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Antibiotic Sensitivity of Bacteria Isolated from Otitis Media Patients of Southern Punjab, Pakistan

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A B S T R A C T

Background: Otitis media (OM) is considered as one of the most common prevalent infection causing serious complications. It is a major health issue in health care centers and is associated with a high incidence and prevalence in both developed and developing countries. In this era of growing drug resistance, susceptibility pattern of etiological agents of OM is gradually changing. Adequate usage of antibiotics based on the knowledge of the latest antibiotic sensitivity of bacteria is necessary in order to control the spread of resistant bacteria and enhance efficacy of the treatment.

Objective: This study was conducted to determine the prevalence and antibiotic sensitivity of bacteria isolated from OM patients of Southern Punjab, Pakistan.

Methodology: A total of 300 ear samples including children and adults were collected from ENT department of Nishtar Hospital, Multan with standard microbiological practices and processed for aerobic bacterial culturing and characterization. Kirby-Bauer disc diffusion method was used for antibiotic susceptibility profiling of isolates and results were interpreted according to CLSI guidelines.

Results: It was observed that Gram negative bacteria (73%) were predominant in comparison with Gram-positive bacteria (27%). Pseudomonas aeruginosa (35%) was the most predominant in patients of OM, followed by Staphylococcus aureus (27%), Proteus vulgaris (11%), Escherichia coli (8%), Enterobacter spp (8%), Klebsiella spp (5%), Proteus mirabilis (4%), Citrobacter spp (2%), and Serratia spp (1%). Out of all, 34% were resistant to more than three different classes of drugs and hence, were MDR. The majority of the bacterial isolates were sensitive to Amikacin, Aztreonam, Cefaclor, Imipenem and Levofloxacin. However, most of them exhibited resistance towards Amoxicillin/Clavulanic acid, Cefixime, Ceftriaxone and Clarithromycin.

Conclusion: The high prevalence of drug resistance among OM pathogens necessitates the enhancement of surveillance systems and promotion of antibiotic stewardship programs.

Key words: Antibiotic Resistance, Antibiotic Sensitivity, Multidrug Resistant, Otitis Media

Introduction

Otitis media (OM) is an inflammatory disease of the middle ear which is common among children and is categorized into two subtypes based on whether or not the infection is present and duration of disease: acute OM (AOM) and OM with effusion (OME).[1] AOM refers to acute onset of symptoms due to infection of middle ear whereas OME is characterized by effusion from middle ear without infection, both of which is clinically related but requires different strategies for treatment.[2]

OM is associated with a high morbidity rate among children which is reflected by the fact that among patients visiting pediatrics and otorhinolaryngology departments, the second highest incidence rate has been reported for OM.[3] It has been reported that around 80% of the children experience AOM during first five years of their life and the incidence rate of 14.52% has been described for South Asia.[4] In Pakistan, the incidence of AOM was reported at 17.80 % among children less than two years old.[5] M is linked to a multifactorial etiology

involving anatomical differences, microbe-host interactions as well as cell biology of middle ear and nasopharynx.[6]

Haemophilus influenzae, Streptococcus pneumoniae and *Moraxella catarrhalis* are the three most frequently isolated bacterial pathogens from OM, although other microbes including fungi and anaerobic bacteria may also be involved.[7] While bacteria are considered as the most common cause of OM, viral infections of upper respiratory tract can enhance the predisposition for bacterial infection because they can lead to dysfunction of eustachian tube thereby supporting the attachment of bacteria to epithelial cells and facilitating bacterial colonization of nasopharynx.[8]

OM is the leading cause for antibiotic prescription and surgical treatment among children.[9] In 2004, AAP and AAFP Clinical Practice Guidelines on AOM provided principles for observation versus antimicrobial therapy which recommended restricted and deliberated use of antibiotics among children. However, this has not led to a significant decrease in antibiotic prescription in subsequent years.[10] Antibiotic use is still considered the first-line and second-line approach for management of OM highlighting the widespread and problematic antibiotic usage.[11] Consequently, antibiotic treatment of OM has been linked to encouragement of antibiotic resistance among pathogenic microbes and earlier exposure to antibiotic drugs can also enhance the risk for antibiotic resistance.[12]

