Effectiveness of Hyperbaric Oxygen Therapy for the Management of Chronic Osteomyelitis: A Systematic Review of the Literature

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abstract

Hyperbaric oxygen has been used as an adjunctive measure in the treatment of chronic osteomyelitis. The aim of this systematic literature review was to analyze the outcome and the complications of hyperbaric oxygen for chronic osteomyelitis. Forty-five of 96 studies reporting the use of hyperbaric oxygen for 460 patients with chronic osteomyelitis met the inclusion criteria and were analyzed qualitatively. All patients previously received antibiotics and surgical debridement. Mixed bacterial flora was detected in most of the studies. *Staphylococcus aureus* was the isolated pathogen in 12 (60%) of the 20 cohort and in 4 (20%) of the 20 case studies. Adjuvant hyperbaric oxygen was effective in 16 (80%) of the 20 cohort and 19 (95%) of the 20 case studies. Overall, 308 (73.5%) of 419 patients with complete data had a successful outcome and no reported relapse. Available evidence supports a potentially beneficial role of adjunctive hyperbaric oxygen, especially in refractory cases of chronic osteomyelitis. [*Orthopedics*. 2018; 41(4):193-199.]

Chronic osteomyelitis is considered one of the most difficult orthopedic conditions to treat, despite significant progress being made with surgery and antibiotic therapy in the past decade.[1] Successful management of chronic osteomyelitis usually requires a combination of multiple surgical interventions at the affected bone site coupled with stabilization through a variety of methods, closure of dead space, soft tissue flap coverage, and bone reconstruction followed by the administration of antibiotics either locally or systemically.[2] Susceptibility testing of the microorganisms cultured from the infected site guides antibiotic administration.[3] Because efficient concentrations at the site of infection may be obtained for only a short period, antibiotic therapy may not always lead to long-term arrest of the disease.[4] Delivery at the local level via various vehicles has been effective in the management of refractory cases.[5,6] Nevertheless, failure of an antibiotic treatment is not uncommon.[7,8]

Intermittent hyperbaric oxygen has been proposed as an adjuvant treatment option for chronic osteomyelitis. The

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European Society of Clinical Microbiology and Infectious Diseases Study Group on Biofilms currently investigates the benefits of hyperbaric oxygen in the management of biofilm infections.[9]

Hyperbaric oxygen therapy is defined as the inhalation of 100% oxygen at pressures above the normobaric pressure of 101.3 kPa measured at sea level.[10] This leads to a significant increase in the tissue partial oxygen pressure and in the arterial blood oxygen pressure.[10] Hyperbaric oxygen counteracts the hypoxia-related inhibition of angiogenesis by inducing neovascularization; it promotes the mobilization of vasculogenic and progenitor cells from bone marrow in either healthy human subjects or diabetic patients and in those treated with radiation.[11-13] Furthermore, hyperbaric oxygen reduces tissue edema by suppressing the expression of pro-inflammatory cytokines,[14] activates macrophage chemotaxis, increases the bactericidal activity of leukocytes,[15] and inhibits toxin production.[16] Finally, hyperbaric oxygen prevents tissue reperfusion injuries by inhibiting the neutrophil ß2-integrin adhesion without an adverse effect on the antibacterial function of the neutrophils.[14]

Hyperbaric oxygen has been widely used in the treatment of chronic osteomyelitis during the past few decades. However, a clear appraisal of its effectiveness is lacking. The aim of this study was to systematically review and evaluate published studies on the overall efficacy and possible complications of hyperbaric oxygen for the treatment of chronic osteomyelitis.

Materials and Methods

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17,18] The following databases were thoroughly searched: Medline (via PubMed), Web of Science, the Cochrane Library, Embase, Ovid, Google Scholar, and the World Health Organization International Clinical Trials Registry. The search methodology was performed using the following combination of terms: "chronic osteomyelitis [all fields]," "hyperbaric oxygen [all fields]," and "treatment [all fields]." The titles and the abstracts of the studies were identified and reviewed independently by 2 of the authors (O.D.S., A.K.), who used predefined criteria to select the relevant publications. Inclusion criteria were as follows for the human studies: (1) an appropriate description of the etiology and pathogenesis of the disease; (2) reporting of the pathogen associated with chronic osteomyelitis development; (3) description of the treatment and follow-up protocol used; and (4) reporting of the final outcome of the therapeutic approach (ie, success vs failure). Case reports were reviewed and are reported separately from other types of studies. All articles in English published in peer-reviewed journals were considered. Articles in languages other than English, literature reviews, technical notes, and letters to the editor or expert opinion publications were excluded. Articles with insufficient details regarding type of infection, therapeutic procedure, follow-up, and clinical outcome were also excluded.

The Cochrane Collaboration's tool was used to assess the quality of the studies to ascertain the risk of bias in nonrandomized studies. For each study, patient selection, methodology, follow-up, data, and other issues that could be characterized as having a risk for bias were evaluated. These were defined as low risk, moderate risk, high risk, or unclear risk.[1,19]

For further minimization of selection bias, all articles were reviewed a third time and then assessed and discussed by all of the authors. If a disagreement occurred regarding the inclusion and exclusion criteria, the senior author (S.T.) made the final decision. Data extraction was performed and data were recorded independently by all of the researchers. Study design, demographic characteristics, surgical intervention, causative microorganism, disease severity, and treatment effectiveness and safety were recorded. Animal studies were examined separately from human studies.

