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Treatment of Multi-Drug Resistant Microorganisms in Chronic Suppurative Otitis Media

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ABSTRACT

Objective: The aim of the study was to investigate the bacterial profile of patients who have resistant otorrhea despite the administration of topical antibiotics, antiseptics, and ear cleaning (aural toilet) and to discuss the topical and systemic therapy used for the eradication of treatment-resistant bacteria.

Methods: A swab culture was obtained from the external ear canal in 544 patients with resistant otorrhea. All bacterial isolates were identified by conventional microbiological methods. Multidrug-resistant microorganisms were identified, and a systemic or topical antibiotic therapy was initiated based on the culture results.

Results: *Pseudomonas aeruginosa* was the most commonly isolated pathogen (n=128; 24%), followed by *Staphylococcus aureus* (n=98; 18%). Since otorrhea could not be resolved with outpatient treatment, broad-spectrum antibiotics were applied in 54 (4%) of 1290 patients, 54% of whom were infected with *P. aeruginosa*. Recovery time was similar in intravenous treatment and topical piperacillin/tazobactam treatment in patients with ear discharge and multidrug-resistant *P. aeruginosa* infection ($P = .82$).

Conclusion: In medical treatment of chronic suppurative otitis media, obtaining a dry ear can be highly difficult in some patients. Antibiotic resistance was relatively greater in gram-negative bacteria. In particular, multidrug-resistant *P. aeruginosa* can remain unresponsive to treatment. Data from future prospective studies and clinical trials may provide useful information on the results of topical piperacillin/tazobactam treatment in patients with chronic suppurative otitis media caused by multidrug-resistant *P. aeruginosa* infections to further improve clinical practice and off-label prescribing decisions.

Introduction

The goals of chronic suppurative otitis media (CSOM) treatment are to eradicate infection, prevent complications, restore the eardrum, and improve hearing. Inactive chronic otitis media (COM) includes no active inflammation or suppuration of the eardrum, and thus, it is referred to as dry. In contrast, active COM includes an active inflammation in the middle ear and is characterized by a mucopurulent discharge defined as wet.[1]

Bacterial inflammation is a leading etiological factor for the development of active COM, which is mostly caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Bacterial eradication is mandatory for the prevention of this inflammation. Of note, the importance of bacteria that can cause treatment difficulties and clinical unresponsiveness by forming antibiotic resistance is gradually increasing in the development of active COM.[2] Accordingly, the severity of the disease may increase in proportion to the resistance of a pathogen to antibiotics. Multidrug-resistance (MDR) is defined as acquired non-susceptibility to at least 3 different classes of antibiotics, namely carbapenems, penicillins, cephalosporins, aminoglycosides, and quinolones.[3-5] Bacterial strains such as *P. aeruginosa* and *S. aureus* can rapidly develop resistance to antimicrobial agents and may cause problems in the treatment of patients with CSOM. For this reason, the assessment of the susceptibility of bacteria to the commonly used antibiotics is highly important.[4-6]

Topical antibiotherapy and topical steroids are often used with topical antiseptics to obtain a dry ear before ear surgery. However, sometimes a dry ear cavity cannot be obtained by the use of topical ear drops (ciprofloxacin, ofloxacin, gentamicin, and dexamethasone). The aim of this study was to investigate the bacterial profile of patients who have resistant otorrhea despite the administration of topical antibiotics,