Vaccination has been introduced as a preventive solution to the universal problems of OM which can protect against OM as well as its complications and reduce the burden of growing antibiotic resistance.[11] A multitude of vaccines have been tried against OM and some of them have resulted in decreased frequency of OM, however, they have not proved to be highly efficacious due to several challenging problems including involvement of multiple pathogens and frequent occurrence in infants with poorly established host defense mechanisms.[13] The *H. influenzae* type b (Hib) vaccine was introduced in Pakistan in 2009 and in the post-vaccination era, a rise in polymicrobial cultures and *H. influenzae* has been described in children less than five years of age which is surprising and requires further studies to ascertain.[14] Other vaccines have also been introduced in Pakistan in ensuing years against pathogens that can cause OM, among other diseases.[15] The present study was undertaken to investigate the prevalence and antibiotic sensitivity of bacteria isolated from OM patients of Southern Punjab, Pakistan.

Materials and Methods

For this observational study, samples were collected from ENT indoor/outdoor ward of Nishtar Medical University, Multan, Pakistan between September 2020 and April 2021. Subsequently, they were processed at Department of Microbiology and Molecular Genetics, The Women University, Multan, Pakistan. The study was approved by the Research Ethical Committee of The The Women University (WUM/REC/23-03). All procedures were in compliance with the declaration of Helsinki. Informed written consent was taken from participants or their relatives. Patients were included after confirmation of OM diagnosis by respective clinicians irrespective of age and gender. The clinical subtypes of OM including acute OM and OM with effusion were included among the samples. Additionally, only the patients experiencing pus discharge within last three months were included. Patients receiving antibiotic treatment or having systemic infections were excluded. Patients who had experienced surgery for treatment of OM were also excluded. A total of 300 pus samples were taken with the help of an aural speculum from middle ear following complete aseptic precautions by disinfecting the outer surface of ear with 70% alcohol swab. Data regarding age and gender was obtained from the hospital management system. Patients were categorized into five age groups: Group 1, less than 10 years; Group 2, 10-30 years; Group 3, 30-50 years; Group 4, 50-70 years and Group 5, greater than 70 years. Samples were cultured using blood and MacConkey agar and incubated at 37°C for 24-48 hours after which colony morphology was observed. Subsequently, Gram staining was performed to discriminate between Gram-positive and Gram-negative bacteria.

Further characterization was done using biochemical tests. Catalase and coagulase tests were performed for identification of Gram-positive cocci whereas triple sugar iron (TSI), Simmon's citrate, sulphide indole motility (SIM), oxidase and urease tests were done for identifying the Gram-negative rods. Identity of bacterial isolates was established based on their morphological, cultural as well as biochemical characteristics. Antibiotic sensitivity profile was established by using Kirby-Bauer disc diffusion method using Mueller-Hinton agar. 0.5 McFarland standard was included. The antibiotics used for this purpose were purchased from Oxoid™ and these included Amikacin (30ug), Amoxicillin/clavulanic acid (20/10ug), Azithromycin (15ug), Aztreonam (30ug), Cefaclor (30ug). Cefixime (5ug), Ceftriaxone (30ug), Clarithromycin (15ug), Imipenem (10ug), Levofloxacin (5ug), Linezolid (30ug) and Piperacillin/Tazobactam (30/10ug). Zones of inhibition were measured and documented according to Clinical Laboratory Standard Institute (CLSI) guidelines. The isolates which were resistant to more than three groups of drugs were termed as Multidrug Resistant (MDR) pathogens [16]. All experiments were done in triplicates and data was analyzed on Statistical

Package for Social Sciences (SPSS), version 18.0. Results were documented as frequency and percentage.

Results

Patients from the entire Southern Punjab region become admitted to Nishtar Hospital, Multan, thus making our study population representative of Southern Punjab, Pakistan. Out of 300 patients, 56% were males while 44% were females as shown in Table I which indicated greater prevalence of OM among males as compared to females. In general, OM was more prevalent among younger individuals as compared to the older ones. Majority of the patients belonged to the age group of 10 to 30 years among both males and females. The disease was least prevalent among individuals who were 50 to 70 years old or those older than 70 years, irrespective of gender. All of the samples were positive for bacterial culturing. Results for gram staining revealed that majority (73.33%) of the isolates were Gram-negative while some (26.67%) of them were Gram-positive. Bacterial pathogens isolated from OM patients included *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., *Proteus vulgaris*, *Proteus mirabilis, Serratia* spp. and *Staphylococcus aureus*. In terms of bacterial frequency, *Pseudomonas aeruginosa* (34.67%) was the most prevalent followed by *Staphylococcus aureus* (26.67%), *Proteus vulgaris* (11.0%), *Escherichia coli* (8.33%), *Enterobacter* spp. (7.67%), *Klebsiella* spp. (4.67%), *Proteus mirabilis (4.33%)*, *Citrobacter* spp. (1.66%) and *Serratia* spp. (1.0%) as summarized in Table II.

