Chronic Refractory Osteomyelitis

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Background

Osteomyelitis is defined as an infection of bone and bone marrow with microorganisms (39). This infection can be acute, subacute or can merge into a chronic form as a complex disease state (38). Chronic refractory osteomyelitis is still not well defined despite the conglomerate of different symptoms and wide variability of the etiology (4, 39). There is still no consent about the detailed definition, criteria of diagnosis or universally accepted staging system (1, 26, 38, 39). Various types of osteomyelitis require different therapeutic approaches (31, 33, 40). This makes is challenging to compare published studies and the total number of literature reviews and studies is scarce. Most authors define refractory osteomyelitis as a bone infection which lasts more than 6 weeks of adequate therapy (2) or with persistence or recurrency of infection after treating properly with debridements and antibiotics for several weeks (3, 4).
To date we don't have any tool to determine exactly the extension of infected bone or soft tissue. This poses challenges in eradicating all affected structures (41). Inadequate debridement is one cause of high recurrence rates (40). Even nowadays treating osteomyelitis remains still challenging and is long lasting and expensive (39, 40). Experience in septic operations of the surgeon is highly important and reduces costs (14).
There are 2 relatively new possible mechanisms which may cause chronic refractory infections of bones which have been detected during the last years: Some recent published articles reported the problem of biofilm. Biofilm is a complex microbial community which produces a matrix of sugars and proteins. Furthermore the microorganisms are able to communicate and to coordinate their reaction. The matrix protects the microorganisms from antibiotics, antibodies and phagocytosis (39). Underlying mechanisms are largely unknown and further research is necessary (4, 15, 40).
Another kind of hard detectable bacteria are "small colony variants". They grow very slow and are able to penetrate cells and to persist intracellular so that antibiotics and endogenous defence can't harm them (1, 39).

Incidence

Haematogenous osteomyelitis decreased to less than 20 % in industrial countries due to antibiotic treatment (1, 39). Haematogenous osteomyelitis occurs predominantly in children (38). In contrast haematogenous vertebral osteomyelitis is more frequently seen in the elderly (37).
Trauma is the origin of most of bone infections: open fractures, surgical procedures or after implanted prosthesis. Infection rates increase in stabilizing

fractures from 1.5 % in closed fractures up to more than 30 % in open fractures (5, 50). The infection rate of prosthesis of the hip is about 0.5 to 2 % (6, 40). 10 to 30 % of acute bone infections will result in chronic osteomyelitis (4, 7). In Germany 1500 new diagnosed cases of chronic osteomyelitis per year are assumed (9).
As population is growing older and the use of more surgical/orthopaedic implants is raising the incidence of chronic osteomyelitis will increase during the next years (39, 40). Older persons are predisposed to osteomyelitis because of an increased incidence of associated disorders that predispose to osteomyelitis (e.g. diabetes mellitus, peripheral vascular disease, malnutrition etc.) (37, 39).

Clinical presentation

Clinical symptoms are often less impressive and variable (37, 39, 40). Classical findings like rubor, calor, tumor and dolor are often missing. Most reported symptoms are recurring local dull pain, soft tissue inflammation, drainage, swelling or abscess formation (39, 40). A fistula with conjunction to the bone or missing soft tissue coverage is a pathognomonic finding. Late findings are loosening of implants, pathological fractures, cancer of fistulae (37).
Inflammation parameters like leucocytes or C-reactive protein may be elevated in blood samples but not necessarily (39, 40). X-rays show typically osteolysis and destruction beside zones of sclerosis and periostal appositions (8). X-rays are useful for diagnostic and follow up (40). Sonography, MRI, CT, PET or scintigraphy may also detect pathological findings and can be used supplementary for special issues (38, 39, 40).
Despite the widespread symptoms chronic osteomyelitis must be diagnosed by synopsis of patient history, patient risk factors, clinical findings, various imaging techniques, microbiologic and histopathologic analysis (9, 38). Biofilm and “small colony variants” are difficult to detect (1).
Several classifications are trying to categorize the complexity of chronic osteomyelitis. A staging system should not only be a useful graduation but also allow for extrapolating treatment regimes. The Cierny Mader classification had been revolutionary as they combined elements of anatomical findings with the health status of the patient (26). But new classifications are still coming up (10).

Table 1. Cierny and Mader osteomyelitis staging system.

Classification	Description
Anatomic type	
Stage 1	Medullary osteomyelitis
Stage 2	Superficial osteomyelitis
Stage 3	Localized osteomyelitis
Stage 4	Diffuse osteomyelitis
Physiological class	
A host	Normal host
B host	Systemic compromise (Bs), local compromise (Bl), or systemic and local compromise (Bls)
C host	Treatment worse than the disease

Table 2. Systemic and local factors in class B hosts that affect immune surveillance, metabolism, and local vascularity.

Type of compromise	Factors
Systemic (Bs)	Malnutrition
	Renal, hepatic failure
	Diabetes mellitus
	Chronic hypoxia
	Immune disease
	Malignancy
	Extremes of age
	Immunosuppression or immune deficiency
Local (B1)	Chronic lymphedema
	Venous stasis
	Major-vessel compromise
	Arteritis
	Extensive scarring
	Radiation fibrosis
	Small-vessel disease
	Neuropathy
	Tobacco abuse (≥2 packs/d)

Standard management and outcome

There are still no evidence based guidelines for the therapy of chronic osteomyelitis available. Two guidelines - one concerning acute haematogenous osteomyelitis and bacterial arthritis of children and another one concerning osteomyelitis of the jaw exist in Germany (16, 42). Both guidelines don't mention hyperbaric oxygen therapy.