Results

The literature search and cross-referencing resulted in a total of 96 references. On evaluation, 51 articles were excluded and 45 articles were retained. These consisted of 14 retrospective and 6 prospective cohort studies (**Table A**, available in the online version of the article),[20-39] 20 case reports (**Table B**, available in the online version of the article),[40-59] and 5 animal studies (**Table C**, available in the online version of the article).[60-64] The included studies were published between 1971 and 2017.

Experimental Models

Five studies examined the use of hyperbaric oxygen in an experimental model of chronic osteomyelitis (**Table C**). All studies examined *Staphylococcus aureus*–associated chronic osteomyelitis.[60-64] One study additionally examined the effectiveness of hyperbaric oxygen for implant-associated chronic osteomyelitis caused by the gram-negative pathogens *Klebsiella* species and *Pseudomonas* species known to be implicated in biofilm formation.[61] In 4 animal experiments, the effectiveness of hyperbaric oxygen was increased when it was used in combination with systemic antibiotics.[60,62,63] Hyperbaric oxygen for implant-associated chronic osteomyelitis led to contradictory results.[60,62] Regarding surrogate laboratory parameters evaluating inflammation, 1 animal study reported that hyperbaric oxygen therapy led to a reduction of oxidative stress and inflammatory indices, revealing a potential pathophysiologic explanation for the positive effect of hyperbaric oxygen.[60]

Human Data

Twenty cohort studies and 20 case studies examined the effectiveness of hy-

perbaric oxygen for chronic osteomyelitis. A total of 460 patients treated with hyperbaric oxygen were identified. Overall, 308 (73.5%) of 419 patients with complete data had a successful outcome and no reported relapse.

Only 4 studies reported the grade of chronic osteomyelitis according to the Cierny Mader system, classifying 3 patients as having grade II, 26 patients as having grade III, and 30 patients as having grade IV. In addition, only 1 study described the severity of the concurrent pedal ulcers with the calcaneal chronic osteomyelitis in diabetic patients based on the Wagner classification, with 11 patients having grade II and 12 having grade III.

The follow-up period was reported in 27 studies, being a mean of 28.3 months (range, 1-108 months).

The anatomic locations of chronic osteomyelitis, in order of frequency, were as follows: (1) the mandible (62 patients); (2) the tibia/fibula (58 patients); (3) the spine (32 patients); (4) the jaw (30 patients); (5) the hip joint (28 patients); (6) the femur and the calcaneus (23 patients each); (7) the sternum (16 patients); (8) the elbow (14 patients); (9) the pelvis (6 patients); (10) the chest and the humerus (5 patients each); (11) the foot and the ankle (3 patients); (12) the sinus and the temporal bone (3 patients); and (13) the knee joint (2 patients). In 2 studies, the exact location was not clarified. In 3 patients, chronic osteomyelitis developed in more than 1 site (**Tables A-B**).

Staphylococcus aureus was the predominant pathogen associated with chronic osteomyelitis in the studies reviewed (**Tables A-B**). Other implicated pathogens included streptococci species, *Pseudomonas aeruginosa*, *Proteus* species, enterococci, *Escherichia coli*, and other microorganisms (gram-positive cocci [eg, *Staphylococcus epidermidis*, *Propionibacterium acnes*]; gram-negative pathogens [eg, *Klebsiella* species, *Serratia* species]; anaerobes [eg, clostridia species]; and fungi-like *Candida* species, *Saccharomyces cerevisiae*, and *Rhizopus* species). Mixed flora was also isolated. In 3 studies, the infective organism was not reported.[22,32,33]

Sixteen cohort studies[2,21-23,27-31,33-39] and 19 case studies[40-43,45-48,50-59] reported increased rates of successful treatment when combining hyperbaric oxygen with intravenous antibiotics and surgical debridement. Three studies reported the resolution of chronic osteomyelitis with hyperbaric oxygen plus surgical intervention[20] or hyperbaric oxygen plus antibiotic administration.[26,32] Two studies reported that the extra hyperbaric oxygen application did not improve the results of surgical and antibiotic treatment.[24,49] In 1 case study, where no surgical intervention was undertaken, hyperbaric oxygen did not lead to any clinical improvement.[44] In 29 (6.3%) of 458 patients, failure of the hyperbaric oxygen treatment was reported.[20,22,24,25,27,28,34,37,49] In 20 (4.4%) of 458 patients, recurrence of chronic osteomyelitis was observed.

Failure of hyperbaric oxygen treatment was reported in 7 cases of *Staphylococcus aureus*–associated chronic osteomyelitis,[25,28,37] 6 cases with *Pseudomonas aeruginosa,*[20,25,31,34] 5 cases with mixed bacterial flora,[20,24,27,28,31] and 1 case each with isolation of *Escherichia coli*[34] and *Serratia marcescens.*[37] Finally, in 9 patients for whom hyperbaric oxygen failed, culture did not reveal any bacteria.[22,31,37,49]

Few occurrences of adverse events were noted. Middle ear barotrauma and ear or sinus pain were most commonly reported,[36,38] followed by changes in visual acuity in 2 patients[34] and cataract development in 1 patient.[65] In 1 case, hyperbaric oxygen was discontinued due to the development of convulsions.[39]

All of the studies were either prospective or retrospective case series or case reports. Compared with randomized clinical trials, these study designs are prone to selection bias. Only 1 study used a control group.[23] No study tested the outcome statistically. The mean quality assessment score of the studies was low, indicating that their quality was fair. The weakness of the methodology quality and the low assessment score indicated increased risk of bias. There were not significant differences between the mean values of the scores estimated by the 2 examiners. The summary of the potential biases is presented in **Table D**, available in the online version of the article.

