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Antimicrobial Agents in Malignant Otitis Externa: A Systematic Review

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ABSTRACT

This systematic review determined the main antimicrobial agents resulting in MOE and spectrum antimicrobial therapy covering drug resistance in the disease. All the articles published in three electronic databases, including PubMed, Web of Science, and MEDLINE, were searched within November 15 to December 15, 2020. Eventually, 27 reports were identified assessing the clinical outcomes of patients with MOE. Generally, the mean age of patients with MOE in different studies was within the range of 59–82 years, and the male/female ratio was 1.8:1. The frequency of diabetes among patients with MOE was within the range of 40%-100%, and the frequency of facial nerve involvement was up to 60.7% in various studies. *Pseudomonas aeruginosa* is the most commonly reported causative organism in MOE. Methicillin-resistant *Staphylococcus aureus* is another organism leading to MOE. The main concerning issue in antibiotic therapy is the increasing isolation of bacterial strains resistant to this therapeutic approach. Generally, patients undergoing initial combination therapy have better outcomes compared to those receiving single therapy. Furthermore, the risk of ciprofloxacin resistance increased, especially when used as a monotherapy agent. The early diagnosis and treatment of patients with MOE are very crucial. In this regard, it is necessary to consider the management of diabetes for controlling the infection with antibiotics and debridement of necrotic tissue. Aggressive surgical management is suggested in some patients with MOE.

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Introduction

The malignant otitis externa (MOE) or necrotizing otitis externa is a high morbidity progressive infection of the external auditory canal that can extend to the surrounding soft tissues, cranial nerves, and adjacent skull base (1, 2). The frequency of MOE is higher among elderly patients with diabetes mellitus (2).

The MOE is not a neoplastic condition; however, the disease rapidly spreads and deteriorates similar to a malignancy. Severe otalgia, purulent otorrhea, aural fullness, hearing loss, and involvement of various cranial nerves are the main clinical features of MOE (3). The infection is commonly observed among immunocompro mised individuals, such as patients with diabetes, human immunodeficiency virus/acquired immune deficiency syndrome (AIDS) subjects, patients undergoing chemotherapy, and cases with anemia and leukemia (4).The MOE was reported in 1959 for the first time (5). *Pseudomonas aeruginosa* is reported as a causative organism in MOE (6).

The first case of nonpseudomonal MOE has been reported in 1982 (7). *Klebsiella species, Staphylococcus aureus*, and *Staphylococcus epidermidis* are other causative organisms in MOE (8-10). Fungal agents are also rare causes of MOE, the most common of which includes *Aspergillus fumigatus*, *Aspergillus niger*, and

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Aspergillus flavus (11,12).

Wide surgical debridement of necrotic tissues and even canal wall down mastoidectomy are the classic treatments for MOE. However, the prognosis of patients undergoing surgery is poor and in some cases leads to mortality and high morbidity. Moreover, outcomes were unsatisfactory following facial nerve decompression.Various studies completely cover potent broad-spectrum antimicrobial therapy, including bacterial (i.e.,Gram-negative pathogens) and fungal pathogens, and drug resistance to antimicrobial therapy.

This systematic review determined the main antimicrobial agents resulting in MOE and spectrum antimicrobial therapy covering drug resistance in the disease. The main issues discussed in this study are as follows:

-Relationship between MOE and demographic factors

-Main comorbidities in patients with MOE

-Assessment of antimicrobial agents (including bacterial and fungal pathogens) resulting in MOE

-Assessment of drug-resistant antimicrobial agents in MOE.

Materials and Method

This systematic review was performed to investigate studies assessing antimicrobial agents (including bacterial and fungal pathogens) resulting in MOE and drug-resistant antimicrobial agents in MOE. The guideline of Cochrane Handbook for Systematic Reviews of Interventions was used for the searching process. The guideline contains various stages of article eligibility, searching process, removal of unrelated papers, evaluation of the risk of bias, extraction of the information, and discussion (13).

Inclusion and exclusion criteria

This review included all the studies focusing on antimicrobial agents (including bacterial and fungal pathogens) resulting in MOE and drug-resistant antimicrobial agents in MOE. Participant-Intervention-Comparison-Outcome-Study design was used for the determination of inclusion and exclusion criteria. Only the articles published in English were entered into this study. Additionally, the papers focusing on patients with MOE were entered in this study, and studies conducted on subjects with external otitis were removed from the study.

The current study only included the articles assessing antimicrobial agents, and the papers without this information were excluded from the study. Moreover, the studies without enough information were ruled out from this study. Concerning MOE as a relatively rare infection, all types of observational, cross-sectional, prospective, and retrospective designs were entered into this study.

This study also excluded the papers with inaccessible full-texts and insufficient data, articles with a sample size of lower than 10, in vitro articles, animal studies, editorial letters, short communications or brief reports, books, narrative articles, systematic reviews and meta-analyses, and case reports or case series. Moreover, quantitative studies and papers providing a technical note, treatment protocol, or therapeutic evolution were removed from this study.

Literature search

Three electronic databases, including PubMed, MEDLINE, and Web of Science, were searched within November 15 to December 15, 2020. The research process was performed using the keyword, including “Malignant Otitis Externa” and “Necrotizing Otitis Externa” Along with “Antimicrobial Pathogens,” “Bacterial Pathogens,” and “Fungal Pathogens .” All stages of the searching process were conducted by two researchers, who were in contact with each other to discuss the selection of databases, topic issues, eligibility criteria, selection of studies, and data extraction.

Study design and data extraction

This systematic review focused on the papers assessing the clinical outcomes, antimicrobial pathogens, resulting in MOE, and drug-resistant antimicrobial agents. The databases, including MEDLINE, PubMed, and Web of Science, were searched using the selected keywords within November 15 to December 15, 2020. In the first step, duplicates and unrelated articles were removed, and then reference lists of identified papers were gathered to determine the studies relevant to the issues of the current study. The articles were entered this study reporting demographic data, antimicrobial pathogens, and clinical outcomes.

Out of the remaining papers, studies in which bacterial and fungal culturing was not assessed were excluded from the current study. The titles and abstracts were reviewed to remove unrelated papers considering the eligibility. The full-texts of the related articles were obtained for further evaluation. The selected studies were assessed by two researchers. They discussed together for the determination of the eligibility criteria, selection of the articles, data extraction, and topic issues.

chronic renal failure, antimicrobial pathogens, drug resistance, outcome, and mortality). PRISMA flowchart represents the stages of the selection of the articles (Figure 1).

