NHS England

Evidence review: Hyperbaric Oxygen Therapy for Malignant Otitis Externa

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1 Introduction

Indication and epidemiology

- Malignant otitis externa (MOE), an aggressive infection involving the external auditory canal and the surrounding skull base, mainly the temporal bone, was first reported in the literature by Toulmouche in 1838. The condition was described and characterised as a unique clinical entity by Chandler in 1968. This type of otitis externa was termed malignant, due to the high mortality rate, aggressive disease progression and poor response to available treatment (Chandler 1968).

- The disease originates in the external ear canal and spreads progressively along the soft tissues and bone of the skull base, ultimately involving intracranial structures (Phillips and Jones 2013). MOE can also be complicated by parotitis[a], mastoiditis[b], jugular vein thrombosis, meningitis and death (Glamarellou 1992). Pseudomonas aeruginosa is isolated from the aural drainage in more than 90% of MOE cases. Diagnosis is made upon clinical, microbiological and radiological grounds (Ali et al 2010).

- MOE is an uncommon condition mainly found in the elderly or in diabetics (Phillips and Jones 2013). It is generally suspected in diabetic patients with pseudomonal otitis externa, especially when pain is a prominent feature. Recent reviews have quoted the prevalence of diabetes in MOE cases as 90% to 100% (Berenholz, Katzenell and Harell 2002, Mani et al 2007). Other immunocompromised states also represent risk factors for MOE development (with or without diabetes) (Shpitzer et al 1993), including human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), neoplasia, leukaemia, lymphoma, splenectomy and post-transplantation immunosuppression (Hollis and Evans 2011). MOE is more common in males than females. The mortality of MOE has been reported to be as high as one third, but when cranial nerves are affected it may be as high as 80% (Phillips and Jones 2013).

- MOE is rarely seen in paediatric practice. However, when encountered it is commonly associated with immunocompromise (either malignancy or malnutrition). Diabetes is a less common comorbid factor in paediatric cases (Sobie, Brodsky and Stanievich 1987).

- The mainstay of treatment for MOE has been prolonged antibiotic therapy, stringent diabetes control, the repeated removal of dead tissue and surgical management (Glamarellou 1992, Illing and Olaleye 2011, Phillips and Jones 2013). Hyperbaric oxygen has been proposed as adjunctive therapy for MOE and has been included in treatment pathways in places where a therapeutic pressure chamber is available (Shupak et al 1989).

The intervention

- Hyperbaric oxygen therapy (HBOT) is increasingly being used for the treatment of MOE, in addition to traditional treatments, where facilities exist.

- HBOT is the administration of 100% oxygen for respiration at pressures above one atmosphere absolute (ATA) (~100 kilopascals [kPa]). HBOT involves placing the patient in a compression chamber, increasing the environmental pressure within the chamber and administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased partial pressure of oxygen to the tissues. Typically, treatments involve pressurisation to between 203 to 304 kilopascals (kPa) [two and three atmospheres absolute (ATA)] for periods between 60 and 120 minutes once or twice daily. A typical course might involve 15 to 30 such treatments (Phillips and

[a] Parotitis is an inflammation of one or both parotid glands, the major salivary glands located on either side of the face, in humans. The parotid gland is the salivary gland most commonly affected by inflammation.

[b] Mastoiditis is the result of an infection that extends to the air cells of the skull behind the ear. Specifically, it is an inflammation of the mucosal lining of the mastoid antrum and mastoid air cell system inside the mastoid process. The mastoid process is the portion of the temporal bone of the skull that is behind the ear which contains open, air-containing spaces.

Jones 2013).

- There are two types of chambers used for administering HBOT: a monoplace chamber for a single patient; or a multiplace chamber used for multiple patients and medical personnel.

- It is postulated that HBOT works by increasing oxygen supply to avascular tissues. This leads to efficient leukocyte function which is essential for soft tissue and bone healing as well as infection resolution (Phillips and Jones 2013).

Existing national policies and guidance

- There are no national evidence-based policies or guidance for the management of patients with malignant otitis externa.

2 Summary of results

Clinical effectiveness

- The literature search for this rapid evidence review found one systematic review (Phillips and Jones 2013), one retrospective controlled study (Sabra et al 2015) and one case series (Saxby et al 2010) which assess the use of HBOT in the management of MOE.

- A variety of outcomes were reported including pain, ear discharge, complications of HBOT and mortality.

