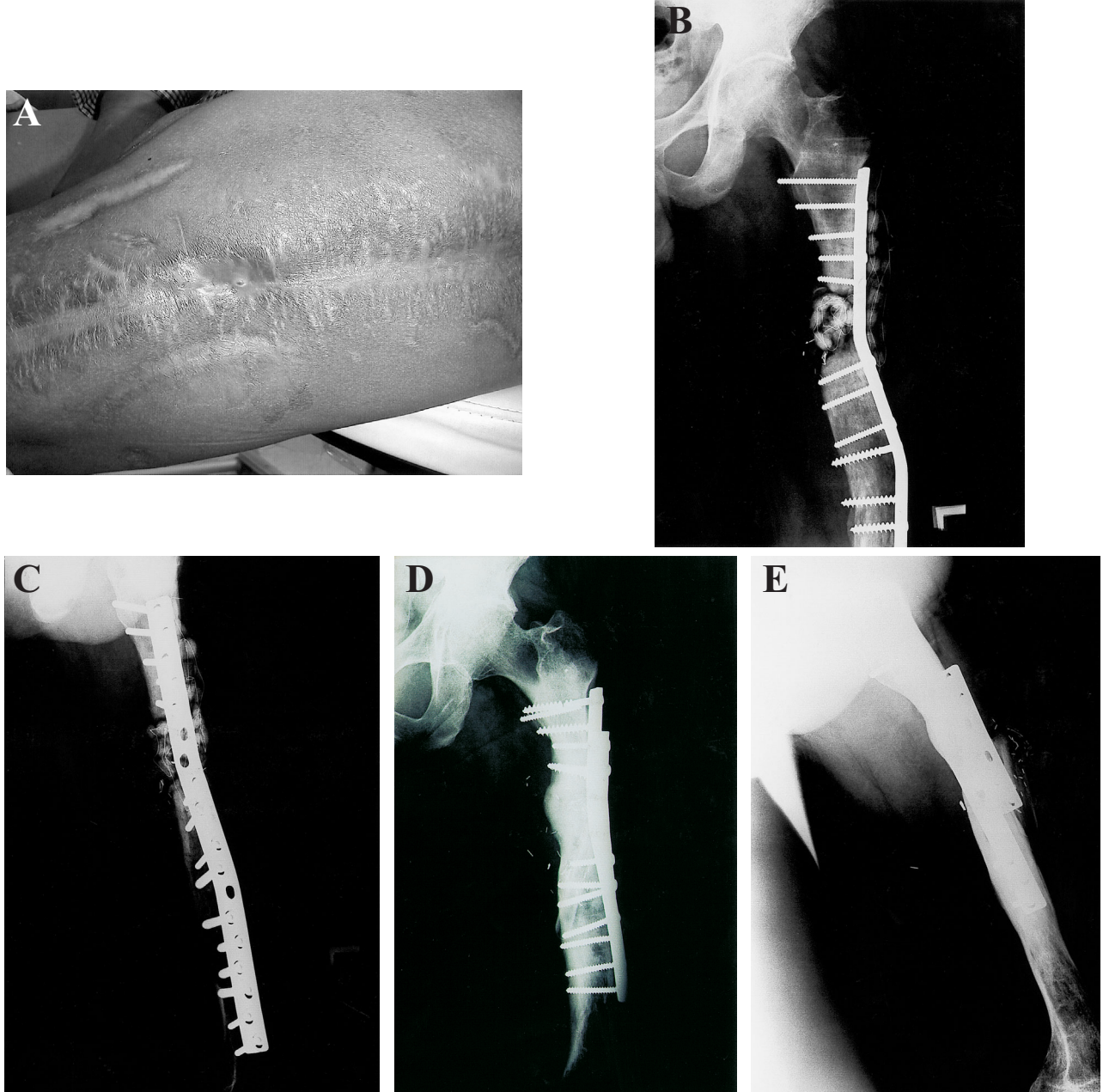
In addition to surgical debridement and parenteral antibiotic, all patients received adjunctive HBO therapy in a diving chamber (Haux-Starmed 2000 Hyperbaric Chamber, Germany). The treatment regimen was designed according to the suggestions by the UHMS.<sup>(12)</sup> In the compression chamber, 100% oxygen was delivered using a mask system, with 2.5 atmospheres absolute (ATA), for a 2-hour duration with an intermittent schedule of 25 minutes of 100% oxygen breathing and 5 minutes of air breathing, one dive per day, 5 days per week. All patients were followed for a minimum of 1 year with an average of 22 months (range, 12 to 42 months). Success of treatment was defined in patients who had good wound healing with no discharge, and no recurrence of infection during the follow-up period after HBO therapy.