Discussion

To the best of the authors' knowledge, this is the first systematic review focusing on the impact of hyperbaric oxygen in the treatment of chronic osteomyelitis. Despite the fact that the design of the studies included in this review was not optimal to identify the efficacy of hyperbaric oxygen for chronic osteomyelitis, it appeared that the combination of hyperbaric oxygen, intravenous antibiotics, and surgical debridement led to remarkable improvement in clinical and laboratory findings in both animal models and human studies.

Experimental models evaluated in this study used *Staphylococcus aureus* as the implicated pathogen (ie, the main pathogen evaluated in most human studies). *Staphylococcus aureus* is known to be a significant pathogen in chronic osteomyelitis. In animal models, hyperbaric oxygen was always used in combination with antibiotics[61,64] or ozone.[61] Effects on local and systemic inflammation were highlighted in some of these experiments as mediating the therapeutic effect of hyperbaric oxygen. Hyperbaric oxygen not only reduced the histopathological score and the bacterial count of chronic osteomyelitis but also decreased the oxidative (malondialdehyde, superoxidase dismutase, and glutathione peroxidase) and inflammatory (interleukin-1ß, interleukin-10, and tumor necrosis factor-α) indices.[61] However, these effects could work both ways; in some reports, hyperbaric oxygen was associated with either a delayed improvement of outcome with antibiotic treatment[60] or bacterial growth stimulation[62] in

implant-associated chronic osteomyelitis. Nevertheless, in implant infections, surgical debridement probably has the primary therapeutic role.

In human subjects, the results of this systematic review indicated that hyperbaric oxygen had at least a moderate beneficial effect on the management of posttraumatic and postoperative chronic osteomyelitis. In spinal,[21] tibial,[31] or femoral[27] chronic osteomyelitis caused by either gram-positive or gram-negative bacteria, adjuvant hyperbaric oxygen often resulted in eradication of the infection, even after the failure of antibiotics.[21] Hyperbaric oxygen therapy was additionally moderately effective in patients who developed chronic osteomyelitis after closed and open fractures[34] or trauma of various etiologies (eg, war) or after orthopedic operations such as hip arthroplasty.[37] Adjuvant hyperbaric oxygen resulted in complete healing of not only the patients with lower extremity chronic osteomyelitis but also the patients with chest, sinus, and mandible chronic osteomyelitis.[33,35,38,39,43,48,53,58,59] This beneficial effect may be attributed to either neovascularization of the ischemic tissues or the hyperoxygenation that results in the direct suppression of anaerobic bacteria and stimulation of leukocytes.[66]

Sternal infection and osteomyelitis in patients undergoing cardiothoracic surgery increases the mortality rate.[67] Hyperbaric oxygen is considered a safe adjuvant treatment for sternal chronic osteomyelitis of gram-positive, gram-negative, or mycobacterial etiology, minimizing the intensive care unit stay.[23,47,52,54,57]

In diabetic patients, vascular insufficiency is the major reason for secondary chronic osteomyelitis infection. This is due to severe ulcers of the lower extremities, which lead to amputation. The combination of hyperbaric oxygen, surgical debridement of the necrotic tissues, and intravenous antibiotics may prevent amputation in difficult cases of *Pseudomonas aeruginosa*–associated chronic osteomyelitis[20] or in the absence of an effective antibiotic regimen.[42]

In immunocompromised patients and in children, chronic osteomyelitis is usually caused by hematogenous spread. Hemodialysis-dependent patients have high rates of chronic osteomyelitis because of phagocyte dysfunction.[68] Although the use of hyperbaric oxygen in these populations is controversial,[24] the reviewed reports indicated that adjuvant hyperbaric oxygen can lead to remarkable clinical improvement[25] or complete recovery.[29]

The effectiveness of hyperbaric oxygen therapy has also been studied in osteopetrosis, which is a rare genetic disease caused by metabolic imbalances and complicated by chronic osteomyelitis in approximately 10% of patients.[40,41] The combination of surgical debridement[40] or endoscopic lavage[41] of the necrotic tissue and hyperbaric oxygen has been associated with increased success rates, even in the absence of high doses of antibiotics.[41] Nevertheless, in such difficult cases, when a combination of surgical and antibiotic treatment fails, hyperbaric oxygen is controversial.[49]

In addition to adjuvant hyperbaric oxygen, other factors, such as the secure immobilization of the infected area[27,28] and the removal of the infected implants, may contribute to a successful outcome in difficult cases of chronic osteomyelitis. The combination of hyperbaric oxygen, antibiotics, and debridement[35] with full or partial removal of internal[35,48,53] or external[20] fixation devices and hardware[23,30,37,47,50,52,54,57] was correlated with increased clinical improvement. The exact contribution of hyperbaric oxygen in such cases, which are almost always complicated by biofilm development, is difficult to elucidate. In vitro studies have shown that hyperbaric oxygen can be used as an adjuvant to ciprofloxacin on biofilms caused by *Pseudomonas aeruginosa*, enhancing the bactericidal activity of ciprofloxacin.[69,70] Although there is an increasing acceptance of the advantages of hyperbaric oxygen on biofilm infections, its use remains controversial.