Table I: Age and gender-wise distribution of otitis media patients.

Age in years	Males (%)	Females (%)	Total (%)
Less than 10	30 (10%)	25 (8.33%)	55 (18.33%)
10-30	73 (24.33%)	59 (19.67%)	132 (44%)
30-50	37 (12.33%)	24 (8%)	61 (20.33%)
50-70	16 (5.33%)	12 (4%)	28 (9.34%)
Greater than 70	13 (4.33%)	11 (3.67%)	24 (8%)
Total	169(56.33%)	131 (43.67%)	300(100%)

Table II: Distribution of bacterial isolates among otitis media patients.

Bacterial isolate	Number	Percentage
Pseudomonas aeruginosa	104	34.67%
Staphylococcus aureus	80	26.67%
Proteus vulgaris	33	11.00%
Escherichia coli	25	8.33%
Enterobacter spp.	23	7.67%
Klebsiella spp.	14	4.67%
Proteus mirabilis	13	4.33%
Citrobacter spp.	5	1.66%
Serratia spp.	3	1.00%
Total	300	100%

The antibiogram of Gram-positive and Gram-negative isolates is shown in Table III. Majority of the Gram-positive isolates were resistant to Aztreonam and a considerable degree of resistance was observed against Amoxicillin/clavulanic acid, Azithromycin, Cefixime and Ceftriaxone. However, they were completely susceptible to Amikacin, Cefaclor and Clarithromycin. Among the gram-negative bacteria, *Pseudomonas aeruginosa* were highly resistant against Amikacin, Amoxicillin/clavulanic acid, Cefixime and Levofloxacin as well as substantially against Azithromycin, Imipenem and Piperacillin/Tazobactam. *Proteus vulgaris* were, to a large extent, resistant against Amoxicillin/clavulanic acid, Azithromycin and Cefixime and extensively against Aztreonam, Ceftriaxone and Levofloxacin.

Most of the *Escherichia coli* isolates demonstrated resistance against Cefixime, Ceftriaxone and Amoxicillin/clavulanic acid as well as several of those were resistant to Azithromycin, Aztreonam and Levofloxacin. However, they were highly susceptible to Imipenem. Regarding *Enterobacter* spp., a great deal of resistance was manifested against Amikacin, Amoxicillin/clavulanic acid and Azithromycin. They were also largely resistant against Cefixime and Piperacillin/Tazobactam but quite susceptible to Cefaclor, Imipenem and Levofloxacin. *Klebsiella* spp. were observed as being highly resistant to Levofloxacin and considerably resistant to Amikacin, Azithromycin, Cefixime and Ceftriaxone. *Proteus mirabilis* isolates exhibited complete resistance against Cefaclor and Clarithromycin as well as great susceptibility to Amikacin and Aztreonam. *Citrobacter* spp. were entirely resistant to Cefaclor and Clarithromycin as well as highly resistant to Amoxicillin/clavulanic acid, Cefixime and Ceftriaxone. Regarding *Serratia* spp., it was observed that they were completely resistant against Amoxicillin/clavulanic acid, Cefaclor, Cefixime, Ceftriaxone and Clarithromycin. Out of all, 104 (34%) isolates were observed as being resistant to more than three different classes of antibiotics and hence, were documented as being MDR pathogens.

Discussion

OM is considered one of the most common disorders for patients to contact doctors and undergo antibiotic treatment. It is one of the most common health issues in hospitals, being associated with a high frequency and incidence in both developed and developing countries.[16] Regarding treatment of OM, the universal therapy of choice is antibiotic therapy due to its proven effectiveness.[17] However, heavy reliance on empirical antibiotic treatment and neglect of the approach of watchful waiting has led to adverse consequences and treatment failure due to rise in antibiotic resistance among pathogens.[18] It is important to keep abreast of the dynamic

Table III: Antibiogram showing percentage of resistant bacteria isolated from otitis media patients.

