ANTIBIOTIC RESISTANCE IN CSOM IN A TEACHING HOSPITAL

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ABSTRACT

BACKGROUND

Antibiotic resistance pattern of CSOM has been changing according to geographical variation and differences in patient population. Increased and irrational use of broad spectrum antibiotics, as well as resistance in bacterial isolates, has become very common. *Staphylococcus* is one of the most important bacteria in CSOM and MRSA is a common pathogen in otologic diseases. Continuous and periodic surveillance of MRSA is necessary to reduce the spread of antibiotic resistant pathogens in CSOM cases.

OBJECTIVES

To identify the bacteria causing CSOM, to determine the antibiotic resistance of the isolates from CSOM samples and also to determine the methicillin resistance of the isolates.

MATERIALS AND METHODS

Prospective study of 30 samples from clinically suspected cases of CSOM was performed over a period of two months. Samples were processed by microscopy and culture and the culture isolates were identified by standard biochemical reactions. Antibiotic susceptibility test of the isolates was performed as per CLSI guidelines.

RESULTS

73.33% of the isolates were *Staphylococcus aureus*. 26.66% of the isolates were *Enterococcus*. 100% resistance to Cotrimoxazole, Ampicillin sulbactam, Azithromycin, Cefuroxime, Cefazolin, Doxycycline, Tetracycline and Cefepime was observed followed by 50% resistance to Amikacin and 43.3% resistance to Amoxiclav and Ceftazidime. MRSA constituted 50% of the total isolates.

CONCLUSION

Cotrimoxazole, Ampicillin sulbactam, Azithromycin, Cefuroxime, Cefazolin, Doxycycline, Tetracycline and Cefepime should not be considered for treatment of CSOM in our hospital area. There is an over use of Cefepime and Ceftazidime in our hospital area. Increased isolation of MRSA warrants potential interventions to reduce the prevalence of MRSA in our hospital area.

KEYWORDS

CSOM, Antimicrobial Resistance, Methicillin Resistance.

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INTRODUCTION

Chronic Suppurative Otitis Media (CSOM) is a common disease of childhood. It is a persistent or intermittent infection of ear for more than three months' duration. There is purulent or mucopurulent discharge through the perforated tympanic membrane. Causative micro-organism may be bacteria, fungi and virus resulting in inflammation of mucosal lining of middle ear. If not treated it leads to partial or total loss of the tympanic membrane and ossicles resulting in acquired hearing loss. It is a highly prevalent condition and an important cause of preventable hearing loss. Chronic Suppurative Otitis Media (CSOM) has assumed world-wide importance. In the developing countries, it has continued to constitute a heavy disease burden with the prevalence of

chronic ear infections being up to 72 cases per 1000 inhabitants.

According to a classification by World Health Organization (WHO) for burden of CSOM, India has been placed in highest (>4%) prevalence group.¹ Several organisms have been implicated in the causation of CSOM, posing a challenge to the management. Commonly isolated bacteria include *Staphylococcus aureus* (Methicillin-resistant [MRSA] and methicillin-sensitive [MSSA]), *Pseudomonas*, *Proteus*, *Coagulase-negative staphylococci*, *Enterococcus*, and Anaerobes (Including *Peptostreptococcus*, *Fusobacterium*, *Prevotella* and *Porphyromonas*).² Polymicrobial growth is common.³ With the emergence of antibiotic resistance as well as the ototoxicity of antibiotics and the potential risks of surgery, there is an urgent need to develop effective therapeutic strategies against CSOM.² The indiscriminate and haphazard use of antibiotics in CSOM have resulted in persistence of low-grade infections. Further the changes in the microbiological flora with the advent of new antimicrobials made the evaluation of bacterial flora of CSOM and their antibiotic resistance pattern very important. This evaluation will contribute to rational usage of antibiotics, success of treatment and prevention of the complications in CSOM patients.⁴ Often, the primary care physicians are usually the first to see these patients and mostly rely on

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empirical antibiotic therapy and only refer to the otolaryngologist when their treatments fail. Due to the recurrent nature of CSOM and the development of resistant pathogenic organisms, control of infection poses a greatest therapeutic challenge. The challenges of resistance have even been compounded by the activities of quacks where they engage in uninformed administration of antibiotics to these patients.⁵ Hence, the present study was conducted to detect the antibiotic resistance pattern of the isolates of CSOM in our hospital area. Identification and detection of MRSA is also important before treatment of CSOM cases, as cases with these infections are resistant to routine beta-lactam antibiotics and Penicillin.⁶ Moreover, empirical antibiotic treatment of patients with antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), which have been increasingly identified in infectious diseases may result in treatment failure or complications.⁷ Knowledge of local bacteriological pattern and their antibiotic resistance is essential for effective and low cost treatment.