In this study, hyperbaric oxygen therapy was found to be generally safe and well tolerated; most of the side effects reviewed were mild and reversible. Awareness is necessary because, in a few of the cases, potentially severe side effects (eg, barotrauma, seizures, congestive heart failure and pulmonary edema, and infantile purpura fulminans and pulmonary toxicity) were reported. Some additional minor adverse events were found with the use of hyperbaric oxygen, including transient vision changes, occasional earache and sinus pain in patients with colds or allergies that resolved after their symptomatic treatment with decongestants[38] or application of tympanostomy tubes,[34] and cataract development.[39] Minor symptoms improved shortly after the interruption of hyperbaric oxygen.[32]

The most serious contraindication to using hyperbaric oxygen is the suspicion of an untreated or undiagnosed pneumothorax. Relative contraindications include any febrile illness that may potentially cause reduction of the central nervous system seizure threshold, poorly controlled seizure disorder, hyperthyroidism, congestive cardiac failure, chronic obstructive pulmonary disease, and claustrophobia.[71] Concurrent administration of hyperbaric oxygen with chemotherapeutic agents such as doxorubicin, bleomycin, or cisplatin should be avoided because of their interference in mechanisms of free oxygen radical scavenging. On the other hand, malignancy is not a contraindication for hyperbaric oxygen use, as hyperbaric oxygen is not implicated in the induction of tumor growth or cancer pathogenesis.[72] It was reported that hyperbaric oxygen use in patients with a malignancy was not associated with cancer expansion or recurrence.[46]

Cost-effectiveness issues may counteract the beneficial effect of adjuvant hyperbaric oxygen for chronic osteomyelitis identified in this review; no studies

exist regarding this. Compared with standard of care treatment, adjuvant hyperbaric oxygen therapy was cost-effective in studies of its therapeutic use for diabetic ulcers.[73,74] In these studies, hyperbaric oxygen therapy correlated with an increased quality-adjusted life years index and a lower proportion of major amputation. When considering financial gains for a relatively expensive therapy, direct and indirect medical costs need to be addressed, such as savings in wound dressing materials, hospital admissions, travel, and rehabilitation. These have been favorably affected in diabetic ulcer and chronic wound studies.[75] Treatment for diabetic ulcers and treatment for chronic osteomyelitis have many similarities.

The major limitation of this review was the heterogeneity of the included studies, which made their accurate comparison difficult. More specifically, great variability in treatment protocols, selection criteria, and follow-up periods and missing classification of disease severity and statistical analysis of the outcomes and recovery rates were observed. Other limitations of this review included the large number of case reports, the low level of evidence, and the small number of patients in the included surveys. Finally, a significant amount of the data were derived from studies before 2000. Thus, considerable information about the current treatment protocols is lacking.

Conclusion

Hyperbaric oxygen appears to be a safe and potentially useful adjunctive intervention for the management of chronic osteomyelitis of various etiologies. Hyperbaric oxygen combined with other important therapeutic interventions, such as antibiotics and/or surgical debridement, was associated with high recovery rates of chronic osteomyelitis, especially when followed by a secure stabilization of the bone and removal of the infected implant. Nevertheless, quality data regarding this finding are scarce. Randomized controlled trials should be conducted to investigate the efficacy of hyperbaric oxygen for chronic osteomyelitis.

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Table A: Overview of the causative agents, classification, interventions, follow-up and outcome of the included cohort studies

Author, year, location	Type of study	Participants	Microorganism	Classification system	Intervention	Follow – up	Summary outcome
Akkurt et al 2017, Turkey [20]	Retrospective	Chronic calcaneal osteomyelitis in diabetic patients with severe pedal ulcer (n=23)	*Staphylococcus aureus* *Klebsiella pneumoniae* *Escherichia Coli* *Pseudomonas aeruginosa*	11 pts with grade II and 12 pts with grade III Wagner classification	Surgical debridement Application of ILIZAROV external fixation No antibiotics administration HBOT	Not reported	Complete clinical cure in 18 pts (78%) with painless and functional foot Partial recovery in 3 pts Failure in 2 pts - amputation
Onen et al 2015, Turkey [21]	Retrospective	Spinal osteomyelitis not improved by antibiotic therapy (n=19) Cervical:1 Thoracic:4 Lumbar:14	Gram negative *MRSA* *Enterococcus* spp. *Pseudomonas aeruginosa* *Acinetobacter* spp	Not reported	Antibiotics administration (IV Cefazoline) HBOT (in cases that were intractable to3 weeks of antibiotic therapy)	23 months	The combination of antibiotics and HBOT led all cases to a successful outcome. No recurrence and no signs of infection
Skeik et al 2015, USA [22]	Retrospective	Chronic refractory osteomyelitis (n=23)	Not reported	Not reported	Surgical debridement Antibacterial therapy HBOT	Not reported	19 (82.6%) of the patients showed a successful out come 4 (17.4%) failed to demonstrate any improvement

Yu et al 2011, Taiwan [23]	Retrospective	Osteomyelitis of the sternum after sternotomy and cardiothoracic surgery (n=12)	*MRSA* *Staphylococcus aureus* *Klebsiella pneumoniae* *Escherichia Coli* *Acinetobacter baumannii* *Mycobacterium tuberculosis*	Not reported	Surgical debridement Empiric antibiotic administration HBOT (in six patients)	Not reported	The group on adjuvant HBOT (n=6) appeared to have ↓ length stay in ICU, ↓ duration of positive non-invasive pressure ventilation, ↓ duration of invasive mechanical ventilation No hospital death was noticed (compared with 3 deaths in the non-HBOT group)
Saarinen et al 2011, Finland [24]	Retrospective	Chronic mandibular osteomyelitis mimicking recurrent parotitis (n=6)	*Streptococcus viridans* *Streptococcus anginosus* *Actinomyces* *Fysobacterium* *Candida albicans* *Enterococcus faecalis*	Not reported	Surgical debridement Antibiotic administration(based on the antibiogram) HBOT (in two patients)	60 months	No significant clinical difference in clinical outcome compared to no HBOT group
Chen et al 2008, Taiwan [25]	Prospective	Chronic diffuse osteomyelitis of the tibia (n=7) and humerus (n=3) in hemodialysis patients	*Staphylococcus aureus* *Pseudomonas aeruginosa*	Not reported	Surgical debridement Parental antibiotic administration HBOT	Not reported	In 8 pts arrest of the disease was observed In 2 pts failure of the treatment was observed that led to amputation
Lentrodt et al 2007, Germany [26]	Retrospective cases study	Chronic recurrent mandibular osteomyelitis in childhood (n=3)	No microbiological investigation was taken due to lack of pus or abscesses	Not reported	No surgical debridement Antibiotic therapy (teicoplanin, clindamycin, penicillin G)	41 months	All patients free of symptoms

