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Identification and Role of Antimicrobial Susceptibility Patterns of Aerobic Bacteria in the Management of Refractory Chronic Suppurative Otitis Media – A Tertiary Hospital-based Retrospective Study

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Keywords

Chronic Suppurative Otitis Media
CSOM
Ear discharge
Pseudomonas aeruginosa
Antibiotic Sensitivity Testing
Ototopical antibiotics

Abstract

Objectives: This study identifies aerobic bacteria that cause refractory chronic suppurative otitis media (CSOM) and compares the treatment outcomes of patients treated with antibiotic sensitivity testing (AST) directed antibiotics against those treated with empirical antibiotics.

Methods: This retrospective study was conducted at the departments of ENT and Microbiology, AIIMS, Patna. Data were collected from clinical and microbiological laboratory records of patients with complaints of persistent ear discharge from September 2018 to February 2020. Ear discharge samples were cultured and AST data from all patients were examined. Antibiotics were administered to those patients diagnosed with refractory CSOM based on their AST reports. Patients were followed up, and their treatment responses were assessed and recorded. Data were analyzed by using IBM SPSS Statistics software Version 20.0. Descriptive analysis was performed and Pearson Chi-square tests were applied and *p*-values were determined to draw relevant conclusions.

Results: A total of 90 patients were examined, of which 70 showed significant bacterial growth and were prescribed AST-directed antibiotics. The remaining 20 patients with insignificant growth were treated empirically. Common microorganisms isolated in our study were *P. aeruginosa* and *S. aureus*. Gram-negative and Gram-positive isolates were highly resistant to commonly used fluoroquinolones. Among intravenous (IV) formulations, piperacillin-tazobactam and cefoperazone-sulbactam had the highest sensitivity (>80%) against Gram-negative isolates. There was a statistically significant ($p < 0.05$) difference in cure rates between patients treated with AST-directed antibiotics (n = 54; 77.1%) and empirical therapy (n = 9; 45%). Route of antibiotic administration (oral versus IV) had no statistically significant effect on treatment outcomes ($p > 0.05$).

Conclusion: In the management of refractory CSOM, AST-directed antibiotic therapy is more effective than empirical treatment. Oral and IV antibiotics were equally effective when combined with aural toileting and ototopical antibiotics. Therefore, when treating such cases, AST-directed antibiotics should always be used to prevent widespread antibiotic resistance caused by injudicious antibiotic use.

1 Introduction

Otitis Media (OM) is defined as an inflammation of the middle ear cleft that is accompanied by fluid effusion into the middle ear due to infection, which may or may not be associated with tympanic membrane (TM) perforation [1]. OM is the most common cause of temporary hearing loss in children and leads to a spectrum of disorders such as acute otitis media (AOM), chronic suppurative otitis media (CSOM), and otitis

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media with effusion (OME) [2]. OM can be caused by various causative agents (bacterial, viral, or fungal), depending on the route of infection through which it reaches the middle ear cavity. The most common route is via ascending infections through the eustachian tube, in which the primary infection may be in the nose, paranasal sinuses, or oropharynx [3-5].

OM is a major chronic condition in low and middle-income countries. About 1.23 billion people worldwide, mostly children under the age of 5 are affected by OM. The highest rates of OM incidence have been reported in Sub-Saharan Africa and South Asia [6]. The WHO estimates that 28,000 children die every year in developing countries due to complications from otitis media [7].

Chronic Suppurative Otitis Media (CSOM) is a chronic inflammation of the middle ear or mastoid cavity, which results in tympanic membrane perforation with persistent otorrhoea from the middle ear for more than 6 weeks [8]. CSOM complications are classified as extracranial (EC) or intracranial (IC). EC complications include mastoid abscess, petrositis, labyrinthitis, facial nerve paralysis (FNP), and Bezold's abscess. IC complications comprise intracranial abscess (including extradural, epidural, subdural, perisigmoid sinus, and brain abscesses), lateral sinus thrombophlebitis (LST), meningitis, and otitic hydrocephalus [9]. Poverty, overcrowding, illiteracy, poor living conditions, ignorance, poor hygiene, malnutrition, and lack of medical facilities have been suggested as a basis for the widespread prevalence of CSOM [10]. CSOM is estimated to affect 31 million people worldwide each year (4.76 cases per thousand people), with a higher incidence of 22% among children under the age of 5 [11].

