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Review

Hyperbaric Oxygen in Otorhinolaryngology: Current Concepts in Management and Therapy

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Abstract: Background: In otorhinolaryngology and head and neck surgery, oxygen is a therapeutic tool used for various pathologies. Oxidative stress is the imbalance between the production of free radicals (ROS) and the antioxidant capacity of the body, which can represent the pathogenesis of several pathologies or contribute to their worsening. This narrative review aims to analyze the benefits, indications, and side effects of hyperbaric oxygen therapy (HBOT) in different head and neck disorders. Methods: The search was carried out on multiple electronic databases such as PubMed and Google Scholar, and prospective, randomized, and reviewed studies were analyzed from January 1982 to February 2024. Results and Conclusions: The most common tools used to manage oxidative stress in the ear, nose, and throat (ENT) field are continuous positive airway pressure (CPAP) and HBOT. A common ENT pathology, while the latter can be used for osteoradionecrosis treatment in head and neck cancer patients, infections, malignant external otitis, head and neck reconstruction, facial cosmetic surgery, and among patients with sudden sensorineural hearing loss. From our analysis, it emerged that HBOT is a currently used effective therapy in various ENT pathologies' treatment, alone or in association with other treatments; it can guarantee functional recovery and healing depending on the type of pathology for which it is used and on its severity.

Keywords: hyperbaric oxygen therapy; ENT; oxidative stress

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1. Introduction

Mitochondrial dysfunction and oxidative stress are considered key etiological factors in the pathogenesis of several head and neck disorders. For example, many studies suggest that oxidative stress could be the main cause of sudden sensorineural hearing loss (SSHL) even though it is not completely clear the pathophysiological mechanism and the main cause of this pathology [1]. The lack of balance in the aerobic metabolism is caused by constant stressful agents that determine a biological stress response. Hair cells of the inner ear are high energy-demanding and oxygen-consuming cells; a condition of hypoxia that increases ROS levels can trigger cell death or damage to biomolecules and DNA. The predominant ROS molecule is the superoxide radical ($O_2^{\bullet -}$), which is generated by univalent reduction of molecular oxygen, mainly during mitochondrial respiration but also by several enzymatic systems, such as xanthine oxidase, "uncoupled" endothelial nitric oxide synthase (eNOS) and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase from leukocytes and endothelial cell's function [1]. The superoxide is a relatively weak radical, but reacting with other molecules can yield additional, more potent ROS molecules and oxidants such as hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), and lipid peroxides. Additional toxic radicals, such as peroxynitrite (OONO-),

which is formed by the reaction of superoxide with the primary vasodilator nitric oxide (NO), also contribute to oxidative/nitrosative stress. This reaction results in diminished NO availability and severely affects endothelial function [1]. Hyperbaric oxygen therapy could be potentially used to correct the molecular alterations mentioned above. A study conducted by Yamamoto et al. [2] aims to identify the effects of the hyperbaric treatment on the microcirculation and oxygenation of the tissues by examining the changes in peripheral blood flow and on the transcutaneous partial pressure of oxygen ($TcPO_2$), demonstrating that the peripheral blood flow decreases while $TcPO_2$ increases when the treatment is applied for a short duration. Increased $TcPO_2$ at the beginning of treatment is followed by an increase in the levels of nitric oxide (NO) and superoxide ($O_2^{\bullet-}$) that are produced by endothelial cells. $O_2^{\bullet-}$ reacts with NO to generate peroxynitrite (ONOO-) between the endothelium and vascular smooth muscle cells, leading to vasoconstriction while the vasodilatory effects of NO were antagonized [2]. This reaction has been considered the cause of decreased peripheral blood flow during a short duration of HBO exposure [2]. During HBO exposure, extracellular superoxide dismutase (SOD) is gradually activated between the endothelium and vascular smooth muscle cells [2]. SOD scavenges $O_2^{\bullet-}$ allows the improvement of NO effect. The restoration of the vasodilatory effect of NO during a longer HBO exposure allows an increase in peripheral blood flow and an increase in dissolved O_2 in blood (Figure 1).

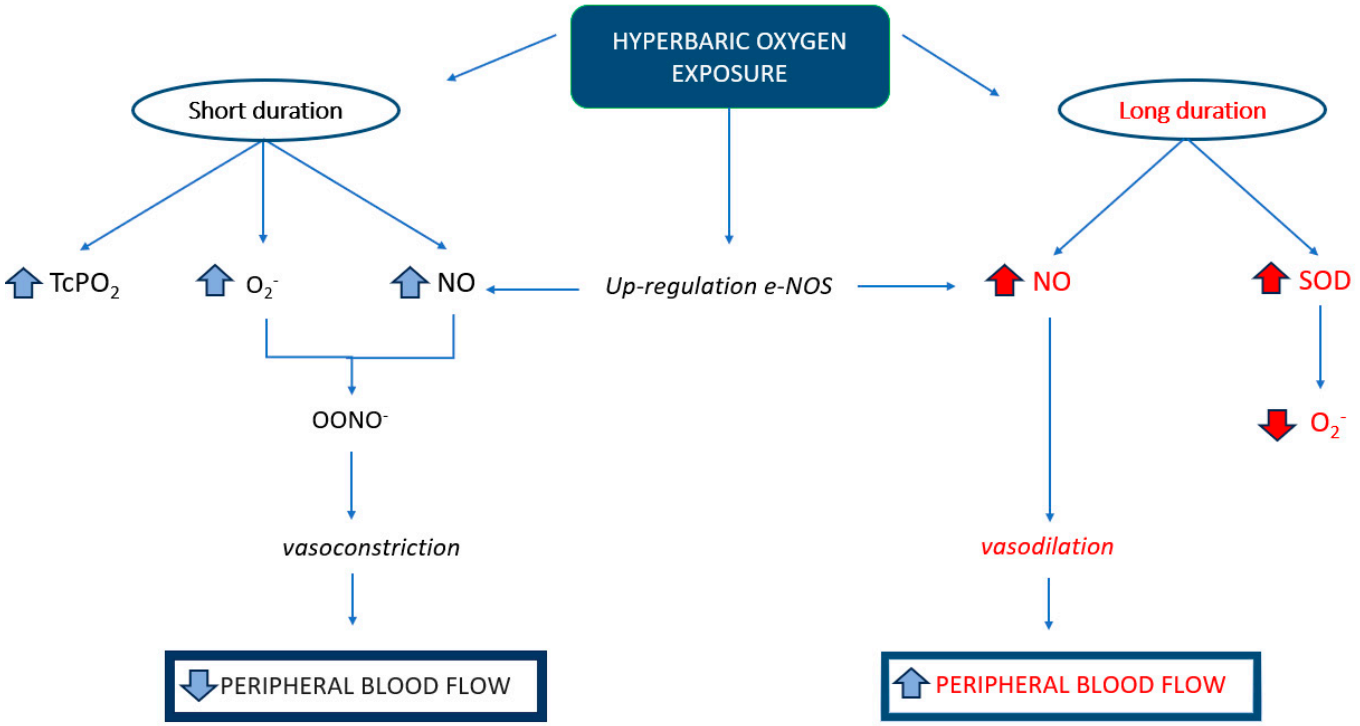

Figure 1. The diagram shows the effect of the HBOT on peripheral blood flow.

