REVIEW

Outcome predictors of treatment effectiveness for fungal malignant external otitis: a systematic review

Predittori di efficacia nel trattamento dell'otite esterna maligna fungina: una review sistematica

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SUMMARY

The aim of this review is to summarise literature data on clinical aspects and traditional management of fungal malignant external otitis (FMEO), and to identify potential predictive factors of positive treatment outcome. Articles were initially selected based on their titles or abstracts. Full articles were then retrieved and further scrutinised according to predetermined criteria. Reference lists of selected articles were searched for any missed publications. The selected articles were methodologically evaluated. Of an initial 143 references, 14 were selected that focalised on the management of FMEO. The majority of studies demonstrated a correlation between treatment effectiveness, assessed as symptom resolution, and clinical and management variables: abstention from surgical debridement, absence of facial palsy, Aspergillus spp. as causative pathogen and absence of imaging findings at diagnosis and follow-up. The effectiveness of FMEO treatment depends on the assessment of cranial nerve state, the causative pathogen and imaging findings. Above all, absence of facial nerve palsy, Aspergillus spp. and absence of radiological signs at diagnosis and during follow-up correlate with symptom resolution. The fact that conservative treatment may be associated with a better outcome than surgical debridement could purely reflect that patients with more aggressive and advanced illness required debridement, whereas milder disease was treated conservatively. Thus, caution should be advised in the interpretation of data due to the need for further trials on the topic.

KEY WORDS: *Fungal • Malignant external otitis • Predictive factors • Review • Treatment*

RIASSUNTO

Obiettivo dello studio è stato riassumere i dati della letteratura sugli aspetti clinici e la gestione abituale dell'otite esterna maligna fungina (OEMF), ed identificare possibili fattori predittivi di esito positivo del trattamento. Gli articoli sono stati inizialmente selezionati sulla base del titolo e degli abstract. Sono poi stati recuperati ed analizzati per intero seguendo criteri predeterminati. È stata stilata una lista di riferimento degli articoli selezionati per cercare eventuali pubblicazioni mancati. Gli studi raccolti sono stati infine valutati metodologicamente. Dei 143 articoli iniziali, ne sono stati selezionati 14 focalizzati sulla gestione dell'OEMF. La maggior parte di questi ha dimostrato una correlazione tra l'efficacia del trattamento, inteso come risoluzione dei sintomi, ed alcune variabili cliniche e di gestione della patologia quali l'astensione da procedure chirurgiche invasive, l'assenza di paralisi facciale, l'Aspergillus spp come patogeno causante e l'assenza di segni radiologici alla diagnosi e nel corso del follow-up. L'efficacia del trattamento dipende dalla valutazione dello stato dei nervi cranici, dal patogeno alla base e dai segni radiologici, più precisamente: l'assenza di paralisi facciale, l'Aspergillus spp e l'imaging negativo alla diagnosi e durante il follow-up correlano con la risoluzione dei sintomi. L'evidenza che il trattamento farmacologico possa associarsi ad un miglior outcome rispetto a procedure chirurgiche invasive potrebbe semplicemente riflettere il fatto che pazienti affetti da una patologia più avanzata richiedono un approccio più aggressivo mentre le forme più lievi possono essere trattate in modo conservativo. È necessario quindi prestare attenzione nell'interpretazione dei dati a causa della necessità di ulteriori studi sull'argomento.

PAROLE CHIAVE: *Fungina • Otite esterna maligna • Fattori predittivi • Review • Trattamento*

Introduction

Malignant external otitis (MEO) is an aggressive and potentially fatal infection that originates in the external ear canal and spreads progressively along the soft tissue and bone of the skull base[1]. Since Chandler's publication of the first comprehensive case series of MEO in 1968[1], the most commonly reported causative pathogen is *Pseudomonas aeruginosa*.