					HBOT		
Chen et al 2004, Taiwan [27]	Prospective	Chronic refractory osteomyelitis of the femur (n=13)	Staphylococcus aureus *Escherichia coli (most common)* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Enterococcus* spp *Morganella morganni* *Enterobacter cloacae* *Citrobacter freudii*	Grade IIIA: 2pts,IVA: 9 pts, IVB: 2pts according to Cierney Mader classification	Surgical debridement Cancellous bone grafting Antibiotic therapy (Vancomycin, Gentamycin, Cefamezide, Piperacillin, Ampicillin) HBOT	22 months	Good wound healing No discharge No recurrence or infection
Chen et al 2004, Taiwan [28]	Prospective	Chronic refractory osteomyelitis of the tibia (n=14) due to close (n=5) and open II, IIIB, IIIC open fractures (n=9)	*Staphylococcus aureus (most common)* *Escherichia coli* *Pseudomonas aeruginosa* *Enterococcus* spp *Serratia mercescens* *Aeromonas sobria*	Grade IIIA: 2 pts, IIIB:3 pts IVA: 3 pts, IVB: 6 pts according to Cierney Mader classification		15 months	No recurrence in 11 (78.6) patients Extra HBOT sessions in 2 patients 1 patient with mixed flora after open IIIB fracture received above knee amputation
Baltenspenger et al, 2004, Switzerland [29]	Retrospective	Chronic osteomyelitis of the jaw (n=30)	*Staphylococcus coagulase (-)* *Enterococci* spp *Klebsiella* spp *Actinomyces* spp *Neisseria* spp *Haemophilus* spp *Fusobacterium* *Propionibacterium* No bacterial growth in 3 cultures	Not reported	Surgical debridement-decortication, partial resection Antibiotic therapy (Clindamycin+Trimethoprim-sulfamethoxazole, amoxicillin, doxycycline) HBOT	48 to 56 months	11(36.7%) patients completely free of symptoms Moderate effect in 14 (46.6%) patients Recurrence in 5 (16.7%) patients

Aitasalo et al, 1998, Finland [30]	Retrospective	Chronic osteomyelitis of the mandible/maxilla (n=33)	*Staphylococci* spp *Streptococcus viridans* *Streptococcus* spp *Enterococci* spp *Actinomyces* spp *Klebsiella* spp *Bacteroides* spp *Peptostreptococcus* spp	Not reported	Surgical debridement Decortication with periosteal grafting Antibiotic therapy HBOT	Over than 10 months	Success in 26 (79%) patients No signs for oxygen toxicity
Maynor et al, 1998, USA [31]	Retrospective	Chronic osteomyelitis of the tibia (n=34)	*Staphylococcus aureus* *Staphylococcus coagulase (-)* *Escherichia coli* *Pseudomonas* spp *Serratia marcescens* *Enterobacter* spp *Bacteroides* spp *Clostridia* spp Yeast	Grade IIB: 3pts, IIIB: 17 pts, IVB: 14 pts according to Cierney Mader classification	IV Antibiotics based on the antibiogram Tobramycin beads Microsurgical muscle transplantation in 20 pts HBOT	24 to 84 months	21/26 (81%) at 24 months were drain free
Dan Waisman et al, 1998, Israel [32]	Retrospective	Chronic osteomyelitis of femur/toe in children (n=5) suffering from familiar dysautonomia (n=2), septic arthritis of the hip(n=1), open wound (n=1) and paraplegia (n=1)	Not reported	Not reported	Antibiotic therapy (Aminoglycosides) HBOT	Not reported	5/5 (100%) patients recovered without surgical intervention
Berg et al 1989, USA [33]	Retrospective cases study	Case 1: chronic osteomyelitis of the tibia after IIIB open fracture	Not reported	Not reported	Open debridement and curettage Antibiotic administration HBOT	18 months	Drain free