One of the largest prospective studies evaluated all oxidative mechanisms in patients affected by SSHL [3]. There is evidence that endothelium is the tissue that is mostly affected by ROS, inducing cell death. In this study, ROS levels were significantly elevated compared to healthy patients, suggesting that vascular impairment might be involved in the pathogenesis of SSHL. In this study, it was demonstrated, by taking blood samples between the two groups of patients, that total oxidant status (TOS) levels were higher in the group suffering from sudden sensorineural hearing loss compared to the healthy group. The data was statistically significant, although there were some limitations; for example, blood samples were taken from the systemic circulation while the deep position of the cochlea in the temporal bone does not allow the study of the cochlea microcirculation [3]. A

condition of oxygen reduction (hypoxia) can stimulate a metabolic activation to re-establish tissue homeostasis, which determines the increase in ROS levels, it starts a mechanism that leads to an increase in levels of HIF-1 α, TNF-α, NF-κB, myeloperoxidase (MPO), intracellular adhesion molecule 1 (ICAM-1), IL-8, vascular cell adhesion protein (VCAM-1), L-selectin, and E-selectin, VE-cadherin cleavage with subsequent endothelial dysfunction and consequently increased endothelial permeability [4]. TNF-α is recognized as a critical factor in the development of atherosclerosis. In general, an increase in oxidative stress and a variation in tissue metabolism, such as observed in the case of infectious or tumor states, can benefit from oxygen therapy. This treatment allows the restoration of a state of equilibrium in case of a lack of balance in the aerobic metabolism caused by constant stressful agents that determine a biological stress response of the organism. This narrative review aims to analyze current scientific literature on the benefits, indications, and side effects of HBOT in different head and neck disorders.

2. Materials and Methods

The study aimed to evaluate the use and effectiveness of HBOT in ENT pathologies through scientific literature research. The search was carried out on multiple electronic databases such as PubMed and Google Scholar using the following keywords "hyperbaric oxygen head and neck", "hyperbaric oxygen oxidative stress", "hyperbaric oxygen sudden hearing loss", "hyperbaric oxygen palsy's bell", "hyperbaric malignant otitis externa", "hyperbaric oxygen infections", "hyperbaric oxygen in osteoradionecrosis" and "hyperbaric ear avulsion". Limitations on the publication date, study design, and language were applied in the search strategy. We limited the search to articles published in the English language over the past forty years. The title and abstracts of the identified records were initially screened and selected by two independent reviewers (F.Z., A.C.) based on their relevance to the review topic. The following set of inclusion criteria, chosen in a shared way, was applied individually to the selected articles in their full-text versions. The literature search produced 136 records. Subsequently, 102 studies were excluded because they did not meet the objective of our review. In total, 34 studies were included and discussed because they compared the clinical outcomes of using HBOT, either when pharmacological or surgical treatments failed or as a combination treatment (Figures 2 and 3).

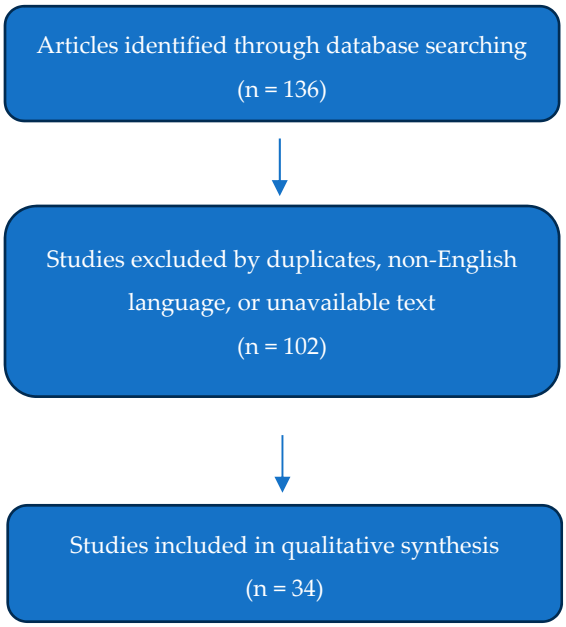

Figure 2. The diagram shows the information flow through different phases of the review and illustrates the number of records that were identified and included.

3. Results

3.1. HBOT in Obstructive Sleep Apnea Syndrome (OSAS)

OSAS is a common sleeping sickness disease that can be caused by obesity, craniofacial malformations or changes, pharyngeal neuropathy, altered muscle function in the upper airway, and fluid shift to the neck. Around 1 billion people are affected worldwide, aged 30–60 years (24% in men and 9% in women) [5,6]. OSAS is a pathology caused by at least five episodes per hour of airway obstruction (apnea) or reduction (hypopnea), in which there is a reduction in ventilation of at least 50%, resulting in oxygen desaturation $\geq$ 4%, with consequent intermittent hypoxemia, sympathetic hyperactivation, and sleep fragmentation. Blood oxygen desaturations are common findings after apnea and hypopnea events [7]. OSAS occurs mainly during REM sleep, in which there is a condition of muscle atony, and the severity of the pathology is defined by the number of sleep apneas and hypopneas per hour; this index is named the Apnea-Hypopnea Index (AHI). When the index is between 5 and 15, the disease is listed as mild, moderate between 15 and 29, and as severe when more than 30 episodes occur per hour of sleep [8]. These episodes are identified by polysomnography (PSG) monitoring, which represents the goal standard for diagnosing OSAS. CPAP could represent an important tool in treating this disease; it applies continuous positive airway pressure, expanding the alveolar surface area; in fact, increasing surface area aids oxygen diffusion over tissues [9]. Ryan S. et al. [10] showed that using CPAP for at least 6 weeks allowed a decrease in serum levels of TNF-α and IL-8. The role of inflammatory molecules in the development of atherosclerosis is well established. So, CPAP represents an effective treatment to lower this inflammatory response. CPAP has been confirmed as a valid antioxidant therapy, having the ability to reverse some of the alterations induced by oxidative stress, like eNOS, nitro-tyrosine, and NF-κB in the endothelium and circulating TNF-α [11].