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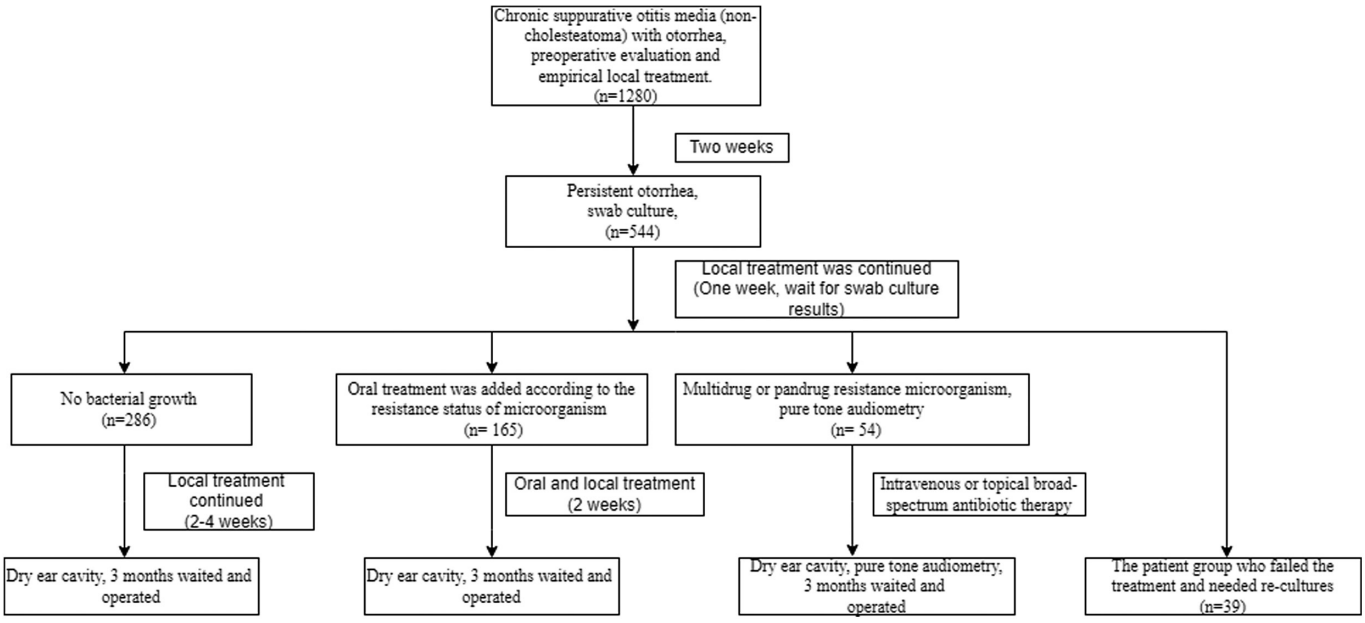

Figure 1. Study flow diagram.

antiseptics, and ear cleaning (aural toilet) and to discuss the topical and systemic therapy used for the eradication of treatment-resistant MDR bacteria.

Methods

The study evaluated 1290 patients who were diagnosed with non-cholesteatoma-active CSOM in our tertiary referral center between January 2015 and February 2021. The diagnosis of CSOM was made based on the presence of a perforated tympanic membrane and otorrhea lasting more than 3 months. Patients were prepared for surgery to obtain a dry middle ear cavity and those who were operated on 3 months after obtaining a dry middle ear cavity were included in the study. Exclusion criteria were as follows: (i) a diagnosis of cholesteatoma, (ii) prior middle ear surgery, and (iii) immunosuppressive (uncontrolled diabetes, chemotherapy) conditions. During their first admission, all the patients were examined for otorrhea and were initiated on empirical treatment. Following the aspiration of ear discharge, patients were prescribed ear drops containing dexamethasone (Onadron simple 0.1% eye ear drops®, İ.E Ulugay®) and ciprofloxacin (Siprogut 0.3% ear drops®, Bilim Pharmaceuticals, Istanbul, Turkey) (3 drops 3 times a day) and 3% boric acid solution (3 drops 3 times a day). They were also recommended to keep their ears as dry as possible. After topical treatment, patients were re-evaluated at the end of the second week. If otorrhea persisted, topical treatment was administered again and a swab culture was obtained from the external ear canal. Patients who were detected with resistant otorrhea at the end of the third week were accepted as having resistant CSOM. An additional systemic or local treatment was initiated in the patients based on the culture results (Figure 1).

After cleaning the auricle and external ear canal with an alcohol wipe, swab samples were obtained from the external ear canal, at a location closest to the eardrum. Samples were embedded in Stuart Transport Medium (Oxoid, Hampshire, UK) and stored under appropriate storage conditions (24 hours, +4 °C). Samples were then incubated for 18-24 hours at 36.5-37°C under aerobic conditions. For bacteriological examination, cultures were inoculated into blood agar, chocolate agar, and eosin methylene blue agar and the samples with suspected fungal growth were inoculated into 2 separate sabouraud dextrose agar. The results were evaluated in our microbiology laboratory according to the results of VITEK 2 antibiogram device (BioMérieux, Marcy-l'Etoile, France) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) diagnostic criteria. Colonies isolated from the samples were identified with the Phoenix 100 ID/AST system (Becton Dickinson, Sparks, MD, USA). Antibacterial sensitivities were studied in accordance with the Clinical and Laboratory Standards Institute criteria and the EUCAST Standards defined in January 2015. Minimum inhibitory concentrations (MICs) were determined using MIC test strips. Appropriate antibiotic therapies were initiated in patients with resistant otorrhea according to culture and MIC results.