The standard management of osteomyelitis includes surgical debridement and thoroughly removal of nonviable tissue, potential removal of hardware, obliteration of dead space, adequate soft-tissue coverage and additional organism-specific, sensitivity proven antibiotic regime for 4 to 6 weeks (4, 41, 38, 39). New surgical methods are jet lavage and vacuum-assisted wound therapy (28, 39). Vacuum-assisted wound therapy has several advantages: it is easy to handle, widely applicable and cost effective. Removal of excess fluid and debris decreases tissue bacterial levels and increases tissue perfusion, reduces soft-tissue edema, enhances granulation tissue formation and improves wound healing. A controlled study about clinical efficacy of vacuum-assisted closure therapy in the management of osteomyelitis has been published by Tan et al. (28). It is a non-randomized controlled study with 68 patients total. The vacuum-assisted therapy showed significantly better results concerning the recurrence rate, the number of needed plastic flaps and converted negative bacterial cultures .

There are two approaches concerning the aim of therapy: cure or palliative care depending on the health status of the patient and acceptance/compliance of patient (1, 37, 39). Surgery is composed of 2 steps: First, the infection of bone and soft tissues must be eradicated. The second step is stabilisation and/or reconstruction for example with arthrodesis, (vascularised) bone grafts, free or local muscle flaps or bone segment-traction (9, 40, 41). Limb salvage is not always possible (37, 39). Several partly extended complex surgical procedures are necessary. Some patients are in poor condition that only allows limited procedures or sometimes patients refuse the burden of long-lasting therapy. In such cases the therapeutic goal is to pacify infection and to perform a conservative treatment (37, 39).
Most recommendations for the treatment of osteomyelitis are based on expert opinion rather than the results of randomized, controlled studies (38).

Haematogenous osteomyelitis is primarily treated conservatively with antibiotics. A failure of conservative treatment leads to surgical treatment similar to the above described treatments (1, 16, 38, 39).

A Cochrane report on antibiotics for treating chronic osteomyelitis in adults concludes a lack of evidence to determine regimen of antibiotics, their treatment duration or application (19).

Outcome is dependent on co-morbidities, compliance of patient and efficiency of surgical and microbiological treatment. Interdisciplinary collaboration is essential (40). Extreme variations of recurrence rates of 2 to 44 % are reported (1, 18, 21, 22). This wide range is based on the variable experience of surgeons, different surgical approaches, inhomogeneous patient population with distinctive risk factors. Osteomyelitis patients are not identical (13). Years of follow-up are necessary to demonstrate sustained remission (38).

Eckhard et al. treated 13 patients with an aggressive surgical approach with no recurrency in long term follow up of an average of 58 months (11 to 89 months) (18). The authors conclude that recurrency is well-founded by inadequate removal of infected tissue, insufficient reconstruction of tissue and inappropriate antibiotic therapy.

Rationale for HBO use

The rationale for the use of adjunctive HBO-therapy has been well described in the past (2, 3). There are several mechanisms which can be responsible for observed positive effects by HBOT. In infected bone the oxygen tension levels are reduced to 10 to 20 mm Hg (47). However, for the neutrophil killing mechanism oxygen tension levels of 30 – 40 mm Hg are needed (48). HBOT elevates significantly the oxygen tension of bone (43, 46). These effects have been demonstrated in *in vitro* and *in vivo* animal studies. Other animal data suggest improvement of osteoclasts and osteoblasts functions (57). HBOT acts synergistic with aminoglycosides or cephalosporines (44, 45). Furthermore high oxygen levels have a direct suppressive effect on anaerobic bacteria (55, 56). Tissue edema will be also reduced by using hyperbaric oxygen (60, 61). At least HBOT promotes new collagen formation and capillary angiogenesis (58,59).

Some published animal studies do have better quality than human studies (23, 24). But they have some limitations: In none of these studies surgical debridement is performed which is the main treatment with antibiotics in the management of osteomyelitis of humans. A tibial bone of a rabbit has a dimension of a metacarpale bone of a human. An infection of a human tibia or femur has a much greater dimension and it is debatable if comparison is possible (13).

Evidence – Based review of HBO use

Search for literature was performed using the following electronic databases: Pub Med, Rubicon Foundation, GTUEM-Database, Cochrane Database of systematic reviews and additional manual search. Date of search was 15th November 2015. The key words had been: “osteomyelitis and HBOT”, “osteitis and HBOT”, “osteomyelitis and hyperbaric oxygen” and “osteitis and hyperbaric oxygen”.

Systematic reviews concerning hyperbaric oxygen treatment in chronic refractory osteomyelitis had been published (11, 17, 30). They assess the quality of the few available studies as low to moderate with various flaws and inconsistent findings so that the evidence for the benefit of an additional hyperbaric oxygen treatment is low to moderate and further research is necessary before this can be recommended.

Until now there is no study if HBOT alone or in combination with other therapies may have any effect on biofilm in osteomyelitis. But one study evaluated the effect of HBOT on periodontal disease (12). The periodontic plaques constitute also a bacterial biofilm. The results showed that HBOT therapy in combination with surgical intervention reduced the gram-negative anaerobe microflora and

this persisted for at least 2 months – the end of this study. The gingival index as a marker of inflammation showed also gingival health in the HBO groups. Additional studies are missing. Furthermore it remains unclear if therapies for periodontal disease are transferable for chronic refractory osteomyelitis.

Several preliminary reports have been published (25, 32, 33). Unfortunately no further data from these groups had been rolled out. It remains unanswered why.

There is still no published prospective randomized controlled clinical trials.