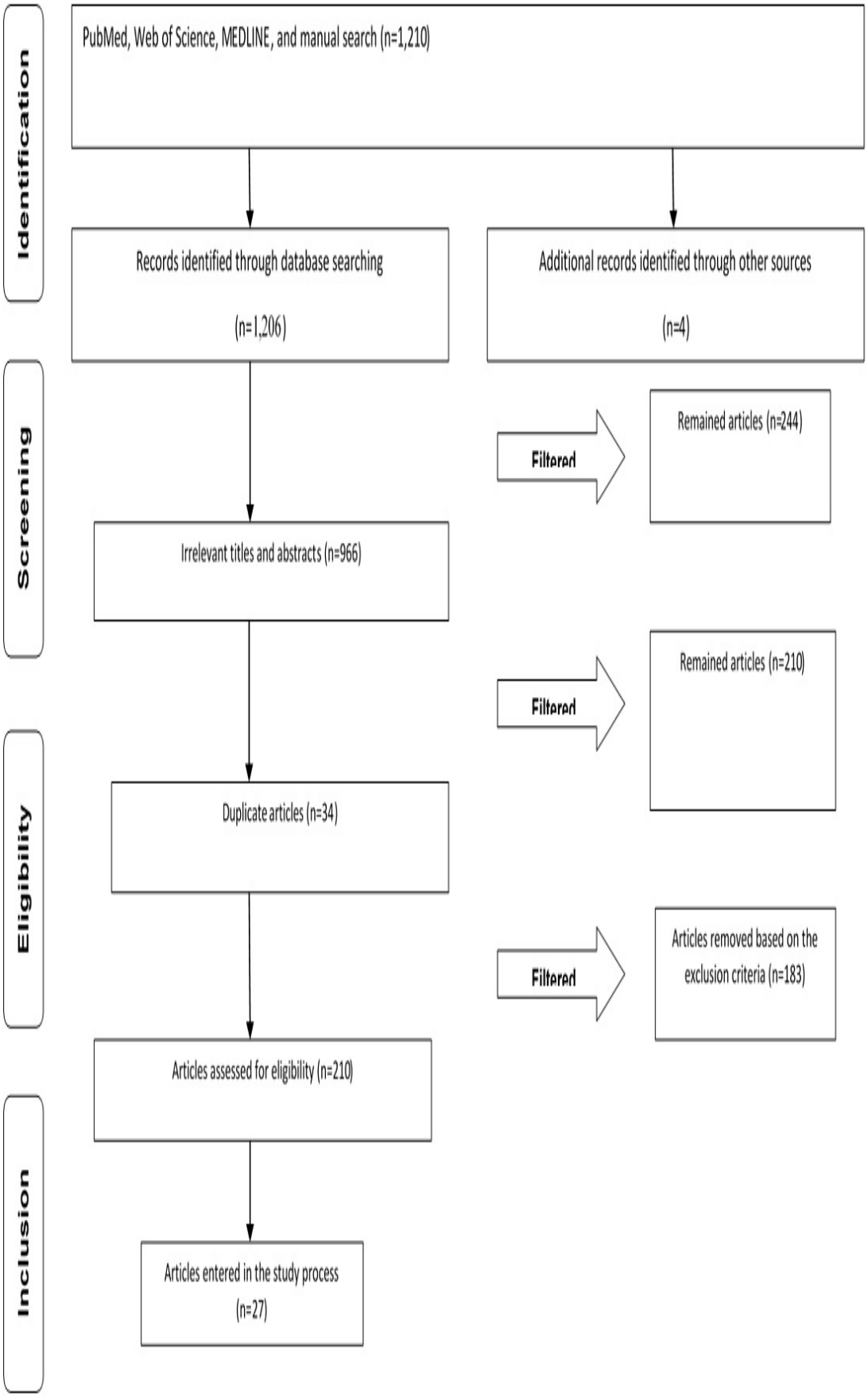

Figure 1. PRISMA flowchart representing selection process of the review

Quality assessment

In this study, the guideline of Cochrane Handbook for Systematic Reviews of Interventions was used to determine the risk of bias based on the seven categories, including bias due to confounders, bias due to the selection of participants, bias due to the measurement of intervention, bias due to missing data, free of selective reporting, and other sources of bias (14).The risk of bias was assessed in each study and categorized into high, low, and undetermined, which were marked as "Yes", "No," and "Unclear," respectively. Table 2 and Figure 2 show the risk of bias of the included studies by the evaluation of quality assessment.

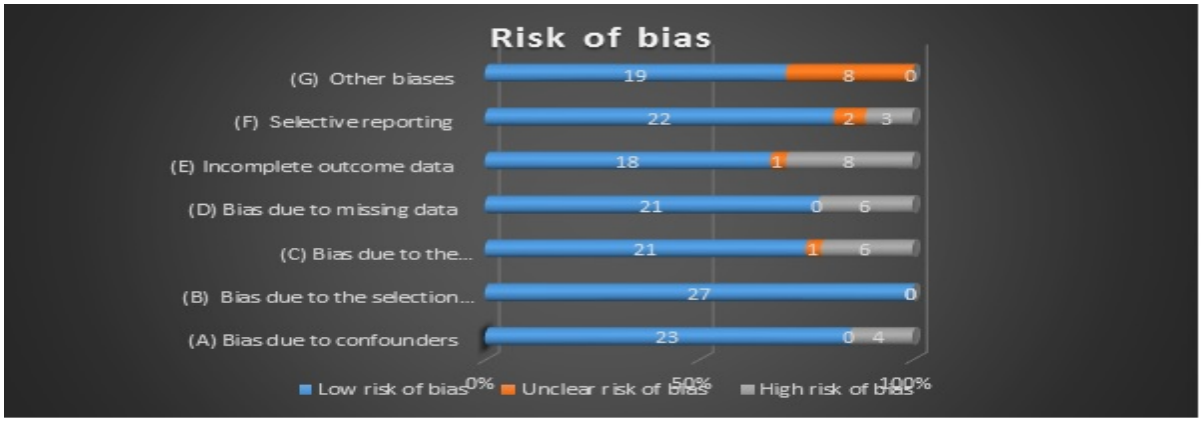

Figure 2. Quality assessment of entered studies in the review

Table 2. Quality assessment of entered studies in the reviewe.

