Hyperbaric oxygen treatment: Results in seven patients with severe bacterial postoperative central nervous system infections and refractory mucormycosis

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Abstract
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Introduction: Resistant bacterial infections following brain and spine surgery and spontaneous mucormycosis with central nervous system (CNS) involvement represent a serious treatment challenge and more efficient therapeutic approaches ought to be considered. Hyperbaric oxygen treatment (HBOT) has shown promise as a complementary therapy. This case series evaluated whether HBOT contributed to infection resolution in seven patients with refractory CNS infectious conditions.
Methods: Clinical results for seven patients referred for HBOT between 2010 to 2018 to treat refractory postoperative brain and spine infections or spontaneously developing mucormycosis were retrospectively analysed. The patients' clinical files and follow-up consultations were reviewed to assess evolution and outcome.
Results: Seven patients were referred with a median age of 56 years. The median follow-up was 20 months. Four patients had postoperative infections and three had rhino-orbital-cerebral mucormycosis (ROCM). HBOT was used as an adjunctive treatment to antimicrobial therapy in all patients. Prior to HBOT, all patients had undergone an average of four operations due to infection refractoriness and had completed an average of five months of antimicrobial therapy. After HBOT, infection resolution was obtained in six patients without additional operations, while one patient with ROCM stopped HBOT after the third session due to intolerance. Three patients stopped antimicrobial therapy while four were maintained on prophylactic treatment.
Conclusions: Infection resolution was reached in the six patients that completed HBOT as prescribed. HBOT may serve as an effective complementary treatment in CNS refractory postoperative and spontaneous infections.

Introduction

Resistant infections remain a challenge to neurosurgical and neurological care. The use of less conventional techniques can be an adjuvant option to consider when standard treatments are ineffective. Albeit seldom used in complex cases, there is evidence to support hyperbaric oxygen treatment (HBOT) as a complementary therapy.

The 2016 European Committee for Hyperbaric Medicine (ECHM) guidelines[1] strongly recommend HBOT use in anaerobic or mixed bacterial infections and the 2013 European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM)[2] joint guidelines for the diagnosis and management of mucormycosis express marginal support for HBOT in refractory infections.

Previous studies have also shown HBOT can be of value in complicated brain and spine infections.[3–6]

HBOT provides beneficial pathophysiological changes in the context of infection and inflammation, such as the correction of tissue and cellular hypoxia and the enhancement of polymorphonuclear leukocyte activity.[7,8] Concomitantly, a release of anti-inflammatory cytokines occurs, microvascular perfusion is enhanced and wound healing improves. Hyperbaric oxygen has also bacteriostatic and bactericidal properties.[8–10]

Larsson et al. reported fewer reinterventions for infection control following HBOT in complicated postoperative neurosurgical infections.[6] However, evidence remains scarce regarding hyperbaric oxygen impact on chronic central nervous system (CNS) infection morbidity. Therefore, the present study evaluated the impact of a complementary therapy that has been somewhat overlooked by the medical community, despite its potential effectiveness and safety, in achieving infection resolution in four patients with complicated postoperative infections and three patients with rhino-orbital-cerebral mucormycosis (ROCM) that had proved refractory to conventional treatment.

Methods

This study was approved by the institutional Ethics Committee of the Centro Hospitalar Universitário São João.

The patient database of the Hyperbaric Medical Unit (HMU) at Pedro Hispano Hospital (PHH) in Matosinhos, Portugal was accessed to identify patients referred by the Department of Neurosciences and Mental Health of Centro Hospitalar Universitário São João (CHUSJ) since 2006 (when the HMU started its activity) and those cases in which the hyperbaric department had acted as consultant due to CNS involvement.

Demographic and clinical data were collected including: age and gender; past medical history; active disease; HBOT clinical indication; number of HBOT sessions; number of operations before and after HBOT; presence or absence of surgical heterologous material; microbiologic results; and antibiotic treatment. Patients and physicians were contacted to assess clinical improvement. Serum inflammatory markers, temperature charts, computed tomography (CT) and magnetic resonance imaging (MRI) scans were evaluated to gauge whether infection resolution had been achieved.

The primary endpoint was infection resolution. Infection resolution was defined by clinical improvement, normalisation of elevated inflammatory markers when applicable, and by the lack of active infection on MRI imaging. All cases of infection resolution were confirmed by infectious diseases specialists.