- Sabra et al (2015) carried out a retrospective controlled study to assess the usefulness of HBOT as an adjunctive treatment in diabetic patients with MOE. 28 patients received ciprofloxacin (antibiotics) only while 15 patients were treated with ciprofloxacin and HBOT. HBOT was administered at 2.5 ATA (~253 kPa) for 90 minutes per session every other day for two months. All the patients were evaluated clinically (in terms of ear discharge, granulations, and pain severity) and radiologically by a temporal bone computed tomography scan. The patients were followed up for at least two months.

- The authors reported the following in patients treated with ciprofloxacin plus HBOT versus those treated with ciprofloxacin only: an improvement in pain in 86.7% vs. 32.1% of patients at one month after 15 sessions (no p-value was reported); freedom from pain in 46.7% vs. 0% of patients at one month and 93.3% vs. at 28.5% two months ($p<0.001$ for both follow up periods); the absence of purulent ear discharge in 80% vs. 0%[c] ($p<0.001$) at one month and 93.3% vs. 28.5% ($p<0.001$) at two months (Sabra et al 2015).

- The systematic review did not identify any RCTs; it described four case reports and five case series which included a total of 73 patients (range was not reported). The authors reported that the individual papers described the use of HBOT as adjuvant therapy with antibiotics in the majority of cases. Most regimens used 20 to 40 doses of hyperbaric oxygen treatment. Each treatment was of 90 minutes duration at 2.5 ATA (~253 kPa). However due to the poor quality of studies, lack of randomisation or other controls, they were unable to assess statistically the effectiveness of treatment with HBOT compared with other treatments (Phillips and Jones 2013).

- The retrospective case series of patients with a diagnosis of MOE, referred to a hyperbaric unit for treatment over a period of six years, conducted by Saxby et al included 17 patients. All the patients received HBOT once daily on Monday to Friday on a standard 90-minutes schedule at

[c] Not reported to one decimal place therefore inconsistent with other results

243 kPa (2.4 ATA).They reported that 12 patients (70%) were disease-free at follow up, so were considered cured of their disease; this included four patients who had died of other causes but were symptom-free at the time of death. Three patients (18%) died from MOE, one after a recurrence of their disease. Two further patients (12%) had recurrent disease, both successfully treated with a second cycle of HBOT and antibiotics (Saxby et al 2010).

Safety

- The study carried out by Sabra et al did not report any complications associated with HBOT. The case reports and case series described in the Cochrane review did not report any complications or adverse events related to hyperbaric oxygen treatment (Phillips and Jones 2013).

- However, the retrospective review conducted by Saxby et al reported that five out of 17 patients (29%) had complications attributable to HBOT; acute pulmonary oedema (n = 2), seizure (n = 1), tympanic membrane perforation (n = 1) and claustrophobia (n = 1).

Cost-effectiveness

- We did not identify any cost-effectiveness studies.

3 Methodology

- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane Library, TRIP and NICE Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st January 2007 and 28th March 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).
- Conference abstracts, commentaries and editorials were excluded.

4 Results

A total of three papers matching the PICO were identified; one systematic review (Phillips and Jones 2013), one retrospective controlled study (Sabra et al 2015) and one case series (Saxby et al 2010).

In the patient populations of interest, what is the effect of adding HBOT into the management pathway on the specified outcomes?

Sabra et al (2015) carried out a retrospective controlled study to assess the usefulness of HBOT as an adjunctive treatment in patients with MOE. They included 43 diabetic patients (on insulin) treated

for MOE between January 2011 and December 2014. 28 patients received ciprofloxacin (antibiotics) only, while 15 patients were treated with ciprofloxacin and HBOT. HBOT was administered at 2.5 ATA (~253 kPa) for 90 minutes per session every other day for two months. All the patients were evaluated clinically (in terms of ear discharge, granulations, and pain severity) and radiologically (by a temporal bone computed tomography scan). The patients were followed up for at least two months.