Only 5 studies concerning osteomyelitis and hyperbaric oxygen treatment in men have been published since the last Consensus Conference in 2004 (20, 34, 35, 53, 36). Three of them are retrospective case series without controls (two of them only published in German), one of them has matched controls and one has not randomized or matched controls. All studies included only a small number of patients with a maximum of 32 patients (34). The 5 studies analyse various types of osteomyelitis: Barili and Yu studied organ/space sternal surgical site infections (34, 36), Handschel and Jamil chronic osteomyelitis of the jaw (35, 54), Sandner advanced skull base osteomyelitis (20) and Ahmed haematogenous and postoperative spinal osteomyelitis (53).

The level of the 5 studies published since 2004 is low that means Grade C due to study design and small number of patients.

The only prospective study by Barili (34) showed inconsistent findings. The HBO group had a lower rate of infection relapse (0 versus 33,3 %) but no differences in the duration of infection and the time to wound closure could be detected. The duration of intravenous antibiotic use and the total hospital stay was significantly shorter in the HBO group. One flaw is the choice of control group: it consists of 2 patients with contraindications und 16 patients who refused a hyperbaric treatment because of claustrophobia or risks of this treatment. The other group may be at least much more motivated. We can also find differences in the preoperative clinical characteristics: the control group contains more patients with diabetes (61.1 % versus 42.8 %) but in the HBO treatment group are more patients with chronic obstructive lung disease or peripheral vascular disease.

Yu analysed also organ/space sternal surgical site infections in his retrospective case series with not randomized or matched controls (36). He reports outcomes of only 6 patients of each group. His control group was founded by insurance and risk for HBOT without any further details. Barili started HBOT within 30 days postoperatively after sternotomy. Yu's patients started from 2 weeks to several months later after diagnosis. He concluded that mortality rate is higher in the control group but 2 of 3 deaths had not been related to sternal infection (ischemic bowel disease, acute pancreatitis). He also concluded that length of intensive care unit stay and invasive ventilation is higher without HBOT. But the HBO patients were treated with face masks. It remains totally unclear at what point in time during hospital stay patients had been mechanically ventilated. A difference from an average of 4 days with mechanical ventilation in the HBO group to 34.8 days in the control group presumes more critical ill patients in the control group. The rate of diabetes was also higher in the control group.

Surprisingly the debridement frequency, hospital admission frequency and length of hospital stay were not significantly different between the two groups.

Ahmed presented a retrospective case series of 6 patients over a 10 year period without controls (53). His target had been haematogenous and postoperative spinal osteomyelitis which means a case mix of different entities. Follow up was possible from 5 months to 5 years with an average follow up of 1.9 years. 5 of 6 patients had been cured. Ahmed concluded that HBOT as an adjunctive therapy is effective in previous failure of standard treatment but it is important to determine patients who will benefit from this therapy.

Sandner et al. used for the life-threatening indication advanced skull base osteomyelitis HBOT as an adjunctive therapy (20). 6 from 8 patients had been immunocompromised and 7 patients showed cranial nerve palsies. All patients could be cured and in only 2 patients cranial nerve palsies persisted.

Handschel treated 3 groups of osteomyelitis of the jaw (13 patients with primary diagnosis, 5 patients with relapse after antibiotic treatment and 9 patients with relapse after surgical and combined antibiotic treatment) with antibiotics, decortication if necessary and HBOT. Unfortunately he didn't specify the hyperbaric oxgen treatment (pressure and duration of breathing oxygen per session). No resection of the jaw was necessary. Only one patient with osteomyelitis after treatment with bisphosphonats could not be cured with his protocol: he concluded that other treatments are indicated for such cases. Follow up had been 2 to 4 years. In 59 % of patients no surgical intervention had been necessary. Better results had been achieved in patients older than 30 years. But HBOT is a long lasting therapy as 40 sessions seem to be the minimum.

All these studies are extremely inhomogeneous, examine different types of osteomyelitis, have only small numbers of patients and mostly no control group. But if we take all published studies under consideration (also the previous studies which are listed in the table) evidence enhances that adjunctive HBOT leads to better results especially in compromised hosts. The bias is often against HBOT as most patients referred to an HBOT are of poor prognosis due to comorbidities (52, 53).

Only one study by Esterhai couldn't show remarkable effects in a prospective study with matched pairs. Hyperbaric oxygen had no effect on length of hospitalization, rapidity of wound repair, initial clinical outcome or recurrence of infection (13). But he didn't publish the number of HBO sessions. He only described that treatment failures occurred in 3 of 4 patients with 20 HBO sessions. But there is established evidence that a minimum of 40 sessions for this type of osteomyelitis are needed to show a beneficial effect. So it is an immediate suggestion that the oxygen dose was not sufficient.

The overall published literature shows inconsistent results but mostly results are described as encouraging. But the patient population with osteomyelitis is heterogeneous (13, 53). Treatment needs to be individualized due to the condition and compliance of patients. Compromised hosts may benefit from an additional HBOT. It is a task to identify these patients.

Nevertheless having not many alternatives as standard therapy often fails in these patients HBOT should be considered in chronic refractory osteomyelitis.

Looking at these data the outcome and the needed number of HBOT sessions seems to be dependent on localisation and origin of chronic osteomyelitis. Well designed studies with randomized controls and usage of new established surgical standard treatment procedures e.g. vacuum-assisted closure therapy are necessary.

Patients selection for HBO

According to several reports hyperbaric oxygen therapy seems to have a better outcome for patients with Cierny Mader classification 3 B and 4 B and in special cases with high morbidity and mortality associated with complicated infections of sternum, skull and spine. These patients should receive additional HBOT (20, 53). In chronic refractory osteomyelitis which cannot be pacified by standard treatment HBOT should be taken into consideration (2, 3, 33).