Author (year) Reference	Bias due to confounders	Bias due to the selection of participants	Bias due to the measurement of intervention	Bias due to missing data	Incomplete outcome data	Free of selective reporting	Other sources of bias
Yu et al. (15)	Yes	No	Yes	Yes	Unclear	No	Unclear
Berenholz et al. (36)	No	No	No	No	No	Yes	No
Mani et al. (24)	Yes	No	Yes	Yes	Yes	Unclear	No
Joshua et al. (35)	Yes	No	Yes	Yes	Yes	Yes	Unclear
Sudhoff et al. (32)	No	No	Yes	Yes	Yes	Yes	No
Chen et al. (10)	No	No	No	No	No	Yes	No
Karaman et al. (2)	Yes	No	Yes	Yes	Yes	Yes	No
Chin et al. (26)	No	No	No	No	No	Unclear	No
Cheng Chen et al. (16)	No	No	Yes	No	Yes	No	Unclear
Hobson et al. (1)	No	No	No	No	No	Yes	Unclear
Glikson et al. (31)	No	No	No	No	No	Yes	No
Williams et al. (23)	No	No	No	Yes	Yes	No	No
Stevens et al. (34)	No	No	No	No	No	Yes	Unclear
Bhat et al. (3)	No	No	No	No	Yes	Yes	Unclear
Shavit et al. (33)	No	No	No	No	Yes	Yes	No
Hopkins et al. (30)	No	No	No	No	Yes	Yes	No

Bhasker et al. (27)	No	No	No	No	No	Yes	No
Shamanna et al. (19)	No	No	No	No	Yes	Yes	Unclear
Hatch et al. (18)	No	No	No	No	Yes	Yes	No
Kaya et al. (28)	No	No	No	No	Yes	Yes	No
Hutson et al. (29)	No	No	No	No	No	Yes	Unclear
Carlton et al. (22)	No	No	No	No	No	Yes	No
Marina et al. (17)	No	No	No	No	Yes	Yes	No
Amaro et al. (21)	No	No	No	No	Yes	Yes	No
Peled et al. (37)	No	No	No	No	Yes	Yes	No
Arsovic et al. (20)	No	No	No	No	Yes	Yes	No
Cheema et al. (25)	No	No	No	No	Yes	Yes	No

Findings and research outcomes

During the searching process, 1,210 articles were identified (1,206 through searching the databases and 4 by manual searching), 966 of which were excluded due to irrelevance. Out of 244 remaining papers, 34 articles was ruled out due to duplicacy, and 210 papers remained and were reviewed for eligibility. In addition, one study was published in a non-English language.

The articles with inaccessibility to the full-text version and insufficient data (n=2), papers with a sample size of lower than 10 (n=3), in vitro articles (n=3), animal studies (n=0), editorial letters and short communications or brief reports (n=9), books (n=3), narrative articles (n=41), systematic reviews and meta-analyses (n=2), and case reports or case series (n=84) were removed from this study. The other exclusion criteria included quantitative studies and papers providing a technical note, treatment protocol, or therapeutic evolution (n=11).

Out of the remaining papers, the studies in which the bacterial and fungal culturing was not assessed were excluded from the current study (n=24). Eventually, 27 studies assessing the clinical outcomes of patients with MOE were included in this review. PRISMA flowchart represents the selection process of the articles in this review (Figure 1). The majority (96%) of the selected papers had a retrospective design, and there was only one prospective study. Most studies (29.6%) were conducted in East Europe (United Kingdom [26%; n=7]; Ireland [4%; n=1]). One (4%) and five (18.5%) studies were conducted in Serbia and Israel, respectively. Additionally, four studies (15%) were conducted in North America.

Moreover, nine studies (33%) were conducted in Asia (India [11.5%; n=3]; Turkey [8%; n=2]; Taiwan [11%; n=3]; Pakistan [4%; n=1]). The included studies were conducted on a total of 1,553 patients with MOE (range: 10–789 subjects). The mean age of the participants in different studies was within the range of 59.3-82.4 years. In general, 64.8% (n=971) and 35.2% (n=526) of the patients were male and female, respectively. Therefore, the male/female ratio was reported as 1.8:1.

The frequency of gender was not reported in two studies. The duration of studies was within the range of 1–26 years. The frequency of diabetes in patients with MOE was within the range of 40-100%, and the frequency of facial nerve involvement was reported as up to 60.7% in various studies. Chronic renal failure was observed up to 40% among the patients with MOE.

P. *aeruginosa* was responsible for MOE in 26%-90% of the cases. In the reviewed papers, methicillin-resistant S. aureus (MRSA) was isolated from 7%-34% of the patients' specimens (1, 10, 15–1915-19). *S. aureus and Enterococcus faecalis* were isolated from 2%-40% (10, 20–28) and 4%-10% (2, 21, 23, 24, 29-32) of the patients' specimens, respectively. *Streptococcus* types (i.e., S. Milleri, S. epidermidis, S. pyogenes, and S. pneumoniae) were isolated from 1.3%-10% of the patients' specimens (18, 20, 21, 24, 26, 29, 32, 33). *Candida* was responsible for MOE in 3%-26.7% of the cases (18, 20, 21, 25, 26, 29–31, 33). Moreover, *Klebsiella* was isolated from 6.6%-23% of the cases (3, 10, 17, 19), and *Aspergillus* types (i.e., A. flavus, A. niger, and A. fumigatus)

were isolated from 3%-17% (18, 21, 23, 25, 26, 28, 31, 33, 34) of the patients' specimens. In addition, Escherichia coli was responsible for MOE in 7% of the subjects (17, 20), and Proteus mirabilis is responsible for MOE in 3%-6% of the cases (10, 20, 23, 30). Enterobacteriaceae was reported in one study in 23% of the MOE patients' specimens (33). The pathogens rarely reported included Enteroccocus (3%), Methicillin-sensitive S. aureus (11.6%), Acinetobacter baumannii complex (4%), Bacillus cereus (8%), Morganella (6.2%), Diphtheroids (7%), Serratia (8%), Nontuberculous mycobacteria (9%), Corynebacterium (4%), yeasts (13%), Coagulase-negative staphylococcal species (6%), and Proteus mirabilis (6.67%) (3, 10, 16, 22, 23, 26, 29). Furthermore, mixed pathogens were isolated from 3%-38% of the cases (22, 23, 26, 30, 31, 35). About 4%-32% of MOE patients have no causative agent (1, 16, 17, 19, 20, 22, 24-30, 33).