The authors reported that the degree of improvement after adjuvant HBOT with antibiotics was higher, both clinically and symptomatically, compared with the antibiotics only group. They reported the following in patients treated with ciprofloxacin plus HBOT versus those treated with ciprofloxacin only: an improvement in pain[d] in 86.7% (13/15) vs. 32.1% (9/28) of patients at one month after 15 sessions (no p-value reported); freedom from pain in 46.7% vs. 0% of patients at one month and 93.3% vs. at 28.5% two months ($p<0.001$ for both follow up periods); the absence of purulent ear discharge in 80% vs. 0%[e] ($p<0.001$) at one month (after 15 sessions) and 93.3% vs. 28.5% ($p<0.001$) at two months. They reported that granulations in the external ear improved and that computerised tomography (CT) scans of the temporal bone indicated considerable improvement with HBOT treatment, with less infection, opacity, fluid in the mastoid, and osteomyelitic changes; however; no further details were provided (Sabra et al 2015).

Phillips et al (2013) carried out a systematic review to assess the effectiveness of adjunctive HBOT for MOE. They did not find any randomised controlled trials, they found four case reports and five case series (N = 73). The authors stated that the studies described the use of HBOT as adjuvant with antibiotics in the majority of cases. In general, most regimens used 20 to 40 doses of hyperbaric oxygen treatment. Each treatment was of 90 minutes duration at 2.5 ATA (~253 kPa). Alternative regimens differed very little.

The authors did not fully report the results of the studies. They stated that the quality of the studies was poor, lacking randomisation or other controls. In view of this, they could not assess statistically the effectiveness of treatment with HBOT compared with treatment with antibiotics and surgical debridement. They concluded that 'no clear evidence exists to demonstrate the efficacy of hyperbaric oxygen therapy when compared to treatment with antibiotics and/or surgery' (Phillips and Jones 2013).

Saxby et al conducted a retrospective review of all patients with a diagnosis of MOE referred to the Prince of Wales Hospital (New South Wales, Australia) hyperbaric unit for treatment over a period of six years (August 2001 to October 2007).

They found and included 17 patients with confirmed MOE of whom 15 (88%) completed therapy, one did not tolerate HBOT and one was withdrawn due to pulmonary complications. All the patients received HBOT once daily on Monday to Friday on a standard 90-minutes schedule at 243 kPa (2.4 ATA). A variety of different antibiotic regimens were employed with varying time courses. The most commonly used antibiotics were Timentin™ and ciprofloxacin. The authors report that 12 patients (70%) were considered cured of their disease, being disease-free at follow up. This included four patients who had died from other causes but were free of MOE symptoms at the time of death. The authors reported that three patients died from MOE (18%), one after a recurrence of their disease. Two further patients (12%) had recurrent disease, both successfully treated with a second cycle of HBOT and antibiotics. Long-term outcomes were determined by medical chart/full medical record review, patient assessment and telephone interviews (Saxby et al 2010).

The authors concluded that "HBOT confers minimal morbidity, but its role in MOE remains uncertain. The high mortality of MOE despite maximal therapeutic intervention highlights the need for more effective treatment protocols" (Saxby et al 2010).

[d] These results refer to patients with mild or no pain from having severe pain

[e] Not reported to one decimal place therefore inconsistent with other results

Is there evidence to identify a group of patients who are most likely to benefit?
We did not identify any studies which suggest that any group of patients are more likely to benefit from HBOT for MOE than others. The studies identified for inclusion in this review assessed diabetic patients diagnosed with MOE as well as any patients diagnosed with the condition.

Which treatment schedules were the most effective in achieving best outcomes?
We did not identify any studies that compared treatment schedules of HBOT in the management of MOE, however the studies included in the review generally used 20 to 40 doses of HBOT; each treatment was of 90 minutes duration at about 253 kPa.

Safety

The case reports and case series described in the systematic review by Phillips et al and the controlled study by Sabra et al did not report any complications or adverse events related to HBOT (Phillips and Jones 2013). However, the retrospective review conducted by Saxby et al reported three deaths from MOE, they also reported that five out of 17 patients (29%) had complications attributable to HBOT: acute pulmonary oedema (n = 2), seizure (n = 1), tympanic membrane perforation (n = 1) and claustrophobia (n = 1).

What is the cost effectiveness of HBOT for the management of MOE?
We did not identify any cost-effectiveness studies.

5 Discussion

The evidence currently available on the effectiveness of HBOT in MOE is of low quality. The systematic review identified no randomised trials so the authors were not able to assess statistically the effectiveness of HBOT in the management of MOE. One study was a single-centre case series with no comparator and the third study was a retrospective single-centre controlled study in which there was no randomisation or blinding of participants or assessors.