The aerobic microorganisms most commonly isolated in CSOM are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, Gram-negative organisms such as *Proteus* spp., *Klebsiella* spp., and *Escherichia* spp., *Haemophilus influenzae*, and *Moraxella catarrhalis*. *Bacteroides* spp. and *Fusobacterium* spp. were the most commonly isolated anaerobic organisms [12]. Resistance is increasing among pathogens such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, and other Gram-negative organisms commonly responsible for CSOM due to the widespread use of broad-spectrum antibiotics [13]. Fungi such as *Aspergillus* spp. and *Candida* spp. were also commonly isolated in CSOM patient cultures. Immunosuppressive therapy, prolonged and irrational use of topical antibiotics or antibiotic-steroids ear drops inhibit the bacterial flora and allow the opportunistic fungal flora to emerge [14].

CSOM is a chronic inflammation and often polymicrobial infection. Ototopical quinolone in combination with aural toilet is the first-line therapy for CSOM for at least 3 weeks. Systemic oral or parenteral antibiotics are second-line therapy for CSOM if primary treatment fails to resolve otorrhoea. Systemic antibiotics should be used for various degrees of first-line treatment failure or when intracranial complications occur during CSOM. Overuse of systemic antibiotics leads to increased bacterial resistance in the community and hospital-acquired pathogens. Whenever possible, systemic antibiotics should be prescribed based on the AST report, otherwise empirically. Knowledge of the local incidence, bacterial spectrum, and antimicrobial susceptibility patterns is essential for both effective empirical treatment and a better understanding of the disease [15,16]. To the best of our knowledge, no studies have been conducted in this region that show a difference in treatment outcomes between AST-directed and empirical antibiotic therapy. Hence, this study was carried out to compare the treatment outcomes of AST-directed and empirical antibiotic therapy for refractory CSOM.

2 Materials and Methods

This retrospective study was conducted at the departments of ENT and Microbiology of AIIMS Patna, a tertiary healthcare center in Bihar. The data collected and analyzed in this study was for a period of 1 year and 6 months, from September 2018 to February 2020. Data were collected from clinical and microbiological laboratory records of patients. Patients diagnosed with refractory CSOM during that period were analyzed.

A total of 90 patients were enrolled in this study. Among the participants 48 (53.33%) were males and 42 (46.66%) were females. of which 70 showed significant bacterial growth and the remaining 20 patients with insignificant growth. Relevant demographic data were recorded. Patients who visited the ENT department with complaints of persistent ear discharge even after topical and/or systemic antibiotic treatment for 2–3 weeks were evaluated. Patients diagnosed with refractory CSOM who had failed to respond to initial antibiotic therapy administered at primary or secondary healthcare facilities. Aspirate or swabs of middle ear discharge was collected under strict aseptic conditions and sent to the microbiology laboratory for culture and sensitivity testing. Primary smears were prepared directly from clinical specimens and first examined by Gram stain for the presence of any suspected pathogen and/or pus cells. They were then cultured on blood agar, chocolate agar, MacConkey agar, SDA with chloramphenicol and nutrient broth and incubated at 37^0C for 18-24 hrs. Culture plates that showed positive growth were further investigated to identify the microorganism using standard microbiological procedures.

Antibiotic susceptibility testing of isolated organisms was performed by the Kirby–Bauer disc diffusion method on Mueller–Hinton agar plates using commercially available antibiotic discs (Hi-Media, Mumbai) following CLSI guidelines 2017 [17].

The treating ENT surgeon has conveyed the obtained laboratory results. Further management was determined based on culture and sensitivity reports, following standard protocols for these patients in the ENT department. The treatment strategy implemented after receiving the AST report is outlined in Fig. 1.