Current protocol

HBOT treatment regimes reported in the literature include daily hyperbaric sessions (5 to 7 sessions per week) for a minimum of 4 to 6 weeks which means 20 to 40 sessions minimum (32, 34, 53). Utilization review should be done after 30 to 40 sessions (35, 52).
Oxygen dose should be 90 to 120 minutes using 2.0 – 3.0 ATA. Most centres use a pressure of 2.4 to 2.5 ATA for 90 minutes of oxygen supply. This regime seems to be the best balance between positive effects of oxygen and its toxicity. HBOT should start after thorough surgical debridement including removal of any existing osteosynthesis material in the infected zone if possible. Serial debridements and treatment with antibiotics based on microbiology results have to be continued.
In special cases where extensive surgical procedures are not possible it can be useful to administer more HBO sessions (2, 3, 52).

Cost impact

Actual estimated costs per case of chronic refractory osteomyelitis are round about 500.000 to 700.000 Euros in Germany (9, 14). This cost assessment includes outpatient and inpatient treatment costs, rehabilitation, pension as well as non-productive-time (9). Hyperbaric treatments calculated with 40 sessions would generate costs round about 8.000 to 16.000 Euros – which is negligible given the total costs.
Schenker et al. estimated lifetime costs of $680.000 in the most severe open fracture injuries due to musculoskeletal infections (50).

Chung et al. performed a cost-utility analysis of amputation versus salvage for Gustilo type IIIB and IIIC open tibial fractures (49). This group calculated that amputation will be more expensive than salvage of the limb concerning the estimated life time costs so their recommendation is the strategy of limb salvage.

Larsson et al. estimated less than half of the costs for hyperbaric oxygen treatment compared to 2 additional surgical interventions for removal of bone/acrylic flaps and secondary cranioplasty in osteomyelitis of the cranial bone with a moderate failure rate (52).

If by using hyperbaric oxygen for adjunctive treatment length of hospital stay, duration of antibiotic treatment and/or number of serial debridements, limb salvage could be reduced, HBOT would be cost effective. Well designed studies have to demonstrate this in the future.

References

1. Walter G, Kemmerer M, Kappler C et al.: Treatment algorithms for chronic osteomyelitis. Dtsch Arztebl Int 2012; 109(14): 257-64; DOI: 10.3238/arztebl.2012.0257.

2. Kemmer A, Stein, T Hierholzer C : Persistent Osteomyelitis. From Daniel Mathieu, Editor. Handbook on Hyperbaric Medicine. Springer-Verlag, 2006. ISBN-10: 1402043767.

3. Brett Hart: Refractory Osteomyelitis. From Gesell, LB, Chair and Editor. Hyperbaric Oxygen Therapy Indications, 12th Edition. The Hyperbaric Oxygen Therapy Committee Report. Durham, NC: Undersea and Hyperbaric Medical Society, 2008. ISBN-10: 0930406230.

4. Fang RC, Galiano RD. Adjunctive therapies in the treatment of osteomyelitis. Semin Plast Surg 2009;23:141-7

5. Papakostidis C, Kanakaris NK, Pretel J, Faour O, Morell DJ, Giannoudis PV.Injury. Prevalence of complications of open tibial shaft fractures stratified as per the Gustilo-Anderson classification. Injury. 2011 Dec;42(12):1408-15. doi: 10.1016/j.injury.2011.10.015. Epub 2011 Oct 22.

6. Parvizi J, Ghanem E, Azzam K, Davis E, Jaberi F, Hozack W. Periprosthetic infection: are current treatment strategies adequate? Acta Orthop Belg. 2008 Dec;74(6):793-800

7. Hofmann G. Chronische Osteitis. Infektionen der Knochen und Gelenke. München: Jena Urban & Fischer; 2004: 59-83

8. Schmidt HG, Tiemann AH, Braunschweig R, et al.: Zur Definition der Diagnose Osteomyelitis-Osteomyelitis-Diagnose-Score (ODS). Z Orthop Unfall 2011; 49: 449-60

9. Tiemann AH, Braunscheig R, Hofmann GO. Knocheninfektionen. Unfallchirurg 2012; 115:480-488

10. Schmidt HGK, Diefenbek M, Krenn V et al. Klassifikation der Osteomyelitis und Osteitis. Z Orthop Unfall 2014; 152 334-342

11. Phillips JS, Jones SEM. Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa (Review). Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD004617.DOI: 10.1002/14651858.DD004617.pub3.

12. Signoretto C, Bianchi F, Burlacchini G, Canepari P. Microbiological evaluation of the effects of hyperbaric oxygen on periodontal disease. New Micobiologica, 2007; 30: 431-437

13. Esterhai, JL, et al.. Adjunctive hyperbaric oxygen therapy in the treatment of chronic refractory ostomyelitis. J Trauma, 1987. 27(7): 763-8

14. Heppert V, Wagner C, Glatzel U, Wentzensen A. Prinzipien der operativ-chirurgischen Therapie der Osteitis. Trauma Berufskrankh 2002; 4: 321-328

15. Leaper DJ, et al.. Extending the TIME concept: what have we learned in the past 10 years? Int Wound J. 2012 Dec; 9 Suppl 2:1-19. doi: 10.1111/j.1742-481X.2012.01097.x.

