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Research Paper

Methicillin-resistant *Staphylococcus aureus* in acute otitis externa[☆]



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KEYWORDS

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Abstract *Objective:* Otolgic methicillin-resistant *Staphylococcus aureus* (MRSA) infection has historically been rare, but given the rise in community-acquired MRSA carriage and infection at other body sites, prevalence rates may be changing. The goal of this study was to determine the prevalence of MRSA in recent otologic cultures from patients with acute otitis externa (AOE). *Study design:* Retrospective review of an institutional microbiologic database. *Methods:* A retrospective analysis was performed on serial culture isolates taken from the ear at a quaternary care hospital from January 2014 to April 2016. The causative pathogen and antibiotic sensitivity was determined by culture isolation and end point mean inhibitory concentration (MIC) testing. Medical records were reviewed to document patient characteristics, chronicity of infection, symptomatology, and previous treatments.

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Results: Over the study period, 173 patients were diagnosed with AOE and underwent otologic cultures of the ear. Fifty-three (30.6%) of cultures grew *S. aureus* (SA). Of SA infections, 15 (28.3%) were identified as MRSA. MRSA patients were typically older than patients with methicillin-sensitive SA (MSSA) (mean age 46.7 ± 17.9 vs 29 ± 19.4 , $P = 0.003$) and had more medical comorbidities (4 vs 1.7 , $P = 0.001$). Compared to patients with MSSA, patients with MRSA were significantly more likely to have had prior ototopical antibiotic exposure (37% vs 73%, $P = 0.019$).

Conclusion: Contemporary ear culture isolates at quaternary care center show higher rates of MRSA compared to historical reports in the literature. Clinicians should consider ear cultures to identify MRSA AOE.

Level of Evidence: IV.

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Introduction

Acute otitis externa (AOE) is a common otologic condition, affecting 1 of every 10 individuals.¹ Defined as an infection of the skin and soft tissue of the external auditory canal, AOE can be caused by a variety of bacteria or fungi. While most symptoms of AOE are mild, complications of AOE may be serious, including necrotizing infection, facial nerve paralysis, osteomyelitis, and rarely death.¹

The implicated pathogens in acute bacterial otitis externa vary geographically, but most commonly involve *Pseudomonas* and *Staphylococcus aureus*.¹ *Pseudomonas* species are estimated to be responsible for 20%–71.3% of cases.^{2,3} *S. aureus* is thought to be the second most common pathogen in acute bacterial otitis externa, with case series identifying *S. aureus* in up to 40% of cases.^{3–13} Studies from Pakistan, Korea and New Zealand found rates of *S. aureus* AOE above 30%,^{10–12} while the most recent study in the U.S. reported rates of 7.8%.³

Current guidelines for treatment of otitis externa focus on *Pseudomonas* spp. and *S. aureus* because of their high incidence in AOE. Generally, empiric management with topical antibiotics targeting non-resistant strains of these bacteria is recommended.² A 2014 update of the clinical practice guidelines (American Academy of Otolaryngology-Head and Neck Surgery [AAO-HNS]²) identifies topical fluoroquinolones, aminoglycosides, and/or polymyxin B for empiric treatment. While most systematic reviews have found no significant difference in treatment outcomes with antiseptic or different types of antibiotic drops treating AOE, two meta analyses by Rosenfeld et al¹⁴ and Mösgen et al¹⁵ suggest that quinolone drops resulted in higher rates of bacteriologic and clinical cure – defined as the absence of pathogen on follow up and resolution of clinical symptoms. At present, empiric treatment with ototopical antibiotic drops is recommended, unless there is extension of infection outside the ear canal, or the patient has concerning host factors such as immunocompromise or diabetes. In such cases, the inclusion of systemic antibiotics is appropriate.