## RESULTS

The average number of surgical procedures was 1.5 (range, 0 to 2) during the HBO therapy. The average number of treatments with HBO therapy was 32.2 times (range, 18 to 75 times). The length of treatment averaged 50 days (range, 31 to 109 days).

One patient failed to respond to the treatment despite combined surgical debridement, parenteral antibiotic treatment and HBO therapy. The osteomyelitis in this patient resulted from an open type IIIA fracture treated with plating. The infecting microorganisms were mixed oxacillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Multiple surgical procedures including free osteocutaneous flap reconstruction were performed, however, the infection persisted despite aggressive treatment.

The remaining 12 patients achieved wound healing and showed no recurrence of osteomyelitis at an average follow-up period of 22 months after HBO therapy (Fig. 1). The success rate of treatment in this series was 92%. None of the patients exhibited signs of oxygen toxicity or barotraumas during HBO therapy.



**Fig. 1** Case 5 (A) Photograph of the thigh of a 46-year-old male showing a discharge sinus over the lateral aspect of the thigh. (B,C) Radiographs of the femur showing internal fixation and local antibiotic beads for infected nonunion of femoral shaft fracture. (D,E) Bone grafting and 30 sessions of hyperbaric oxygen therapy were performed to promote bone union. At 30 months of follow-up, no recurrence of infection was noted and the fracture was united.

## DISCUSSION

The most important principles in eradicating chronic osteomyelitis are adequate debridement and

appropriate antibiotic treatment.<sup>(1,2,13,14)</sup> Soft tissue reconstruction or osteocutaneous transfer is necessary if there are soft tissue or bone defects. However, optimal surgical results are not always

achievable due to recurrent infection. The recurrence rate of chronic refractory osteomyelitis is high because the chronic nature of the disease renders osteomyelitis resistant to conventional treatment.<sup>(15)</sup>

Normal oxygen tension in healthy bone is about 45 mmHg of oxygen under ambient conditions.<sup>(16)</sup> The infected bone and necrotic tissue produces an area of lower oxygen tension.<sup>(10)</sup> The level of oxygen tension under ambient conditions in chronic osteomyelitis is 23 mmHg or less.<sup>(16)</sup> The causes of low oxygen tension in chronic osteomyelitis include initial trauma, vascular compromise, dense fibrous scarring and unbridged infected bone. Intermittent oxygen tensions of 30 to 40 mmHg are necessary for neovascularization in an ischemic environment.<sup>(17)</sup> Also, elevating the oxygen tension above 30 to 40 mmHg further improves leukocytes ability to kill microorganisms.<sup>(18)</sup>

Although antibiotics can kill microorganisms in the soft tissue around the focus of infection and surgery can remove the macroscopic portion of dead and infected bone, HBO improves host response by making the environment more favorable for leukocyte oxidative killing, neovascularization, and resorption of dead and infected bone.<sup>(19)</sup> Small bone debris can be resorbed under HBO therapy, but persistent sequestrum should be surgically removed.<sup>(19)</sup> In addition, access of aminoglycoside to the bacterial wall is oxygen-dependent and is inhibited in a hypoxic environment. Therefore, HBO therapy can enhance transport and augments the antibiotic efficacy.<sup>(20)</sup>

Many *in vitro* and *in vivo* studies have shown that HBO therapy increases tissue oxygen tension and promotes bone and soft tissue healing in ischemic tissue.<sup>(7,9,21-23)</sup> The probable mechanisms of HBO in treating osteomyelitis are: (1) HBO raises the tissue oxygen tension, (2) HBO enhances the leukocyte phagocytic mechanisms in bones and wounds with low oxygen tension,<sup>(5)</sup> (3) optimal oxygen tension enhances osteogenesis or neovascularization to fill the dead space with vascular or bony tissue,<sup>(21)</sup> and (4) HBO enhances osteoclastic activity to remove bony debris.<sup>(21)</sup> HBO also directly inhibits the growth of anaerobic organisms in hypoxic tissue.