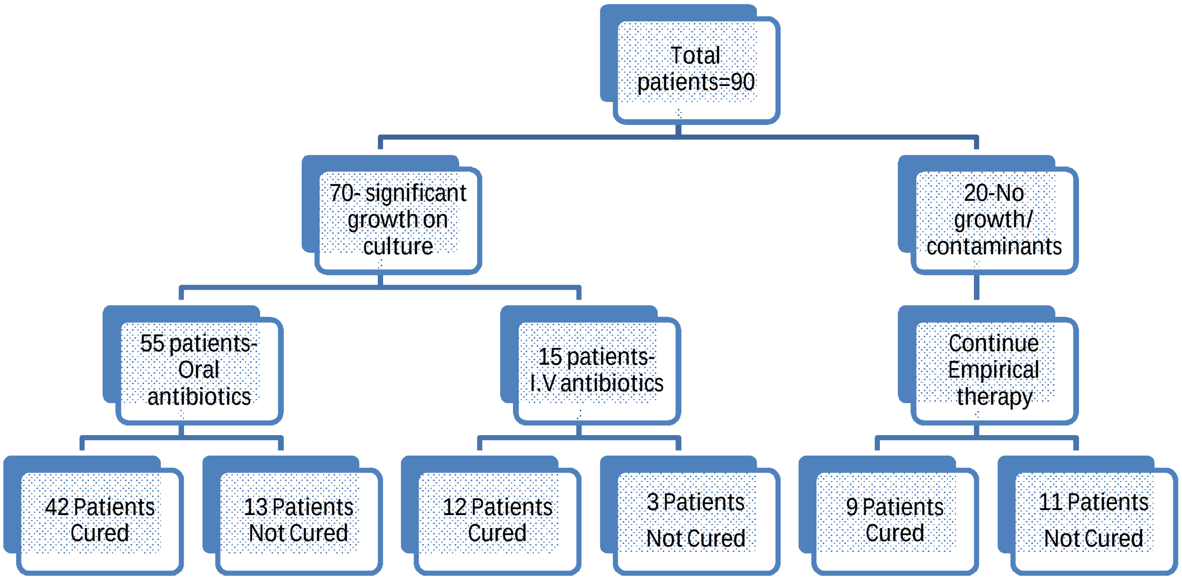

Fig. 1: Treatment strategy in CSOM patients.

In this study, patients (n = 70) with confirmed bacterial infections were prescribed a 2-week course of AST-directed systemic antibiotics, which included oral or IV antibiotics. Patients (n = 20) with insignificant culture growth were treated empirically. For empirical therapy, broad-spectrum antibiotics such as quinolones/ aminoglycosides, which exhibit high activity against the most commonly cultured microorganisms such as *P. aeruginosa* and *S. aureus*, were prescribed [16].

All patients enrolled in this study were given oral antihistamines, an aural toilet, and a topical antibiotic. Topical antibiotics were combined with topical steroids if granulation tissue was present [18]. Topical therapy is beneficial because the high concentration of topical agents can directly reduce the rate of bacterial resistance into the middle ear as well as limit systemic absorption [19]. Topical steroids combined with topical antibiotics may reduce inflammation in the outer or middle ear, improve penetration of the antibiotic agent and decrease allergic sensitivity to the antibiotic component [20]. Therefore, we have used this combination in all of our patients irrespective of culture sensitivity results. Antibiotics that were prescribed as well as the patient's response to treatment were recorded. All of these patients were followed for two weeks to see if their symptoms had resolved. A completely dry ear was considered a successful treatment with the resolution of associated symptoms such as ear fullness, itching, or pain.

Data analysis was performed using IBM SPSS statistical software Version 20.0 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics were carried out for the analysis of basic variables. The statistical significance of the association was determined by using the Pearson Chi-square test. A p-value of < 0.05 at a 95% confidence level was considered statistically significant.

3 Results

A total of 90 patients of various ages participated in this retrospective study. Among the participants 48 (53.4%) were males and 42 (46.7%) were females. The mean age of patients (n = 90) was 25.09 years (SD = 14.38; range 64). The mean age of male patients (n = 48) was 22.31 years (SD = 13.54; range 56) and females patients (n = 42) was 28.26 years (SD = 14.82; range 60). Therefore, the age and gender distributions of our patient population were comparable (Table 1).

Table 1: Age and gender distribution of CSOM cases.

Age group (years)	Male (n=)	Female (n=)	Total (n=)
0-20	27	12	39
21-40	16	25	41
41-60	03	03	6
>60	02	02	4
Total	48	42	90

The microorganisms most frequently isolated from patient's ear discharge are listed in Table 2. The most common pathogens detected in patient population were *Pseudomonas aeruginosa* (n = 31; 44.3%) and *Staphylococcus aureus* (n = 17; 24.3%).