Ciprofloxacin-resistant Pseudomonas was the most common resistance, which was reported to be within the range of 12.5%-50% in various studies (10, 22, 29, 34, 36); however, it was not observed in some studies (1, 26). Levofloxacin-resistant Pseudomonas was reported as 4%-5% in various articles (1, 26). Clindamycin-resistant MRSA and gentamicin-resistant Pseudomonas were reported among the 44% of the subjects (1, 29). According to the findings of a study, Clarithromycin- and erythromycin-resistant Streptococcus milleri was observed in 4% of the patients (29). Another study showed that imipenem-resistant Pseudomonas was reported in 16.7% of the cases, and Pan-resistant and Zosyn-resistant Pseudomonas was observed in 8.3% of the subjects (22). No doxycycline-, trimethoprim/sulfamethoxazole-, or vancomycin-resistant MRSA was reported in this regard (1). The mortality rate due to MOE was reported within the range of 0%-23% in various studies. Table 1 tabulates the extracted data obtained from the reviewed studies in detail.

Table 1: Extracted data obtained from reviewed studies.

Sample size	Mean age (year)	Male/female ratio	Duration	Facial nerve involvement	Diabetes	Chronic renal failure	Antimicrobial pathogen	Drug resistance	Summary of outcomes	Mortality
12	65.3	--	8 years (1990-1997)	--	11 (92%)	1 (8%)	*P. aeruginosa*1: 66% MRSA2: 33%	--	Renal failure, meningitis, pneumonia, and upper gastrointestinal bleeding leading to death in four patients	--
28	68.6 (86-52)	19/9	13 years (2001-1988)	--	28 (%100)	--	P: %75	Ciprofloxacin-resistant P:7 (33%)	Resistance to ciprofloxacin in patients with MOE3 increased over time	1 (%3.5)
23	71 (39-87)	4/19	10 years	10 (%43.5)	21 (%91)	--	*P. aeruginosa*: 18 (78%) *Staphylococcus*: 1 (4%) *F Streptococcus*: 1 (4%) *Enterococcus faecalis*: 1 (4%) No growth: 2 (8%)	--	All patients were treated; Facial nerve palsy was significantly less likely to improve by medical treatment	0%
75	65	46/29	14 Years (1990-2003)	7 (9.3%)	61 (81%)	8 (12%)	*P. aeruginosa*: 45% Mixed (*Aspergillus/Candida*): %12	--	The worse prognosis of Type 1 MOE was compared to that of Type 2	--
23	71 (39-87)	19/4	--	10 (43%)	21 (91%)	--	*P. aeruginosa*: 18 (78%) *F streptococcus*: 1 (4%) *Enterococcus faecalis*: 1 (4%)	--	All patients had local treatment along with long-term systemic antibiotic therapy; local debridement of the necrotized and granulating tissue in two patients	0%

19	67.3 (38.83)	12.7	16 Years (1995-2010)	26%	14 82.3%	21%	*P.* *S.* *Kl* (6 *Pr* Pr (6 N(	25	73.5 (37-94)	16/9	5 years (2007-2011)	3 (12%)	10 (40%)	2 (8%)	P. aeruginosa: 1 %57.9 S. aureus: 2 (6%) Aspergillus flav (6%) Coagulase-nega staphylococcal s (6%) Candida albican Proteus mirabili S. epidermis7, a bacteria: 1 (%3)
10	(64-83)	7/3	5 years (2007-2012)	4 (40%)	9 (90%)	4 cases under-going dialysis	*P. aeruginosa*: 9 (90%) *Enterococcus faecalis*: 1 (10%)				--	Local debridement and local and systemic antibiotic; hyperbaric oxygen therapy for facial paralysis; all patients improved		1 (10%)	
24	64.3 (93-29)	--	9 years (2007-1998)	1 (4%)	13 (54%)	1 (4%)	*P. aeruginosa*: 15 (62%) *Serratia*: 2 (8%) *S. pneumonia*: 1 (4%) *Corynebacterium*: 1 (4%) *S. aureus*[5]4 (2%) Yeast: 3 (13%) *Candida*: 1 (4%) *Aspergillus fumigatus*: 3 (13%) *Aspergillus niger*: 1 (4%) Mixed skin flora: 1 (4%) No growth: 1 (4%)				P: Ciprofloxacin: None Levofloxacin: 1	The majority of patients were treated		1 (4%)	
55	65	21/14	12 years (1990-2001)	--	35 (64%)	--	*P. aeruginosa*: 20 (36%) MRSA: 19 (34%) Nontuberculous mycobacteria: 5 (9%) Negative culture: 5 (9%)				--	All patients were treated		0%	
20 P4: %45 MRSA: %15	64.9	12/8	18 years (1995-2012)	Total: %25 P: %33 MRSA: %0 (P=0.51)	Total: %75 P: %100 MRSA: %33 (P=0.04)	--	*P. aeruginosa*: 9 (45%) MRSA: 3 (15%) Other: 5 (25%) No growth: 3 (15%)				P: Ciprofloxacin: None Levofloxacin: 1 MRSA: Clindamycin: 1 Doxycycline, trimethoprim / sulfamethoxazole, or vancomycin: 0	NonPseudomonas-infected patients had longer treatment duration than Pseudomonas-infected patients (P=0.25); one patient infected with MRSA and Acinetobacter died		1 (5%)	
25	73.8 (27-93)	18/7	7 years (2009-2015)	2 (8%)	21 (84%)	1 (4%)	*P. aeruginosa*: 10 (40%) *Enterococcus faecalis*: 1 (4%) *Candida species*: 3 (12%) *Aspergillus flavus*: 3 (12%) Aspergillus fumigatus: 1 (4%) Mixed pathogens: 4 (16%)				Multidrug-resistance rate of P. aeruginosa: 30%	80% of the patients were clinically recovered; the majority (%68) of patients were operated out of whom five patients needed extensive surgery under general anesthesia		2 (8%)	
25	73.5 (37-94)	16.9	5 years (2007-2011)	3 (12%)	10 (40%)	2 (8%)	*P. aeruginosa*: 11 (57.9%) *S. aureus*: 2 (6%) *Aspergillus flavus*: 2 (6%) Coagulase-negative *staphylococcal* species: 2 (6%) *Candida albicans*, *Enterococcus, Proteus mirabilis*,*S. epidermis*7, and *diphtheroid* bacteria: 1 (3%)				--				