Whilst the results suggest that HBOT (20 to 40 doses administered at 253 kPa for 90 minutes) may be effective as adjunct in the management of MOE, it is not clear if they are reliable or generalisable. The studies reported on different outcomes (including improvement in pain, ear discharge and complications of treatment) in very small numbers of patients.

The published literature on the use of HBOT in MOE is limited to very small unrandomised studies; it is therefore not robust enough to make blanket recommendations.

6 Conclusion

The evidence for the clinical effectiveness of HBOT as adjunctive treatment in the management of MOE is limited to small case series and retrospective studies. Although the reported results suggest that this intervention may be effective, the studies have a number of limitations. For this reason the results may not be reliable or generalisable.

In summary, while HBOT may be useful as an adjunct in the management of MOE, there is insufficient evidence to make clear recommendations particularly in comparison to alternative treatments.

7 Evidence Summary Table

Studies of hyperbaric oxygen therapy plus antibiotics for malignant otitis externa (MOE) compared with antibiotics alone									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Sabra et al 2015 Egypt	Retrospective controlled study	Diabetic patients on insulin who had MOE treated between January 2011 and December 2014	Ciprofloxacin + HBOT (90 min at 2.5 ATA) every other day for 2 months n=15 vs. Ciprofloxacin only n=28	Primary Clinical effectiveness	Improvement in pain or having only mild pain Pain scores 3=severe pain 0= no pain	**Cipro + HBOT vs. Cipro only** **At one month (after 15 sessions)** 86.7% (13/15) vs 32.1% (9/28) reported improvement in pain or having only mild pain, no p-value reported. These results refer to patients with mild or no pain from having severe pain	7/10	Direct	This was a controlled single centre study; however; there was no blinding or randomisation. This study is likely to have been subject to selection bias as this is common with retrospective studies. The right patients may not have been identified or the patients may have been classified wrongly. Although patient-reported outcomes are very useful, they are likely to be subject to reporting bias.
				Primary Clinical effectiveness	Freedom from pain Having no pain Pain scores 3=severe pain 0= no pain	**Cipro + HBOT vs. Cipro only** **At one month (after 15 sessions)** 46.7% vs.0% p<0.001 **At two months (after 30 sessions)** 93.3% vs 28.5% p<0.001			
				Secondary Clinical effectiveness	Absence/ cessation of purulent ear discharge	**Cipro + HBOT vs. Cipro only** **At one month (after 15 sessions)**[f] 80% vs. 0% p<0.001 **At two months (after 30 sessions)** 93.3% vs. 28.5% p<0.001 The authors reported that granulations in the external ear improved but no details were provided.			

[f] Not reported to one decimal place therefore inconsistent with other results

Studies of hyperbaric oxygen therapy for malignant otitis externa (MOE) with no comparator									
Phillips et al 2013	Systematic review Four case reports, five case series	Adults undergoing HBOT therapy for MOE n= 73 the range was not reported Details of patient characteristics were not stated	HBOT Various regimens but most used 20 to 40 doses for 90 minutes at 2.5 ATA.	Primary Clinical effectiveness	Not reported	Not reported	8/10	Direct	The quality of studies was poor, lacking randomisation or other controls. In view of this the authors could not assess statistically the effectiveness of treatment with HBOT compared with treatment with antibiotics and surgical debridement.
				Primary Safety	None reported	No data found			
Saxby et al 2010	Case series	Patients with a diagnosis of MOE referred to hyperbaric centre for treatment between August 2001 and October 2007 n=17 (15 completed therapy)	HBOT All patients received HBOT once daily on Monday to Friday on a standard 90-minutes schedule at 243 kPa (2.4 ATA).They also received broad-spectrum & culture directed antibiotics	Primary Clinical effectiveness	Disease-free	12 patients (70%) were disease-free at last follow-up. Mean follow-up =47 months (range 1 to 94)	6/10	Direct	The authors addressed a clear question. Study methods were mostly reported. A narrative synthesis was appropriate given the methodology and the number of participants included in the study. However it should be noted that these data were not derived from prospective or controlled studies but from a retrospective uncontrolled case series of 17 patients from a single centre. Without a control arm, it is impossible to make any comparison between treatment regimens with HBOT and those without HBOT. The single centre possibly introduces a selection bias. These sources of bias mean that the findings reported may not be valid and/or generalisable to a larger population of patients.
				Primary Safety	Complications	5 patients (29%) had complications; Acute pulmonary oedema=2 Seizure = 1 Claustrophobia =1 Tympanic membrane perforation = 1			
				Primary Safety	Mortality	3 patients died of MOE (18%)			