3.2. HBOT in Bell's Palsy

Bell's palsy is an acute unilateral facial disease, which may include a unilateral lower motor neuron weakness of the face. The pathophysiology includes facial nerve hypoxia caused by swelling in the facial canal of the temporal bone. This leads to a phenomenon of reversible neuropraxia due to ischemia and inflammation of the nerve. HBOT could be an alternative tool to reduce nerve hypoxia levels. In the literature, there are not numerous studies to study the use of HBOT in Bell's palsy. An important study conducted by Racic in 1997 [12] suggested that hyperbaric oxygen therapy may be an effective treatment for moderate to severe Bell's palsy, but this study was excluded because treatment allocation was not blinded. The trial involved 79 participants in which the use of steroids was compared with the HBOT. The trial divided participants into two groups, each of whom was assigned the same treatment program. The HBOT group (n = 42) was exposed to 2.8 atm abs of 100% oxygen for 60 min, twice a day, 5 days a week, and was given a placebo orally, while the prednisone-treated group (n = 37) was exposed to 2.8 atm abs of 7% oxygen (equivalent to 21% oxygen in air at normal pressure). Prednisone was given orally (total of 450 mg in 8 days): 40 mg twice daily on days one to four; 30 mg twice daily on day five; 20 mg twice daily on day six; 10 mg twice daily on day seven; 10 mg once on day eight. Placebo tablets in the HBOT group were divided in the same manner. The group treated with HBOT received placebo tablets, not prednisone. Both study groups underwent equivalent dosing schedules of hyperbaric treatment. The patients were followed for nine months, and the dives were stopped when facial function returned to normal (maximum 30 dives). Nerve excitability testing (NET) was performed daily to determine the degree of facial nerve degeneration and subsequent recovery. Positive NET was found in 2 of 42 participants treated with HBOT at nine months and 9 of 37 treated with prednisone at nine months. The average time to complete the recovery in the HBOT group was 22 days as opposed to 34.4 days in the control group ($p < 0.001$). Those subjected to the hyperbaric oxygen treatment recovered more quickly (95% versus 76%), but the assessors of facial function knew what treatment the participants had undergone [12,13]. Despite the low

quality of the study due to the mentioned bias, it suggests, however, that HBOT may have a more valid effect than the use of corticosteroids [12,13].

3.3. HBOT in the Treatment of Sudden Sensorineural Hearing Loss

Sudden sensorineural hearing loss (SSNHL) is an acute, usually unilateral, deficit of the hearing. It develops suddenly, within a few hours, or occurs upon awakening. Many patients complained of tinnitus, and some had dizziness, vertigo, or both. Diagnostic criteria include a hearing loss of at least 30 decibels or greater over at least three contiguous test frequencies occurring within 72 h.

The incidence of SSNHL is 5–27 per 100,000 people annually. The main causes of this pathology are various and include viral infections, tumors, acute acoustic trauma, vascular occlusions, immune-mediated mechanisms, and cochlear membrane damage, but in more than 90%, it is idiopathic. So, a correct medical anamnesis is the basis for the choice of the best therapy and to improve symptoms [14–16]. Nowadays, there is no standard treatment for ISSHL: therapy can be based on a rational approach.

Systemic steroids are historically the primary therapy, although the mechanism of action is not known; probably, the reduction of cochlear and auditory nerve inflammation or reducing oxidative stress and the reversing of the apoptotic pathway of the injured cochlear hair cells could explain their effectiveness [17].

Over the last two decades, intratympanic steroids (ITS) and hyperbaric oxygen therapy (HBOT) have been proposed as salvage treatments in case of failure of systemic steroids.

The hypothesis that SSHL may occur due to hypoxia in the cochlea makes the use of the HBOT an effective therapeutic opportunity. The antioxidant systems can lead to alterations of the microcirculation, such as the increase in peroxynitrite, which is noticed especially in OSAS patients and causes an increase in NO and superoxide in the endothelial tissue [18,19].

It has been found that untreated OSAS can lead to damage to the hearing system; the oxidative stress caused by intermittent hypoxia is the main pathogenetic mechanism of damage [19]. pO2 in the perilymph during HBOT is inclined to increase. Oxygen is diffused from various terminal cochlear capillary networks into the perilymph and cortilymph, supplying the sensor and peripheral neuronal structures of the inner ear. About this, the pO2 in the perilymph and cortilymph will show a constant increase only after an extreme increase in the arterial pO2 and, thus, the arterio-perilymphatic difference in oxygen concentration. This condition can only be achieved by HBO therapy [20].

A study investigated the effects of the hyperbaric oxygen in some substructures of the cochlea regarding the upregulation of constitutive nitric oxide synthase (NOS), which is a protective enzyme, on adult male albino guinea pigs. NO released from constitutive NOS, such as eNOS, protects the cochlear circulatory system; it was upregulated after HBOT [21]. In 2023, it was conducted a major study that analyzed the medical charts of patients who suffered from SSNHL between 1 January 2012 and 31 December 2021, and these were subjected, early, within 72 h of symptoms, to the HBOT alone, without corticosteroids, for at least 10 sessions of 85 min each, with pure oxygen inhalation at 2.5 atmospheres absolute pressure, observing that 71.4% patients had complete hearing recovery; it suggests that HBOT could have a positive impact on patients with idiopathic SSNHL [22]. A retrospective analysis was conducted on patients with Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) between January 2016 and December 2021 and underwent HBOT. Data were analyzed for 102 patients after 1 to 5 therapy sessions and for 46 patients after 6 to 10 therapy sessions. Results showed an improvement of 44.1% in the first group and similar in the second group. It was highlighted that the improvement was more significant when the severity of the pathology was greater and, above all, if the therapy was started early [23]. Another study conducted by Cavaliere et al. [24] confirmed what has just been described above; it was conducted in a randomized controlled trial in which the use of steroids alone, the HBOT alone, and steroids + HBOT were compared, evaluating them among patients who received therapy within 7 days, 14 days and beyond 14 days from

the onset of symptoms. The HBOT (either alone or with steroids) was a more effective treatment than steroids alone, especially if it was started within 14 days of onset.

Thus, it is shared that the effectiveness of HBO is time-dependent, also Capuano et al. demonstrated that recovery is certainly more significant if treatment with HBOT is started within the first 14 days of symptoms compared to those treated after 14 days [25]. Holy et al. found an improvement if treatment was started within the first 10 days [26].

The American Academy of Otolaryngology-Head and Neck Surgery guidelines for the treatment of SSHL suggest that HBOT is recommended as adjunctive therapy with steroid therapy for either initial or salvage therapy after the failure of pharmacological treatment [27]. In literature, several studies confirm the indications of the American Academy of Otolaryngology-Head and Neck Surgery guidelines. Ajduk et al. measured the effect of hyperbaric oxygen therapy as salvage therapy after the failure of steroid therapy on ninety-three patients, in which 43 patients received additional HBO therapy while 50 did not. There was a great recovery in patients with a hearing loss of >61 dB, while those with a hearing loss of <60 dB had a significant improvement only at 250 and 500 Hz. Patients not undergoing HBO treatment showed no hearing improvement [28].

Pezzolli et al. [29] studied 58 patients who failed to recover after primary treatment with IV steroids. Patients treated with HBO had a mean improvement of 15.6 dB, while those who had not been treated had a spontaneous mean improvement of 5.0 dB. Patients with worst hearing had a greater degree of improvement if they were treated in the first 10 days after the onset of the hearing loss or between 11 and 30 days.

Zirong Huo et al. analyzed 92 patients with SSNHL. All patients were managed by intravenous dexamethasone, and 72 cases were treated with additional HBOT for 10 consecutive days. The overall hearing recovery rate was higher in the Intravenous steroids + HBOT group than in the IV-only group, suggesting that HBOT may have additional therapeutic benefits when it is combined with intravenous steroids. In this study, the level of hemoglobin (HGB), hematocrit (HCT), and superoxide dismutase (SOD) was significantly higher after HBOT in patients with better hearing improvements. It suggests that higher HGB, HCT, and SOD might be protective factors for hearing recovery, and HBOT may be more efficient when the level of available oxygen transporter is sufficient in blood [30].