HYPERBARIC OXYGEN THERAPY

All patients were treated at the multiplace hyperbaric chamber of the HMU of Pedro Hispano Hospital. The sessions' duration was 90 minutes and took place on consecutive weekdays. Treatment was given at 243.1 kPa (2.4 atmospheres absolute) pressure breathing 100% oxygen.

Before treatment all patients were examined by an anaesthesiologist to rule out relative contraindications such as Eustachian tube dysfunction, uncontrolled epilepsy and pulmonary conditions like pneumothorax.

ANTIBIOTIC AND ANTIFUNGAL TREATMENT

Prior to and throughout HBOT, patients with infections were treated with antibiotics and/or antifungal therapy based on the susceptibility of the isolated agents. When no microbial pathogen could be isolated patients were treated empirically taking into account the most likely pathogen and local resistance patterns. The antimicrobial treatment was optimised by infectious diseases specialists in all cases.

Results

A total of seven patients (median age 56) with relevant infectious pathology were consecutively treated with HBOT from 2011 to 2018 inclusive. The median follow-up was 20 months. Key patient and pathology characteristics are provided in Table 1 and the history of surgical intervention and selected biochemistry results in Table 2.

Patients one to four had refractory postoperative infections following neurosurgical intervention at our department while patients five to seven had complex ROCM that had not been controlled with antifungal treatment.

Previous to HBOT, all patients had undergone an average of four operations and had completed an average of five months of antimicrobial therapy indicating the refractory nature of the infections. Addition of HBOT was associated with infection resolution in six patients without additional subsequent operations, while one patient with ROCM stopped HBOT after the third session due to intolerance. Three patients stopped all antimicrobial therapy while four were maintained on prophylactic treatment.

CASE SUMMARIES

Patient 1

A 65-year-old female patient with no relevant past medical history underwent craniotomy for drainage of a chronic subdural hematoma.

One month later she underwent surgical site debridement due to infection and two years later she underwent bone flap, cranioplasty and surgical drainage of a subdural empyema. Because of infection persistence she underwent two additional operations for refractory empyema drainage and superficial wound infection revision and cleansing.

Before HBOT initiation she had completed five months of multiple antibiotic regimens while sulfamethoxazole and trimethoprim were added before HBOT. The patient completed 60 sessions of HBOT and has remained on prophylactical sulfamethoxazole and trimethoprim during the follow-up period of 20 months.

Following HBOT complete wound closure and infection resolution were obtained.

Table 1

Relevant clinical data for seven patients treated with HBOT for refractory CNS infections. F – female; m – months; M – male; MR – multidrug resistant; MRSA – methicillin-resistant *Staphyloccocus aureus*, MSSA – methicillin-sensitive *Staphyloccocus aureus*; NSES – nasosinusal endoscopic surgery; PLF – posterior lumbar fusion; RA – rheumatoid arthritis; ROCM – rhino-orbital-cerebral mucormycosis; T1DM – type 1 diabetes mellitis; T2DM – type 2 diabetes mellitus, TLIF – transforaminal lumbar interbody fusion; TPF – transpedicular fixation

Case	Sex	Age	Condition	Past history	Antibiotic treatment pre-HBOT	Antimicrobials during HBOT	HBO#	Microbe	Operations prior to HBOT
1	F	65	Subdural empyema	Chronic hypochromic microcytic anemia	5 m vancomycin, meropenem, metronidazole, ceftriaxonesulfamethoxazole + trimethoprim	Sulfamethoxazole + Trimethoprim	60	Could not isolate	4
2	M	56	Brain abscess	Glioblastoma (Grade IV)	6 m vancomycin, ceftazidime, flucloxacillin, ceftriaxone, cefepime and meropenem	Ceftriaxone	40	*Enterobacter aerogenes* (surgical site)	5
3	F	51	L4 – L5 osteomyelitis + soft tissue infection + paravertebral muscles abscesses	T2DM + RA Lumbar TLIF, PLF, TPF	5 m levofloxacin, ceftazidime, vancomycin, ciprofloxacin, ceftriaxone and daptomycin	Flucloxacillin Rifampicin	40	*MSSA* (surgical site) *MRSA* (surgical site)	4
4	M	69	Sepsis and meningitis + L4-5 osteomyelitis and spondylodiscitis	T2DM	3 m meropenem, vancomycin, linezolid and rifampycin	Vancomycin	40	*MRSA* (blood culture) *MSSA* (surgical site)	2
5	M	73	ROCM	Diffuse large B cell lymphoma	1 m liposomal amphotericin B, meropenem, vancomycin and posaconazole	Vancomycin Posaconazole	40	All surgical site *Aspergillus fumigates Mucor sp.,* MRSA, *MR Corynebacterium Tuberculostearicum*	2
6	F	20	ROCM	T1DM	3 m ceftriaxone, clindamycin, meropenem, liposomal amphotericin B, ceftriaxone, ampicillin, metronidazole, cefepime and posaconazole	Liposomal amphotericin B Ceftriaxone, Cefepime Isavuconazole	40	MSSA *Serratia marcensens MR – S. epidermidis*	5
7	M	14	ROCM	Anaplastic T-cell lymphoma	6 m vancomycin, posaconazole, linezolid and meropenem	Liposomal Amphotericin B and isavuconazole	3	*Rhizopus sp.* (Left NSES) *Staph. warneri* (Surgical site dura)	3