Topical and/or systemic antibiotic therapies were administered in line with the recommendation of the infectious diseases department. Clinical improvement was evaluated based on both subjective and objective criteria. Subjective criteria consisted of pain, itching, otorrhea, and hearing loss, and objective criteria included complete recovery of edema, erythema,

Main Points

- Occasionally, bacteria with multidrug resistance may require intravenous broad-spectrum antibiotic therapy.
- There has been a widespread increase in the prevalence of multidrug-resistant *Pseudomonas aeruginosa* infection.
- In this study, patients with otorrhea caused by multidrug-resistant *P. aeruginosa* as a result of chronic suppurative otitis media were treated with piperacillin–tazobactam drops.
- Similar outcomes were obtained between the groups treated with topical piperacillin–tazobactam and intravenous piperacillin–tazobactam.

debris and discharge in the external auditory canal as confirmed by otoscopic examination and improvement in hearing test. After 3 months of follow-up, clinical success was defined as non-recurrence of otorrhea and improvement of the clinical condition of the middle ear. After obtaining a dry ear cavity, patients who had recurrent otorrhea during the 3-month waiting period were assigned to a different group due to the growth of different microorganisms and the emergence of different resistance states. Prior to antibiotic therapy, pure tone audiometry was performed at the time of first admission after obtaining a dry ear. Audiological data were calculated based on the data obtained by pure tone audiometry. Audiograms were obtained both before and after treatment. Air conduction thresholds were routinely measured at 0.5, 1, 2, 3, 4 kHz, and the bone conduction thresholds were measured at 0.5, 1, 2, 3, and 4 kHz with adequate masking. The study was approved by Ethics Committee of Van Research and Training Center (Date: August 1, 2019; No. 2019-15), and an informed consent was obtained from each patient prior to the study.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences for Windows version 26.0 (IBM Corp., Armonk, NY, USA). Descriptives were expressed as mean ± standard deviation (SD) for continuous variables and as frequencies (n) and percentages (%) for categorical variables. The activity types of the drugs according to the pathogen types were summarized using cross-tabulations. Variables were compared using chi-square analysis. Differences among the groups with regard to clinical improvement were compared using Mann–Whitney *U* test. A *P* value of <.05 was considered significant.

Results

Of the 1290 patients evaluated, 544 patients were detected with resistant otorrhea at the second outpatient visit and were included in the study.

These 544 patients comprised 290 (53%) women and 254 (47%) men with a mean age of 32.4 ± 15.6 (range, 5-84) years.

In the swab culture, bacterial growth was detected in 258 (47%) and no bacterial growth was detected in 286 (53%) patients. *P. aeruginosa* was the most commonly isolated pathogen (n=128; 24%), followed by *S. aureus* (n=98; 18%), *Aspergillus* spp. (n=18; 3%), *Escherichia coli* (n=17; 3%), and *Proteus mirabilis* (n=17; 3%). Of all patients, 12 were detected with multiple bacteria, 14 patients had bacterial and fungal growth, and 26 (7.9%) patients had mixed-type bacterial growth. At the second outpatient visit, an additional oral antibiotic therapy or intravenous (IV) treatment was initiated based on the culture results. The topical treatment was continued in the same way in patients with no bacterial growth. In 54 (4.1%) out of 1290 patients, a broad-spectrum IV antibiotic therapy was initiated due to uncontrollable otorrhea. Of the 544 patients, more than 1 culture was obtained from 39 patients and these patients underwent different treatment modalities depending on their culture results. After obtaining a dry ear cavity and planning the surgery for the patient, he/she could not protect his/her ear and thus required retreatment.