The concentration and dosage of antibiotics prescribed for CSOM patients are shown in Table 3. The antibiotic sensitivity pattern of the isolates is shown in Table 4. Among the Gram-positive isolates, orally administered antibiotics such as ciprofloxacin, cotrimoxazole, and clindamycin showed higher sensitivity (>50%), whereas, vancomycin (IV), linezolid (IV), and cefoperazone-sulbactam (IV) showed the highest sensitivity (≥80%). In the case of Gram-negative isolates, commonly used fluoroquinolones such as ciprofloxacin and levofloxacin showed poor sensitivity (<50%), whereas, IV formulation of piperacillin-tazobactam showed the highest sensitivity (>80%).

Table 2: Clinically significant microorganisms from CSOM patients.

Age group (years)	Microorganism	Male	Female	Total
0-20	*Pseudomonas aeruginosa*	11	05	16
	Staphylococcus aureus	05		05
	Citrobacter koseri	01		01
	Acinetobacter baumannii		02	02
	Candida spp.	01		01
	Proteus vulgaris		01	01
	Proteus mirabilis	01		01
	Moraxella catarrhalis	01		01
	Enterococci		01	01
	Streptococcus pneumoniae	01		01
21-40	*Pseudomonas aeruginosa*	03	05	08
	Staphylococcus aureus	04	03	07
	Methicillin-resistant *Staphylococcus aureus* (MRSA)		04	04
	Acinetobacter baumannii		02	02
	Escherichia coli		03	03
	Proteus vulgaris		04	04
	Moraxella catarrhalis	02		02
	Haemophilus spp.		01	01
41-60	*Pseudomonas aeruginosa*	03	01	04
	Staphylococcus aureus	01		01
>60	*Pseudomonas aeruginosa*	01	02	03
	Moraxella catarrhalis		01	01

Table 3: The following antibiotics were used in the below-mentioned concentration and dosage.

ORAL	INJECTABLES
Cotrimoxazole (800mg/160mg) - BD	Piperacillin (4000mg) + Tazobactam (500mg) - TDS
Ciprofloxacin (500mg) - BD	Cefotaxime (1000mg) - TDS
Levofloxacin (500mg) - OD	Ceftazidime (500mg) - BD
Erythromycin (500mg) - BD	Amikacin (500mg) - BD
Clindamycin (300mg) - TDS	Imipenem (500mg) - BD
Linezolid (600mg) - BD	Gentamicin (80mg) - TDS
Ampicillin (500mg) - TDS	Cefepime (1000mg) - BD
Ampicillin (500mg) + clavulanic acid (125mg) - TDS	Cefoperazone (1000mg) + Sulbactam (500mg) - BD
Azithromycin (500mg) - OD	Aztreonam (1000mg) - BD
	Meropenem(1000mg) - BD
	Vancomycin (500mg) - OD

OD - Once daily (q24hr); BD - Twice daily (q12hr); TDS - Thrice daily (q8hr)

Table 4: Antimicrobial susceptibility pattern (Sensitivity %) of clinically significant isolates in CSOM patients.

Antibiotics	Gram-positive Isolates	Gram-negative Isolates	
	***S. aureus, S. pneumonia, Enterococcus* spp.**	**Enterobacteriaceae (*E. Coli*, *Proteus* spp., *Citrobacter* spp.)**	**Non-fermenters (*P. aeruginosa, Acinetobacter* spp., *Haemophilus, Moraxella* spp.)**
Gentamicin	73.7	40	42.9
Amikacin	78.9	40	45.7
Levofloxacin	36.8	50	35.9
Ampicillin	21.1	30	22.9
Ciprofloxacin	63.2	40	48.6
Cefoperazone-Sulbactam		80	82.9
Aztreonam		60	71.4
Cefepime		40	40
Ceftazidime		70	77.1
Imipenem		60	51.4
Meropenem		70	64.9
Cotrimoxazole	78.9	70	15.4
Piperacillin-Tazobactam		80	80
Cefotaxime		30	27.03
Azithromycin	42.1		
Clindamycin	84.2		
Erythromycin	36.8		
Linezolid	100		
Ampicillin-Clavulanate	47.4	40	34.1
Vancomycin	100		

Out of 90 patients, middle ear discharge of 70 patients had significant microbial growth on culture and was treated with oral or IV antibiotics based on their AST pattern. The remaining 20 patients were treated empirically based on insignificant or contaminant growth. The treatment response of patients on AST-directed antibiotics and empirical therapy is shown in Table 5. There is a statistically significant ($p < 0.05$) difference in the recovery rate between patients treated with AST-directed antibiotic therapy (n = 54; 77.1%) and those treated with empirical therapy (n = 9; 45%).