Table 2

Case surgical timelines and procedures and pre- post-HBOT C-reactive protein and white cell counts. CRP – C-reactive protein; CSDH – chronic subdural hematoma; GBM – glioblastoma; L – lumbar; NSES – nasosinusal endoscopic surgery; PEEK – polyetheretherketone; PLF – posterior lumbar fusion; ROCM – rhino-orbital-cerebral mucormycosis; TLIF – transforaminal lumbar interbody fusion

Case	Initial surgery/ diagnosis	1st operation	2nd operation	3rd operation	4th operation	5th operation	Pre-HBOT Post-HBOT CRP / WBC $mg{\cdot}L^{-1}$ / L^{-1}
1	April 2016 CSDH drainage with craniotomy	May 2016 Surgical site debridement	May 2018 Empyema drainage	July 2018 Empyema drainage	September 2018 Surgical debridement	–	9.9 / 5,820 2.2 / 7,000
2	February 2015 Right frontal GBM removal	June 2015 Reopening of craniotomy with abscess drainage	July 2015 Reopening of craniotomy with surgical cleansing of right frontal abscess	September 2015 Surgical site cleansing and debridement	December 2015 Surgical right frontal abscess drainage	February 2016 Surgical site cleansing	3.0 / 4,900 8.2 / 5,300
3	August 2011 L4-5 left synovial cyst excision + L5 laminectomy	September 2011 Surgical subcutaneous and subfascial cleaning	November 2011 L2-4 PEEK bars removal and L2-3 left screws removal TLIF L4-5, PLF L5-S1	January 2012 Purulent epidural hematoma drainage Subfascial abscesses drainage	February 2012 Infected seroma drainage and L5 epidural cyst removal	–	101.2 / 7,740 30 / 8,850
4	January 2012 TLIF L4 -5	February 2012 Subcutaneous and paravertebral abscesses drainage	July 2012 Surgical site cleansing with paravertebral muscles abscesses drainage and cage removal	–	–	–	77.7 / 8,290 28.8 / 7,260
5	March 2017 ROCM diagnosis	March 2017 NSES– right unciformectomy and right anterior and posterior ethmoidectomy	April 2017 Orbital apex biopsy and sphenoidotomy	–	–	–	17 / 1,770 2.8 / 6,310
6	August 2018 ROCM diagnosis	August 2018 Right NSES with unciformectomy and right maxillary sinus antrostomy	September 2018 Right NSES Anterior and posterior ethmoidectomy	October 2018 Right orbitotomy for right orbit abscess drainage	October 2018 Right orbitotomy revision with drainage of small orbital abscess	October 2018 Right orbit exenteration	18.8 / 4,840 2.3 / 3,620
7	November 2018 ROCM diagnosis	November 2018 Left NSES with ethmoidectomy and sphenoidectomy	November 2018 Microsurgical removal of intracranial infectious component Left superior and lateral orbitotomy. Left temporal pole abscess drainage	November 2018 Total left orbit exenteration	–	–	NA

Patient 2

A 56-year-old male had a right frontal glioblastoma removed via craniotomy. In the following weeks he started chemoradiotherapy, but treatment had to be stopped once the diagnosis of brain abscess at the surgical site was made (Figure 1).