Fungi are rarely involved in MEO, but have been identified in immunocompromised patients, such as those with AIDS or acute leukaemia. *Aspergillus fumigates* is the most common cause of fungal malignant external otitis (FMEO)[2]. *Aspergillus* FMEO occurs in immunocompromised patients, usually with profound and long-lasting neutropenia or under long-term steroid therapy, as well as in individuals with uncontrolled diabetes mellitus[2].

The disease manifests as a painful inflammation of the external ear canal, associated with purulent otorrhoea and granulation polyps. Otalgia is presenting symptom in 75% of cases [3]; it is intense, particularly during the night, and associated with severe temporal or occipital headache. The purulent otorrhoea appears with a frequency ranging from 50 to 80% and varies from a moist and modest secretion to greenish malodorous and abundant exudates. Histologically, granulation tissue is characterised by non-specific inflammation with inflammatory cell infiltration and hyperplasia of squamous epithelium [3].

The progression of the disease has been divided into three clinical stages: in the first, there is infection of the external auditory canal and adjacent soft tissues with severe pain, with or without facial nerve palsy. The second stage is characterised by extension of infection with osteitis of skull base and temporal bone, or multiple cranial nerve neuropathies. In the third stage, the infection reaches the intracranial structures, neck spaces and large blood vessels. This stage is always associated with poor prognosis. The most frequent causes of death are meningitis, large vessel septic thrombophlebitis or rupture, septicaemia, pneumonia caused by inhalation for vagal paralysis and cerebrovascular accident [3].

The treatment of FMEO classically includes extensive surgical debridement and intensive long-term antifungal therapy with amphotericin B and/or itraconazole and/or voriconazole. Despite this management, FMEO is associated with substantial morbidity and mortality, mostly due to late diagnosis and patient comorbidities [2]. Treatment failure can also be a result of suboptimal therapeutic management as a consequence of antifungal agent toxicity. In particular, the side effects of amphotericin B, particularly renal failure, may require interruption of antifungal agents or decrease in dosage [2], even if newer liposomal amphotericin formulations have largely eliminated renal failure as a side effect of this therapy.

Based on these premises, the aim of this review was to summarise literature data on clinical aspects and traditional management of FMEO, and to identify potential predictive factors of positive treatment outcome.

Materials and methods

Search strategy

The search strategy was designed to include papers on the basis of their relevance for answering the clinical research question: "Can FMEO treatment effectiveness, assessed as symptoms' resolution, be predicted by any clinical and/or management variable?"

The inclusion criteria were based on the type of the study: articles that were published after 2000, focusing on clinical manifestations, diagnostic tools, possible therapies and pitfalls of FMEO. The choice to limit the included studies to those publishing after 2000 was due to the need for an updated approach to the disease.

In order to identify relevant studies, as the first step, a search was carried out in the Medline databases using a combination of MeSH and keyword terms related to FMEO (i.e., fungal or mycotic malignant external otitis). No language limitations were set.

This first search step allowed the identification of a list of potential citations for inclusion in this review. Titles and abstracts on this list were screened by one independent reviewer (MM), who then determined whether to retrieve the full-text or not on the basis of the citations' potential relevance to the review's clinical research question.

As a further expansion of the search, searches were performed "by hand" within the Scopus database, the authors' personal libraries, and the references lists of the full-text studies were performed to identify potential additional relevant citations.

All the retrieved full-texts were included in the review by consensus of all authors.

Data extraction from the included publications was performed by the same author who performed the initial search. Data regarding the demographic features of the sample, comorbidities, pathogens, complications, imaging findings, treatments and symptoms resolution were put into descriptive tables. All data have been represented as they appeared in the original publication.

Table I. Grading of evidence statements.

Level of evidence	Type of evidence
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conduced meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*.
2++	High-quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is casual.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is casual.
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is casual*.
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion, formal consensus.

* Studies with a level of evidence "-" are not used as a basis for making recommendation; RCT: randomised controlled trial

Quality assessment

As a quality assessment strategy, the included studies were methodologically appraised according to the National Institute for Health and Clinical Excellence's levels of evidence (Table I).