The *P. aeruginosa* strains grown in ear cultures were most susceptible to colistin (75%) and piperacillin/tazobactam (66%) and were most resistant to ciprofloxacin (66%) and cefepime (58%) (Figure 2). In patients (n=128; 24%) with resistant *P. aeruginosa* infections, the initial ciprofloxacin therapy failed and thus no additional ofloxacin therapy was attempted. In those patients, oral antibiotics were administered along with aural toilet, boric acid, and dexamethasone (trimethoprim and sulfamethoxazole, amoxicillin and clavulanic acid, or amoxicillin, rifampin, levofloxacin, clindamycin, linezolid, doxycycline, azithromycin, or penicillin alone). In total, 70 patients improved with additional oral antibiotherapy. In 37 patients, IV antibiotic therapy along with daily aural toilet, boric acid, and dexamethasone (3 drops 3 times a day) was administered due to the presence of MDR in culture. One patient was treated with ertapenem, 2 patients with cefepime, 3 patients with meropenem, 4 patients with imipenem, 6 patients with colistin, and 11 patients were treated with piperacillin/tazobactam intravenously until a dry ear was obtained. These patients recovered in 10 ± 2.1 days. In 10 other patients, an alternative therapy

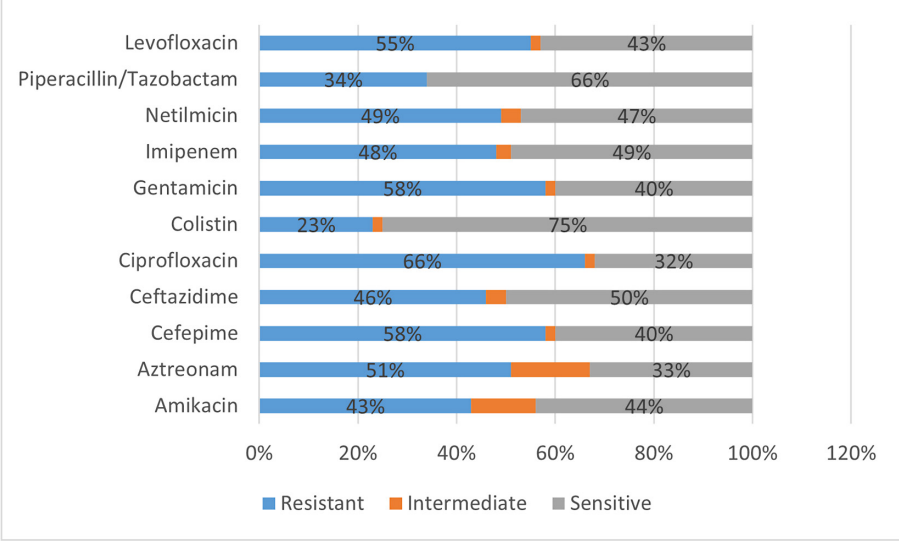

Figure 2. Antibiotic resistance rates of Pseudomonas aeruginosa in the first culture.

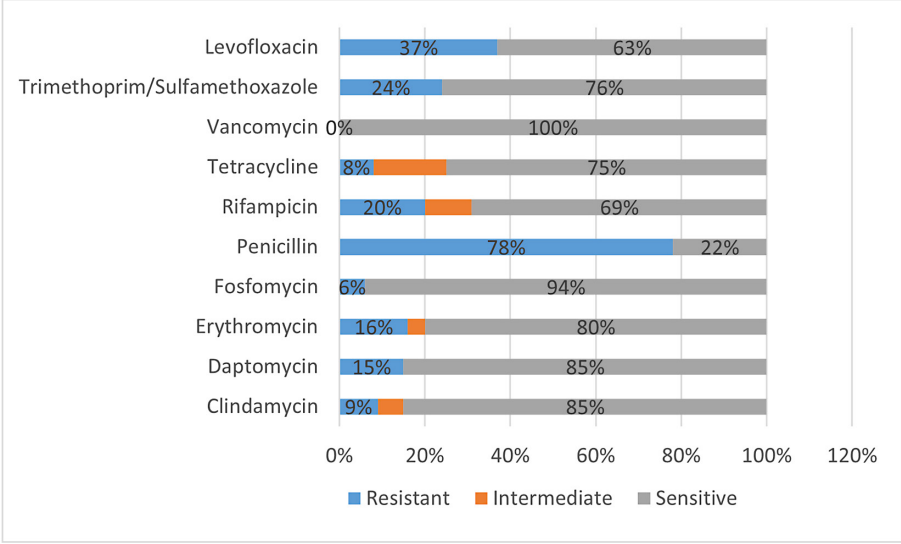

Figure 3. Antibiotic resistance rates of Staphylococcus aureus in the first culture.