Subsequently, the patient underwent four operations for abscess drainage and surgical locus cleansing and completed 10 months of varied antibiotics.

He underwent 40 HBOT sessions while maintaining the antibiotic regimen that had previously failed to achieve infection control. Infection resolution was reached following HBOT (Figure 1) and the patient was kept on prophylactic levofloxacin. He remained infection-free during the follow-up period of six months but passed away due to tumour progression.

Patient 3

A 51-year-old female with past history of type II diabetes, rheumatoid arthritis treated with steroid sparing agents and previous operations for spine instrumentation underwent L4-5 left synovial cyst excision and L5 laminectomy.

Due to surgical locus infection and osteomyelitis she was kept on wide spectrum antibiotics for five months and underwent four operations with removal of previous spine instrumentation hardware and new instrumentation performed at adjacent levels. Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from the surgical site and rifampicin was introduced prior to HBOT.

Owing to refractory infection she was prescribed hyperbaric oxygen therapy and completed 40 sessions that led to infection resolution. No further surgical or antibiotic treatment was necessary.

Patient 4

A 69-year-old male with past history of type II diabetes mellitus underwent a L4-5 transforaminal lumbar interbody fusion (TLIF). He developed a postoperative infection with formation of paravertebral abscesses and subcutaneous tissue empyema.

He underwent two operations for surgical site cleansing and hardware removal and completed six months of multiple courses of different antibiotics, without successfully achieving infection control.

The patient underwent HBOT while on antibiotics that had previously failed to resolve the infection and upon completing 40 sessions of hyperbaric oxygen, the infection was successfully cured with no further need for surgical operation or antimicrobial treatment.

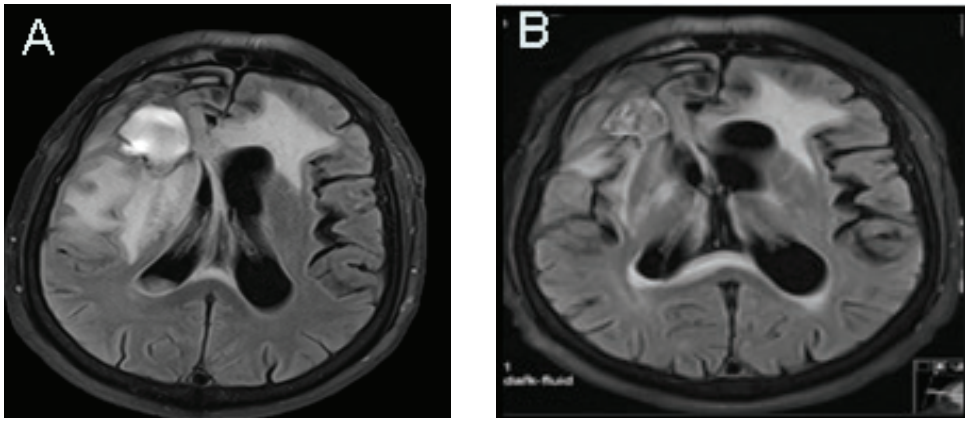
Patient 5

A 73-year-old male with a year long history of diffuse large B-cell lymphoma developed sudden onset of right-sided vision loss, extreme ocular pain and proptosis. Orbital and brain MRI demonstrated a diffuse infiltrate of the right optic nerve, sphenoid and ethmoidal sinuses and discreet cerebral invasion (Figure 2). Endonasal endoscopic biopsy confirmed the diagnosis of mucormycosis with isolation of *Aspergillus fumigates* and *Mucor spp*.

The patient underwent two operations for infection control and had completed one month of antifungal and antibiotic treatment due to bacterial superinfection prior to HBOT initiation.

Infection resolution was obtained after 40 HBOT exposures and the patient maintained prophylactic antifungal therapy with oral posaconazole.

Figure 1
Patient 2. Brain abscess at glioblastoma excision site. A – final MRI before HBOT; B – first MRI post HBOT (FLAIR sequence)



Patient 6

A 20-year-old female with poorly controlled type I diabetes mellitus presented with a two week history of right sided facial pain, hypoesthesia, oedema and purulent drainage from the right superior dental arch, with right ocular pain and ptosis. Brain and orbital MRI demonstrated a diffuse infiltrate arising from the paranasal sinuses with ocular and cavernous sinus invasion on the right side.