8 Grade of evidence table

Hyperbaric oxygen therapy for malignant otitis externa (MOE) compared with ciprofloxacin					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Improvement in pain (Having only mild pain) Freedom from pain (Having no pain)	Sabra et al 2015	7/10	Direct	B	Pain was measured according to its severity, degree of improvement or cessation. A pain score of 3 indicated severe pain (preventing patients from sleep and normal activities), a pain score of 2 indicated moderate pain (controlled sometimes with powerful analgesics), a pain scored of 1 indicated mild pain (bearable without analgesics), and a pain score of 0 indicated no pain. The results provide an estimate of the proportion of patients who had an improvement in their pain and to what extent after HBOT. Sabra et al reported the following in patients treated with ciprofloxacin plus HBOT versus those treated with ciprofloxacin only: an improvement in pain[g] in 86.7% (13/15) vs. 32.1% (9/28) of patients at one month after 15 sessions(no p-value reported); freedom from pain in 46.7% vs. 0% of patients at one month and 93.3% vs. at 28.5% two months ($p<0.001$ for both follow up periods). The results suggest that after one month of HBOT (15 sessions administered on alternate days), almost two thirds of patients on HBOT and ciprofloxacin had an improvement in their pain compared to a third of patients taking ciprofloxacin only, and about half of patients were free from pain compared to none taking ciprofloxacin only. At two months, over 90% of patients on HBOT had no pain at all compared to just over a quarter in the ciprofloxacin only group. However, these results should be interpreted with caution as, despite the presence of a control group, the patients were not randomised and the participants and assessors not blinded. Pain scores were self-reported therefore intra- and/or inter-patient error could not be ruled out. In addition, the rationale for the treatment choice was unclear, for example whether the treatment received was wholly or partly based on severity of clinical presentation and/or prognosis. These results may therefore not be generalisable.

[g] These results refer to patients with mild or no pain from having severe pain

Hyperbaric oxygen therapy for malignant otitis externa (MOE) compared with ciprofloxacin					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Purulent ear discharge	Sabra et al 2015	7/10	Direct	B	Purulent ear discharge is a known symptom and it is usually clinically assessed in MOE. The results provide an estimate of the effect of HBOT plus antibiotic therapy versus antibiotic therapy alone on ear discharge. Sabra et al reported an absence of purulent ear discharge in 80% vs. 0%[h] (p<0.001) at one month (after 15 sessions) and 93.3% vs. 28.5% (p<0.001) at two months. The results suggest 80% of patients who received HBOT no longer had purulent ear discharge after one month of treatment compared to none of those who did not receive HBOT. At two months, almost 95% of those who had HBOT had no purulent ear discharge while only a third of those who did not were free of ear discharge. However, care must be taken interpreting these results as this was an unrandomised single-centre study and there was no blinding. In addition the rationale for the treatment choices made is unclear; therefore the results may not be generalisable.
Hyperbaric Oxygen therapy for malignant otitis externa (MOE) with no comparator					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Disease-free	Saxby et al 2010	6/10	Direct	C	Disease-free refers to when the patient is free of symptoms. The authors did not clearly define this outcome. Saxby et al reported that 12 patients (70%) were considered cured of their disease, being disease-free at follow up. This included four patients who had died from other causes but were free of MOE symptoms at the time of death. The results suggest that over two thirds of patients who received HBOT were disease free at last follow-up (mean follow up 47 months, range 1 to 94 months). However, these findings should be interpreted with