16. http://www.awmf.org/uploads/tx_szleitlinien/027-054l_S1_Akute_h%C3%A4matogene_Osteomyelitis_bakterielle_Arthritis_2013-01.pdf

17. Kay Tetzlaff K, Jüttner B. Hyperbare Therapie und Tauchmedizin – Hyperbare Therapie Teil 2: adjuvante Therapieoptionen. Anästhesiol Intensivmed Notfallmed Schmerzther 2015; 50(10): 628-636 DOI: 10.1055/s-0041-107111

18. Eckardt JJ, Wirganowicz PZ, Mar T: An aggressive surgical approach to the management of chronic osteomyelitis. Clin Orthop Relat Res, 1994 (298):229-39

19. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD004439. DOI: 10.1002/14651858.CD004439.pub3.

20. Sandner A, Henze D, Neumann K, Kösling S. Nutzen der HBO bei der Therapie der fortgeschrittenen Schädelbasisosteomyelitis. Value of hyperbaric oxygen in the treatment of advanced skull base osteomyelitis. Laryngorhinootologie. 2009 Oct;88(10):641-6

21. Tice AD, Hoaglund PA, Shoultz DA. Outcomes of osteomyelitis among patients treated with outpatient parenteral antimicrobial therapy. Am J Med 2003;114:723-728

22. Lipsky BA, berendt AR, Deery HG, et al. Diagnsis and treatment of diabetic foot infections. Plast Reconstr Surg 2006; 117 (7, Suppl): 212S-238S

23. Mendel V, Reichert B, Simanowski HJ, Scholz HC. Therapy with hyperbaric oxygen and cefazolin for experimental osteomyelitis due to Staphylococcus aureus in rats. Undersea Hyper ed. 1999 Fall; 26 (3): 169-74

24. Adams KR, Mader JT. Aminogycoside potentiation with adjunctive hyperbaric oxygen therapy i experimental ps. Aerugiose osteomyelitis. Abstract of the Undersea and Hyperbaric Medical Society Inc. Annual Scientific Meeting held May 26-30, 1987. Baltimore.

25. Chen CE, Ko JY, Fu TH, Wang CJ. Results of chronic osteomyelitis of the femur treated with hyperbaric oxygen: a preliminary report. Chang Gung Med J. 2004 Feb;27(2):91-7.

26. Mader JT, Shirtliff M, Calhoun JH. Staging and Staging Application in Osteomyelitis. Clin Infect Dis. 1997 Dec;25(6):1303-9.

27. Tieman A, Diefenbeck M, Mückley T, Hofmann GO. Use of Hyperbaric Oxygenation in the Therapy of Osteitis – Are there any New aspects?. Zentralbl Chir 2008; 133: 396-397.

28. Tan Y, Wang X, Li H, Zheng Q, Li J, Feng G, Pan Z. The clinical efficacy of the vacuum-assisted closure therapy in the management of adult osteomyelitis. Arch Orthop Trauma Surg. 2011 Feb;131(2):255-9. doi: 10.1007/s00402-010-1197-x. Epub 2010 Dec 23.

29. Tiemann AH, Hofmann GO. Principles of the therapy of bone infections in adult extremeties. Are there any new developments? Strategies Trauma Limb reconstr. 2009 Oct; 4 (2): 57-64.

30. Goldman RJ. Hyperbaric oxygen therapy for wound healing and limb salvage: a systematic review. PM R. 2009 May; 1 (5): 171-89. doi: 10.1016/j.pmrj.2009.03.012.

31. Van Merkesteyn P, et al.. Hyperbaric oxygen treatment of chronic osteomyelitis of the jaws. Int J Oral Surg. 1984 Oct; 13(5): 386-95.

32. Chen CE, et al.. Hyperbaric Oxygen Therapy in the Treatment of Chronic Refraktory Osteomyelitis: A preliminary Report. Chang Gung Med J Vol. 2003; 26 No. 2:114-120.

33. Morrey BF, Dunn JM, Heimbach RD, Davis J. Hyperbaric oxygen and chronic osteomyelitis. Clin Orthop Relat Res. 1979 Oct;(144):121-7.

34. Barili F, et al.. Role of hyperbaric oxygen therapy in the treatment of postoperative organ/space sternal surgical site infections. World J Surg. 2007 Aug;31(8):1702-6.

35. Handschel et al.. Hyperbare Sauerstofftherapie bei Unterkiefer-Osteomyelitis. Mund Kiefer GesichtsChir (2007); 11: 285-290.

36. Yu WK, Chen YW, Shie HG, Lien TC, Kao HK, Wang JH. Hyperbaric oxygen therapy as an adjunctive treatment for sternal infection and osteomyelitis after sternotomy and cardiothoracic surgery. J Cardiothorac Surg. 011 Oct 17;6:141.

37. Cunha BA. Osteomyelitis in elderly patients. Clin Infect Dis. 2002 Aug 1;35(3):287-93. Epub 2002 Jul 11.

38. Carek PJ, Dickerson LM, Sack JL. Diagnosis and management of osteomyelitis. Am Fam Physician. 2001 Jun 15;63(12):2413-20.

39. Lazzarini L, Mader JT, Calhoun JH. Osteomyelitis in long bones. J Bone Joint Surg Am. 2004 Oct;86-A(10):2305-18.

40. Lew DP, Waldvogel FA. Osteomyelitis. Lancet. 2004 Jul 24-30;364(9431):369-79.

41. Tiemann AH, Schmidt HG, Braunschweig R, Hofmann GO. Strategies for the analysis of osteitic bone defects at the diaphysis of long bones. Strategies Trauma Limb Reconstr. 2009 Apr;4(1):13-8. doi: 10.1007/s11751-009-0054-3. Epub 2009 Mar 14.