(topical piperacillin/tazobactam) was administered since the patients did not accept to undergo long-term IV treatment. The piperacillin/tazobactam solution was prepared by dissolving 4.5 g of piperacillin/tazobactam powder in 20 mL of sterile distilled water to obtain a working solution with a concentration of 225 mg/mL. The solution was administered at a dose of 3 drops 3 times a day (total daily dose = 101 mg). After instillation, patients were asked to remain in the same position for 10 minutes to facilitate penetration of the drops into the ear canal. Patients who received IV piperacillin/tazobactam only recovered in 9.8 ± 3.1 days and patients who received topical piperacillin/tazobactam recovered in 9.5 ± 1.2 days. However, no significant difference was found between these 2 patient groups with regard to time to recovery ($P = .82$).

The *S. aureus* strains grown in ear cultures were most susceptible to vancomycin (100%) and were most resistant to penicillin (78%) (Figure 3). Ten out of 98 cultures with *S. aureus* were detected with methicillin-resistant *S. aureus* (MRSA), which had a prevalence of 2.1% MRSA among all isolated microorganisms. Topical vancomycin therapy was administered in patients with MRSA. The vancomycin solution was prepared by dissolving 500 mg of vancomycin powder in 20 mL of sterile distilled water to obtain a working solution with a concentration of 25 mg/mL. The solution was administered at a dose of 3 drops 3 times a day (total daily dose, 11.25 mg). The patients recovered in 9.9 ± 1.7 days.

The *E. coli* strains grown in ear cultures were most susceptible to colistin, imipenem, and ertapenem (88%) and were most resistant to ceftazidime (82%), cefepime (82%), and ciprofloxacin (77%) (Figure 4). In a patient with *Klebsiella pneumoniae* carbapenemase resistance, IV piperacillin/tazobactam was administered due to the growth of *E. coli* and resistant otorrhea. Ertapenem was administered in 3 patients with extended-spectrum beta lactamase (ESBL) resistance.

One patient with pandrug resistance (PDR) showed resistance to all antibiotics and was detected both *Serratia marcescens* and *Enterobacter cloacae*. The patient was treated with

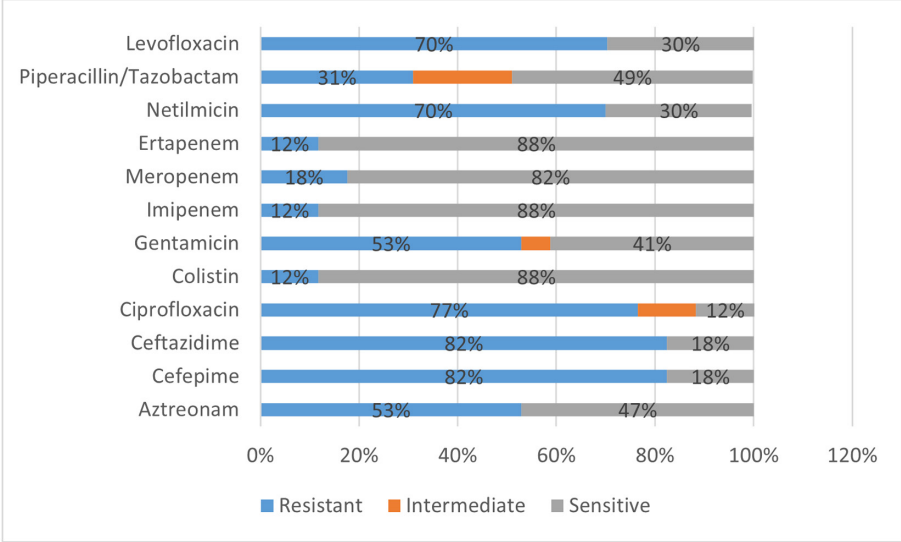

Figure 4. Antibiotic resistance rates of Escherichia coli in the first culture.