MATERIALS AND METHODS

A prospective study of 30 patients with clinical evidence of CSOM attending the Outpatient Department of Apollo General Hospital, Jubilee Hills, Hyderabad, was done for a period of 2 months from April to June 2015. The processing of the samples was done in the Microbiology Department of AIMSR. Institutional Ethics Committee approval was obtained for the study. Patients of all ages and either gender suffering from CSOM as determined by otoscopic examination were included in the study. Patients with current febrile illness, antibiotic usage in the preceding 2 weeks, ear surgery or any other relevant ear problems were excluded from the study. Two sterile swabs were used to collect ear discharge from each patient. The first swab was used to make a smear on a clean, grease-free slide for preliminary differentiation of bacteria by Gram staining. The second swab was plated on 5% blood agar, MacConkey's agar and chocolate agar and the plates incubated at 37°C for 48 hours, after which a part of the colony is picked up with a sterile loop for making a smear. The smear was stained by Gram staining again and findings recorded.⁴ The bacterial colonies isolated in culture were identified by standard biochemical reactions. Antibiotic susceptibility testing is done by modified Kirby-Bauer disc diffusion technique using Mueller-Hinton agar as per CLSI guidelines. Pure colonies of the isolates were suspended in sterile normal saline and the turbidity of the suspension adjusted to 0.5 McFarland standard. A sterile cotton swab was dipped into the suspension and squeezed against the side of the bottle and then used to inoculate a Mueller-Hinton agar before the application of antibiotic discs and subsequently incubated at 37°C for 18-24 hours. The standard antibiotic discs as recommended by CLSI guideline were used. The antibiotics used were Ampicillin sulbactam (10 µg), Amoxiclav (30 µg), Ciprofloxacin (5 µg), Ofloxacin (5 µg), Vancomycin (30 µg), Cefazolin (30 µg), Cefotaxime (30 µg), Ceftazidime (30 µg), Netilmicin (30 µg), Chloramphenicol (30 µg), Amikacin (30 µg), Doxycycline (30 µg), Tetracycline (30 µg), Cotrimoxazole (1.25 + 23.75 µg), Azithromycin (15 µg), Ceftriaxone (30 µg), Cefuroxime (30 µg) and Cefepime (30 µg). Results of the antibiotic susceptibility test were

interpreted and antibiotic resistance of the isolates determined in accordance with Clinical and Laboratory Standards Institute Guidelines. Reference strains such as *S. aureus* ATCC 25923 and *Enterococcus faecalis* ATCC 29212 were used for quality control for antibiotic susceptibility testing. Detection of methicillin resistance in staphylococcal isolates was done by cefoxitin disc method as per CLSI guidelines.⁸

All dehydrated media, reagents and antibiotic discs were procured from Hi-Media Laboratories Pvt. Ltd., Mumbai, India.

RESULTS

A total of 30 ear swabs from cases of CSOM were studied to identify the bacterial agents causing CSOM and to determine the antibiotic resistance of these isolates. Out of the 30 samples of CSOM processed, *Staphylococcus aureus* was isolated from 22 (73.33%) of the isolates. *Enterococcus* was isolated from 8 (26.66%) of the isolates.

Organism	No. of Cases	Percentage of Cases
<i>Staphylococcus aureus</i>	22	73.3%
<i>Enterococci</i>	8	26.6%

Table 1: Organisms Isolated in CSOM Cases

When the antibiotic resistance of the isolates in our study was analysed, highest degree of resistance (100%) to Cotrimoxazole, Ampicillin sulbactam, Azithromycin, Cefuroxime, Cefazolin, Doxycycline, Tetracycline and Cefepime was observed. Isolates also showed increased resistance to Amikacin (50%), Amoxiclav (43.3%) and Ceftazidime (43.3%). Table 1 shows the antibiotic resistance of the isolates and Table 2 shows the methicillin resistance of the isolates.