Statistical analyses

Descriptive baseline and follow-up data were presented for each patient. Statistical analyses were conducted with the aim to identify potential predictors of treatment effectiveness.

Numerical continuous variables were expressed as means ± standard deviation and nominal variables were described by the absolute and relative (%) frequency.

For all statistical procedures, symptom resolution was the main outcome variable which is adopted in a regression analysis to be predicted by the dichotomic study variables (i.e. sex [M/F], diabetes [yes/no], pathogen [*Aspergillus*/no *Aspergillus*], facial palsy [yes/no], imaging findings [yes/no], treatment [monotherapy/no monotherapy] [surgical debridement/no surgical debridement]).

For dichotomic variables, single variable regression analysis was performed, with the aim to screen among the potential predictors of the outcome variable. For all statistical analyses, the level of significance was set at $p < 0.05$. All statistical procedures were performed with the Statistical Package for the Social Sciences (SPSS 19.0; SPSS Inc., Chicago, Ill).

Results

Literature search

One hundred forty-three citations were retrieved from the first phase of the search. A total of 132 references were excluded after screening of the titles and abstracts because they were clearly not relevant for this review, published before the year 2000, were not relevant to the clinical research question, or were duplicate studies. Full texts of the remaining 11 references were retrieved, along with three additional full text articles that were identified as potentially relevant by the second-step search expansion. Based on the inclusion criteria, 14 articles were selected for inclusion in this review (Fig. 1).

Overview of analysed studies

Of the 14 studies included in the review, all except three [2 4 5] are case reports. The average age of the 25 subjects is 62.6 ± 18, with 19 males and six females (Tables IIa, IIb). 80% of patients had diabetes mellitus.

Regarding the pathogen implicated, in the majority of cases *Aspergillus* spp. was found (61%), followed by *Candida* spp. (27%) and *Scedosporium apiospermum* (7%). Only one study [6] described *Malassezia sympodialis* as the cause of the disease.

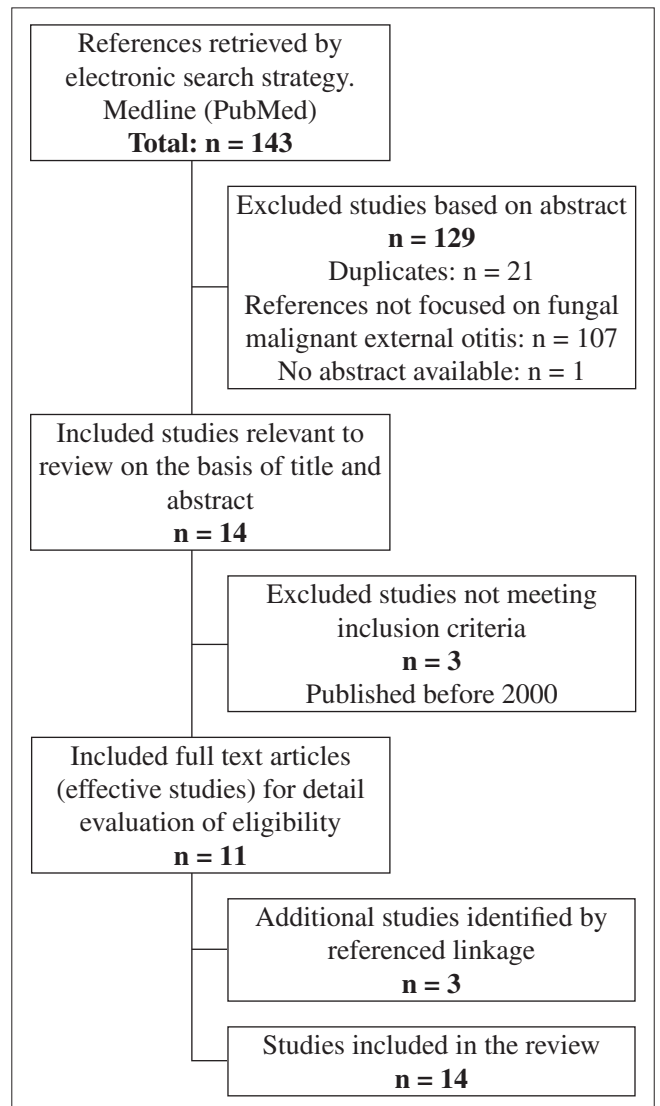52% of the subjects developed facial nerve palsy.