While sensitive *S. aureus* may be treated similarly to other gram positive bacteria, methicillin-resistant *S. aureus* (MRSA) otitis externa, represents a greater therapeutic challenge.¹⁶ Since their initial detection in the 1960's,

MRSA infections in the U.S. have been typically associated mainly with hospitalized patients.¹⁷ MRSA represents a significant healthcare burden worldwide, as patients with MRSA have more difficult-to-treat infections, associated with longer hospital stays, and a much higher cost-of-care.¹⁸ Another risk factor for MRSA is recent exposure to antibiotics, especially quinolones.^{19,20}

While MRSA remained mainly nosocomial in nature through the 1980's, community-acquired MRSA (CA-MRSA) emerged in the 1990's and has become increasingly common in soft tissue and otolaryngologic infections since.^{16,21,22} In 2002, Hwang et al¹⁶ reported >8.5% increase in CA-MRSA incidence in otologic infections in Taiwan. Similarly, in 2007 a group from Hawaii²¹ noted a rapid increase in CA-MRSA head and neck infections from 21% to 64% over a five-year period.

Despite the rise of MRSA soft tissue infections, few studies have examined contemporary clinical features and incidence patterns of MRSA in AOE. In the UK, an English 2007 study and an Irish 2001 study have reported rates of 0.7% and 6%, respectively.^{6,7} The most recently published work on uncomplicated AOE, a 2012 study from Singapore, reported a MRSA AOE rate of 4.2%.¹³ Studies in South Africa, Pakistan and Korea found no MRSA in AOE cultures, consistent with the low levels of MRSA colonization of their populations.^{8,10,11}

The aim of the current study was to determine contemporary incidence rates, resistance patterns and clinical features of MRSA AOE diagnosed and treated at a quaternary care center in the United States.

Materials and methods

A retrospective chart review was performed on all patients at a quaternary care center with an available otologic culture between January 2014 and April 2016. Inclusion criteria included patients presenting with acute otologic symptoms who were clinically diagnosed with AOE, and who underwent an ear culture. Exclusion criteria included patients presenting with otitis media, chronic otitis externa, primarily non-otologic symptoms, hospitalized patients, and post-operative patients. While all patients presented from the community, some had recent outpatient exposure to antibiotic agents, and a thorough review of their chart

included topical antibiotics used in the affected ear over the preceding 6 months. Other information gathered from the patient chart included demographics, comorbidities, symptomatology, physical exam findings, and otologic outcomes. Comorbidities evaluated included otologic disease (*i.e.*, chronic otitis, existing hearing aid or other prosthesis) and systemic disease (with special attention given to diabetes, immunocompromise, and malignancy).

Bacterial culture findings and antibiotic resistance patterns on included patients were reviewed. Swabs were taken from the site of infection and cultured on various agars, following standard institutional microbiological analysis protocols. Bacterial identification and antibiotic susceptibility testing were performed using the MicroScan WalkAway 40 Plus System (Beckman Coulter).

Statistical analysis of the collected data was performed using Stata statistical software (StataCorp, 2015). Pearson's χ^2 test and unpaired *t*-tests were performed to determine significant associations in the microbial patterns and patient data. A *P* value of <0.05 was considered statistically significant. This study was approved by the Human Subjects Committee of our Institutional Review Board (Protocol #914379).

Results

Patient demographics

From 2014 to 2016, 179 patients had a clinical diagnosis of AOE and available culture data supporting the diagnosis of a bacterial infection. Six patients with concomitant chronic otitis media were excluded from the study. Of the remaining 173 patients, 45.7% (79/173) were male. The mean age was 34.2 ± 23.8 . Adult patients (defined as patients >18 years old) comprised 66% of the study population.