Table 1. Pathogens Isolated in the First Cultures

	No of Isolated, n	Intravenous Antibiotherapy, n	Oral and Topical, n	Topical Broad-Spectrum Antibiotherapy, n	The Patient Group Who Failed the Treatment and Needed Re-culture n
Pseudomonas aeruginosa	128	27 (MDR)	70	10 (MDR)	21
Staphylococcus aureus	98	-	70	10 (MRSA)	18
Aspergillus spp.	18	-	-	-	-
Escherichia coli	17	3 (ESBL), 1 (KPC)	13	-	-
Proteus mirabilis	17	1 (MDR)	16	-	-
Candida spp.	15	-	-	-	-
Klebsiella spp.	10	1	9	-	-
Enterobacter cloacae	5	1 (PDR), 1 (MDR)	3	-	-
Serratia marcescens	2	1 (PDR)	1	-	-
Other	12	-	12	-	-

MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; PDR, pandrug resistance; other, *Acinetobacter baumannii*, *Alcaligenes faecalis*, *Cedecea lapagei*, *Citrobacter freundii*, *Citrobacter koseri*, *Enterococcus avium*, *Morganella morganii*, *Providencia rettgeri*, *Serratia liquefaciens*, *Streptococcus pyogenes*.

tigecycline IV since the patient was resistant to all antibiotics except for tigecycline. Another patient who was detected with *P. mirabilis* was administered meropenem IV due to high resistance to commonly used antibiotics. In 1 patient who had MDR and was detected with *E. cloacae*, the otorrhea resolved after the administration of piperacillin/tazobactam IV. In another patient who had MDR and was detected with *K. pneumoniae*, ertapenem therapy was administered. Table 1 presents the treatments administered and the microorganisms isolated in the patients. In pure tone audiometry, no ototoxic symptoms or hearing loss was observed in any patient after treatment. Table 2 presents pre- and post-treatment pure tone hearing levels. During the administration of IV antibiotic therapies, an increase was observed in some parameters of liver function tests and kidney function tests in some patients; however, no liver and kidney failure occurred in any patient. No hearing loss, tinnitus, or vertigo was observed in any patient who received topical or IV antibiotic therapy.

Discussion

In patients with active CSOM, alternative methods should be considered when otorrhea cannot be treated by topical therapies. Systemic antibiotics are a second-line treatment for CSOM. There are numerous factors affecting drug efficacy in chronic disease, including bioavailability, organism resistance, scarring of middle ear tissues, and decreased vascularization of middle ear mucosa. Systemic therapy has not been as efficacious as direct administration of topical antibiotics due to the inability to achieve effective concentrations in the infected tissues of the middle ear.[7]

Topical application has the advantage of delivering high concentrations of antibiotics to the potentially affected area

Table 2. Pre- and Post-treatment Pure Tone Hearing Levels

		Pre-treatment				Post-treatment			
		500 Hz	1000 Hz	2000 Hz	4000 Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz
Intravenous treatment	**Bone conduction**	20 ± 15	20 ± 14	22 ± 17	20 ± 17	22 ± 16	20 ± 16	24 ± 18	20 ± 20
	Air conduction	47 ± 24	47 ± 24	44 ± 26	47 ± 26	47 ± 29	47 ± 29	44 ± 30	50 ± 30
Topical vancomycin	**Bone conduction**	16 ± 11	15 ± 9	19 ± 11	14 ± 8	17 ± 9	16 ± 9	18 ± 10	16 ± 14
	Air conduction	59 ± 28	55 ± 19	49 ± 12	50 ± 15	48 ± 24	48 ± 24	40 ± 15	46 ± 23
Topical piperacillin/tazobactam	**Bone conduction**	26 ± 21	28 ± 23	33 ± 24	31 ± 24	27 ± 22	27 ± 25	34 ± 24	30 ± 26
	Air conduction	51 ± 28	59 ± 28	58 ± 27	62 ± 29	59 ± 31	59 ± 31	57 ± 29	61 ± 28

(100-1000 times more), whereas systemic antibiotics are absorbed and distributed throughout the body.[8,9] However, in some patients, systemic treatment can be performed due to lack of response to topical treatment.[7] Aminoglycosides and quinolones are the 2 groups of licensed antibiotics used in topical treatment of CSOM. Literature has shown that topical quinolones are equal to or more effective than aminoglycosides and also have less potential ototoxic effects.[10] Although topical applications of broad-spectrum antibiotics are not approved by the Food and Drug Administration, they are used by clinicians in some clinical cases. The use of topical vancomycin in resistant MRSA infections in CSOM has been practiced in some centers since 2004. Although intravitreal or intraabdominal applications of topical piperacillin/tazobactam are available in the literature, its topical applications for the ear has never been reported.[11,12]