Some studies do not confirm the evidence found by other authors, as in the case of the study by Dova et al. [31], in which two groups of patients were compared: those who received therapy with intravenous steroids alone and those with combined therapy (hyperbaric oxygen therapy + IV steroids). No significant hearing improvements were observed. These results agree with other studies, which did not show a significant improvement after the addition of HBOT [32,33].

3.4. HBOT in Radiation Necrosis

The HBOT may represent a therapeutic intervention that manages one of the late complications of Radiation Therapy (RT), like radiation necrosis (RN), through three mechanisms, including angiogenesis, anti-inflammatory modulation, and cellular repair [34].

RT causes a hypoxic, hypocellular, and hypo-vascular environment.

One of the most severe complications of radiation therapy in the head and neck field is osteoradionecrosis (ORN).

The radiation can generate hypo vascularization and necrosis, creating negative sequelae for the patient's quality of life, such as areas of exposed bone in the mouth, loss of teeth and supporting structures, or soft tissue oro-cutaneous fistula [35].

HBOT can increase cellular oxygen levels in osteoblasts and fibroblasts, promoting angiogenesis and, consequently, the production of new tissue [36].

The use of hyperbaric oxygen has been suggested as a means of prevention and treatment.

It seems that the HBOT may have a better therapeutic effect on early-stage lesions because they can benefit from conservative treatment. The most severe stage lesions probably

need to be managed by early bone debridement or bone resection and subsequently treated with HBOT. Early surgery can reduce the number of HBOT sessions [37].

An important study was conducted by the University of Pennsylvania between 1989 and 1994 on hyperbaric oxygen therapy for the treatment of radiation-induced sequelae in children. HBO treatment has been studied both in the form of prophylaxis and in the therapeutic field. The outcome was excellent, as demonstrated by the disappearance of signs and symptoms of radio necrosis and new bone growth on a follow-up computed tomography scan. It is a potentially valuable tool both in the prevention and treatment of radiation-related complications [38].

Several pieces of evidence showed that HBOT improves local tumor control and mortality for cancers of the head and neck, reducing the chance of local tumor recurrence in cancers of the head and neck after receiving radiation therapy with HBOT [39].

Leach et al. [40] recommend preventing mandibular osteonecrosis after surgery on irradiated facial and neck tissue by 30 preoperative 90-min sessions and 10 postoperative sessions. In fact, in their research, they point out that comparing osteoradionecrosis at six months postoperatively, the incidence was 5% in patients receiving 30 preoperative hyperbaric oxygen treatments compared with 30% in patients who received only preoperative antibiotics.

Forner et al. [41] compared a group of patients with surgical removal of necrotic mandibular bone supplemented by 30 pre- and 10 postoperative HBO exposures at 243 kPa for 90 min each with a group with surgical removal of necrotic bone only. In the first group, 70% healed compared to 51% in the second group. They showed that a combination of HBO + surgery had a beneficial effect on RT-induced xerostomia, unstimulated salivary flow rate, and dysphagia. Unfortunately, the trial was underpowered, and the results were not significant, but the results obtained encouraged the benefits that HBOT could have on RT.

A study conducted on 9 years of experience and 30 patients, observed how the hyperbaric chamber is useful in the management of osteoradionecrosis and post-irradiation wounds and it is therapeutic in some post-irradiated wounds where we cannot offer surgical correction [42].

3.5. Could the HBOT Be an Effective Treatment for Malignant Otitis Externa?

Malignant otitis externa (MOE) is an aggressive necrotizing infection of the soft tissues of the external auditory canal and surrounding structures, which spreads to involve the periosteum and bone of the skull base. The most common causative agent is *Pseudomonas aeruginosa* followed by *Aspergillus* spp., *Staphylococcus aureus*, *Candida* spp., and fungi and affected patients are typically elderly, uncontrolled diabetics or immunocompromised [43].

They complain of symptoms such as pain, otalgia, purulent otorrhea, edema, exudate, granulations, micro abscess (when operated), positive bone scan, or failure of local treatment, often for more than 1 week [44].

The primary treatment of MOE is long-term antimicrobial therapy, including topical and systemic administration, close follow-up of blood glucose levels and inflammation markers, and surgical debridement of the external auditory canal. In cases where antibiotic or surgical therapy fails, adjuvant treatment has been proposed with hyperbaric oxygen therapy [45]. The pathogenesis of MOE in diabetics is based on the impairment of leukocyte activity and on microangiopathy, which causes tissue hypoperfusion and hypoxia and further impairs the oxygen-dependent antimicrobial activity of leukocytes. Thus, hyperbaric oxygenation has been shown to increase the oxygen partial pressure in infected tissues, enhancing oxygen-mediated leukocyte killing of pathogens [46].

A retrospective study of 42 diabetic patients who were treated either by only antibiotic therapy (23 cases) or with both antibiotic therapy and hyperbaric oxygen therapy (19 cases) observed a 100% recovery in patients treated with HBOT compared to 74% of patients treated with antibiotic therapy alone and improving a typical complication such as facial nerve paralysis by 75%. There was also a rapid disappearance of clinical symptoms in

the group treated with hyperbaric oxygen. This testifies to the effectiveness of hyperbaric oxygen therapy in this disease [47].

Another retrospective study conducted on 16 patients (15 had diabetes) found similar results. This suggests how necessary it is to support and standardize HBOT treatment protocols [48]. However, in the Tenth European Consensus Conference, it was decided that there is no indication for the use of the HBOT in malignant otitis externa owing to very low levels of evidence [49].

Some literature supports the effectiveness of HBOT as a treatment modality for MOE, highlighting how it is a promising and effective tool [50–55].

Unfortunately, most of these studies had a limited number of samples, which prevented the results obtained from being objectified. The difficulty of organizing prospective, randomized, or double-blind studies due to the rarity of the disease must certainly be recognized.

	Positive scientific evidence	Accepted Indications	Possible use of the treatment	Effects
Bell's Palsy [12,13,49]	x		using HBOT instead of steroids	recovery quickly
Sudden Sensorineural Hearing Loss [21,22,23,24,25,26,27,28,29, 30,49]	x	x	adjuvant treatment with steroid therapy for either initial or salvage therapy after the failure of pharmacological treatment.	increased pO2 levels in the perilymph and up-regulation of NOS
Radiation Necrosis [37,38,39,40,41,42,49]	x	x	both in the prevention and treatment of radiation necrosis	increased cellular oxygen levels in osteoblasts and fibroblasts, promoting angiogenesis,anti-inflammatory modulation, and cellular repair to produce new tissue
Malignant otitis externa [45,46,47,48,50,51,52,53,54, 55,49]	x		adjuvant treatment if antibiotic or surgical therapy fails	increased the oxygen partial pressure in infected tissue
Ear Avulsion [56,57]	x		adjuvant treatment to surgery	good aesthetic and functional outcomes

Figure 3. The diagram shows the main information obtained from the analysis of the articles evaluated among the main ENT fields in which HBOT therapy is currently applied.

3.6. Primary Repair of Ear Avulsion with Adjuvant Hyperbaric Therapy

Ear avulsion can represent a serious and difficult problem to afford, given the different techniques described in the literature; primary repair is almost always the first choice, although viable tissue is not always available to allow the operation to be successful. Adjuvant hyperbaric oxygen therapy has been an option for some years.