Bacterial isolates in otitis externa

Of the 173 patients, 73 (42.2%) yielded *Pseudomonas aeruginosa* as the primary pathogen identified. *S. aureus* was the second most commonly isolated pathogen (53/173, 30.6%). Of the 53 *S. aureus* isolates, 38 (71.7%) were methicillin-sensitive *S. aureus* (MSSA) and 15 (28.3%) were methicillin-resistant *S. aureus* (MRSA). Thus, 22.0% (38/173) of all AOE patients analyzed were infected with MSSA, and 8.7% (15/173) with MRSA. The next most common species isolated from AOE cases was *Enterococcus faecalis* (5.2%). *Escherichia coli*, *Stenotrophomonas maltophilia*, and *Streptococcus pneumoniae* each were isolated from 2.3% of patients (Table 1).

Comparison of demographics and symptomatology of MSSA and *P. aeruginosa* AOE versus MRSA AOE

The average age of the 38 patients with MSSA was 29.0 ± 19.4 (range 5–74), and 13/38 (34%) were pediatric patients. The average age for the 73 patients with *P. aeruginosa* was 31.2 ± 22.7 (range 1–90), and 28/73 (38%) were pediatric patients. In contrast, the average age of

Table 1 Distribution of isolates in patients diagnosed with acute otitis externa.

Culture isolate	<i>n</i>	Percentage of OE (%)
<i>Pseudomonas aeruginosa</i>	73	42.0
Methicillin-sensitive	38	22.0
<i>Staphylococcus aureus</i>		
Methicillin-resistant	15	8.7
<i>Staphylococcus aureus</i>		
<i>Enterococcus faecalis</i>	9	5.2
<i>Escherichia coli</i>	4	2.3
<i>Stenotrophomonas maltophilia</i>	4	2.3
<i>S. pneumoniae</i>	4	2.3
Coagulase negative	4	2.3
<i>Staphylococcus</i> species		
<i>Staphylococcus epidermidis</i>	4	2.3
<i>Serratia marcescens</i>	3	1.7
<i>Achromobacter xylosoxidans</i>	2	1.1
<i>Citrobacter koseri</i>	2	1.1
<i>Acinetobacter</i>	1	0.6
<i>baumannii/haemolyticus</i>		
<i>Actinomyces odontolyticus</i>	1	0.6
<i>Alcaligenes</i> species	1	0.6
<i>Enterobacter aerogenes</i>	1	0.6
<i>Enterococcus casseliflavus</i>	1	0.6
<i>Haemophilus influenzae</i>	1	0.6
<i>Klebsiella oxytoca</i>	1	0.6
<i>Proteus mirabilis</i>	1	0.6
<i>Pseudomonas stutzeri</i>	1	0.6
Resembles <i>Aspergillus</i> species	1	0.6
<i>Staphylococcus warneri</i>	1	0.6
<i>Streptococcus</i> group G	1	0.6

patients with MRSA was 47.7 ± 17.9 (range 13–68), and included only one pediatric patient. Of patients with MSSA, 36% were male (Table 2), whereas there was a slight male predominance (54%) among MRSA AOE cases.

The average number of comorbidities (defined as systemic chronic conditions at the time of culture) for AOE associated with MRSA was 4 (range 0–12), which was significantly higher than for MSSA patients at 0.8 (range 0–3), $P < 0.01$ and *P. aeruginosa* patients at 1 (range 0–2), $P < 0.01$. Of 15 AOE patients with MRSA, one was diabetic and two were immunocompromised. No patient with MSSA had either diabetes or was immunocompromised.

All three groups of AOE patients presented with similar symptoms (Table 3). The most common symptoms were otorrhea, otalgia, swelling, and hearing loss/blocked ear. Swelling was more common in MRSA associated cases (33.3%) compared MSSA cases (5.3%, $P = 0.01$). and *P. aeruginosa* cases (19.2%, $P = 0.2$). Patients with *Pseudomonas* were more likely to present with otalgia than MRSA patients (83.6% vs 60.0%, $P = 0.04$). Data on time to resolution of symptoms was available for only a subset of patients who had several follow up visits. Mean time to resolution was calculated from the point in the clinical history at which the patient reported no longer being symptomatic. Resolution of symptoms appeared to take

Table 2 Demographics presentation, and previous exposure to antibiotic drops of *S. aureus* acute otitis externa infections. Nine out of 11 patients with MRSA exposed to otic drops were exposed to quinolone drops. **Significantly different from MRSA.