28	62.7	24.4	11 years (2004-2014)	9 (32%)	26 (93%)	--	The most frequently observed organisms: P. aeruginosa, MRSA, and Escherichia coli Aspergillus: 3 (10%)	Seven patients with ciprofloxacin-resistant P	High mortality and longer treatment courses among patients with severe MOE	5 (17.8%)
15	25-82	12/3	8 years (2006- 2013)	1 (7%)	14 (93%)	No	P. aeruginosa: 11 (73%) patients Klebsiella species: 1 (7%) Diphtheroids: 1 (7%)	--	All patients were treated with antibiotic therapy	--
88	73	61/27	5 years (2013-2009)	15 (17%)	%75	--	P. aeruginosa: 39 (%50) Enterobacteriace: 18 (%23) Candida: 10 (%13) S. aureus7 :5 (%9) Aspergillus: 2 (%3) Streptococcus: 1 (%1.3) Coagulase Negative: 1 (%1.3) Normal flora/Negative: 20 (%23)	--	Poor prognosis of the presence of diabetes mellitus, facial nerve palsy, positive computed tomography scan, and age of over 70 years	12 (%14)
30	82.4	25/5	10 years (2006-2015)	27%	70%	--	P. aeruginosa: 20 (66.7%) Candida: 8 (27.6%) Mixed anaerobes: 4 (13.3%) Enterococcus species: 2 (6.7%) Coagulase Negative Staph: 2 (6.7%) Proteus mirabilis: 1 (3.3%) No growth: 2 (6.7%)	--	MOE affected by old age, diabetes, male gender, and smoking	7 (23%)
11	77 (38-97)	5/6	9 years (2004-2012)	2 (18%)	36%	--	P. aeruginosa: %64 S. aureus: 2 (18%) No causative agent: 2 (18%)	All pathogens were sensitive to ciprofloxacin	All patients responded well to treatment	0%
34	48-61	30/4	4 years (2014-2017)	2 (6%)	24 (71%)	11 (32%)	P. aeruginosa: 18 (53%) Klebsiella: 8 (23%) MRSA: 5 (15%) No growth: 3 (9%)	--	All patients responded well to medical line of management	0%
786	--	465/312	3 years in 187 hospitals (2012-2015)	15/5 %	506 (%64/4)	182 (23%)	Out of %34 of patients (n=267) P. aeruginosa: 153 (57/3%) MRSA: 46 (17/2%) MSSA31 :6 (11/6%) Streptococcus infection: 27 (10%)	--	Length of hospital stay and mortality rate in MOE patients are affected by several factors, such as age, gender, cranial neuropathies, and underlying comorbidities	20 (2.5%)
25	69.6	18/7	11 years (2006-2017)	9 (36%)	100%	--	P. aeruginosa: 11 (44%) S. aureus: 3 (12%) Aspergillus flavus: 2 (8%) Acinetobacter baumannii complex: 1 (4%) No growth: 8 (32%)	--	After 6 weeks of treatment with intravenous antibiotherapy, all patients were treated with ciprofloxacin, piperacillin / tazobactam, and meropenem; two (%8) patients with cholesteatoma were operated	0%

16	72 (89-40)	11.5	1 year	--	11 (%69)	-	*P. aeruginosa*: 12 (75%) *Enterococcus*: 1 (6.2%) *Streptococcus milleri*: 1 (6.2%) *Morganella*: 1 (6.2%) *Candida*: 1 (6.2%) No growth: 2 (12.5%)	P. aeruginosa: Gentamicin: 1 Ciprofloxacin: 2 Streptococcus milleri: Clarithromycin/ Erythromycin: 1	Minimal antibiotic therapy complications, allergic rash, acute kidney injury, and clostridium difficile infection were reported each in one case; one mortality was reported	%0
12	68.9	11.1	7 years (2010- 2016)	7 (58%)	9 (92%)	4 (33%)	*P. aeruginosa*: 6 (67%) No growth: 3 (25%) *Bacillus cereus*: 1 (8%) Mixed pathogens: 2 (16%) *S. aureus*: 1 (8%)	Ciprofloxacin:4 Imipenem: 2 Pan-resistant:1 Zosyn:1	All patients were treated with intravenous antibiotics for recalcitrant disease; secondary outcomes were drug resistance and complications of MOE	1 (8%)
14		13/1	5 years (2017-2013)	4 (28%)	14 (100%)	1 (7%)	*P. aeruginosa*: %50 MRSA:%7 *Klebsiella*: %7 *Escherichia coli*: %7 No growth: %29	--	Reduction in the symptoms of otalgia and decrease in ear discharge in the majority of patients within 2 weeks; relapse rate was %21	0%
16	71 (58-84)	15.1	19 years (2016-1998)	No	100%	--	*P. aeruginosa*: 7 (43.7%) *Candida albicans*: 2 (12%) *Aspergillus favus*: 1 (6%) *Enterococcus faecalis*: 1 (6%) *S. aureus*: 1 (6%) *Streptococcus epidermidis:* 1 (6%)	--	Nine (%56.25) patients underwent surgery for local debridement or/ and decompression of the facial nerve	1 (6%)
81	68.2 (40-90)	48/33	26 years (2015-1990)	5 (11%)	75 (92.5%)	--	*P. aeruginosa*: 40 (49%) Fungal factor: 10 (12%)	--	Elderly patients with MOE are at increased risk for conservative treatment failure; aging, duration of hospitalization, and rates of readmission were associated with surgery	2 (2.5%)
30	71 (52-88)	27/3	11 years (2008-2018)	5 (17%)	23 (76%)	--	*P. aeruginosa*: 14 (47%) *S. aureus*: 3 (10%) *Candida*: 5 (17%) *Enteroccocus*: 1 (3%) *Escherichia coli*: 2 (7%) *Proteus mirabilis*: 1 (3%) *Streptococcus pyogenes*: 1 (3%) Normal findings: 8 (27%)	--	The treatment and prognosis of MOE patients are affected by cranial nerve involvement, erosion of temporal bone, and presence of comorbidities	2 (6%)
28	59.36	17/11	4 years (2016-2019)	17 (60.7%)	28 (85.7%)	--	*P. aeruginosa*: 14 (50%) *Staph*: 7 (25%) *Aspergillus*: 2 (7%) *Candida*: 1 (3.57%) None: 4 (14.3%)	--	All patients who improved had mild to moderate hearing loss	5 (17%)