Organism	Amikacin	Levofloxacin	Amoxicillin/clavulanic acid	Azithromycin	Aztreonam	Ceftriaxone	Cefixime	Linezolid	Imipenem	Piperacillin/Tazobactam	Clarithromycin	Cefaclor
Pseudomonas aeruginosa	56/104 53.8%	57/104 54.80%	59/104 56.73%	42/104 40.38%	20/104 19.23%	29/104 27.88%	71/104 68.26%	-	50/104 48.07%	34/104 32.69%	31/104 29.80%	31/104 29.80%
Staphylococcus aureus	5/80 6.25%	21/80 26.25%	28/80 35%	37/80 46.25	63/80 78.75%	34/80 42.5%	27/80 33.75%	20/80 25%	20/80 25%	22/80 27.5%	3/80 3.75%	3/80 3.75%
Proteus vulgaris	8/33 24.24%	12/33 36.36%	17/33 51.51%	18/33 54.54%	13/33 39.39%	16/33 48.48%	18/33 54.54%	-	8/33 24.24%	9/33 27.27%	7/33 21.21%	7/33 21.21%
Escherichia coli	3/25 12%	12/25 48%	13/25 52%	9/25 36%	11/25 44%	17/25 68%	14/25 56%	-	2/25 8%	6/25 24%	7/25 28%	7/25 28%
Enterobacter spp.	12/23 52.17%	3/23 13.0%	14/23 60.86%	12/23 52.17%	7/23 30.43%	7/23 30.43%	10/23 43.47%	-	3/23 13.0%	11/23 47.82%	5/23 21.7%	3/23 13.04%
Klebsiella spp.	5/14 35.71%	7/14 50%	3/14 21.42%	5/14 35.71%	2/14 14.28%	6/14 42.85%	6/14 42.85%	-	2/14 14.28%	2/14 14.28%	4/14 28.57%	4/14 28.57%
Proteus mirabilis	1/13 7.69%	2/13 15.38%	3/13 23.0%	-	1/13 7.69%	3/13 23.0%	2/13 15.38%	-	-	-	13/13 100%	13/13 100%
Citrobacter spp.	1/5 20%	1/5 20%	4/5 80%	-	-	4/5 80%	4/5 80%	-	1/5 20%	-	5/5 100%	5/5 100%
Serratia spp.	1/3 33%	1/3 33%	3/3 100%	-	-	3/3 100%	3/3 100%	-	1/3 33%	1/3 33%	3/3 100%	3/3 100%

patterns of antibiotic resistance among bacterial pathogens causing OM so that well timed alternative management options may be devised conveniently and keeping this in view, 300 ear samples of OM patients were collected and processed to determine the prevalence and antibiotic sensitivity pattern of bacterial pathogens in a local population of Southern Punjab, Pakistan. Kadhim *et al* reported in 2018 that OM was more prevalent among males (63%) in comparison with females (37%) representing age-based differences in prevalence of

OM.[19] According to the findings of our study, OM was more common among males (56.33%) than the females (43.67%). This may be attributed towards their greater likelihood of being exposed to the external environment and involvement in activities like swimming etc. owing to the cultural norms of Pakistan.

According to the observation of this study, 18.33% cases were less than 10 years of age, 44% cases were in the age range of 10-30 years, 20.33% cases were in the age range of 30-50 years, 9.34% cases were in the age range of 50-70 years while 8% cases were above 70 years of age. Overall, OM infection was more prevalent in younger population than in adults. This is in line with the results of another study where age of 18 (20%) patients was less than 15 years, age of 62 (69%) patients was in the range of 15-40 years and age of 9 (11%) patients was greater than 40 years [20]. The main reason is that eustachian tube is shorter, narrower and straighter in younger children as comparable to adults increasing the possibility of disease occurrence.[16]