Antibiotic	No. (%) of Resistant Isolates
Ampicillin sulbactam	30(100%)
Amoxiclav	13(43.3%)
Ciprofloxacin	0(0%)
Ofloxacin	0(0%)
Vancomycin	12(40 %)
Cefazolin	30(100%)
Cefotaxime	7(23.3%)
Ceftazidime	13 (43.3%)
Netilmicin	0(0%)
Chloramphenicol	12(40%)
Amikacin	15(50%)
Doxycycline	30(100%)
Tetracycline	30(100%)
Cotrimoxazole	30(100%)
Azithromycin	30(100%)
Ceftriaxone	7(23.3%)
Cefuroxime	30(100%)
Cefepime	30(100%)

Table 2: Antibiotic Resistance of the Isolates

No. of <i>Staphylococcus aureus</i> Isolates	No. of MSSA Isolates among <i>Staphylococcus aureus</i> Isolates	% of MSSA Isolates among <i>Staphylococcus aureus</i> Isolates	No. of MRSA Isolates among <i>Staphylococcus aureus</i> Isolates	% of MRSA Isolates among <i>Staphylococcus aureus</i> Isolates
22	7	31.3%	15	68.2%

When methicillin resistance of the staphylococcal isolates was analysed, 68.2% of the staphylococcal isolates were MRSA and 31.3% were MSSA.

DISCUSSION

Among the 30 samples of CSOM processed, *Staphylococcus aureus* was isolated from 22 (73.33%) of the isolates. *Enterococcus* was isolated from 8 (26.66%) of the isolates. Predominant bacterial aetiology of CSOM in this region is *Staphylococcus aureus* (73.3%). In contrast, other studies from India.⁹ revealed about 16% isolation of *staphylococcus*, a study from Nigeria revealed 13.5% *Staphylococcus aureus*.¹⁰ and another from Pakistan.¹¹ revealed 41.5% *Staphylococcus aureus*. All these studies showed a different trend in which *Pseudomonas* was the most prevalent organism and this could be due to the variation in micro-organisms in different regions and effect of climate. However, *Pseudomonas* does not usually inhabit the upper respiratory tract and it probably gains access to the middle ear through a defect in the tympanic membrane. It is usually a secondary invader.³ Since *Staphylococcus aureus* is the predominant isolate in our study and it being a primary pathogen in CSOM, CSOM in our hospital area can be considered as a primary infection.

A study from South India (Coastal AP).¹² revealed *Pseudomonas* as the predominant organism. In a study conducted in hot and dry regions of AP.¹³ *Staphylococcus aureus* was the major isolate. Our place being a relatively dry place and the predominant isolate in our study being *Staphylococcus aureus*, it can be concluded that *Staphylococcus aureus* is the predominant pathogen of CSOM in the dry and less humid regions.

In the present study, *Enterococcus sp.* were isolated in 26.6% cases. Other workers who had isolated *Enterococci* in CSOM are Hiremath et al (2001).¹⁴ in 0.79% cases and Loy et al (2002) in 2.2% cases.¹⁵ There is an increased isolation of *Enterococci* in our study compared to the previous studies conducted by Hiremath et al and Loy et al. From this we conclude that *Enterococci*, generally regarded as normal flora of gastrointestinal and genitourinary tract of humans, is emerging as the etiogen of several nosocomial as well community-acquired infections since last two decades.

In the era of antibiotics, the emergence of antibiotic resistance is becoming more common. Patient non-compliance is an important factor responsible for the development of antibiotic resistance. As soon as symptoms subside, many patients stop taking antibiotics before completion of therapy and allow partially resistant microbes to flourish. Such practice should be condemned strongly and patients should be educated to avoid the same for the antibiotics commonly available locally as topical eardrops.

In our study maximum resistance was observed to Cotrimoxazole, Ampicillin-sulbactam, Azithromycin, Cefuroxime, Cefazolin, Doxycycline, Tetracycline and Cefepime (100%) followed by high resistance to Amikacin (50%), Ceftazidime (43.3%) and Amoxiclav (43.3%). The antibiotic

resistance pattern in our study was in collaboration with the studies of Gulati et al¹⁶, Nandy et al¹⁷, Hiremath et al¹⁴, Saurabh et al¹⁸ and Poorey et al.¹⁹ Increased resistance to these drugs suggests that these drugs should not be considered in the treatment of CSOM cases. When the results of various workers were compared, one fact became evident that the antibiotic resistance pattern of CSOM has been changing from time to time. The strains of yesterday, which exhibited least resistance to Tetracyclines and Chloramphenicol no longer exhibited the old, less resistance pattern today. Previously amoxicillin /ampicillin was used frequently than quinolones for acute and chronic middle ear infections in our setup. But the present study has clearly shown a changing behaviour of microorganisms with resistance to ampicillin and amoxicillin. Amoxicillin/clavulanate combination was found to be among the least effective antibiotic not only in our study but also in other studies.⁵ Incidentally, this antibiotic enjoys high patronage by general duty physicians, being the most often prescribed empirical antibiotic in CSOM. Hence, its use should be abandoned in CSOM cases.