P. aeruginosa and *S. aureus* are the most common aerobic microbial isolates in CSOM patients.[13] In a study of 289 patients with CSOM, *S. aureus* was the most dominant microorganism (44.9%), followed by *P. aeruginosa* (16.9%).[14] In another study, *P. aeruginosa* was the most common isolate (57.6%), followed by *S. aureus* (16.5%).[15] Similarly, Orji and Dike[16] reported that *P. aeruginosa* was the most common isolate (44%) followed by *S. aureus* (17%) and *P. mirabilis* (15%). In addition, in studies conducted in Angola and Malawi, *Proteus* spp. strains were the most dominant microorganisms.[17,18] Although the rates of *P. aeruginosa*, *S. aureus*, and other bacteria isolated in our study were similar to those of some studies in the literature, different rates of bacterial isolation were observed, which could be attributed to sample size and geographical differences.

P. aeruginosa readily exploits the middle ear environment and is difficult to eradicate. *P. aeruginosa* is naturally resistant to many antibiotics (antistaphylococcal penicillins, amoxicillin-clavulanate, and cephalosporins) and shows high resistance to other antibiotic groups. Beta-lactamase production, reduced membrane permeability for the drug, and active pumping systems are among the mechanisms of drug resistance that play a role in the production of a high level of resistance.[19] Quinolones are particularly effective against *P. aeruginosa* and do not have potential side effects such as cochleotoxicity and vestibulotoxicity. However, management of *P. aeruginosa* strains that are resistant to fluoroquinolones may be difficult since there is a limited choice of effective topical and oral antibiotics. Noonan et al[20] used non-ciprofloxacin ear drops (tobramycin, neomycin, and polymyxin B sulfates) with hydrocortisone and gentamicin otic or ophthalmic suspensions in ciprofloxacin-resistant microorganisms in addition to oral antibiotic therapy and achieved a 70% cure rate. The authors found that ciprofloxacin otic suspension had no significant effect in the treatment of ciprofloxacin-resistant bacteria and also noted that the potentially high concentrations achieved with the administration of topical ciprofloxacin in vivo were not sufficient to overcome antibiotic resistance. These findings support the need for obtaining culture samples and using adjunctive or alternative therapy for resistant infections. In another study, broad-spectrum antibiotic therapy and topical therapy were administered for the eradication of ciprofloxacin-resistant *P. aeruginosa* in 88 of 231 patients, among whom 49 patients were treated with self-prepared topical amikacin ear drops for 7 days and intramuscular amikacin for 5-7 days, 29 patients were treated with imipenem IV for 5-7 days, 9 patients were treated with piperacillin/tazobactam IV, and 1 patient was treated with aztreonam IV.[21] Cavel et al[22] administered ceftazidime, meropenem, piperacillin/tazobactam IV against ciprofloxacin-resistant *P. aeruginosa* in 11 ears of 8 patients and could not obtain a dry ear cavity in any patient despite the administration of extensive topical and IV therapy. In our study, *P. aeruginosa* showed a higher antibiotic resistance compared to other microorganisms. In such patients, we administered a broad-spectrum systemic antibiotic therapy and obtained a dry ear. In an animal study, Jang et al evaluated albino guinea pigs treated with topical piperacillin/tazobactam using the auditory brainstem response (ABR) test and electron microscopy and reported that topical piperacillin/tazobactam did not affect the ABR threshold before and after treatment. The authors also noted that electron microscopy revealed almost normal stereociliary arrangements and surface structure on the inner and outer hair cells. Based on these outcomes, the authors suggested that fortified piperacillin/tazobactam solution could be effective in topical treatment of ciprofloxacin-resistant *P. aeruginosa* (CRPA) otorrhea in patients with CSOM.[23] A previous in vitro study compared the use of piperacillin/tazobactam-coated tympanostomy tubes with the use of silver oxide-coated tubes and uncoated control tubes and reported that piperacillin/tazobactam-coated tympanostomy tubes showed good resistance to CRPA biofilm formation.[24] In our study, we obtained a dry ear with topical piperacillin/tazobactam in 10 patients for whom systemic antibiotherapy could not be performed. Although no significant difference was found between IV and topical application of piperacillin/tazobactam in terms of clinical improvement, the topical therapy was relatively more advantageous since it required a lower dose and did not require hospitalization. Additionally, the topical therapy can be considered in difficult-to-treat patients such as those with malignant external otitis.