1-Pseudomonas aeruginosa; 2- Methicillin-resistant Staphylococcus aureus; 3- Malignant otitis externa; 4- Pseudomonas; 5- Staphylococcus aureus; 6-Methicillin-sensitive Staphylococcus aureus; 7- Staphylococcus epidermis

Discussion

Relationship between MOE and demographic factors

Based on the obtained results of the current study, the mean age of the patients with MOE in different studies was within the range of 59-82 years. Some hypotheses have been proposed on the physiologic connection between aging and MOE, such as the reduced epithelial migration of the ear canal and microvascular disease disturbing immune response (38). Although MOE is commonly observed in elderly patients, the disease may be noticed among young individuals. In a study conducted by Bhat et al., the age of the patients was within the range of 25-82 years (3). In general, MOE patients younger than 30 years of age were reported in only 3 studies (3, 26, 31) out of 27 papers.

According to the findings of this study, the male/female ratio was 1.8:1. Nearly in all studies, the frequency of male patients was higher compared to that reported for female subjects, except for one study by Cheema et al., in which the frequency of females was higher than that of males (25). Moreover, based on the evidence, it was recommended that the male gender may be associated with a more severe type of MOE (34).

In this study, reported patients with MOE were identified from different areas across the world. The majority of the studies was conducted in the UK. It seems that there is a relationship between race and presentation of MOE; however, this factor was not evaluated in this study due to the lack of data in the selected studies. Only in one study conducted in the USA, four races (i.e., Caucasian, African, American, and Asian) were assessed in terms of the incidence of MOE indicating the higher frequency of MOE among Caucasian, African, American, and Asian individuals, respectively (18). Therefore, it is suggested to perform further studies in this regard.

Main Comorbidities in patients with MOE

Based on the literature, a steady increase was reported in the admission of patients with MOE, and this upward trend continues (39). This upward trend should be explained by a multifactorial approach, including increased awareness of MOE, aging population, diabetes epidemic, and possible antibiotic resistance (29). The MOE usually affects elderly patients with diabetes, and diabetes, along with an immunocompromised state, is introduced as the most frequent risk factor of MOE (38). Diabetic patients are vulnerable to MOE due to endarteritis, microangiopathy, impaired blood circulation, and small vessel obliteration due to the disease (38). Pseudomonal vasculitis leads to poor vascular supply because microvascular disease restricts tissue fusion in patients with diabetes. Moreover, there is an association between diabetes mellitus and impaired polymorphonuclear cell function (32).

Previously, it was suspected that the disease is limited to diabetic patients (40). However, recently , some cases of MOE have been reported among non-diabetic subjects. In this regard, there are various findings showing the incidence of diabetes among patients with MOE within the range of 40%-100% (2, 8, 41, 42). Hatch et al. demonstrated that the severe type of MOE is associated with a history of diabetic vascular complications (18). The aforementioned finding is confirmed by previous studies (2, 8, 35, 41, 42).

Facial nerve involvement is the other comorbidities associated with MOE. Due to the proximity of the external auditory canal to the facial nerve, it is the most common cranial nerve in MOE patients. Commonly, cranial nerve involvement in the patients is associated with the occurrence of dysphagia, dysphonia, and facial paralysis (24).The frequency of facial nerve involvement in MOE patients was within the range of 0-60.7% in various studies. Based on the results of a study by Sudhoff et al., there was further morbidity in MOE patients with palsy in comparison to that of the subjects without palsies (32). Hatch et al. observed no increase in mortality rate among MOE patients with cranial nerve involvement (18). However, several studies confirmed the association between facial nerve involvement and higher mortality (18, 33, 43). It is shown that the lower cranial neuropathies lead to worse outcomes (34). The mortality rate of MOE patients with the involvement of the facial nerve might be higher than that reported for those without facial nerve involvement if follow-up data in the long term are available. Moreover, chronic renal failure was observed among up to 40% of patients with MOE in various studies. Congestive heart failure and coagulopathy are other comorbidities significantly impacting complications and mortality rate in patients with MOE, which are affected by aging (34).

Assessment of antimicrobial agents (including bacterial and fungal pathogens) resulting in MOE

Bacterial pathogens: There is no consensus over the diagnostic criteria, prognostic indicators, or treatment approaches for MOE. The diagnostic criteria and risk factors of MOE are not similar in different reports (44). The cases suspected of MOE should undergo both bacterial and fungal culture testing, antibiotic sensitivity

testing, and biopsies via aural microsuction and swabbing. In general, P. aeruginosa is the most common isolated microbiological agent responsible for MOE, the frequency of which is estimated to be within the range of 36%-90% in various studies (2, 3, 33). Based on an old review of Rubin and Victor, 99.2% of the patients with MOE were infected by Pseudomonas (38). P. aeruginosa and S. aureus were isolated from 44.3% and 8% of MOE patients in a study by Shavit et al., respectively (33). In another similar study, P. aeruginosa was isolated from the majority (73%) of MOE patients (3). Nevertheless, it was isolated in less than half (44%) of MOE patients in a study by Kaya et al. (28). In a study conducted by Hutson et al., P. aeruginosa was the most common organism cultured on the microscopy of external auditory canal swabs, which were isolated from 75% of MOE patients (29).