She had urgent surgery with nasosinusal endoscopic unciformectomy and right maxillary sinus antrostomy for diagnostic and therapeutic purposes. Due to the refractory infection pattern the patient underwent four subsequent operations, including right orbital exenteration.

Polymerase chain reaction (PCR) was run on a surgical microbial isolate that was positive for *Mucor spp* and, due to suspected bone osteomyelitis, she was treated with antibiotics alongside multiple antifungal medication during a three-month period.

The patient completed 40 HBOT sessions and was considered infection-free upon treatment completion. She was kept on prophylactic isavuconazole for 12 months.

Patient 7

A 14-year-old male with past history of anaplastic T-cell lymphoma presented with rapid onset of left-sided ophthalmoplegia, complete amaurosis and proptosis. He underwent three operations, including brain abscess drainage due to intracerebral invasion from a rhinosinusal fungal infection that had also invaded the left orbit and later required left ocular exenteration. *Rhizopus spp*. was isolated from the first endoscopic nasosinusal intervention.

After referral for HBOT, the patient could only complete three sessions and sadly was not able to accomplish treatment as prescribed due to nausea, vomiting and generalised discomfort while in the hyperbaric chamber.

Up to the end of the current follow-up period of 20 months, the patient had undergone two further operations for encephalocele and cerebrospinal fluid (CSF) fistula correction and remained on amphotericin B and isavuconazole for ROCM treatment.

Discussion

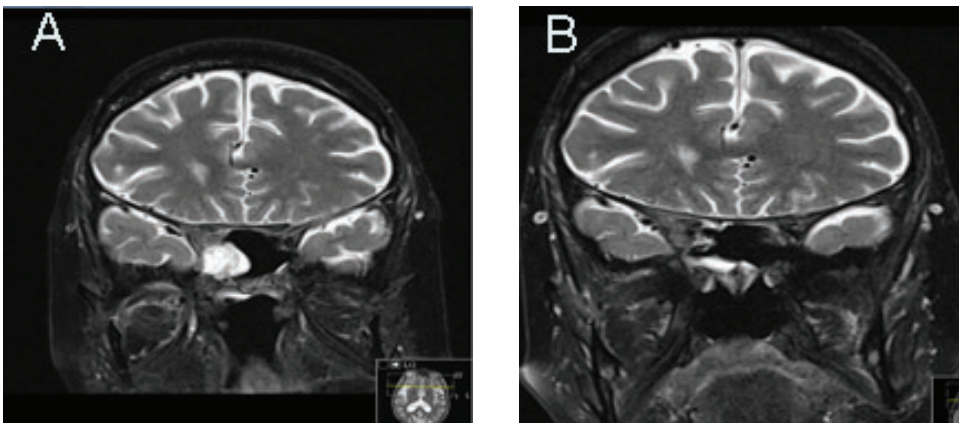
The aim of this case series was to evaluate the impact of HBOT in resolving complex refractory postoperative or spontaneous infections with CNS involvement. The cohort is small and lacks a control group; therefore, caution is needed when interpreting the results. However, with resistant infections following neurosurgical interventions and mucormycosis with CNS involvement representing rare events and thus rendering randomised controlled trials difficult to undertake, case series of this nature are likely to provide the best evidence for potential efficacy of HBOT.

As previously mentioned, there are multiple potentially relevant physiological effects of HBOT. In patients with a compromised immune system, HBOT may enhance elements of immune system activity and also lead to improvement in tissue oxygenation, wound healing and neovascularization.[7,10,11] Hypoxia leads to deficient neutrophil activity and by inducing hyperoxia, HBOT seems to optimise neutrophil antimicrobial activity through enhancing their release of reactive oxygen species.[7,11] In addition, animal studies have shown hyperbaric oxygen to dampen inflammation through cytokine downregulation. HBOT also seems to increase the efficacy of certain antimicrobial agents.[11–15]

Notwithstanding its relative safety, HBOT is not devoid of shortcomings. Besides side effects that include middle ear barotrauma, transient visual acuity changes and pulmonary

Figure 2

Patient 5. Mucormycosis in right sphenoid sinus. A – MRI taken a few days after starting HBOT; B – first MRI post HBOT (T2 sequence)



oxygen toxicity[16] it may be burdensome to obtain for patients whose local hospital or clinic does not possess a hyperbaric chamber. In this series HBOT proved safe and tolerable to all but patient seven. None of the other patients reported symptoms from HBOT.