		Case 2: chronic osteomyelitis of the great toe in a patient with Diabetes Mellitus type I			Amputation at the first metatarsal/skin graft Antibiotic administration HBOT	12 months	Drain free
Davis et al, 1986 USA [34]	Prospective	Chronic non-hematogenous osteomyelitis (n=38) after open fractures(n=2), closed fractures treated with open reduction and internal fixation(n=8) and abscess or infection at the side of a prosthesis (n=10)	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Proteus mirabilis* *Escherichia coli* *Staphylococcus epidermidis* *Serratia marcescens* *Enterobacter cloacae*	Not reported	Surgical debridement Parenteral antibiotic administration based on the antibiogram HBOT	34 months	34 pts remained clinically free of infection The treatment of 3 pts with *Ps. aeruginosa* infection and one patient with *E. coli*, failed
Seftel et al 1985, USA [35]	Retrospective cases study	Case 1: chronic osteomyelitis of the tibia and humerus after open fracture in a patient with chronic malnutrition	*MRSA* *Proteus mirabilis*	Stage IIIB according to Cierney Mader classification	Surgical debridement Antibiotic administration (Vancomycin+Tobramycin) HBOT	14 months	Without clinical symptoms
		Case 2: chronic osteomyelitis of the acetabulum and proximal femur after osteotomies due to osteonecrosis	*MRSA* *Escherichia coli* *Pseudomonas aeruginosa* *Enterococcus sp.*	Stage IVA according to Cierney Mader classification	Surgical debridement Antibiotic administration (Vancomycin+Tobramycin) HBOT	32 months	Without clinical symptoms sedimentation rate <10mm/h
		Case 3: chronic osteomyelitis of the femur after external fixation	*MRSA* *Staphylococcus epidermidis* *Pseudomonas aeruginosa*	Stage IIIA according to Cierney Mader classification	Surgical debridement/bone graft Antibiotic administration (Vancomycin+Tobramycin)	35 months	Without clinical symptoms

					HBOT		sedimentation rate<5mm/h
		Case 4: chronic osteomyelitis of the femur after open reduction and internal fixation revision surgery for non-union fracture	*MRSA*	Stage IVA according to Cierney Mader classification	Surgical debridement with hardware removal and intramedullary pinning Antibiotic administration (Vancomycin) HBOT	23 months	union of the fracture site sedimentation rate<5mm/h
		Case 5: chronic osteomyelitis of the ankle after open fracture pinning	*MRSA* *Streptococcus pyogenes* *Streptococcus morbillorum* *Pseudomonas aeruginosa* *Enterococcus* spp *Bacteroides fragilis*	Stage IVA according to Cierney Mader classification	Surgical debridement Antibiotic administration (Vancomycin + Tobramycin + Clindamycin) HBOT	2months	No clinical or laboratory osteomyelitis signs
Eltorai et al 1984, USA [36]	Retrospective	Chronic osteomyelitis of the hip (n=28) Pelvis (n=6), lumbar spine (n=3), sacrum (n=5), knee joint(n=2), tibia (n=2), elbow(n=14) in patients with paraplegia (n=30) and tetraplegia (n=14) after spinal cord injury	*Staphylococcus aureus* *Streptococcus* spp *Escherichia coli* *Pseudomonas aeruginosa* *Enterococcus* spp *Klebsiella* spp *Serratia* spp	Not reported	Surgical debridement, osteotomies, muscle grafts Antibiotic administration based on antibiogram HBOT	6 to 108 months	No side effects of the treatment 30 pts considered cure Recurrence in 5 patients Amputation in 5 patients
Morrey et al 1979, USA [37]	Prospective	Chronic refractory osteomyelitis of the femur, tibia , spine, and foot (n=53, 40 patients treated with adjuvant HBOT)	*Staphylococcus aureus* *Escherichia coli* *Pseudomonas aeruginosa* *Serratia* spp *Proteus* spp	Not reported	Surgical debridement, sequestrectomy, autologous bone graft, soft tissue procedures	23 months	33 patients: clinical free 7 patients recurrence of osteomyelitis

					Antibiotic administration based on antibiogram HBOT	
Depenbusch et al, 1972, USA [38]	Prospective	Chronic refractory osteomyelitis of the extremities (n=25), Spine-pelvis(n=4), Chest wall (n=5), Frontal sinus(n=2) Mandible (n=13) (Total n=59)	*Staphylococcus aureus* *Escherichia coli* *Pseudomonas aeruginosa* *Proteus* *Klebsiella* *Enterobacter* spp	Not reported	Surgical debridement, sequestrectomies, Antibiotic administration based on antibiogram HBOT	Excellent results-healing in 35 patients In 24 patients decreased drainage and pain reduction No side effects
Hamblen, 1971, UK [39]	Retrospective cases study	<u>Case 1</u>: chronic osteomyelitis of the tibia after open comminuted fracture and extensive soft-tissue damage after a military missile trauma	*Staphylococcus pyogenes* *Pseudomonas pyocyanea*	Not reported	Surgical debridement, sequestrectomies, skin graft, bone graft Antibiotic administration (Penicillin, lincomycin, fucidic acid) HBOT	The HBOT treatment was discontinued after 6 days due to convulsions Complete healing
		<u>Case 2:</u> patient with lasting 47 years chronic osteomyelitis of the femur	*Streptococcus faecalis* *Proteus* spp	Not reported	Surgical debridement Antibiotic administration (Ampicillin) HBOT	The osteomyelitis sinus was not healed Rapidly decrease of the drainage and the sedimentation rate Amputation was not avoid

Case 3: chronic osteomyelitis of the fibula following surgical treatment of an ankle fracture-dislocation	Not reported	Not reported	Surgical debridement, sequestrectomies, Antibiotic administration (cloxacillin) HBOT	The sinus of the osteomyelitis was healed within 10 days Healthy surrounding tissues, No clinical or laboratory findings of the infection

Table B: Overview of the causative agents, classification, interventions, follow-up and outcome of the included case studies.