Group	Average age (y)	Sex	Average number of comorbidities	Average time to resolution of symptoms (days)	Previous exposure to otic drops
MRSA	46.7 (13–68; 1 pedi patient)	54% M; 46% F	4 (0–12)	21.5 (3–42; data available for $n = 6$)	11 (73%)
MSSA	29.0 (5–74; 13 pedi patients, $P < 0.01$)**	36% M; 64% F	1.7 (0–6, $P < 0.01$)**	11.2 (1–42)	14 (37%, $P = 0.019$)**
<i>P. aeruginosa</i>	31.2 (1–90; 28 pedi patients, $P = 0.014$)**	46.6% M; 53.4% F	1 (0–2, $P < 0.01$)**	15 (2–56, $P = 0.04$)**	35 (48%)

Table 3 Symptoms of *S. aureus* acute otitis externa infections. * $P < 0.05$; **Significantly different from MRSA.

Group	n	Otorrhea cases (%)	Otalgia cases (%)	Swelling* cases (%)	Hearing loss cases (%)
MRSA	15	9 (60.0)	9 (60.0)	5 (33.3)	4 (26.7)
MSSA	38	23 (60.5)	19 (50.0)	2 (5.3)**($P < 0.01$)	5 (13.2)
<i>P. aeruginosa</i>	73	47 (64.3)	61 (83.6%)** ($P = 0.04$)	14 (19.2)	23 (31.5)

Table 4 Proportion of *S. aureus* isolates resistant to listed antibiotics. NA: Not applicable. * $P < 0.05$.

Antibiotic	MRSA Number (%) of specimens showing resistance to antibiotic	MSSA Number (%) of specimens showing resistance to antibiotic	P value
Amikacin	13 (100)	1 (100)	NS
Amoxicillin/Clavulanate	NA	22 (100)	NA
Ampicillin	NA	5 (71.4)	NA
Clindamycin	0 (0)	7 (18.4)	0.51
Daptomycin	0 (0)	0 (0)	NS
Erythromycin*	12 (80)	9 (25.7)	<0.001
Gentamicin	1 (6.67)	0 (0)	0.11
Levofloxacin*	5 (33.3)	2 (5.26)	0.007
Linezolid	0 (0)	0 (0)	NA
Penicillin*	NA	28 (73.68)	NA
Tetracycline	1 (6.67)	2 (5.4)	0.51
Trimethoprim/sulfamethoxazole	1 (6.67)	1 (2.7)	0.86
Vancomycin	0 (0)	0 (0)	NA

longer in MRSA infected patients (21.5 days) than in patients with *P. aeruginosa* (15 days) and patients with MSSA (11.2 days). The difference in resolution of symptoms was statistically significant for *P. aeruginosa* versus MRSA patients ($P = 0.04$). Due the smaller numbers of MSSA patients included, the difference between MRSA and MSSA patients did not achieve significance ($P = 0.11$).

Antibiotic sensitivities

MRSA isolates were significantly more likely ($P < 0.05$) than MSSA isolates to be resistant to multiple antibiotics, including erythromycin and levofloxacin. Both groups

exhibited high proportions of resistance to amikacin (Table 4).

A sub-analysis of AOE patients with prior exposure to otic antibiotic drops (ciprofloxacin, ofloxacin, tobramycin, neomycin, gentamicin) was performed. Of 53 total patients infected with *S. aureus*, 25 (47.1%) had a prior history of antibiotic otic drops within the past 6 months. Of those using drops, 11 were infected with MRSA (73.3% of MRSA isolates) and 14 were infected with MSSA (36.8% of MSSA isolates, Table 2). The most common exposure was to quinolone drops, in 9 out of 11 previously exposed patients with MRSA isolates. This was significantly different from patients with MSSA, in which 8 out of 14 previously exposed patients had been exposed to quinolone drops ($P = 0.019$).