Fig. 1. Study flow diagram.stract

Table IIa. Baseline and follow-up data on the study population.

	All
No. of patients	25
Sex	19 (M) / 6 (F)
Age (range)	62.6 ± 18 (7-85)
Diabetes	80%
Aspergillus spp.	16 (61%)
Candida spp.	7 (27%)
S. apiospermum	2 (7%)
M. sympodialis	1 (4%)
Facial nerve palsy	13 (52%)
Imaging findings	9 (36%)
Monotherapy	16 (64%)
Duration	178.4 days
Combination therapy	9 (36%)
Duration	151.62 days
Surgical debridement	14 (56%)
Symptom resolution	15 (60%)

Table IIb. Summary of reviewed studies.

Main author	Year of paper	Age (y)	M/F	Comorbidity	Pathogen	Nerve palsy	CT or MRI findings	Therapy	SD	Symptom resolution
Walton et al. [7]	2014	83	M	DM2	A. flavus	VII	Y	Voric iv (2 wk) then oral (11 mo)	N	Y
Tarazi et al. [4]	2012	77	M	DM2	Aspergillus	No	Unspec	AmB then voric	N	Y
Tarazi et al. [4]	2012	85	F	DM2	Aspergillus	VII	Unspec	AmB then voric	N	Y
Tarazi et al. [4]	2012	70	F	DM2	Aspergillus	No	Unspec	Voric	N	Y
Bovo et al. [3]	2012	69	M	DM2	A. fumigatus	VII	Y	Voric iv (400 mg x2 l day, then 200 mg x2 for 3 mo)	Y	No - facial palsy
Lilic et al. [8]	2012	70	M	DM2	S. apiospermum	VII	Y	Ciprofloxacin (oral + topical)	N	No - died
Halsey et al. [9]	2011	62	M	AML	A. wentii	VII	Unspec	AmB (2 wk) then Itz (8 wk)	Y	No - facial palsy
Hamzany et al. [5]	2011	68	M	DM2	Candida	VII	Y	Voric + cloxacillin (42 days)	Y	No - died
Hamzany et al. [5]	2011	68	M	DM2	Candida	VII	Y	Voric (42 days)	Y	No
Hamzany et al. [5]	2011	68	M	DM2	Candida	VII	N	Voric(42 days)	Y	No
Hamzany et al. [5]	2011	68	M	DM2	Candida	VII	N	Ciproflox + ceftaz (110 days) then ceftaz + ofloxacin + vanco (66 days) then flucon + meropenem (60 days) then AmB (30 days)	Y	Y
Hamzany et al. [5]	2011	68	M	DM2	Candida	VII	N	Flucon (75 days) then flucon + rifampicin + fusidic ac (30 days)	Y	Y
Hamzany et al. [5]	2011	68	M	DM2	Candida	No	N	Ceftaz (78 days) then meropenem (55 days) + Itz (225 days)	Y	Y
Hamzany et al. [5]	2011	68	M	DM2	Aspergillus	No	Unspec	Meropenem (40 days) then flucon (42 days) then flucon + rifampicin + linezolid (60 days)	Y	Y
Hamzany et al. [5]	2011	68	F	DM2	Aspergillus	No	Unspec	Voric + cotrimox (130 days)	N	Y
Hamzany et al. [5]	2011	68	F	Nil	Aspergillus	No	Unspec	Ceftaz (42 days) then flucon + ampicillin (30 days)	N	Y
Parize et al. [2]	2009	48	M	Polychondritis	A. niger	No	Y	Voric (19 wk at 400 mg/day)	N	Y
Parize et al. [2]	2009	40	F	IDDM, renal tx, CRF	A. niger	No	Y	Voric (52 wk at 600 mg/day)	Y	No - hearing loss
Ling et al. [10]	2008	77	M	NIDDM, HTN, gout	Candida, A. flavus	VII	Y	Voric (14 wk at 400 mg/day) + caspofungin	Y	Y
Narozny et al. [11]	2006	65	M	NIDDM	Aspergillus	VII, IX, X	Unspec	AmB + Itz	Y	No - died
Tzuku et al. [12]	2006	17	F	IDDM	S. apiospermum	No	Y	AmB	Y	No – died
Bellini et al. [13]	2003	73	M	NIDDM	A. niger	Unspec	Unspec	AmB (2 g in 3 wk) then Itz (13 wk at 600 mg/day)	N	Y
Shelton et al. [14]	2002	58	M	Nil	A. niger	Unspec	Unspec	Itz (6 wk)	N	Y
Finer et al. [15]	2002	7	M	Neuroblastoma	A. flavus	Unspec	Unspec	AmB (6 days) then Itz (77 wk at 200 mg/day)	N	Y
Chai et al. [6]	2000	53	M	NIDDM	M. sympodialis	VII, IX, X, XII	Unspec	AmB than flucon	N	No - facial palsy