Author, year, location	Type of study	Participants	Microorganism	Intervention	Follow – up	Summary outcome
Sun et al 2016, China [40]	Case study	Patient with osteopetrosis complicated with chronic mandibular osteomyelitis (n=1)	Negative culture	Surgical debridement Antibiotics administration (Cefuroxim + ornidazole) HBOT	6 months	Complete healing without recurrence
Liu et al 2016, China [41]	Case study	Patient with osteopetrosis complicated with chronic maxillary osteomyelitis (n=1)	Not reported	Surgical lavage Low-doses antibiotics administration (cefazolin 1 gr every 8hs) HBOT	2 months	Complete healing without recurrence
Goerger et al 2016, France [42]	Case study	Patient with Diabetes Mellitus type II, complicated with skin infection and osteomyelitis of the midfoot (n=1)	*Klebsiella pneumoniae*	Surgical debridement Daily wound cleaning HBOT No antibiotics administration	1 month	Negative bacteriological cultures of the wounds
Seng et al 2016, France [43]	Case study	Chronic osteomyelitis after a distal humeral fracture (n=1)	*Saccharomyces cerevisiae*	Antifungal therapy (:voriconazole) Antibacterial therapy (Imipenem-cilastin and oral ciprofloxacin)	1.5 months (6 weeks)	The external fixation of the primary treatment was removed after 6 weeks No signs of infection

				HBOT		
Singh et al 2015, Canada [44]	Case study	Chronic sclerosing osteomyelitis of the mandible (n=1)	*Staphylococcus aureus* *Staphylococcus ludgenencis* *Streptococcus viridans*	Antibiotics administration (Ceftriaxone IV and oral Metronidazole) HBOT		No improvement from the conservative therapy Hemimandibulectomy and fibular free flap reconstruction
Lu et al 2015, Taiwan [45]	Case study	Osteomyelitis of posterior mandibular due to arsenic exposure (n=1)	Not reported	Surgical debridement and trimming Antibacterial therapy (Ampicillin) HBOT	48 months	No signs of inflammation and normal bone structure
Ueki et al 2014, Japan [46]	Case study	Osteomyelitis in Cervical spine and epidural abscess on C4-C7 after chemotherapy for hypo pharyngeal carcinoma (n=1)	No microorganism identified in the pharyngeal cultures	No surgical treatment applied Antibiotics administration (Meropenem) HBOT		No recurrence was noted
De Nadai et al 2013, Brazil [47]	Case study	Chronic osteomyelitis of the sternum (n=1)	*Staphylococcus aureus*	Surgical debridement Antibiotics administration (Metronidazole and Cefotaxime) HBOT	1 month	Chest CT and bone sintigram showed bone remodeling and absence of osteomyelitis
Delasotta et al 2013, USA	Case study	Chronic post-traumatic osteomyelitis due to subtrochanderic fracture (n=1)	*MRSA*	Surgical debridement Antibiotics administration (vancomycin)	10 months	Rapid improvement after adjunctive HBOT Without any symptoms

[48]				HBOT		during the follow-up period
García CM et al 2013,Spain [49]	Case study	Chronic osteomyelitis of the mandible in a patient with osteopetrosis (n=1)	Not reported	Surgical debridement, sequestrum, drainage of the abscess Long term antibiotic administration (clindamicyn) HBOT	12 months	Unresolved COM
Grecchi et al 2012, Italy [50]	Case study	Chronic osteomyelitis of the mandible complicated with osteonecrosis due to periimplant infection	*Actinomyces* spp	Surgical debridement-sequestrectomy Antibiotic administration p.os HBOT		Complete healing
Leahy and Sader, 2011, Australia [51]	Case study	Chronic osteomyelitis of the skull base with the involvement of the petrous temporal bone (n=1)	*Pseudomonas aeruginosa*	Antibiotic administration (meropenem+ teicoplanin) plus fluconazole p.os HBOT	2 months	Complete resolution of the infection
Shields et al 2010, USA [52]	Case study	Chronic refractory osteomyelitis of the sternum after median sternotomy (n=1)	*Escherichia Coli*	Multiple surgical debridements Long term antibiotic administration HBOT	16 months	The HBOT was applied due to surgical debridement and antibiotic therapies failure The HBOT resulted in pain relief, healing of the infection and improvement of the

						laboratory indexes No recurrence during the follow-up period
Wilkins et al 2009, USA [53]	Case study	Chronic post-operative osteomyelitis of the distal femur after anterior cruciate ligament repair (n=1)	*Rhizopus species*	Surgical debridement Antifungal therapy (IV Amphotericin B) HBOT	36 months	No evidence of recurrent infection Application of distal femoral endoprosthesis Musculoskeletal functional score: 50%
Sun et al, 2008, Taiwan [54]	Case study	Chronic osteomyelitis of the sternum after coronary artery grafting by-pass	No bacterial growth in cultures	Surgical debridement Antibiotic administration (Vancomycin) Topical antimicrobial dressing HBOT	10 months	Clinical asymptomatic patient C-reactive protein: normalized
Murray and Lieberman 2002, USA [55]	Case study	Chronic anaerobic osteomyelitis of proximal tibia in a child with sickle cell disease (n=1)	*Fusobacterium nucleatum*	Surgical debridement Antibiotic therapy (Clindamycin IV) HBOT		The infection was cured and the patient resumed full activities
Roldan et al, 2001, Germany [56]	Case study	Chronic recurrent multifocal osteomyelitis of the mandible in a patient (n=1) with SAPHO syndrome (Synovitis, Acne, Pustulosis palmoplantaris, Hyperostosis and Osteitis	*Propionibacterium acnes* *Staphylococcus epidermidis*	Decortications of the mandible with application of PMMA beads Immunostimulatory treatment with allogenic blood	18 months	Free of pain The clinical and scintigraphic findings indicate healing.