Discussion

In the current study, we found *S. aureus* as the likely pathogen of AOE in 30.6% of cases, which is higher than previously reported in the U.S., which found a rate of 7.8%.³ This difference could be reflective of changing population demographics and/or changes in the nature of strains of *S. aureus* occurring in the community. Local modifications in the external ear microbial population may also result from the selective pressure imposed by empirical antibiotic treatment. As the likely causative agent of 1 in 3 AOE cases, *S. aureus* should be factored into antimicrobial coverage decisions on initiation of empiric treatment.

Among patients with *S. aureus* otitis externa, we identified MRSA in 8.7% of cases – over three times the last reported U.S. rate, from 2002³ (Table 5). Because the incidence of MRSA in soft tissue infection is reflective of carriage rate in the population, understanding our evolving microbial carriage patterns is critically important. The last large scale study on the microbiology of AOE in the U.S. by Roland et al³ was reported over 15 years ago. Our search of the literature yielded only one other U.S. study examining the epidemiology of MRSA otitis: a 2014 study from Pittsburgh Medical Center, which reported an MRSA rate of 15% among malignant otitis externa cases caused by *S. aureus*.⁴ These findings may indicate that MRSA AOE, when not identified and treated early, may more frequently result in advanced disease and complications.

While little is known about MRSA in AOE, increasing rates of MRSA in soft tissue infections²¹ and in otolaryngology,^{16,22} are well-documented. The increased incidence observed in our study, when compared to the earlier findings of Roland et al³ appear to be consistent with the global trend of increasing prevalence of community-acquired MRSA carriage¹⁸ and infection^{17,22} over the past 20 years.

In general, we found that MRSA AOE presented with a spectrum of symptoms similar to infections caused by MSSA, but was more likely to be associated with significant ($P = 0.006$) ear canal swelling. Rapid onset, severe swelling, tenderness and erythema have been observed before in MRSA head and neck infections, and, when encountered, should raise the index of suspicion of MRSA otitis for the clinician.²² Patients with MRSA tended to experience a longer time to resolution of symptoms. MRSA AOE tended to be associated with diabetes, immunocompromise and comorbidities to a greater degree than MSSA.

In fact, the only case of malignant otitis externa among this cohort was a patient with MRSA AOE. Because of the potential for extended-duration, more severe infection, care providers should consider MRSA AOE when a patient presents and fails to improve quickly with empiric treatment.

We also found that patients with MRSA had a higher exposure to previous otological drops than did patients with MSSA AOE. In fact, 73% of patients with MRSA had been exposed to otic drops in the past 6 months, and of these, most had been exposed to quinolone drops. Exposure to prior otological drops may select for resistant organisms, allowing them to become the primary pathogen during an episode of AOE. The ophthalmology literature studying the use of quinolone drops on corneal ulcers has demonstrated a significant increase in resistant organisms after the use of fluoroquinolone drops.²³ Similarly, a higher level of nasal MRSA colonization has been found in patients exposed to fluoroquinolones.²⁴ Other work by Venezia et al²⁰ has shown a mechanistic link between quinolone usage and selection for oxacillin-resistant organisms, and concluded that exposure to fluoroquinolones greatly increases the likelihood of developing MRSA, even in as short a period as 8 h after exposure. A 2004 meta-analysis of otologic infections,²⁵ concluded that empiric antibiotic drops were unlikely to be associated with the development of resistant organisms. However, this study was limited by very small sample size (2 patients with OE), and is now over 10 years old. It is possible that the microbiologic landscape has changed significantly in intervening years. Larger, contemporary studies in OE should be performed to better understand the relationship between empiric antibiotic therapy and the rise in MRSA infections.