[h] Not reported to one decimal place therefore inconsistent with other results

Hyperbaric oxygen therapy for malignant otitis externa (MOE) compared with ciprofloxacin					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					caution as they are from a retrospective uncontrolled case series of 17 patients from a single centre. Without a control arm, it is unclear how this compares to alternative treatments. The single centre possibly introduces a selection bias. These sources of bias mean that the findings reported may not be valid and/or generalisable to a larger population of patients.
Complications	Saxby et al 2010	6/10	Direct	C	Complications refer to adverse effects associated with HBOT. Saxby et al reported that five out of 17 patients (29%) had complications attributable to HBOT: acute pulmonary oedema (n = 2), seizure (n = 1), tympanic membrane perforation (n = 1) and claustrophobia (n = 1). The results suggest that a third of patients had complications associated with HBOT. However, these findings should be interpreted with caution as they are from a retrospective uncontrolled case series of 17 patients from a single centre. Without a control arm, it is unclear how this compares to alternative treatments. The single centre possibly introduces a selection bias. These sources of bias mean that the findings reported may not be valid and/or generalisable to a larger population of patients.
Mortality	Saxby et al 2010	6/10	Direct	C	Mortality is a measure of the number of patient deaths. Saxby et al reported that three patients died from MOE (18%), one after a recurrence of their disease. Only one study reported numbers of patient deaths and these were deaths which were reported to be associated with MOE rather than with HBOT. We therefore do not know if HBOT is associated with death.

9 Literature Search Terms

Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with: i. Tisch Grade III MOE (local invasion with zygomatic bone or cranial nerve involvement), ii. Tisch Grade IV MOE (diffuse involvement of the cranium with meningitis or sepsis) OR iii. MOE that has failed to respond to, or recurs after, definitive surgical debridement and a period of four to six weeks of appropriate antibiotic therapy (where adequate antibiotic serum and bone concentrations are maintained throughout the four to six week period) and is associated with a high probability for excess morbidity or mortality due to systemic and / or local compromise.** ** Examples of systemic compromise include malnutrition, renal failure, diabetes mellitus, chronic hypoxia, immune deficiency, malignancy, extremes of age, immunosuppression, and tobacco abuse. Examples of local compromise include chronic lymphoedema, venous stasis, major vessel compromise, arteritis, extensive scarring, radiation fibrosis, small vessel disease, complete loss of local sensation.
I – Intervention Which intervention, treatment or approach should be used?	20 or more hyperbaric treatments each delivering a maximum inspired partial pressure of oxygen between 200 and 253 kPa and lasting between 60 and 120 minutes (e.g. Royal Navy Table 66) administered 5 days per week. In the case of rapidly progressive disease, however, consider delivering a maximum inspired partial pressure of oxygen between 280 and 314 kPa lasting between 60 and 150 minutes (e.g. Royal Navy Table 60 or 61) up to twice each day for the first three treatments to halt progress. The Cochrane review suggests that regimes vary between 20 and 40 treatments, stopping when the extent of the infection starts to recede. The hyperbaric oxygen therapy is administered in conjunction with the antibiotics, debridement and management of co-morbidities mentioned in the comparator group.
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Any, including antibiotics, surgical debridement and optimal management of co-morbidities.
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse	<u>Critical to decision-making:</u> Clinical effectiveness including: - Mortality - Morbidity - Time until clinical improvement measured by e.g. resolution of pain and aural discharge

effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	- Time until radiological improvement - Changes in objective scoring tools - Cessation of deterioration and recovery from cranial nerve palsies - Time to disease recurrence and/or symptom free survival - Psychological morbidity - Quality of Life - Activities of Daily Living - Adverse Drug Reactions and other side-effects / complications of treatment - <u>Important to decision-making:</u> Cost effectiveness

Assumptions / limits applied to search

Inclusion Criteria:

Peer reviewed studies published in the last 10 years including:

Systematic Reviews with / without Meta-analysis
Randomised Controlled Trials
Cohort studies (prospective or retrospective)
Case series
Case reports - Published in the last 10 years

Exclusion criteria:

Work that is not available in the English language
Grey literature including conference reports abstracts, letters, posters
Unpublished studies

10 Search Strategy

We searched PubMed, Embase, Cochrane Library, TRIP and NICE Evidence, limiting the search to papers published in English since **1st January 2007 to 28th March 2017**. We excluded conference abstracts, commentaries and editorials.

Search Date: 28th March 2017

Embase Search:

1 external otitis/
2 (otitis adj externa*).ti,ab.
3 1 or 2
4 (malignan* or necrosis or necroti*).mp.
5 3 and 4
6 hyperbaric oxygen/
7 ((hyperbaric adj2 (oxygen* or therap* or treatment)) or hbot or oxygen chamber* or barochamber*).ti,ab.
8 6 or 7
9 5 and 8
10 conference*.pt.
11 9 not 10

11 Evidence Selection

- Total number of abstracts reviewed: 13
- Total number of papers selected for full paper review: 9
- Final number of papers selected for inclusion: 3

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