				Antibiotic administration (tetracycline and amoxicillin-clavunate) HBOT		
Petzold et al, 1999, Germany [57]	Case study	Chronic osteomyelitis of the sternum after orthotopic heart transplantation (n=1)	*Staphylococcus aureus*	Local debridement Partial sternal wire removal Open antiseptic irrigation HBOT	Over than 60 months	The patient was asymptomatic
Goodhart 1993, USA [58]	Case study	Chronic osteomyelitis of the proximal humerus after IIIC open fracture (n=1)	*Mycobacterium fortuitum*	Drainage of the soft tissue abscess Limited debridement of the proximal humerus shaft Oral Antibiotic administration (ciprofloxacin) HBOT	24 months	No side effects No recurrence of osteomyelitis
Neimkin and Jupiter, 1985, USA [59]	Case study	Chronic metastatic osteomyelitis of the left distal radius and septic necrosis of the left lunate	*Clostridium septicum*	Surgical debridement and application of external fixation for joint fusion IV- antibiotic administration (Penicillin and cephalothin) HBOT	19 months	No recurrence of the osteomyelitis Painless pseudarthrosis of the wrist

Table C: Overview of the causative agents, interventions and outcomes of the included animal studies

Author, year, location	Type of study	Animal model/species	Microorganism	Intervention	Summary outcome
Jorgensen et al 2017, Denmark [60]	Experimental animal study	Implant – associated osteomyelitis of the tibia in C57BL6/j mice (n=80)	*Staphylococcus aureus*	Subcutaneous antibiotics administration (Daptomycin and rifampicin) for 14 days	HBOT treatment lead to an initial 3-4% body mass reduction of the animals
				HBOT	HBOT treatment increased the animals' bone turnover
					HBOT reduced the number of animals with abscesses signs
					HBOT treatment did not improve the outcome of antibiotic treatment measured through the bacterial load on implants and bones
Oguz et al 2011, Turkey [61]	Experimental animal study	Osteomyelitis of the femur in Sprague-Dawley rats (n=48)	*Methicillin resistant Staphylococcus aureus (MRSA*)	Intraperitoneal administration of Vancomycin	HBOT treatment was effective in decreasing the oxidative stress indices and the inflammatory cytokine levels of osteomyelitis
				O_3	
				HBOT	The histopathological score of osteomyelitis in the HBOT plus Vancomycin group was lower than the control group
					The bacterial counts in the Vancomycin plus HBOT and Vancomycin plus HBOT and O_3 groups were significantly lower

					than the control group
Shandley et al 2011, USA [62]	Experimental animal study	Implant – associated osteomyelitis of the tibia in C57BL6/j mice	*Methicillin resistant Staphylococcus aureus (MRSA)* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	Prophylactic HBOT treatment Post infection HBOT treatment No antibiotics administration	HBOT does not appeared to be an efficient treatment of an implant-associated osteomyelitis
Mendel et al, 1999, Germany [63]	Experimental animal study	Osteomyelitis of the tibia in Wistar rats (n=104)	*Staphylococcus aureus*	Antibiotics administration (Cefazolin) HBOT	HBOT treatment alone reduce the colony-forming units of S. aureus Cefazolin alone reduce the colony-forming units of S. aureus The effectiveness of the treatment was more pronounced with the combination of HBOT and Cefazolin
Mader et al 1978, USA [64]	Experimental animal study	Osteomyelitis of the tibia in New Zealand white rabbits (n=66)	*Staphylococcus aureus*	Antibiotics administration (Cephalothin) HBOT	The animal mortality rates, the gross severity of osteomyelitis and the killing curves of *S. aureus* were similar in all treatment groups HBOT is as effective as the antibiotic therapy

Table D: Overview of the risk of bias of the included studies

Study	Patient selection	Quality of methodology	Follow-up	Data report	Other issues	Total
Akkurt et al 2017, [20]	+/-	+/-	?	+/-	+/-	4.5
Onen et al 2015, [21]	+/-	+/-	+	+	+/-	3.0
Skeik et al 2015, [22]	+/-	-	?	-	-	7.5
Yu et al 2011, [23]	+/-	+/-	?	+/-	+/-	4.5
Saarinen et al 2011, [24]	+/-	+/-	+	+/-	+/-	4.0
Chen et al 2008, [25]	+/-	+/-	?	+/-	+/-	4.0
Lentrodt et al 2007, [26]	+/-	+/-	+	+/-	+/-	4.0
Chen et al 2004, [27]	+	+	+/-	+	+	1.0
Chen et al 2004, [28]	+	+	+/-	+	+	1.0
Baltenspenger et al, 2004, [29]	+/-	+/-	+	+/-	+/-	4.0
Aitasalo et al, 1998, [30]	+/-	+/-	+/-	+/-	+/-	5.0
Maynor et al, 1998,[31]	+/-	+	+	+	+/-	2.0
Dan Waisman et al, 1998, [32]	+/-	-	?	-	-	7.5
Berg et al 1989, [33]	-	-	+/-	-	-	9.0
Davis et al, 1986[34]	+	+/-	+	+	+	1.0
Seftel et al 1985, [35]	+/-	+	+/-	+	+/-	3.0
Eltorai et al 1984, [36]	+/-	+/-	+/-	+	+/-	4.0
Morrey et al 1979, [37]	+	+/-	+/-	+/-	+/-	4.0
Depenbusch et al, 1972, [38]	+	+/-	?	+/-	+/-	3.5
Hamblen, 1971, [39]	+/-	+/-	?	+/-	+/-	4.5