M: male; F: female; DM2: diabetes mellitus type II; AML: acute myeloid leukaemia; NIDDM: non insulin-dependent diabetes mellitus; tx: transplant; CRF: chronic renal failure; HTN: hypertension; Y: yes; N: no; Unspec: unspecified; Voric: voriconazole; AmB: amphotericin B; Itz: itraconazole; Cirpflox: ciprofloxacin; Ceftaz: caftazidime; Vanco: vamcomycin; Flucon: fluconazole; Cotrimox: cotrimoxazol

In 36% of cases, there was evidence of the disease by imaging, seen as soft-tissue filling of mastoid air cells and middle ear and thickening of the roof of the external ear canal at the magnetic resonance [2] or skull base osteomyelitis with involvement of the temporal bone by CT [7].

64% of patients were treated with monotherapy, i.e. voriconazole or amphotericin B, and the average duration of the treatment was 178.4 days. 36% of cases were treated with associations of antifungal drugs for a mean period of 151.62 days. 56% of subjects underwent surgi-cal debridement. 60% of the 25 cases showed complete resolution of symptoms.

In accordance with the clinical research question underlying this review, correlation between symptom resolution and clinical/management variables was assessed in all studies.

Correlation analysis

In accordance to the main criterion for inclusion in this review, all the studies assessed the correlation between symptom resolution and dichotomic study variables (Ta-

Table III. Single variable correlation analysis. Predictors of symptom resolution.

Predictors	Correlation with symptom resolution	p value
No surgical debridement	5.416	0.022
Absence of facial palsy	5.416	0.022
Aspergillus as causative pathogen	4.250	0.041
Absence of imaging findings	4.250	0.041
Monotherapy	2.097	0.173
Diabetes	1.427	0.307
Male sex	0.412	0.702

ble III). Single variable regression analyses showed that four of the dichotomic predictors were related with treatment outcomes: abstention from surgical debridement and absence of facial palsy (χ^2 = 5.416, p = 0.022), *Aspergillus* spp. as causative pathogen and absence of imaging findings were correlated with resolution of symptoms (χ^2 = 4.250, p = 0.041).

Male sex, presence of diabetes, preference for monotherapy over a combination of anti-fungal agents was not related with treatment outcomes.

Assessment of the quality of studies

All 14 studies could be categorised as evidence level 3 according to the National Institute for Health and Clinical Excellence's levels of evidence. Thus, when considering the quality of those selected, the assessment showed a good level of the reviewed articles as well as their qualitative homogeneity. However, their methodological heterogeneity did not allow for a meta-analysis of data.