Methicillin-resistant *S. aureus* is highly resistant to multiple antibiotics and is also the second most common pathogen in COM after *P. aeruginosa*. Moreover, elimination of MRSA infections is difficult in patients with COM since these infections are resistant to many antibiotics. In a multicenter study, the prevalence of MRSA in various ear cultures was found to be 10.9%.[25] Jang et al[26] used topical vancomycin (25 mg/mL) 2 drops 3 times a day for 10 days for the treatment of MRSA in patients with CSOM and reported that vancomycin was more effective than gentamycin. In another study, MRSA-resistant patients were treated on an outpatient basis with a locally prepared vancomycin otic solution and diluted vinegar irrigation (saline 1 : 1 with vine agar) prior to surgical treatment. After the treatment, the others found that otorrhea resolved in most patients and the success rates of the surgeries performed after treatment were similar to those of patients with non-MRSA.[27] In our study, MRSA was detected in 10% of patients with *S. aureus.* In all of those patients, vancomycin drops were administered locally and a dry ear was obtained in each patient.

Another difficult-to-treat group in our study was the group that included patients with resistant *E. coli*, all of whom were living in low-hygiene conditions and had low socioeconomic

levels. The increase in infections caused by ESBL-producing *E. coli* isolates leads to difficulties in treatment. Moreover, ESBL-producing *E. coli* isolates are often resistant to penicillins, narrow- and extended-spectrum cephalosporins, aztreonams, as well as aminoglycosides and quinolones. Accordingly, carbapenems are often preferred in such infections.[28] Ertapenem has a broad spectrum of activity that includes many aerobic gram-positive and gram-negative organisms and all anaerobes. Moreover, ertapenem has been reported to be highly effective against beta-lactamase-producing gram-negative bacteria including ESBL, excluding metallo-β-lactamase and some other carbapenemases.[29] In our study, systemic ertapenem was administered in 3 patients with ESBL-producing *E. coli* and a dry ear was obtained in all patients.

Among the *Serratia* spp., *S. marcescens* is the most common type isolated in humans. To our knowledge, the production of resistant *S. marcescens* in chronic otitis culture has not been yet reported in the literature. However, production of ESBL and carbapenemases in *Serratia* species has been reported in the literature.[30] The infection can spread quickly and may result in death particularly in neonatal intensive care units.[30] In our study, the patient who had PDR and was detected with *S. marcescens* had a poor hygiene status due to the presence of syndromic features. The patient was treated with IV tigecycline since the infection was resistant to all antibiotics except for tigecycline.

Our study was limited in several ways. First, it was a retrospective and single-center study. Second, systemic antibiotic therapy was administered for each patient separately and there was no standardization of treatment. Accordingly, further prospective, randomized, controlled, and blinded studies are needed for topical application of piperacillin/tazobactam for the treatment of CSOM.

Conclusion

It is commonly known that antibiotic resistance has increased in recent years and the treatment of bacterial infections is becoming more and more difficult. Similarly, serious problems are encountered in the treatment of CSOM and resistant infections can be seen. To prevent or delay the development of antibiotic resistance, it could be more beneficial to plan and initiate the treatment based on antibiotic susceptibility test results. In this study, the results indicated that gram-negative bacteria lead to more resistant infections, particularly *P. aeruginosa* infections. Further prospective, controlled studies are needed to substantiate the efficacy and safety of topical piperacillin/tazobactam therapy for resistant *P. aeruginosa* infections.

Ethics Committee Approval: This study was approved by Ethics Committee of Van Research and Training Center (Approval No: 2019-15).

Informed Consent: Verbal and written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.S.Ç.; Design – Y.S.Ç.; Supervision – U.D.; Resources – U.D.; Materials – Y.S.Ç., S.O.M.; Data Collection and/or Processing – S.O.M., Y.S.Ç.; Analysis and/or Interpretation – S.O.M., U.D.; Literature Search – Y.S.Ç., M.T., N.B.; Writing Manuscript – Y.S.Ç., U.D.; Critical Review – M.T., N.B..

Declaration of Interests: The authors have no conflict of interest to declare.

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