Favede et al. [56] reported 2 cases of pediatric patients with near-total ear avulsion who underwent primary reattachment followed by adjuvant HBOT. These represented the first cases in the literature; the results were favorable to the use of HBOT with good aesthetic and functional outcomes. The authors believe that both treatments may contribute to a positive outcome, but there is a need for further studies to evaluate whether the cost and effort are necessary compared to surgery alone without adjuvant therapy. Unfortunately, there is still no universal consensus. Archibald et al. [57], analyzing the same two cases, underlined how the additional effect of the HBOT and the use of a nitroglycerin ointment

after the surgical treatment achieved a complete graft take for one patient and 90% graft take for the other, obtaining a good aesthetic result.

3.7. HBOT and Infections

HBOT is also effective in the treatment of severe soft tissue infections or necrotizing states of the head and neck. Infections create hypoxia in the tissues, which compromises the phagocytic activity of leukocytes and, consequently, the growth of anaerobic organisms. HBOT provides reoxygenation of the ischemic area, restoring phagocytic activity. HBOT can also act as a bactericidal or bacteriostatic or have a synergistic effect with antibiotics [58,59]. Maroon [60], in his personal case report, found a precipitous decrease in inflammatory protein clusters around session 40. Wound healing is a multifactorial process involving three phases (inflammation, proliferation, and remodeling) with the participation of leukocytes, fibroblasts, and cytokines [61]. The release of chemoattractants into the circulation involves the recruitment of neutrophils (at the beginning) and macrophages (later). The recruitment of leukocytes allows the release of proinflammatory cytokines such as interleukin (IL)-1β and IL-6, tumor necrosis factor-α (TNF-α), and growth factors, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) [62].

Oxygen has an important role in normal wound healing; bacterial killing by phagocytosis depends on a high partial pressure of oxygen. During phagocytosis, the neutrophil membrane produces superoxide, which combines with oxygen molecules and undergoes further changes to produce reactive oxygen species (ROS) [63]. Oxygen in wounds is consumed to produce ROS, which plays a role in killing bacteria, collagen production, and epithelialization [64]. Capò et al. [65] highlighted that HBOT induces an increase in ROS production and reduces inflammation, tissue edema, and oxidative stress. HBOT can also induce an increase in the production of several growth factors, such as hypoxia-inducible factor 1 (HIF-1), which could induce angiogenesis and cell proliferation. It can increase the upregulation of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which contribute to wound healing.

TNF-α and IL-1β, as markers of the inflammatory status, change the effect of HBOT. TNF-α plasma levels decrease after 5 days of treatment and reach their lowest levels 28 days after wound recovery. IL-1β plasma levels also reduced progressively throughout the HBOT [66]. The anti-inflammatory activity associated with HBOT seemed to be mediated by the inhibition of pro-inflammatory nuclear factor κB (NF-κB) [67].

3.8. Side Effects of Hyperbaric Oxygen Treatment

Despite all the positive benefits, the HBOT can induce side effects too and in literature the two most common are certainly barotrauma and claustrophobia. Rarer ones may be concerned with effects on the eye such as progressive myopia and pulmonary dyspnea [68].

A retrospective observational study of 5962 patients who underwent HBO therapy found an incidence of barotrauma of 9% among all patients, and the percentage reached 20% of patients who had hearing problems that pre-existed during the treatment [69].

Middle ear barotrauma (MEB) can represent a common condition responsible for many premature discontinuations of HBOT [70].

HBOT leads to ventilatory dysfunction of the eustachian tube (ET), favoring MEB [64].

Myopia may occur as a direct toxic effect of oxygen on the crystalline lens, and since HBOT can induce reversible myopia and prolonged exposure to HBOT can also induce cataracts but while myopia may be reversible, cataracts may show no signs of regressing [71].

4. Discussion and Conclusions

The literature provides various scientific evidence regarding the benefits that HBOT showed in the treatment of several ENT diseases. Its ability to provide 100% oxygen allows it to oxygenate necrotic or hypoxic tissues, promoting angiogenesis and the proliferation of new vital tissue. From our research, it was possible to deduce that the disease's rarity

and the lack of possibility of having numerous centers that have the hyperbaric chamber available as a treatment do not allow us to provide precise indications on the use of this therapy. The results presented in various trials are promising; the scientific evidence is more concrete regarding sudden sensorineural hearing loss in which it seems that HBOT is more effective when used as an adjuvant treatment to steroid therapy, especially when the hearing loss is severe and if the treatment is used during the first days of symptoms. HBOT up-regulates constitutive nitric oxide synthase [21], increases superoxide dismutase levels, and improves hemoglobin levels [30], and this highlights the ability to oxygenate tissues and, therefore, also be able to heal from infections. Although the Tenth European Consensus Conference does not recommend the use of HBOT in malignant otitis externa [49], we may disagree as there are studies, such as the one by Mardassi et al. [43], which document how there can also be a 100% recovery with HBOT compared to antibiotic therapy alone. However, the small number of cases analyzed in the trials does not allow us to have strong scientific evidence. However, this can stimulate us to work on prospective or randomized studies that could have a higher number of patients to standardize HBOT treatment protocols. HBOT could prevent the use of surgery, which always represents a risk for the patient, thanks to its being bactericidal and bacteriostatic; it can prevent osteoradionecrosis, improving the quality of life of patients. It can also be a tool that works in synergy with surgery, such as in the case of ear avulsion, improving functional and aesthetic outcomes. Multicentric studies, collaboration, additional studies with larger sample sizes, and randomized clinical trials are needed to establish new therapeutic protocols and to confirm the results already obtained. Evaluating the current evidence and clarifying the effect that HBOT may have on hypoxic or necrotic tissues could accelerate the indication of strong recommendations for some ENT diseases. There are currently recommendations to use HBOT in sudden sensorineural hearing loss, osteoradionecrosis of the jaw, and prevention of osteoradionecrosis and infections [49]. There are no indications for its use in malignant otitis externa and Bell's palsy [49], while just two articles [56,57] on ear avulsion are not sufficient to be sure of the effectiveness of HBOT on this pathology.