Many researchers have shown the improvement of chronic osteomyelitis treated with HBO therapy. Davis reported a disease process arrest in 50% which remained so at 5-year follow-up examinations in 98

cases treated with 2 ATA HBO.<sup>(24)</sup> In another report, Davis found that 34 of 38 patients treated with 2 ATA HBO plus wound debridement and antibiotics became free from clinical signs of osteomyelitis within 34 months after treatment.<sup>(7)</sup> Morrey recommended that HBO be used as an adjunct to surgery and antibiotics. In their series of 40 cases treated with HBO, the cure rate at the 2-year follow-up examinations was 85%.<sup>(11)</sup>

Mader et al.<sup>(20)</sup> found that HBO alone was as effective as cephalothin in the treatment of experimental *Staphylococcus aureus* osteomyelitis. The best results were obtained in animals treated using a combination of HBO and cephalothin. They recommended that adjunctive HBO should be used for stages 3B and 4B osteomyelitis but was not indicated for all clinical types of osteomyelitis. However, Esterhai et al.<sup>(6,9)</sup> reported no benefit of HBO therapy in their patients with chronic refractory osteomyelitis. In our series, 12 of the 13 patients (92%) treated with 2.5 ATA HBO showed complete wound healing with no recurrence of infection. No recurrence was observed at an average follow-up period of 22 months after the completion of HBO therapy. One patient, a 27-year-old heavy smoker and diabetic patient with mixed infection, failed to respond to the treatment. The patient sustained a type IIIA open fracture and received multiple surgical procedures including free osteocutaneous flap reconstruction and bone grafting. Despite the aggressive treatments, the infection recurred 3 months after the completion of HBO therapy. The reasons for failure in this patient were unclear. The probable causes included mixed types of infecting microorganisms, duration and severity of infection, and underlying disease.

The weaknesses of this study include that it is a retrospective study with no control, and the series consisted of a small number of patient population. The recurrence of infection was based on clinical observation and the follow-up period was too short to exclude reactivation of osteomyelitis over time. Although HBO therapy has been shown to enhance bone and soft tissue healing in ischemic tissue, the healing in chronic osteomyelitis cannot be attributed solely to the HBO therapy, because all patients had received surgical debridement and antibiotic treatment in addition to HBO therapy. Based on the results of this study, the clinical responses of

osteomyelitis to HBO therapy were used as treatment guidelines.

In conclusion, 12 of 13 patients with chronic refractory osteomyelitis of the femur were successfully treated with surgical debridement, parenteral antibiotics, and HBO therapy. No complications were associated with HBO therapy. HBO therapy is a safe and effective adjunct in the treatment for chronic refractory osteomyelitis.

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## 高壓氧治療股骨慢性復發性骨髓炎的結果：初步報告

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- 背景：** 雖然只有少許的研究報告高壓氧治療的有效性，在台灣已有很多醫院將高壓氧用來治療慢性骨髓炎。在此我們提出以高壓氧治療股骨慢性復發性骨髓炎的臨床結果。
- 方法：** 從1999年12月至2002年5月，我們共收集了13例股骨慢性復發性骨髓炎在本院接受高壓氧治療並能夠追蹤檢查的病例。在我們的病例中最常見的致病菌為金黃色葡萄球菌。所有的病例均為Cierny-Mader classification中type III及type IV的骨髓炎。病患在接受高壓氧治療前平均接受4.6次的手術治療。病患除了接受治療前的清創手術及抗生素使用外，均再使用輔助性的高壓氧治療。治療是以2.5絕對大氣壓，每次2小時，每週5天的方式進行。平均高壓氧治療的次數為32.2次，治療結束後病患接受平均22個月的追蹤。
- 結果：** 追蹤發現其中12位病患傷口癒合而無感染復發，1位病患骨髓炎感染復發。因此治療成功率達92%。治療中未有任何合併症發生。
- 結論：** 對於股骨慢性復發性骨髓炎的治療，如果能夠有適當的外科手術清創及抗生素使用，使用輔助性的高壓氧治療是一種安全又有效的方法。  
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**關鍵字：** 高壓氧，慢性復發性骨髓炎，絕對大氣壓。

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