42. http://www.awmf.org/uploads/tx_szleitlinien/007-045_S2_Osteomyelitis_abgelaufen.pdf

43. Mader, JT et al.. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis, 1980. 142(6): 915-22

44. Mendel V, Simanowski HJ, Scholz HCh. Synergy of HBO2 and a local antibiotic carrier for experimental osteomyelitis due to Staphylococcus aureus in rats. Undersea Hyperb Med. 2004 Winter;31(4):407-16.

45. Mendel V, Reichert B, Simanowski HJ, Scholz HC. Therapy with hyperbaric oxygen and cefazolin for experimental osteomyelitis due to Staphylococcus aureus in rats. Mendel V, Reichert B, Simanowski HJ, Scholz HC.

46. Esterhai JL Jr, Clark JM, Morton HE, Smith DW, Steinbach A, Richter SD. Effect of hyperbaric oxygen exposure on oxygen tension within the medullary canal in the rabbit tibial osteomyelitis model. J Orthop Res. 1986;4(3):330-6.

47. Niinikoski J, Hunt TK. Oxygen tensions in healing bone. Surg Gynecol Obstet. 1972 May;134(5):746-50.

48. Hohn DC, MacKay RD, Halliday B, Hunt TK. The effect of O2 Tension on the microbicidal function of leukocytes in wounds and in vitro. Surg Forum. 1976;27(62):18-20.

49. Chung KC, Saddawi-Konefka D, Haase SC, Kaul G. A cost-utility analysis of amputation versus salvage for Gustilo type IIIB and IIIC open tibial fractures. Plast Reconstr Surg. 2009 Dec;124(6):1965-73. doi: 10.1097/PRS.0b013e3181bcf156.

50. Schenker ML, Yannascoli S, Baldwin KD, Ahn J, Mehta S. Does timing to operative debridement affect infectious complications in open long-bone fractures? A systematic review. J Bone Joint Surg Am. 2012 Jun 20;94(12):1057-64. doi: 10.2106/JBJS.K.00582.

51. Davis JC, Heckman JD, DeLee JC, Buckwold FJ. Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. J Bone Joint Surg Am. 1986 Oct;68(8):1210-7

52. Larsson A, Engström M, Uusijärvi J, Kihlström L, Lind F, Mathiesen T. Hyperbaric oxygen treatment of postoperative neurosurgical infections. Neurosurgery. 2002 Feb;50(2):287-95

53. Ahmed R, Severson MA, Traynelis VC. Role of hyerbaric oxygen therapy of the treatment of bacterial spinal osteomyelitis. J Neurosurg Spine. 2009 Jan;10(1):16-20

54. Jamil MU, Eckardt A, Franko W. Klinische Anwendung in der Behandlung von Osteomyelitis, Osteoradionekrose und der Wiederherstellungschirugie des vorbestrahlten Unterkiefers. Mund Kiefer Gesichtschir. 2000 Sep;4(5):320-3

55. Slack WK, Thomas DA, Perrins D. Hyperbaric Oxygenation Chronic Osteomyelitis. Lancet. 1965 May 22;1(7395):1093-4

56. Park MK, Myers RA, Marzella L. Oxygen tensions and infections: modulation of microbial growth, activity of antimicrobial agents, and immunologic responses. Clin Infect Dis. 1992 Mar;14(3):720-40

57. Ueng SW, Lee SS, Lin SS, Wang CR, Liu SJ, Yang HF, Tai CL, Shih CH. Bone healing of tibial lengthening is enhanced by hyperbaric oxygen therapy : a study of bone mineral density and torsional strength on rabbits. J Trauma. 1998 Apr;44(4):676-81

58. Hohn DC, MacKay RD, Halliday B, Hunt TK. Effect of O2 tension on microbicidal function of leukocytes in wounds and in vitro. Surg Forum. 1976;27(62):18-20

59. Hunt TK, Pai MP. The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis. Surg Gynecol Obstet. 1972 Oct;135(4):561-7

60. Skyhar MJ, Hargens AR, Strauss MB, Gershuni DH, Hart GB, Akeson WH. Hyperbaric oxygen reduces edema and necrosis of skeletal muscle in compartment syndromes associated with hemorrhagic hyptension. J Bone Joint Surg Am. 1986 Oct;68(8):1218-24

61. Nylander G, Lewis D, Nordström H, Larsson J. Reduction of postischemic edema with hyperbaric oxygen. Plast Reconstr Surg. 1985 Oct;76(4):596-603

62. Aitasalo K, Niinikoski J, Grénman R, Virolainen E. A modified protocol for early treatment of osteomyelitis and osteoradionecrosis of the mandible. Head Neck. 1998 Aug;20(5):411-7

Conclusion

HBOT should be considered in chronic refractory osteomyelitis: Type 2 recommendation; Level C Evidence

Compromised hosts must be identified as they may benefit from an additional HBOT: Type 1 recommendation; Level A Evidence

Treatment needs to be individualized due to the condition and compliance of patients: Type 1 recommendation; Level C Evidence

HBOT should last at least 11 to 12 weeks which gives approx. 60 sessions before any significant clinical effect should be expected. Type 1 recommendation; Level B Evidence

Well designed studies and data for standard treatment without HBOT are required: Type 1 recommendation, Level A Evidence

Well designed randomized controlled studies in specialized centres for treating patients with chronic refractory osteomyelitis which have the possibility to offer an adjunctive HBOT are required. Our suggestion is to initiate multicentre studies to get an acceptable number of comparable patients. Type 1 recommendation, Level A Evidence.