However, nonpseudomonal cases of MOE are reported by increasing the frequency of MOE in the next years. In a study conducted by Hobson et al., the second and third most common isolates were S. aureus and MRSA, respectively (1). Based on the literature, the frequency of diabetes in Pseudomonas-infected patients is significantly higher than that of MRSA and non-Pseudomonas infected patients (1). However, there are similar clinical characteristics in MOE caused by Pseudomonas and MRSA, including the age of onset and symptoms. The MRSA is an increasingly important organism leading to MOE. Therefore, the diagnosis of MOE should be considered in all cases with refractory otitis externa even in non-diabetic patients. Moreover, atypical organisms should be suspected in non-diabetic patients suffering from MOE. Various studies showed that MRSA was isolated from 7%-34% of patients' specimens (1, 15–19). The most common pathogen in a study carried out by Cheng et al. was MRSA followed by nontuberculous mycobacteria and P. aeruginosa (16).

In addition, S. aureus is the sole offending organism in MOE (6, 41). In the current study, it was observed that S. aureus, Enterococcus faecalis, and Streptococcus types were isolated from up to 10% of the patients' specimens (2, 18, 20-33). Candida was responsible for MOE in up to 26.7% of MOE cases (10). In a study, concomitant Candida with Pseudomonas was reported in one case and another case grew Enterococcus (28). S. epidermidis, Proteus mirabilis, Klebsiella oxytoca, and Pseudomonas cepacia are other bacteria isolated in MOE (4).

Fungal pathogens: When cases with the MOE symptoms do not respond to the standard treatment, fungal MOE should be considered. The fungal MOE frequency is higher among patients with AIDS compared to that of bacterial MOE, which is more common in diabetic patients. The most common fungal organism causing MOE is Aspergillus fumigatus (45). Aspergillus flavus may be rarely isolated in MOE. In a study conducted by Chin et al., a fungal organism was isolated in 8% of the patients (26). In a study by Kaya et al., Aspergillus flavus was isolated from two patients' specimens (4). Generally, Aspergillus types (i.e., A. flavus, A. niger, and A. fumigatus) were isolated from 3-17% of patients' specimens (18, 21, 25, 28, 33, 34). In some cases, more than one pathogen is responsible for MOE. Chin et al. showed multiple organisms responsible for MOE in 38% of the patients (16, 17, 19, 20, 22–31, 33, 35).

However, MOE may occur without a causative agent. The role of the culture method has not been investigated in MOE. The pathogenic organism infecting the temporal bone in MOE is not always diagnosed by ear-swab culture. The evidence has demonstrated an inconsistency between swab and bone culture in diabetic foot osteomyelitis (46). In this regard, tissue biopsy should be suggested in cases not responding to ear-swab culture.

Assessment of drug-resistant antimicrobial agents in MOE

Drug-resistance Pseudomonas: The optimal duration of MOE treatment is unknown and there are no unified guidelines for treating the disease. P. aeruginosa, as the most common bacterial organism causing MOE, can evade host defenses and confers resistance to antibiotics (47–49). Antibiotherapy is considered the most common treatment usually administered for 4–6 weeks (50). The basis for antibiotic selection is bacterial culturing. Parenteral antibiotics should be administered depending on the culture and sensitivity. Based on the recent evidence, there was an increase (20%-54%) in the resistance rate for some antibiotics, such as fluoroquinolones (20, 51–53).

Ciprofloxacin, newer generation of fluoroquinolones, and third-generation cephalosporin are commonly administered to patients with MOE (54). Oral ciprofloxacin has been a selective treatment for MOE (55); however, ciprofloxacin-resistant P. aeruginosa increased recently. (36). For the first time, MOE caused by ciprofloxacin-resistant Pseudomonas was reported in 33% of the samples in a study by Berenholz et al. (36). Ciprofloxacin-resistant P. aeruginosa is common drug-resistance in MOE patients

reported in up to 50% of patients' specimens (22, 29, 34, 36). However, it was not observed in some reports (1,26).

Fluoroquinolone-resistant P. aeruginosa plays an important role in the poor outcomes in patients with MOE. Great sensitivity to ciprofloxacin in Pseudomonas bacteria was reported in the 1990s. Fluoroquinolone-resistant P. aeruginosa was reported 10 years later (2002). Increasing fluoroquinolone resistance leads to reuse intravenous anti-pseudomonal therapy and frequent debridement (36). A shift from Pseudomonas to culture-negative infections and other Gram-negative species was reported in a study by Carlton et al. They showed fluoroquinolone-resistant Pseudomonas in 50% of the patients. Moreover, P. aeruginosa resistant to fluoroquinolones was reported in two patients after oral ciprofloxacin treatment, both of whom expired (22). Similar treatment failures in fluoroquinolone-resistance were reported in similar studies (1, 10, 36, 55).

Increasing ciprofloxacin-resistant P. aeruginosa may be due to the widespread community use of oral ciprofloxacin for upper respiratory infection, inappropriate use of oral and intravenous fluoroquinolones, and routine topical use for external ear infections (56). In this regard, combination therapy has been suggested against resistance (24, 26). Bhasker et al. used monotherapy only for one patient and combination antibiotic therapy for the majority of patients due to concerns about antibiotic-resistant strains of P. aeruginosa. They showed that the coverage by ciprofloxacin was significantly compromised; accordingly, only 66%-71% of Pseudomonas strains was covered (27, 57). Hutson et al. observed antimicrobial resistance in three cases, ciprofloxacin in two patients, and gentamicin in one subject (29).

There have not been sufficient studies assessing ciprofloxacin-resistant Pseudomonas. It is necessary to give considerable attention to this issue because it will affect treatment strategies. The determination of the relationship between increasing resistance and comorbidity is very important. In some cases, Pseudomonas resistance to ciprofloxacin has required months of intravenous therapy and combination therapy. The selected antimicrobial agent and treatment duration are different in various studies. Tazobactam (Tazocin) is the most frequently used agent for MOE management in the UK. This drug allowed for broader initial treatment, with Gram-positive, anaerobic, and pseudomonal coverage. Before the treatment of the patients, local disease prevalence and sensitivities should be considered case by case.