Discussion

MEO is an insidious disease with frequently delayed diagnosis. Almost 95% of the cases reported in the literature are attributed to *P. aeruginosa*[3]. Nevertheless, other associated bacteria or fungi can have an important role in the aetiology of MEO, particularly in immunocompromised patients, where *Pseudomonas* is not the predominant pathologic organism[3]. Thus, even the isolation of *Pseudomonas* from aural discharge may be not sufficient or specific enough to distinguish between the two forms. In fact, *P. aeruginosa* is frequently a saprophyte in the external auditory meatus, as *Staphylococcus* coagulase negative, diphtheroids, *Micrococcus* spp., *Alternaria* spp., *Penicillium* spp. and miceti.

As emphasised by Leonetti and Marzo[16], patients are either referred with previous cultures and biopsy findings or are extremely tender on external auditory meatus manipulation; general anaesthesia is required to obtain an adequate biopsy. For these reasons, it is tempting to rely either on previous findings or on bacteriologic data to direct therapy. As a consequence, *Pseudomonas* isolation may delay correct diagnosis of fungal infection: the failure to respond to anti-pseudomonal therapy can lead to surgical exploration and detection of miceti[9].

On the other hand, *Aspergillus* spp. is also frequently isolated from external auditory canal smears and diagnosis of FMEO should be based on histopathologic confirmation on deep tissue biopsy or isolation from blood cultures or fistula exudates[17]. Deep tissue specimens obtained at surgery are necessary to diagnose fungi: this should reduce the risk of contamination or isolation of pathogenic saprophytes[12]. Sometimes, fungal cultures at the time of admission are negative and convert to positive only in later samples. In these cases, the primary infection can be caused by a bacterial pathogen, and owing to the prolonged course of the disease and antibiotic treatment, patients acquire an opportunistic fungal infection[5].

Aspergillus fumigatus was once thought to be the most common fungal pathogen in FMEO[10], with *Aspergillus flavus* assumed to be a less frequent cause of the condition. However, recent research reveals that *A. flavus* is about 100 times more virulent than *A. fumigatus* and has an optimum temperature for growth of 37°C, which may explain its particular pathogenicity in humans[7].

MRI and CT can be used in association with other imaging modes for diagnosis and follow-up of FMEO (i.e., Tc[99]MDP bone scanning, Ga[76] citrate scanning and Ga[67] SPECT). It is important to underline that the repeated studies performed in the patients with persistent disease showed that the number of subjects with radiological evidence of bone involvement increased in FMEO and decreased in MEO[5].

The presence of fungal pathogen makes the disease more invasive[5]. This was further confirmed by the higher number of facial nerve palsies in the patients with FMEO: VII nerve palsy is reported in 75% of patients with *Aspergillus* spp. infection, compared with only 34% in MEO due to *P. aeruginosa*[5,9].

The decision between conservative antimicrobial therapy and surgical treatment can present a therapeutic challenge in the management of these life-threatening infections, especially in patients with existing immunodeficiency and illness[3]. Although bone sequestra and abscess are treated surgically, the need for more aggressive treatment is debatable. Some authors suggest that prompt surgical debridement consisting of radical mastoidectomy is indicated in the majority of cases, particularly in fungal diseases, which are more invasive with respect to bacterial pathogens[2,3]. In the series reported by Hamzany[5], extensive surgery was carried out in 78% of FMEO *vs* 18% in bacterial ones. However, other authors stress the fact that extensive surgery may be counterproductive because of the risk of exposing healthy bone to infection[18]. Unfortunately, there are neither guidelines nor definite rec-

ommendations with regards to surgical treatment of the different forms of MEO.