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References

1. Lavie, L.; Lavie, P. Molecular mechanisms of cardiovascular disease in OSAHS: The oxidative stress link. *Eur. Respir. J.* **2009**, *33*, 1467–1484. [CrossRef] [PubMed]
2. Yamamoto, N.; Takada, R.; Maeda, T.; Yoshii, T.; Okawa, A.; Yagishita, K. Microcirculation and tissue oxygenation in the head and limbs during hyperbaric oxygen treatment. *Diving Hyperb. Med.* **2021**, *51*, 338–344. [CrossRef] [PubMed] [PubMed Central]
3. Gul, F.; Muderris, T.; Yalciner, G.; Sevil, E.; Bercin, S.; Ergin, M.; Bababemez, M.A.; Kiris, M. A comprehensive study of oxidative stress in sudden hearing loss. *Eur. Arch. Otorhinolaryngol.* **2017**, *274*, 1301–1308. [CrossRef] [PubMed]
4. Meliante, P.G.; Zoccali, F.; Cascone, F.; Di Stefano, V.; Greco, A.; de Vincentiis, M.; Petrella, C.; Fiore, M.; Minni, A.; Barbato, C. Molecular Pathology, Oxidative Stress, and Biomarkers in Obstructive Sleep Apnea. *Int. J. Mol. Sci.* **2023**, *24*, 5478. [CrossRef] [PubMed] [PubMed Central]
5. Benjafield, A.V.; Ayas, N.T.; Eastwood, P.R.; Heinzer, R.; Ip, M.S.M.; Morrell, M.J.; Nunez, C.M.; Patel, S.R.; Penzel, T.; Pépin, J.L.; et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. *Lancet Respir. Med.* **2019**, *7*, 687–698. [CrossRef] [PubMed] [PubMed Central]
6. Lv, R.; Liu, X.; Zhang, Y.; Dong, N.; Wang, X.; He, Y.; Yue, H.; Yin, Q. Pathophysiological mechanisms and therapeutic approaches in obstructive sleep apnea syndrome. *Signal Transduct. Target. Ther.* **2023**, *8*, 218. [CrossRef] [PubMed] [PubMed Central]
7. Faber, J.; Faber, C.; Faber, A.P. Obstructive sleep apnea in adults. *Dent. Press. J. Orthod.* **2019**, *24*, 99–109. [CrossRef] [PubMed] [PubMed Central]

8. Park, J.G.; Ramar, K.; Olson, E.J. Updates on definition, consequences, and management of obstructive sleep apnea. *Mayo Clin. Proc.* **2011**, *86*, 549–554, quiz 554–555. [CrossRef] [PubMed] [PubMed Central]
9. Truschel, B.; Polkey, M.I. Optimizing Tracheal Oxygen Tension and Diffusion Ratio When Choosing High-Flow Oxygen Therapy or CPAP for the Treatment of Hypoxemic Respiratory Failure: Insights from Ex Vivo Physiologic Modelling. *J. Clin. Med.* **2023**, *12*, 2878. [CrossRef] [PubMed] [PubMed Central]
10. Ryan, S.; Taylor, C.T.; McNicholas, W.T. Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. *Am. J. Respir. Crit. Care Med.* **2006**, *174*, 824–830. [CrossRef] [PubMed]
11. Sivri, B.; Sezen, O.S.; Akbulut, S.; Coskuner, T. The effect of continuous positive airway pressure on middle ear pressure. *Laryngoscope* **2013**, *123*, 1300–1304. [CrossRef] [PubMed]
12. Racic, G.; Denoble, P.J.; Sprem, N.; Bojic, L.; Bota, B. Hyperbaric oxygen as a therapy of Bell's palsy. *Undersea Hyperb. Med.* **1997**, *24*, 35–38. [PubMed]
13. Holland, N.J.; Bernstein, J.M.; Hamilton, J.W. Hyperbaric oxygen therapy for Bell's palsy. *Cochrane Database Syst. Rev.* **2012**, *2012*, CD007288. [CrossRef] [PubMed] [PubMed Central]
14. Rinaldi, M.; Cavallaro, G.; Cariello, M.; Scialpi, N.; Quaranta, N. Metabolic syndrome and idiopathic sudden sensori-neural hearing loss. *PLoS ONE* **2020**, *15*, e0238351. [CrossRef] [PubMed] [PubMed Central]
15. Kuhn, M.; Heman-Ackah, S.E.; Shaikh, J.A.; Roehm, P.C. Sudden sensorineural hearing loss: A review of diagnosis, treatment, and prognosis. *Trends Amplif.* **2011**, *15*, 91–105. [CrossRef] [PubMed] [PubMed Central]
16. Prince, A.D.P.; Stucken, E.Z. Sudden Sensorineural Hearing Loss: A Diagnostic and Therapeutic Emergency. *J. Am. Board. Fam. Med.* **2021**, *34*, 216–223. [CrossRef] [PubMed]
17. Plontke, S.K.; Meisner, C.; Agrawal, S.; Cayé-Thomasen, P.; Galbraith, K.; Mikulec, A.A.; Parnes, L.; Premakumar, Y.; Reiber, J.; Schilder, A.G.; et al. Intratympanic corticosteroids for sudden sensorineural hearing loss. *Cochrane Database Syst. Rev.* **2022**, *7*, CD008080. [CrossRef] [PubMed] [PubMed Central]
18. Ciorba, A.; Gasparini, P.; Chicca, M.; Pinamonti, S.; Martini, A. Reactive oxygen species in human inner ear perilymph. *Acta Otolaryngol.* **2010**, *130*, 240–246. [CrossRef] [PubMed]
19. Mastino, P.; Rosati, D.; de Soccio, G.; Romeo, M.; Pentangelo, D.; Venarubea, S.; Fiore, M.; Meliante, P.G.; Petrella, C.; Barbato, C.; et al. Oxidative Stress in Obstructive Sleep Apnea Syndrome: Putative Pathways to Hearing System Impairment. *Antioxidants* **2023**, *12*, 1430. [CrossRef] [PubMed] [PubMed Central]
20. Lamm, K.; Arnold, W. Successful treatment of noise-induced cochlear ischemia, hypoxia, and hearing loss. *Ann. N. Y. Acad. Sci.* **1999**, *884*, 233–248. [CrossRef] [PubMed]
21. Lin, C.D.; Wei, I.H.; Lai, C.H.; Hsia, T.C.; Kao, M.C.; Tsai, M.H.; Wu, C.H.; Tsai, M.H. Hyperbaric oxygen upregulates cochlear constitutive nitric oxide synthase. *BMC Neurosci.* **2011**, *12*, 21. [CrossRef] [PubMed] [PubMed Central]
22. Aldè, M.; Cantarella, G.; Piatti, G.; Ambrosetti, U. Sudden hearing loss and early hyperbaric oxygen therapy: A preliminary study. *Undersea Hyperb. Med.* **2023**, *50*, 145–153. [CrossRef] [PubMed]
23. Chin, C.S.; Lee, T.Y.; Chen, Y.W.; Wu, M.F. Idiopathic Sudden Sensorineural Hearing Loss: Is Hyperbaric Oxygen Treatment the Sooner and Longer, the Better? *J. Pers. Med.* **2022**, *12*, 1652. [CrossRef] [PubMed] [PubMed Central]
24. Cavaliere, M.; De Luca, P.; Scarpa, A.; Strzalkowski, A.M.; Ralli, M.; Calvanese, M.; Savignano, L.; Viola, P.; Cassandro, C.; Chiarella, G.; et al. Combination of Hyperbaric Oxygen Therapy and Oral Steroids for the Treatment of Sudden Sensorineural Hearing Loss: Early or Late? *Medicina* **2022**, *58*, 1421. [CrossRef] [PubMed] [PubMed Central]
25. Capuano, L.; Cavaliere, M.; Parente, G.; Damiano, A.; Pezzuti, G.; Lopardo, D.; Iemma, M. Hyperbaric oxygen for idiopathic sudden hearing loss: Is the routine application helpful? *Acta Otolaryngol.* **2015**, *135*, 692–697. [CrossRef] [PubMed]
26. Holy, R.; Navara, M.; Dosel, P.; Fundova, P.; Prazenica, P.; Hahn, A. Hyperbaric oxygen therapy in idiopathic sudden sensorineural hearing loss (ISSNHL) in association with combined treatment. *Undersea Hyperb. Med.* **2011**, *38*, 137–142. [PubMed]
27. Chandrasekhar, S.S.; Tsai Do, B.S.; Schwartz, S.R.; Bontempo, L.J.; Faucett, E.A.; Finestone, S.A.; Hollingsworth, D.B.; Kelley, D.M.; Kmucha, S.T.; Moonis, G.; et al. Clinical Practice Guideline: Sudden Hearing Loss (Update). *Otolaryngol. Head Neck Surg.* **2019**, *161* (Suppl. 1), S1–S45. [CrossRef] [PubMed]
28. Ajduk, J.; Ries, M.; Trotic, R.; Marinac, I.; Vlatka, K.; Bedekovic, V. Hyperbaric Oxygen Therapy as Salvage Therapy for Sudden Sensorineural Hearing Loss. *J. Int. Adv. Otol.* **2017**, *13*, 61–64. [CrossRef] [PubMed]
29. Pezzoli, M.; Magnano, M.; Maffi, L.; Pezzoli, L.; Marcato, P.; Orione, M.; Cupi, D.; Bongioannini, G. Hyperbaric oxygen therapy as salvage treatment for sudden sensorineural hearing loss: A prospective controlled study. *Eur. Arch. Otorhinolaryngol.* **2015**, *272*, 1659–1666. [CrossRef] [PubMed]
30. Huo, Z.; Cheng, X.; Gu, J.; Hong, Y.; Wang, Z.; Zhang, Z. Prognostic factors for hearing outcomes in patients that undergo adjuvant hyperbaric oxygen therapy for sudden sensorineural hearing loss. *Laryngoscope Investig. Otolaryngol.* **2022**, *7*, 592–598. [CrossRef] [PubMed] [PubMed Central]
31. Dova, S.; Psillas, G.; Tsaligopoulos, M.; Nikolaidis, V.; Stefanidou, S.; Karagiannis, G.; Kotsiou, M.; Kaltzidis, T.; Markou, K. The effectiveness of hyperbaric oxygen therapy on the final outcome of patients with sudden sensorineural hearing loss. *Am. J. Otolaryngol.* **2022**, *43*, 103564. [CrossRef] [PubMed]
32. Çekin, E.; Cincik, H.; Ulubil, S.A.; Gungor, A. Effectiveness of hyperbaric oxygen therapy in management of sudden hearing loss. *J. Laryngol. Otol.* **2009**, *123*, 609–612. [CrossRef]