The post-HBOT evaluation should use the same diagnostic method as used for diagnosis assuming that it has the sufficient sensitivity in detecting osteomyelitis. Type 1 recommendation, Level A Evidence

Study (authors, year)	Type	Nb patients	Aim(s) / Evaluation criteria	Inclusion / Exclusion criteria	HBO protocol (pressure, time, nb of session)	Results	Conclusion / comment
Morrey 1979 (33)	retrospective case series, no controls	40 (53); 65 % with open fractures or gunshot wounds	outcome: clinically free of disease, no relapse; analysis of treatment failures	patients with refractory osteomyelitis: infection for at least 6 months, undergone at least one surgical procedure , already treated with parenteral antibiotics; No hematogenous osteomyelitis included; 13 patients had been excluded (not mentioned why) ;	2.4 ATA, 90 min oxygen, 20 min oxygen and 5 min air breaks, 5 days a week, average 42 sessions (9 to 208 treatments)	15 % recurrence rate in an average follow up of 2 years (12 – 53 months);	preliminary report; no correlation between site, organisms, mean duration of infection und recurrence rate; cause for relapse was lack of aggressive surgery in 3 of 6 patients; it remains unclear why 13 patients have been excluded author concludes: HBOT may be an adjunct especially in patients in whom ablative surgery is under

							consideration;
Van merkestey n 1984 (31)	retrospective case series no controls	16	evaluation of efficiency of HBOT	chronic osteomyelitis of the jaw, 15 of 16 patients with previous antibiotic and/or surgical treatment	3 ATA, 90 min oxygen, 6 days a week, average 100 sessions (17 to 213 sessions)	7 patients cured, 4 improved, 4 failed	standard treatment is antibiotic and surgical treatment for chronic suppurative osteomyelitis; additional HBOT is indicated in chronic diffuse sclerosing osteomyelitis and in patients in whom decortications and antibiotic therapy have failed; highest number of sessions in literature! standard therapy sufficient? Only a few patients treated multimodal, large number of patients with chronic diffuse

							sclerosing osteomyelitis (difficult to treat)
Davis 1986 (51)	Retrospective case series, no controls	38	evaluation of the infect free interval after a multimodal treatment protocol	chronic refractory non-haematogenous osteomyelitis for at least 6 months, at least one surgical procedure to eliminate the infection before, previous treatment with antibiotics	once daily, 6 days a week, 48 average (8-103) sessions, 2.4 ATA, head tent, 90 min oxygen, 10 min airbreaks, until the bone was fully covered with healthy vascular tissue	follow up average 34 months (24 to 59 months), excellent long term results, 34 of 38 patients remained clinically free of infection (89 %); 2 failures perhaps due to incomplete treatment protocol	author's conclusion: combined treatment protocol is responsible for the good results, no precise documentation of the previous treatments, too short follow up to declare the patients cured,
Esterhai 1987 (13)	prospective study, matched controls based upon the stage of bone involvement at the time of initial debridement	14 with HBOT, 14 without HBOT	effectiveness of adjunctive HBOT: length of hospitalization ; rapidity of open wound soft-tissue granulation repair; clinical outcome; recurrence rate	chronic refractory osteomyelitis of the lower extremities, refractory to antibiotics and surgery;	2 ATA, 2 hours, 6 sessions a week; number of sessions are not published!	average follow up 41.1 months (11-77); 86 % healed; 3 patients refused further indicated surgical procedures; no effect on length of hospitalization, rapidly of wound repair, initial clinical outcome,	3 of the 4 failures had been treated with at least 20 days of adjunctive HBOT; Osteomyelitis patients are not identical; higher recurrence rates in infections of subchondral bone;

						recurrence rate of infection	oxygen dose may be too less to show a beneficial effect of HBOT!!
Aitasalo 1998 (62)	retrospective case series, no controls	33	evaluation of effectiveness of HBOT with combined surgery and antibiotic treatment	chronic osteomyelitis of the jaw	once daily, 5 to 6 times a week,2.5 – 2.8 ATA, first years monoplace 120 min oxygen, then multiplace 90 min oxygen, 10 preoperative and 5 postoperative sessions ; Decortication an free periosteal graft from the tibia	79 % remained symptom free after the first treatment period; Follow up minimum 10 months, average 34 months	reduced number of sessions compared to Marx, lower costs with similar good outcomes, effective treatment
Jamil 2000 (54)	retrospective case series, no controls	16	evaluation of efficiency of HBOT	chronic refractory osteomyelitis of the jaw; all patients treated before: surgical intervention with decortication or sequestrectomy and i.v. antibiotics + oral antibiotic for	2,4 ATA, 90 min oxygen, 5 days a week, 30 sessions	6 patients cured, 8 patients improved, 2 patients with relapse, follow up 9 to 48 months (average 35	only German, no flawless studies possible as patients are not homogenous and several clinical variations of

				minimum of another 4 weeks		months)	osteomyelitis are existing; randomized standardised multicenter studies are necessary
Larsson 2002 (52)	retrospective case series; no controls	39 (1 break off HBOT, 2 died from cancer); Group 1 : 15 patients uncomplicated cranial wound infections, Group 2 : 16 patients with complicated cranial wound infections previous radiotherapy, foreign material, malignant disease, Group 3 : 7 patients with spinal wound infections	usefulness of HBOT in the treatment of postoperative neurosurgical infectious complications	Osteomyelitis of the cranial bone flap and osteomyelitis after spinal surgery with internal fixation	2.5 to 2.8 ATA, 3 x 25 min O2, 10 min air breaks, once daily 5 times a week, life threatening twice daily, 7 to 57 treatments, protocol : designated 40 sessions	Successful treatment of 27 from 36 patients, Group 1 12 of 15 uncomplicated infections healed with retained bone flaps, Group 2 only one could not resolved, Group 3 all infections resolved, 5 of 7 without removal fixation system	Variety of intracranial and intraspinal infections; Some patients overtreated, some would have better more sessions: individual number of sessions would be better; less surgical interventions necessary, HBOT instead of 2 more surgeries can safe costs,
Chen CE 2003 (32)	retrospective case series; no controls	14	evaluation of efficiency of HBOT, no relapse	osteomyelitis of tibia, Cierny Mader III und IV; infection for at least 6 months, parenteral antibiotic, more than 3 surgical procedures	2.5 ATA, 5 sessions a week, 2 hours, 25 min 5 min air breaks, average	no recurrence of infection in 11 patients (79 %), follow up minimum 1 year (12-18 months,	preliminary report, long treatment course, results were unpredictable, treatment was