We examined whether the route of drug administration had an effect on treatment outcomes and found that both oral and IV antibiotics provided similar cure rates (Table 6). Thus, the recovery rates of patients in each group were comparable, with no statistically significant difference between the two groups. We also assessed any potential variation in cure rates of AST-directed and empirical therapy between different age groups. The results showed that AST-directed therapy had better cure rates than empirical therapy in all age groups (Table 7).

4 Discussion

Despite advances in modern medicine, CSOM remains a clinically challenging disease. The molecular mechanisms underlying CSOM are still unknown. There is a need for the development of effective treatment methods against CSOM due to the highly polymicrobial nature, the emergence of antibiotic resistance, and the potential ototoxicity of antibiotics [21]. Refractory CSOM is caused by a combination of factors, including patient non-compliance with medication regimens, treatment with non-antibiotic ear drops, antibiotic-resistant bacterial infections, and deformed ear anatomy [16]. Currently, judicious use of antibiotics is the only way forward, as bacterial infections have been proven to have a significant role in the persistence of CSOM [22].

The present study found that CSOM patients had similar age and gender distribution (male 53.33% and females 46.66%), with the disease being more prevalent in pediatric and under 40-year-old patients, which is consistent with available data on CSOM incidence. Argaw-Denboba *et al.*, (2016) reported an equal risk of middle ear infection in men and women by 50.4% and 49.1%, respectively and the frequency of positive ear discharge cultures was higher in the age group of <5 (14.9%), 5–15 (24.7%) and 16–35 (42.4%) [23]. Similarly, Seid *et al.*, (2013) reported equal distribution between sexes (male 41.9% and females 41.4%), and the majority of the patients were identified as COM cases in the age group of <5 (11.5%), 5–19 (36.6%) and 20–39 (25.2%) [24].

In the present study, 77.78% of the patients showed a definite significant bacterial growth in ear discharge culture, which is in agreement with previously conducted studies. The bacterial isolation rates reported by other authors with a slight variation are 83.6% (Argaw-Denboba *et al.*, 2016) [23], 89.4% (Seid *et al.*, 2013) [24], 80.4% (Hailu *et al.*, 2016) [25], and 92.5% (Gorems *et al.*, 2018) [26]. We found that *S. aureus* (24.3%) and *P. aeruginosa* (44.3%) were the most commonly isolated microorganisms, followed by *Proteus* spp. (8.6%) and *M. catarrhalis* (5.7%). Mittal *et al.*, (2015) [16] conducted a review of recent scientific advances in CSOM and concluded that *P. aeruginosa* and *S. aureus* were the most common aerobic microbial isolates in patients with CSOM, with percentage isolation ranging from 22–44% and 17–37%, respectively, which is consistent with the current study.

Table 5: Comparison of treatment response in AST-directed and empirical therapy.

Therapy	AST-directed	Empirical
Cured	54	09
Not cured	16	11

Pearson Chi square = 7.653; *p*-value = 0.022

Table 6: Treatment response in AST-directed patients.

Antibiotic	No. of Patients	Cured	Not cured	Mean time	P-value
Oral	55	42	13	2 weeks	0.856
I.V	15	12	03	1 week	0.780
Total	70	54	16		1.000

Table 7: Comparison of AST-directed and empirical treatment across different age groups.

Age Group	AST-Directed	Cured	Not Cured	Empirical Treatment	Cured	Not Cured
0-20	30	21 (70%)	09 (30%)	10	4 (40%)	6 (60%)
21-40	31	26 (83.87%)	05 (16.13%)	09	4 (44.45%)	5 (55.56%)
41-60	05	04 (80%)	01(20%)	01	01(100%)	-
>60	04	03 (75%)	01 (25%)	-	-	-
Total	70	54 (77.14%)	16 (22.86%)	20	09 (45%)	11(55%)

In the present study, both Gram-positive and Gram-negative isolates showed high resistance (>50%) to multiple classes of commonly used antibiotics. Against Gram-positive isolates, IV formulations such as linezolid and vancomycin showed the highest sensitivity (100%). These findings are similar to the 100% sensitivity reported in previous studies [27,28]. Piperacillin-tazobactam (80%) and cefoperazone-sulbactam (82.9%) were found to be most effective against Gram-negative isolates including non-fermenters. These findings were very similar to previous studies that found *P. aeruginosa* was sensitive to piperacillin-tazobactam (82%) and cefoperazone-sulbactam (96%) [29]. Similarly, *P. aeruginosa* showed better sensitivity to piperacillin-tazobactam (96.8%) and cefoperazone-sulbactam (96.8%) [30].