33. Yücel, A.; Özbuğday, Y. Comparison of Steroid Treatment with and without Hyperbaric Oxygen Therapy for Idiopathic Sudden Sensorineural Hearing Loss. *J. Audiol. Otol.* **2020**, *24*, 127–132. [CrossRef] [PubMed] [PubMed Central]
34. Hajikarimloo, B.; Kavousi, S.; Jahromi, G.G.; Mehmandoost, M.; Oraee-Yazdani, S.; Fahim, F. Hyperbaric oxygen therapy as an alternative therapeutic option for radiation-induced necrosis following radiotherapy for intracranial pathologies. *World Neurosurg.* **2024**, *186*, 51–61. [CrossRef] [PubMed]
35. Davis, D.D.; Hanley, M.E.; Cooper, J.S. Osteoradionecrosis. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2024. [PubMed]
36. Myers, R.A.; Marx, R.E. Use of hyperbaric oxygen in postradiation head and neck surgery. *NCI Monogr.* **1990**, *9*, 151–157. [PubMed]
37. Jenwitheesuk, K.; Mahakkanukrauh, A.; Punjaruk, W.; Jenwitheesuk, K.; Chowchuen, B.; Jinaporntham, S.; Uraiwan, K.; Limrattanapimpa, P. Efficacy of Adjunctive Hyperbaric Oxygen Therapy in Osteoradionecrosis. *Biores. Open Access* **2018**, *7*, 145–149. [CrossRef] [PubMed] [PubMed Central]
38. Ashamalla, H.L.; Thom, S.R.; Goldwein, J.W. Hyperbaric oxygen therapy for the treatment of radiation-induced sequelae in children. The University of Pennsylvania experience. *Cancer* **1996**, *77*, 2407–2412. [CrossRef] [PubMed]
39. Bennett, M.H.; Feldmeier, J.; Smee, R.; Milross, C. Hyperbaric oxygenation for tumour sensitisation to radiotherapy. *Cochrane Database Syst. Rev.* **2012**, *2012*, CD005007. [CrossRef] [PubMed] [PubMed Central]
40. Leach, R.M.; Rees, P.J.; Wilmshurst, P. Hyperbaric oxygen therapy. *BMJ* **1998**, *317*, 1140–1143. [CrossRef] [PubMed] [PubMed Central]
41. Forner, L.E.; Dieleman, F.J.; Shaw, R.J.; Kanatas, A.; Butterworth, C.J.; Kjeller, G.; Alsner, J.; Overgaard, J.; Hillerup, S.; Hyldegaard, O.; et al. Hyperbaric oxygen treatment of mandibular osteoradionecrosis: Combined data from the two randomized clinical trials DAHANCA-21 and NWHHT2009-1. *Radiother. Oncol.* **2022**, *166*, 137–144. [CrossRef] [PubMed]
42. Korambayil, P.M.; Ambookan, P.V.; Pillai, S.; Karangath, R.R.; George, D. Role of Hyperbaric Medicine for Osteoradionecrosis and Post Irradiation Wounds: An Institutional Experience. *Indian. J. Surg. Oncol.* **2020**, *11*, 469–474. [CrossRef] [PubMed] [PubMed Central]
43. Treviño González, J.L.; Reyes Suárez, L.L.; Hernández de León, J.E. Malignant otitis externa: An updated review. *Am. J. Otolaryngol.* **2021**, *42*, 102894. [CrossRef] [PubMed]
44. Cohen, D.; Friedman, P. The diagnostic criteria of malignant external otitis. *J. Laryngol. Otol.* **1987**, *101*, 216–221. [CrossRef] [PubMed]
45. Arsovic, N.; Radivojevic, N.; Jesic, S.; Babac, S.; Cvorovic, L.; Dudvarski, Z. Malignant Otitis Externa: Causes for Various Treatment Responses. *J. Int. Adv. Otol.* **2020**, *16*, 98–103. [CrossRef] [PubMed] [PubMed Central]
46. Byun, Y.J.; Patel, J.; Nguyen, S.A.; Lambert, P.R. Hyperbaric oxygen therapy in malignant otitis externa: A systematic review of the literature. *World J. Otorhinolaryngol. Head Neck Surg.* **2020**, *7*, 296–302. [CrossRef] [PubMed] [PubMed Central]
47. Mardassi, A.; Turki, S.; Lahiani, R.; Mbarek, H.; Benzarti, S.; Gharsallah, H. Is there a real benefit of hyperbaric oxygenotherapy in the treatment of necrotizing otitis externa? *Tunis. Med.* **2016**, *94*, 863. [PubMed]
48. Amaro, C.E.; Espiney, R.; Radu, L.; Guerreiro, F. Malignant (necrotizing) externa otitis: The experience of a single hyperbaric centre. *Eur. Arch. Otorhinolaryngol.* **2019**, *276*, 1881–1887. [CrossRef] [PubMed]
49. Mathieu, D.; Marroni, A.; Kot, J. Tenth European Consensus Conference on Hyperbaric Medicine: Recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb. Med.* **2017**, *47*, 24–32, Erratum in *Diving Hyperb. Med.* **2017**, *47*, 131–132. [CrossRef] [PubMed]
50. Al Siyabi, A.; Al Farsi, B.; Al-Shidhani, A.; Al Hinai, Z.; Al Balushi, Y.; Al Qartoobi, H. Management of Malignant Otitis Externa with Hyperbaric Oxygen Therapy: A Case Series of 20 Patients. *Oman Med. J.* **2023**, *38*, e512. [CrossRef] [PubMed] [PubMed Central]
51. Davis, J.C.; Gates, G.A.; Lerner, C.; Davis MGJr Mader, J.T.; Dinesman, A. Adjuvant hyperbaric oxygen in malignant external otitis. *Arch. Otolaryngol. Head Neck Surg.* **1992**, *118*, 89–93. [CrossRef] [PubMed]
52. Narozny, W.; Kuczkowski, J.; Stankiewicz, C.; Kot, J.; Mikaszewski, B.; Przewozny, T. Value of hyperbaric oxygen in bacterial and fungal malignant external otitis treatment. *Eur. Arch. Otorhinolaryngol.* **2006**, *263*, 680–684. [CrossRef] [PubMed]
53. Narozny, W.; Kuczkowski, J.; Mikaszewski, B. Hyperbaric oxygen to treat malignant external otitis. *Am. Fam. Physician* **2004**, *70*, 1860. [PubMed]
54. Mader, J.T.; Love, J.T. Malignant external otitis. Cure with adjunctive hyperbaric oxygen therapy. *Arch. Otolaryngol.* **1982**, *108*, 38–40. [CrossRef] [PubMed]
55. Leahy, T.W.; Sader, C. A rare case of bilateral malignant otitis externa and osteomyelitis with lower cranial nerve sequelae. *BMJ Case Rep.* **2011**, *2011*, bcr0320113957. [CrossRef] [PubMed] [PubMed Central]
56. Favede, C.; Bradshaw, C.; Sethia, R.; Kramer, S.; Jatana, K.; Elmaraghy, C.; Grischkan, J. Near-Total Ear Avulsion Repaired with Primary Closure and Hyperbaric Oxygen: A Case Series and Review of the Literature. *Ann. Otol. Rhinol. Laryngol.* **2023**, *132*, 1265–1270. [CrossRef] [PubMed]
57. Archibald, H.; Tibesar, M.; Thacker, J.; Masters, T.; Chinnadurai, S.; Tibesar, R. Primary Repair of Ear Avulsion with Adjuvant Hyperbaric Therapy and Nitroglycerin Ointment. *Facial Plast. Surg. Aesthet. Med.* **2024**. *Epub ahead of print*. [CrossRef] [PubMed]
58. Nedrebø, T.; Bruun, T.; Skjåstad, R.; Holmaas, G.; Skrede, S. Hyperbaric oxygen treatment in three cases of necrotizing infection of the neck. *Infect. Dis. Rep.* **2012**, *4*, e21. [CrossRef] [PubMed] [PubMed Central]