Notwithstanding the effects of quinolones in selecting for MRSA, the fact that in our study almost 1 in 10 patients with AOE had MRSA highlights the importance of adequate treatment and close follow up of the disease. MRSA is a known cause of chronic otitis media (COM) and chronic otorrhea, and clinical algorithms focused on topical vancomycin therapy have been developed to guide clinicians in treating those cases.²⁶ No such algorithm exists for MRSA in otitis externa. However, clinical guidelines on antibiotic use in otolaryngology currently recommend using vancomycin drops in ears affected by MRSA,²⁷ and practitioners should follow this for AOE. At our institution, once external auditory infection with MRSA is confirmed via culture, vancomycin drops (25 mg/ml) twice daily or tobramycin drops (13.6 mg/ml) three times daily for ten days are

Table 5 The prevalence of *S. aureus* acute otitis externa in this study compared to existing studies.

	Year published	Location	Type of institution	Years of data collection	MRSA AOE	MSSA AOE
Duarte et al	2017	United States	Tertiary	2014–2016	8.7% ($n = 15$)	22.0% ($n = 38$)
Roland et al	2002	United States	Various	1998–2000	2.70% ($n = 6$)	7.80% ($n = 215$)
Roland et al	2007	United Kingdom	Tertiary	2006	0.70% ($n = 1$)	9% ($n = 13$)
Walshe et al	2001	Ireland	Primary	2000	6% ($n = 15$)	23.80% ($n = 57$)
Meyer et al	2013	South Africa	Tertiary	2005–2009	0	24% ($n = 5$)
Cheong et al	2012	Singapore	Tertiary	2010–2011	4.20% ($n = 2$)	21% ($n = 16$)
Arshad et al	2004	Pakistan	Primary	2002–2003	0	38% ($n = 41$)
Kim et al	2016	Korea	Tertiary	1995, 2000, 2004, 2013	0	36% ($n = 63$)
Jayakar et al	2014	New Zealand	Various	2007–2011	0	31.90% ($n = 46$)

prescribed, and the patient is followed closely with serial exams. Based on our institution’s guidelines and the data available for MRSA COM, we propose a modified clinical algorithm for AOE that includes consideration of MRSA infections and the implementation of otologic cultures at the point where the current guidelines recommend re-assessing patients who are not improving with standard antibiotic therapy (Fig. 1, modified from the 2014 AAO-HNS clinical practice guidelines). Given the increasing prevalence of MRSA in AOE in this study and in otolaryngologic infections

worldwide, robust trials elucidating the optimal topical antibiotic regimen (vancomycin or otherwise) may be warranted.

This study is limited to only one geographic region in the U.S. (New England), and to patients presenting to our institution who had otologic cultures. While primary cultures are routinely taken on patients presenting to our institution, this practice is not uniform and cultures were not obtained on all patients presenting with AOE. Additionally, many patients with AOE are diagnosed and treated