In our study, the most predominant pathogen isolated from ear swabs was *Pseudomonas aeruginosa* followed by *Staphylococcus aureus* and *Proteus vulgaris*. A small number (<10% each) of *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Proteus mirabilis*, *Citrobacter* spp. and *Serratia* spp. were also present among the isolated pathogens. Similar observations were described in a study conducted by Kaur *et al* in 2016 where *Pseudomonas aeruginosa* was the most prevalent (34.9 %) among OM patients, followed by *Staphylococcus aureus* (24.4%) and *Proteus mirabilis* (6.3%).[20] Likewise, Joseph *et al* in 2017 reported *Pseudomonas aeruginosa* as the dominant (39%) bacterium responsible for causing OM complications.[21] *Pseudomonas aeruginosa* is considered to be well-suited for growth in the auditory meatus of humans and is specifically implicated in the mucosal diseases. It has been projected that *Pseudomonas aeruginosa* possess the ability to evade host defenses by exploiting the shell of surrounding damaged epithelial layer resulting in a decrease in the blood circulation to damaged area and hence, damage to tissues. According to some researchers, OM caused by enteric bacteria is because of fecal contamination of auditory canal instead of nasopharyngeal colonization of bacteria. Incorrect outer ear cleaning, water pollution caused by human and animal waste as well as swimming in ponds are some of the factors associated with high prevalence of *Pseudomonas aeruginosa* and enteric bacteria that are responsible for OM infection.[22]

Antibiotic sensitivity profiling revealed that majority (>50%) of the *Pseudomonas aeruginosa* isolates were resistant to Amikacin, Amoxicillin/Clavulanic acid, Cefixime and

Levofloxacin while the most effective antibiotic against them was Aztreonam. In another South Asian population, Amikacin was found to be quite ineffective but various cephalosporin antibiotics were reported as being efficacious against *Pseudomonas aeruginosa*. With respect to *Staphylococcus aureus,* they reported complete susceptibility to Amikacin, high susceptibility to cephalosporins and considerable susceptibility to macrolides.[23] Our isolates of *Staphylococcus aureus* also showed high susceptibility to Cefaclor (cephalosporin), Clarithromycin (macrolide) and Amikacin as well as high degree of resistance to Aztreonam. We also found that *Proteus vulgaris* was highly resistant to Amoxicillin/Clavulanic acid, Azithromycin and Cefixime whereas *Proteus mirabilis* was completely resistant against Cefaclor and Clarithromycin but highly susceptible to Amikacin and Aztreonam. Previously, *Proteus* spp. have been described as being highly resistant against Amoxicillin as well as various cephalosporin antibiotics but showed variable degree of sensitivity against various macrolide antibiotics.[24]

Pertinent to *Escherichia coli*, we found high degree of resistance against cephalosporins including Cefixime (56%) and Ceftriaxone (68%) as well as Amoxicillin/Clavulanic acid (52%). Yet, they were susceptible to Amikacin (88%) and Imipenem (92%). Another study has reported similar observations where *Escherichia coli* exhibited high resistance to Amoxicillin/Clavulanic acid and various cephalosporin antibiotic drugs but complete susceptibility to Amikacin along with some other antibiotics. With regard to *Enterobacter* spp., they reported complete resistance to Amoxicillin/Clavulanic acid and various cephalosporins but complete sensitivity to Amikacin, Imipenem and Levofloxacin.[25] Our isolates of *Enterobacter* spp. were demonstrated as being highly resistant to Amikacin (52%), Amoxicillin/Clavulanic acid (60.86%) and Azithromycin (52.17%). Nonetheless, they were considerably susceptible to Imipenem (86.9%) and Levofloxacin (86.9%).

Out of all, 34% of the isolates were established as being MDR. Previously, bacteria resistant to multiple drugs have been reported from OM patients in several studies with particular emphasis on *Pseudomonas aeruginosa.*[26] The differences as well as similarities between our observations and the earlier reports highlight the dynamic pattern of antibiotic sensitivity profiles of microorganisms. However, for some organisms, number of isolates was too small to ascertain their sensitivity with certainty. Other limitations were inclusion of all types of OM and all age groups due to which sample size for each category was relatively small. Furthermore, the isolation procedure excluded anaerobic pathogens, the molecular identification was not done, and controls were not considered.

Conclusions

In conclusion, we found that *Pseudomonas aeruginosa, Staphylococcus aureus* and *Proteus vulgaris* were the most common pathogens responsible for causing otitis media in Pakistani population of Southern Punjab. Among these, *Pseudomonas aeruginosa* was the most prevalent. Furthermore, around one-third of all of the isolates were MDR. By understanding the microbial etiology of OM, it is important to design and evaluate the best course of treatment. To avoid irrational use of antibiotics, surveillance and stewardship programs must be implemented. It is now required to track changes in microbial infection patterns, and evolution of resistance among pathogens. Further studies must be conducted in a larger population encompassing a comprehensive strategy for identification of pathogens and assessment of their antibiotic susceptibility profiles.

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