59. Cimşit, M.; Uzun, G.; Yildiz, S. Hyperbaric oxygen therapy as an anti-infective agent. *Expert. Rev. Anti Infect. Ther.* **2009**, *7*, 1015–1026. [CrossRef] [PubMed]
60. Maroon, J.C. The effect of hyperbaric oxygen therapy on cognition, performance, proteomics, and telomere length-The difference between zero and one: A case report. *Front. Neurol.* **2022**, *13*, 949536. [CrossRef] [PubMed] [PubMed Central]
61. Spampinato, S.F.; Caruso, G.I.; De Pasquale, R.; Sortino, M.A.; Merlo, S. The Treatment of Impaired Wound Healing in Diabetes: Looking among Old Drugs. *Pharmaceuticals* **2020**, *13*, 60. [CrossRef] [PubMed] [PubMed Central]
62. Landén, N.X.; Li, D.; Ståhle, M. Transition from inflammation to proliferation: A critical step during wound healing. *Cell Mol. Life Sci.* **2016**, *73*, 3861–3885. [CrossRef] [PubMed] [PubMed Central]
63. Yip, W.L. Influence of oxygen on wound healing. *Int. Wound J.* **2015**, *12*, 620–624. [CrossRef] [PubMed] [PubMed Central]
64. Hunt, T.K.; Hopf, H.W. Wound healing and wound infection. What surgeons and anesthesiologists can do. *Surg. Clin. N. Am.* **1997**, *77*, 587–606. [CrossRef] [PubMed]
65. Capó, X.; Monserrat-Mesquida, M.; Quetglas-Llabrés, M.; Batle, J.M.; Tur, J.A.; Pons, A.; Sureda, A.; Tejada, S. Hyperbaric Oxygen Therapy Reduces Oxidative Stress and Inflammation, and Increases Growth Factors Favouring the Healing Process of Diabetic Wounds. *Int. J. Mol. Sci.* **2023**, *24*, 7040. [CrossRef] [PubMed] [PubMed Central]
66. De Wolde, S.D.; Hulskes, R.H.; Weenink, R.P.; Hollmann, M.W.; Van Hulst, R.A. The Effects of Hyperbaric Oxygenation on Oxidative Stress, Inflammation and Angiogenesis. *Biomolecules* **2021**, *11*, 1210. [CrossRef] [PubMed] [PubMed Central]
67. Camporesi, E.M. Side effects of hyperbaric oxygen therapy. *Undersea Hyperb. Med.* **2014**, *41*, 253–257. [PubMed]
68. Nasole, E.; Zanon, V.; Marcolin, P.; Bosco, G. Middle ear barotrauma during hyperbaric oxygen therapy; a review of occurrences in 5962 patients. *Undersea Hyperb Med.* **2019**, *46*, 101–106. [CrossRef] [PubMed]
69. Edinguele, W.F.O.P.; Barberon, B.; Poussard, J.; Thomas, E.; Reynier, J.C.; Coulange, M. Middle-ear barotrauma after hyperbaric oxygen therapy: A five-year retrospective analysis on 2610 patients. *Undersea Hyperb Med.* **2020**, *47*, 217–228. [CrossRef] [PubMed]
70. Lima, M.A.; Farage, L.; Cury, M.C.; Bahamad, F., Jr. Update on middle ear barotrauma after hyperbaric oxygen therapy-insights on pathophysiology. *Int. Arch. Otorhinolaryngol.* **2014**, *18*, 204–209. [CrossRef] [PubMed] [PubMed Central]
71. Micun, Z.; Dobrzyńska, W.; Sieśkiewicz, M.; Zawadzka, I.; Dmuchowska, D.A.; Wojewodzka-Zelezniakowicz, M.; Konopińska, J. Hyperbaric Oxygen Therapy in Ophthalmology: A Narrative Review. *J. Clin. Med.* **2023**, *13*, 29. [CrossRef] [PubMed] [PubMed Central]