					sessions 33.6 (30-60)	average 15 months)	individualized, HBOT is safe and effective
Chen CE 2004 (25)	retrospective case series, no controls	13	evaluation efficiency of HBOT, no relapse	femoral infection for at least 6 months, parenteral antibiotic, more than 3 surgical procedures, Cierny Mader III und IV	2.5 ATA, 5 sessions a week, 2 hours, 25 min 5 min air breaks, average sessions 32.2 (18 to 75)	12 of 13 (92 %) patients have successfully treated with HBOT, surgery and antibiotics	preliminary report, too short follow up of an average of 22 month, minimum 1 year, small number HBOT is safe and effective
Barili 2007 (34)	prospective study, not randomized controls, matched controls	Group 1:14 patients accepted HBOT, Group 2: 16 patients refused HBOT (due to Claustrophobia and risk of HBOT)+ 2 with contraindicatio n pneumothorax; matched with comparable preoperative clinical characteristics and operative	effect of HBOT on organ/ space sternal surgical site infections	patients with organ/space sternal surgical site infections according to the criteria of the Center for Disease Control, within 30 days postoperatively after sternotomy	one session daily, 90 min per session, 2-3 ATA, average number of sessions 17 (+-5.8) sessions	group 1 no recurrence, group 2 33.3 % recurrence rate, group 1 intravenous antibiotics 48 versus 68 days, length of hospital stay 53 versus 74 days	author's conclusion: lower rate of infection relapse in the HBOT group, but no differences in the duration of infection and the time to wound closure, additional studies with randomized controls are necessary no vacuum suction,

		factors					more patients with diabetes in control group, patients in group 1 better motivated?
Handschel 2007 (35)	retrospective case series; no controls	27 altogether; Group I: 13 patients with primary diagnosis, group II 5 patients already treated with antibiotics and one local relapse; group III: 9 patients with at least one local relapse after antimicrobial and surgical treatment	evaluation of clinical outcome of HBOT: free from clinical symptoms	patients with chronic osteomyelitis of the jaw which received HBOT,	not defined, ca. 40 sessions, more courses after relapse	no resection of jaw necessary, no cure in one patient after therapy with bisphosphonats , all other patients had no relapse after finishing treatment (HBOT, decortication, antibiotics) in a minimum follow up of 2 years (2-4 years); in 16 of 27 pat. (59%) no surgical intervention had been necessary, better results in older patients, pat. < 30 years needed surgery more often;	only in German; 40 HBO sessions seem to be minimum, HBOT can reduce surgical interventions, but long lasting therapy; in patients with osteomyelitis after therapy with bisphosphonats other treatments are indicated
Sandner 2009 (20)	retrospective case series; no controls	8 patients	efficacy of HBOT in the functional	advanced skull base osteomyelitis, 6 of 8 patients had been	2.4 ATA, 90 min oxygen, once daily, 5	cure rate 100 %, functional recovery in	HBOT adjunctive may be highly

			outcome, impact on morbidity and mortality	immunocompromised, all treated before with antibiotics and local treatment, 2 with surgery	days a week, 5 – 41 sessions (average 23 sessions)	cranial nerves in 6 of 8 pat.	effective
Ahmed 2009 (53)	retrospective case series; no controls	6 (of 9: 2 died of significant comorbidities unrelated to spinal infection), 1 patient did not complete the 30 recommended sessions)	efficacy of HBOT	spinal osteomyelitis with HBOT : hematogenous and postoperative	2.0 to 2.4 ATA, 90 min oxygen, hood, 5 sessions a week, once daily, 30 sessions in total	average follow up 1.9 years (5 months to 5 years), 5 of 6 had been cured	author's conclusion: HBOT is effective even in previous failure of standard treatment, it is important to determine pat. who will benefit most from HBOT, number of necessary sessions still not clear small number in a 10 year period, case mix haematogenous and postoperative osteomyelitis;
Yu 2011 (36)	retrospective case series, no randomized controls	12 (6 with and 6 without HBOT)	efficacy of HBOT in patients with sternal infection and osteomyelitis after	patients with organ/space sternal surgical site infections according to the criteria of the Center for Disease Control	90 minutes 2.5 ATA, 5 days a week, facial masks, number of sessions not defined!	better results concerning mortality, length of ICU stay, invasive ventilation and NIV (but HBOT	author's conclusion: favourable results with HBOT as adjunctive

			sternotomy	control group selected: because of insurance or risk of HBOT, no details	Average of 21.3 sessions	with face mask!!!), no difference in overall hospital stay	small number, control group not randomized, control group had been longer invasive ventilated and was more severe ill!!!! HBOT starts 2 weeks to several months later after diagnosis; more patients with diabetes in the control group(50 % to 17 %); 2 of 3 deaths in the control group not related to sternal infection

Used abbreviations:
HBOT = hyperbaric oxygen therapy
ATA = total ambient pressure compared to vacuum