The important principles of FMEO treatment include aggressive control of diabetes, improvement of immunocompetency when possible, and prolonged administration of adequate doses of antifungal agents, although the optimum duration of therapy remains unknown [9]. Amphotericin B and itraconazole were favoured for treatment of FMEO in the earlier case reports, whereas voriconazole has played a role in the therapy of the majority of reported cases since 2008. Voriconazole is currently recommended as first-line treatment in cases of invasive aspergillosis [7]. The intravenous form is recommended for use in systematically unwell patients, with the oral form being reserved for those who are stable or have improved following initial intravenous treatment. Voriconazole is widely distributed throughout tissues and, in its oral form, is not usually associated with worsening of renal function. This is particularly important as patients with comorbidities affecting renal function such as diabetes, who develop aspergillosis FMEO, therefore require treatment with voriconazole. The most commonly reported side effect of this antifungal agent include visual disturbances, particularly to colour vision, abnormal liver function tests, deranged renal function, skin photosensitivity, skin cancer and electrolyte abnormalities [7]. As noted in the literature, amphotericin B was most frequently used, although it has a significantly poorer safety profile, including adverse effects on renal function. Itraconazole and caspofungin have also been used in cases reported in the literature [7].

Regarding hyperbaric oxygen, there is as yet no uniformity in treatment design. Several reports suggested a beneficial effect of hyperbaric oxygen, along with traditional treatment [10][11], whereas the Cochrane Collaboration Database [19] found no clear data supporting its efficacy relative to antibiotics and/or surgery.

According to our research, abstention from surgical debridement and the absence of facial palsy are positive predictors of symptoms resolution, followed by *Aspergillus* spp. as causative pathogen and absence of imaging findings.

The counterproductivity of extensive surgery found from our research confirms the conclusions of Carfrae et al. [18], but the fact that conservative treatment is statistically associated with a better outcome than surgical debridement could purely reflect the disease stage rather than actively contributing to the results: patients with more aggressive and advanced illness required debridement, whereas milder disease was treated conservatively.

Sparing the facial nerve and absence of radiological signs intuitively indicate a less invasive form of FMEO, which correlates with a better prognosis. Even if the presence of fungal pathogen makes the disease more invasive than the bacterial form of MEO, *Aspergillus* spp. is more susceptible to anti-fungal agents than other fungi, i.e. *Candida* spp. The reviewed studies were selected on the basis of their description of clinical aspects and consequent management of FMEO. The choice to limit the included studies to those published after 2000 was due to the need for an updated approach to this disease. In spite of this strategy, unfortunately, the statistical analysis of predictors of outcome is flawed with a small series of case reports and study designs were so heterogeneous that meta-analysis of data could not be performed, and the extraction of sound, clinically-useful, conclusions was hard to perform. As a strength of the review, the studies had the common feature of relying on an accurate characterisation of management, using updated diagnostic techniques and treatments. Also, importantly, despite their methodological heterogeneity, all studies provided an acceptable [3] level of evidence according to the National Institute for Health and Clinical Excellence's grading. Within these limitations, some correlations between the outcomes of FMEO therapy and study variables were reported.

Notwithstanding this interesting information, it must be recognised that the available literature is too limited to permit a recommendation of any particular strategy in the clinical setting: decisions based solely on the studied factors cannot be recommended, especially because an integrated analysis of other risk factors (e.g., age, comorbidities, among others), must be taken into account. More information should be drawn on the amount of the advancement needed to achieve the best balance between benefit and discomfort, which was shown to be a critical aspect in the FMEO literature. Moreover, as a further limitation of this review, it should be pointed out that the external validity is not optimal due to the poor consistency between the reviewed studies as concerns the methodological features.

Conclusions

This systematic review identified 14 studies trying to relate specific clinical and management variables to the effectiveness of FMEO treatment. The outcome depends particularly on absence of facial nerve palsy, *Aspergillus* spp. as causative pathogen and absence of radiological signs at diagnosis and during follow-up. The fact that conservative treatment is statistically associated with a better outcome than surgical debridement could purely reflect the disease stage rather than actively contributing to the results: patients with more aggressive and advanced illness required debridement, whereas milder disease was treated conservatively.

Notwithstanding, the overall conclusions that can be drawn from this review are still limited by the somewhat inconsistent findings and the heterogeneity of study designs. Thus, it is suggested that further trials are performed before recommending any suggestions in the clinical setting.

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