Piperacillin/tazobactam is suggested as an effective alternative anti-pseudomonal antibiotic to ciprofloxacin due to increasing concerns about ciprofloxacin-resistant strains of Pseudomonas (27). A combination of antibiotic piperacillin and the beta-lactamase inhibitor tazobactam was administered to the majority (75%) of patients reported by Hutson et al. The agent was followed by ceftazidime in 25% of the patients. Other antimicrobials (i.e., flucloxacillin, teicoplanin, or metronidazole) were administered to most the subjects (29). Berenholz et al. reported successful treatment with ceftazidime in MOE patients; however, ceftazidime-resistant Pseudomonas has been reported by another study (58). This may be due to the interest in the administration of ceftazidime for simpler infections (e.g., the common cold) and inadequate prescription for simpler ear infections. It is recommended to administer the agent for more resistant infections.

In a study conducted by Glikson et al., multidrug resistance was reported in one-third of MOE cases infected with P. aeruginosa (31). It is possible to demonstrate an association between growing resistance and increasing usage of local quinolones in other clinical conditions. Increasing difficulty in the isolation of causative microorganisms from the external auditory canal is another problem in MOE patients. The antibiotic resistance in patients undergoing systemic antibiotic treatment changes based on culture sensitivity emphasizes the importance of the subsequent modification of treatment and culture-directed therapy (31).

Although increasing the incidence of ciprofloxacin-resistant Pseudomonas as a cause of MOE is reported in some studies (55, 59), Hobson et al. did not report ciprofloxacin resistance in any Pseudomonas specimen; however, an instance of levofloxacin resistance was observed (1). In general, levofloxacin-resistant Pseudomonas was reported in 4%-5% of the subjects (1, 26). Moreover, the developed resistance of P. aeruginosa to sulfa, chloramphenicol, and tetracyclines was reported by Chandler et al. over a period of 10–15 years (40). Drug resistance can lead to poor outcomes among patients with MOE. In a study conducted by Arsovic et al., the majority of patients underwent surgery due to a failure of local treatment and poor antibiotic response (20). However, individual differences are very important in treatment regimes.

Drug-resistance MRSA: There have been a limited number of reports documenting MRSA as a causative organism (1, 6, 15) and restricted data providing treatment guidance for MOE caused by MRSA because it is a rare organism. Therapeutic considerations tailored to the causative

organism should be considered in MOE cases with different etiologies (55). The early-stage of treatment is empirically performed in an outpatient setting. However, due to poor Gram-positive coverage of ciprofloxacin and increasing frequency of ciprofloxacin-resistant Pseudomonas, it is not always an effective therapy, especially against MRSA. In a study by Hobson et al., clindamycin-resistant MRSA and gentamicin-resistant Pseudomonas were reported as 4%. Although there is evidence on the sensitivity of MRSA to antibiotics, the patient's infection was not treated and recovered using intravenous vancomycin. No doxycycline-, trimethoprim/sulfamethoxazole-, or vancomycin-resistant MRSA was reported (1).

Antifungal therapy: Another treatment approach of MOE is antifungal therapy or combination therapy because the disease can be caused by fungal organisms or a mixed bacterial and fungal infection. Fungal MOE can be treated with both intravenous and oral forms of voriconazole, which is the first treatment option for Aspergillus infections (60). An intravenous form of the agent (200 mg twice daily) was used in a study by Kaya et al. Other treatment options for fungal MOE are amphotericin B and itraconazole. Since the administration of amphotericin B and voriconazole may lead to renal side effects, the renal function of patients should be closely monitored during the use of the agents (61).

Since fungal MOE is a refractory disease, radical mastoidectomy may be required in most patients (62). Other therapeutic approaches: Recently, the use of antipseudomonal penicillin (e.g., carbenicillin) and cephalosporins (e.g., ceftazidime and aminoglycosides) has increased as proper agents for MOE. Before using aminoglycosides, nephrotoxicity and ototoxicity should be monitored for patients at risk of compromised renal function. There are no universally accepted criteria for the determination of the time of treatment termination in patients with MOE. In this regard, the improvement of inflammatory markers and disappearance of the symptoms with a normal external auditory canal on examination can be considered factors for disease recovery (63). In serious cases, mastoidectomy should be performed. Although MOE is not traditionally a surgical disease, surgical intervention is the main approach to the treatment of MOE with a trend toward severe cases (64–66). The surgical intervention is commonly performed to obtain adequate cultures, debride necrotic tissue, or rule out an underlying malignancy. Hyperbaric oxygen therapy is another treatment approach for MOE; however, its efficacy has not been proven compared to that reported for antibiotic therapy or surgery (67).

Mortality rate: The mortality rate due to MOE was reported as up to 23% in various studies. The recurrence rate of MOE after complete treatment is within the range of 14%-20% according to the literature (3, 68). There is no difference in the mortality rate among various races (i.e., Asians, Africans, Americans, and Caucasians) (18). Moreover, there is a correlation between aging and increased mortality rates; accordingly, no mortality was reported among the patients of 30 years and younger, and the mortality rate was reported as 4.3% in elderly patients in a study by Hatch et al. (18). The incidence of MOE was higher among male patients compared to female cases; nevertheless, no difference in the complication rate is reported between the two genders except for mortality (18). Male gender can be associated with a more severe form of MOE (34), which may lead to high mortality among male subjects with MOE in comparison to female patients.

Conclusion

The mean age of patients with MOE in different studies was within the range of 59–82 years, and the male/female ratio was reported as 1.8:1. The frequency of diabetes among patients with MOE was within the range of 40%-100%, and the frequency of facial nerve involvement was up to 60.7% in various studies. The main concerning issue in terms of antibiotic therapy is the increasing isolation of bacterial strains resistant to this therapeutic approach. Generally, patients undergoing initial combination therapy have better outcomes in comparison to those with single therapy and the risk of ciprofloxacin resistance increased, especially when used as a monotherapy agent. MRSA is another organism leading to MOE. The early diagnosis and treatment of patients with MOE are very important. In this regard, it is necessary to consider the management of diabetes for controlling the infection with antibiotics and debridement of necrotic tissue. Aggressive surgical management is suggested in some patients with MOE.

Other therapeutic approaches: Recently, the use of antipseudomonal penicillin (e.g., carbenicillin) and cephalosporins (e.g., ceftazidime and aminoglycosides) has increased as proper agents for MOE. Before using aminoglycosides, nephrotoxicity and ototoxicity should be monitored for patients at risk of compromised renal function. There are no univer.

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Conflict of interest

The authors declare that there is no conflict of interest.

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