POSTOPERATIVE INFECTIONS

The four postoperative infection patients reported here were cured after completing HBOT despite long histories of being refractory to multiple interventions. These results are similar to those previously reported in the literature[3–6] and were supportive of the ECHM type I recommendation for HBOT use in anaerobic and mixed anaerobic infections.

Larsson et al.[6] evaluated the results of HBOT both in post-craniotomy and post-spine instrumentation surgery infection with 35 out of a total of 38 patients achieving infection resolution and 23 being able to reach the primary goal of avoiding reoperation for bone flap or spine fixation material removal. Similarly, Bartek et al.[4] set out to assess the efficacy of adjuvant HBOT in resolving deep brain stimulation (DBS) hardware related infections and avoiding material extraction. All 12 patients were cured of their infection and 10 could keep their implants. In a retrospective analysis of two groups of brain abscess patients Bartek et al.[5] showed that those treated with HBOT in addition to surgery and antibiotics had fewer recurrences when compared to surgery and antibiotics alone. Finally, in a series of six patients with spine osteomyelitis treated with HBOT Ahmed et al.[3] reported infection control in one of two patients with spontaneous infection and in four patients with previous spine surgery. All six patients had risk factors for poor infection control.

In complicated postoperative and spontaneous infections, HBOT may serve as an efficient supplementary treatment. Identifying patients with risk factors for developing refractory infections, who may benefit from HBOT, may contribute not only to an earlier cure but also lead to a reduction of antibiotic burden and avoidance of repeated operations, with benefits both to patient well-being and in terms of cost reduction. We believe identifying the correct timing of HBOT application in such complex infections should also be the focus of future studies.

MUCORMYCOSIS

Mucormycosis mostly occurs in immunosuppressed patients, and has high mortality despite antifungal drugs. It follows that alternative supplemental treatments should be sought. HBOT stops fungal growth *in vitro*, augments the efficacy of amphotericin B and through hypoxia reversal and angiogenesis helps to revert the highly hypoxic and hypoperfused infection locus environment. Nevertheless, in spite of a solid pathophysiological case supporting its application[17–21] HBOT use in mucormycosis has been infrequent. The present series, however, adds to a growing number of positive results[17,22–24] that highlight the complementary potential of HBOT in this highly complex infection.

A previous study reported two cases of refractory mucormycosis in diabetic patients that were cured once HBOT was added to the therapeutic armamentarium.[17] Another presented a successful case of mucormycosis control once HBOT was initiated in a child with B-cell precursor acute lymphoblastic leukaemia (ALL).[22] A 60% survival rate in mucormycosis has been reported when HBOT complemented surgical debridement and amphotericin B therapy,[23] representing a significant survival increment when compared to surgical debridement and antifungal therapy alone. Finally, a review of 28 cases of mucormycosis secondary to various immunosupressive states treated with HBOT reported a significant survival benefit for diabetic patients.[24]

Two of three patients in the present series were cured after the completion of HBOT and remarkably patient number six has ceased prophylactic antibiotic treatment. Unfortunately, patient seven could not complete treatment as initially prescribed and has thus far not been able to scale down treatment.

Taking into account the aforementioned results, an earlier introduction of HBOT in mucormycosis treatment might prove beneficial by potentially avoiding the devastating effects of this infection, especially when there is CNS involvement. As recommended for post-op infections, emphasis on the optimal timing for HBOT initiation should be a focus of future studies.

Conclusion

Seven consecutive cases of complex refractory infections with CNS involvement have been reported, of which six were successfully resolved after introduction of HBOT. Previous to HBOT these patients had unsuccessfully undergone prolonged antimicrobial therapy and multiple operations for infection control. After HBOT further reinterventions were not needed and antimicrobial therapy was scaled down or stopped. Moreover, three out of seven patients who achieved infection resolution did not require alteration of their antimicrobial treatment during HBOT, further suggesting hyperbaric oxygen therapy had a positive impact on disease control.

Nonetheless, prospective randomised controlled trials or larger case series are needed to consolidate our findings and more emphasis should be directed towards establishing the correct timing of HBOT initiation in patients with refractory post-operative or spontaneous infections.

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