In the present study, Gram-negative isolates were highly resistant to commonly used fluoroquinolones such as ciprofloxacin (51.4%) and levofloxacin (64.1%) and Gram-positive isolates 36.8% & 63.2% respectively. This is consistent with the findings of Juyal *et al*., (2017) who found that *P. aeruginosa* strains had high resistance to ciprofloxacin (48.7%) and levofloxacin (45.5%) [31]. Similarly, Xu *et al.*, (2021) found that *P. aeruginosa* isolates were highly resistant to ciprofloxacin (40%) and levofloxacin (42.5%) [32]. On the other hand, Kumar *et al*., (2019) found in their study that *S. aureus* was resistant to ciprofloxacin (33.33%) and levofloxacin (41.67%) [33]. An Indian study on CSOM also found that *S. aureus* was highly resistant to ciprofloxacin (64%) and levofloxacin (60%) [30]. Previous antibiotic use has been correlated with increased antibiotic resistance and is associated with higher rates of treatment failure in CSOM patients [34].

CSOM may be treated with topical antibiotics (administered into the ear) with or without steroids, systemic antibiotics (given either orally or intravenously), topical antiseptics, and aural toileting [35]. Patients with CSOM respond to topical therapy more frequently than systemic therapy. Successful topical therapy includes the selection of an appropriate antibiotic drop and aural toileting [36]. In comparison to direct delivery of topical antibiotics, it is difficult to achieve effective antibiotic concentrations in infected middle ear tissues with systemic therapy. Systemic therapy should only be used in patients with CSOM who have failed to respond to topical therapy. As a second-line treatment option, both oral and IV antibiotics are effective against CSOM [16]. In this study, the cure rates of patients resistant to other therapies treated with both AST-directed oral and IV antibiotics formulations were comparable and there was no statistically significant difference in treatment response. Otorrhoea was effectively treated with a combination of aural toilet, topical and systemic antibiotics [37,38]. In children with CSOM, aural toilet and intravenous antibiotics may improve symptoms more frequently than aural toilet alone [39].

Despite the activity of IV antibiotics against the most common infectious agents, these are widely associated with systemic side effects and increased antibiotic resistance [16]. Ear discharge culture should be performed before administering antibiotics, either local or systemic, and antimicrobial susceptibility data should be used to formulate antibiotic policy [40]. Therefore, IV antibiotics should be considered only based on the AST report and not as a standard treatment for refractory CSOM. The present study also concluded that AST-directed therapy had a better treatment response than empirical therapy in both pediatric and adult patient populations and the difference was statistically significant.

This study was limited by the fact that anaerobic culture sensitivity tests were not performed on CSOM patients due to limited healthcare infrastructure at the time. The scope of this study also did not include the follow-up and further definitive management of treatment failure cases of both AST-directed and empirical therapies.

5 Conclusion

In the case of refractory CSOM and its complications, a polymicrobial infection involving both Gram-positive and Gram-negative bacteria is common. The most prevalent etiological agents associated with CSOM were *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Multiple drug therapies using broad-spectrum agents may be required to treat CSOM and its complications. *P. aeruginosa* and *S. aureus* showed high resistance to ciprofloxacin and levofloxacin due to injudicious use of antibiotics and among IV formulations, piperacillin-tazobactam and cefoperazone-sulbactam showed the highest sensitivity. In such patients, AST-guided antibiotic therapy is a promising therapeutic option compared to empirical therapy to achieve cure and prevent antibiotic resistance. The route of antibiotic administration has no significant effect on treatment outcomes and thus should not be considered when choosing an appropriate antibiotic formulation to prescribe.

Conflicts of Interest

The author declares that there is no conflict of interest.

Author Contributions

Conceptualization, data curation, methodology - SS, SD. Formal analysis - KB, SS. Writing original draft - SS, SD. Writing-review and editing - KB, SD, SS.

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