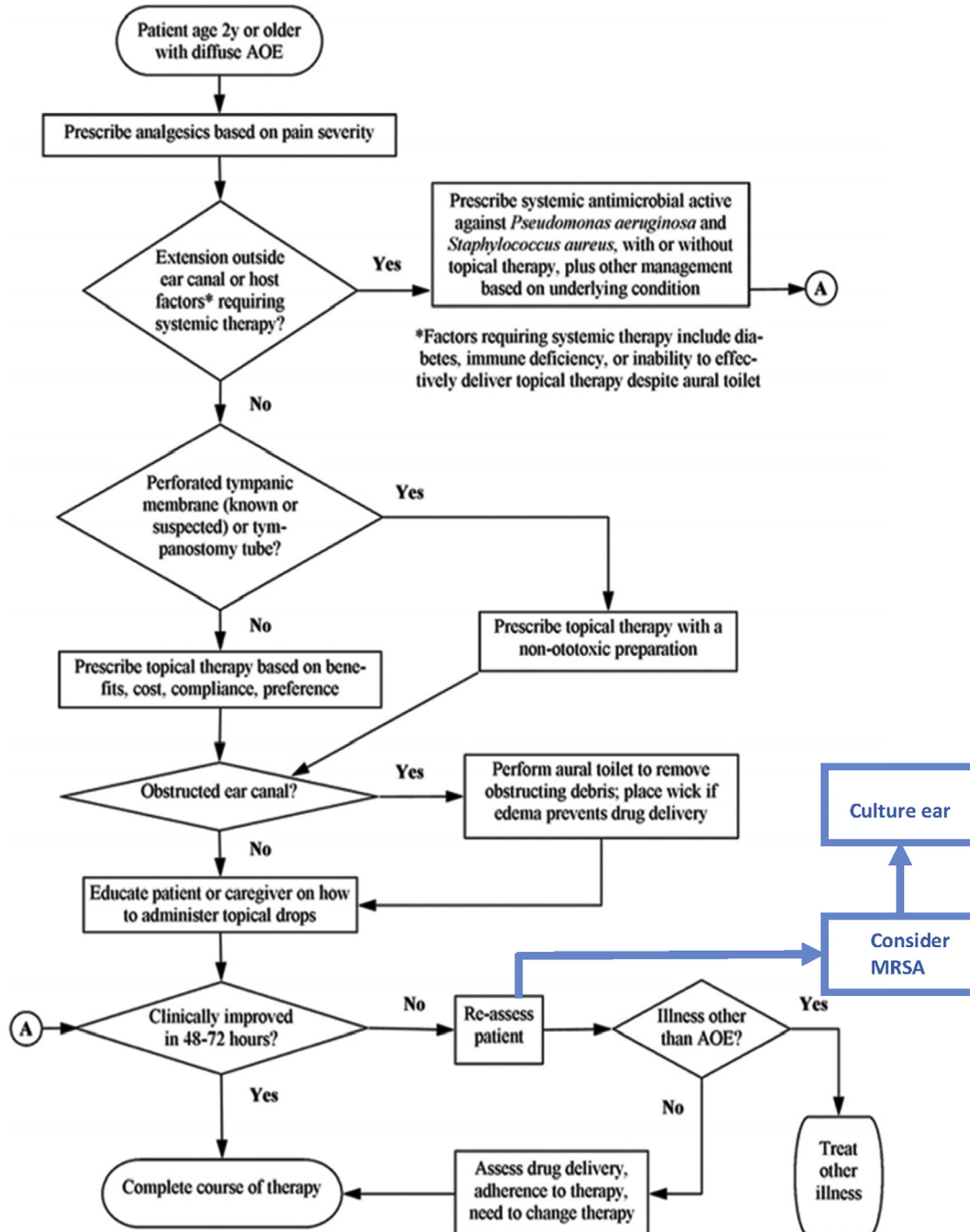


Fig. 1 Clinical treatment algorithm for otitis externa. In Black: Current treatment algorithm for treating acute otitis externa, from the 2014 Clinical Practice Guideline on Acute Otitis Externa, published by the American Academy of Otolaryngology and Head and Neck Surgery. In Blue: Proposed modified AAO-HNS algorithm: if there is no clinical improvement with empiric treatment after 72 h, reassess patient and consider MRSA as a potential source of infection.

clinically by primary care physicians and do not reach our institution for culture, follow up and inclusion in this study. While we focused our analysis on bacterial AOE, and not OE of a fungal etiology, these patients represented a small minority of patients with AOE (Table 1). The review was retrospective, thus some data was incomplete and may be subject to selection bias. In addition, this study was performed in a quaternary care center, which serves as a referral site for community physicians. It is possible that patients were exposed to unknown antibiotic treatment before presentation, and that follow up with community physicians inadequately captured the patient's entire course of disease.

Conclusion

Contemporary ear culture isolates at quaternary care center show higher rates of MRSA compared to historical reports in the literature. Clinicians should consider ear cultures to identify MRSA AOE.

Conflicts of interest

None.

Disclosures

None.

External sources of funding

None.

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