In our study, resistance to Cefepime (100%) and Ceftazidime (43.3%) was more compared to the resistance of Cefotaxime (23.3%) and Ceftriaxone (23.3%). This was in accordance with the study of Manu Chaudhary et al²⁰ over use of Cefepime and Ceftazidime in our hospital area could be the reason for their decreased sensitivity when compared to other studies.²¹

Cotrimoxazole [Trimethoprim-sulfamethoxazole] is a sulfonamide antibiotic that interferes with bacterial folic acid synthesis by inhibiting dihydrofolic acid formation from para-aminobenzoic acid and by inhibiting dihydrofolic acid reduction to tetrahydrofolate. While many organisms are resistant to Cotrimoxazole, *Staphylococcus aureus* bear the inherent trait of resistance against this drug. Moreover, MRSA isolates are often resistant to trimethoprim-sulfamethoxazole. Cotrimoxazole resistance in our study could be attributed partly to the increased isolation rate of MRSA among Staphylococcal isolates and partly to the inherent trait of resistance against the drug borne by staphylococcus. Increased Azithromycin resistance in our study suggests a drift in the antibiotic sensitivity to Azithromycin as observed in other studies also.²²

MRSA is a common pathogen in otologic diseases. The first strains of MRSA were identified in 1961.²³ Since then, the proportion of nosocomial MRSA isolates has increased worldwide from 2% in 1974 to 50% in 1997.²⁴ There has been a steady increase in the number of cases of MRSA otorrhea.²⁵⁻³⁰

For example, studies monitoring staphylococcal isolates in cases of chronic otitis media have reported MRSA incidence rates of 22.3% in Japan.³¹ and 25% in Taiwan.²⁸ In Korea, 70%

of *S. aureus* strains have been MRSA since the mid-1990s and it is one of the most common isolated bacteria in chronic otitis media with an incidence of about 30%.³²

In our study, the isolation of MRSA among Staphylococcal isolates was 68.2%. The study of Swarooparani et al⁶ showed a 51.7% isolation of MRSA. Increased isolation of MRSA in our study suggests increased resistance to not only methicillin, but also to all β lactams and other groups of drugs as well. When MRSA is seen in a significant number of patients, due consideration should be given to it while prescribing empirical drugs to patients with CSOM. These observations may not hold true to all areas, because bacteriology and sensitivity can change from region to region. We advocate improved hygiene, clean clothing, educational campaigns on frequent hand washing, round-the-clock urgent care and dedicated wound clinics as potential interventions to reduce the prevalence of MRSA in our hospital area. Frequent and appropriate aural cleansing and irrigation using diluted acetic acid or other solutions such as Burow's solution can be an effective measure for the medical treatment of MRSA in CSOM.

CONCLUSION

CSOM in our hospital area can be considered as a primary infection. *Staphylococcus aureus* is the predominant pathogen of CSOM in the dry and less humid regions. *Enterococci*, generally regarded as normal flora of gastrointestinal and genitourinary tract of humans is emerging as the aetiological agent in CSOM cases. High degree of resistance to Cotrimoxazole, Ampicillin-sulbactam, Azithromycin, Cefuroxime, Cefazolin, Doxycycline, Tetracycline and Cefepime was observed suggesting that these drugs should not be used for the treatment of CSOM in our hospital area. The strains of yesterday which exhibited least resistance to Tetracyclines and Chloramphenicol no longer exhibited the old resistance pattern today. While many organisms are resistant to Cotrimoxazole, *Staphylococcus aureus* bear the inherent trait of resistance. Though amoxiclav enjoys high patronage by general duty physicians, being the most often prescribed empirical antibiotic in CSOM it was found to be among the least effective antibiotics. Cotrimoxazole resistance in our study could also be attributed to the inherent trait of resistance exhibited by *Staphylococcus aureus* against this drug as well as to the increased isolation of MRSA. Sensitivity to cefepime and ceftazidime in our study was less compared to sensitivity of cefotaxime and ceftriaxone suggesting overuse of these drugs. Hence, the study recommends judicious use of these drugs. The proportion of nosocomial MRSA isolates has increased worldwide. Increased isolation of MRSA in our hospital area necessitates measures to reduce the prevalence of MRSA in our hospital area.

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