

Antibiotic resistance pattern of *Streptococcus pneumoniae* among infants younger than six months of age with acute otitis media in Erbil city

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Abstract

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Background: Acute otitis media (AOM) is one of the most common inflammatory disorders particularly in infants. Multiple factors such as gender, using bottle-feeding formula, and exposure to cigarette smoking are thought to raise the incidence of AOM. In infants at age six months or less, *Streptococcus pneumoniae* is the most common causative bacteria of AOM. The complications of pneumococcal infections are due to increasing the rate of antibiotic resistance among the *S. pneumoniae* strains that coincides with the increased use of antibiotics and multidrug resistant which severely limits the therapeutic options and poses a great threat to public health.

Objective: To determine the antibiotic resistance patterns of *S. pneumoniae* in infants aged six months or less with AOM as the most frequently isolated bacterial pathogens and the most possible risk factors such as parent smoke and bottle feeding that may increase the incidence of acute otitis media in infants.

Patients and Methods: A total of 148 infants six months of age or less, 87 males and 61 females with acute otitis media were enrolled in a current study. Swab from ear discharges were collected and cultured. The bacterial isolates were identified and the antibiotic susceptibility pattern for *S. pneumoniae* isolates was tested.

Results: Among the 148 infants studied with acute otitis media, the frequency of the isolated microorganisms from infants with otitis media in male were higher than female and the majority of the infants were bottle feed and who exposed to cigarette smoke at home. *S. pneumoniae* was comprised the most frequent pathogen (40%) in the selected age, and the antibiotic resistance pattern of 68 *S. pneumoniae* isolates showed high resistance rate against penicillin, erythromycin and cefalothin. On the other hand, imipenem, vancomycin and chloramphenicol were the most effective drugs against *S. pneumoniae* isolates.

Conclusion: The current study has identified *S. pneumoniae* as the most causes isolated pathogen in infants at age six months or less with acute otitis media and the majority of bacterial isolates showed a high rate of resistance against antibiotics and the majority of these isolates revealed multi drug resistance phenotype. It has been found that children exposed to passive smoking in the home and who are bottle-fed were at increased risk of acute otitis media .

Keywords: Acute otitis media, infants, risk factors, *Streptococcus pneumoniae*, multi drug resistance

Introduction

Acute otitis media (AOM) is one of the most common inflammatory disorders particularly in neonates and young infants and can be difficult to diagnose [1, 2]. The two major sub-classifications of otitis media are otitis media with effusion (OME) and acute otitis media (AOM) [3]. Many factors can lead to problems with AOM in neonates and young infants, the infection in this age group may not be localized; it can disseminate and cause a variety of invasive diseases such as bacteremia, sepsis and meningitis which considered a significant cause of morbidity and mortality in infants [4, 5].

Indeed, AOM is a multifactorial, often polymicrobial illness. In the middle ear, both pathogenic bacteria, as well as respiratory viruses can be involved in the infection. Bacteria are retrieved in 50-90% of cases of AOM and the main pathogens are *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae* (NTHi) and *M. catarrhalis* [6, 7]. In infants at age six or less, *Streptococcus pneumoniae* is the most common causative bacteria of AOM [8].

S. pneumoniae is the main cause of pneumonia, meningitis, and otitis media worldwide [5, 9, 10]. In pneumococcal infection, the young children are most susceptible as the nasopharynx in this age group is the main reservoir for pneumococci and the infection occur once the carriage strain moves from nasopharynx to invade another body site [11, 12].

In terms of risk factors, multiple factors such as gender, using bottle-feeding formula, and exposure to cigarette smoking are

thought to raise the incidence of AOM, particularly in young children [13,14]. In children, pneumococcal otitis media results in more damage to the ear and is more likely to lead to recurrent infections, treatment failures and postinfectious complications [15]. The complications of infections are due to increasing the rate of antibiotic resistance among the *S. pneumoniae* strains that coincides with the increased use of antibiotics which severely limits the therapeutic options and poses a great threat to public health as well as imposes a high cost to the AOM patients resulting in greater risk of death [16, 17].

The emergence of drug resistant pneumococci has reported around the world including 13 Asian countries [18, 19], Africa and the Middle East [20] and Ethiopia [21]. Indeed, numerous physicians started to prescribe the antibiotics empirically before the results of microbiological culture are obtained particularly in infants. Penicillin for example was generally the antibiotic of choice, however, the global development of antibiotic resistance (particularly penicillin-resistance) among *S. pneumoniae* isolates has changed the approach to managing AOM. In response to these changes, a combination of two or more antibiotics has been used to treat pneumococcal infections and for longer durations. Interestingly, *S. pneumoniae* strains with increased resistance to penicillin were found to frequently show cross-resistant to other antibiotics. For that reason, resistance to penicillin is reported to be a surrogate marker for the presence of a multidrug-resistant phenotype, this has been

particularly problematic for patients with recurrent AOM, who use antibiotics frequently. These conditions inevitably lead to limitation of treatment options [22].

Several mechanisms may account for the increased rate of pneumococcal resistance against antibiotics. Pneumococcal strains have ability to acquire resistance genes by natural transformation in which pneumococci picked up a specific genome from bacteria that often colonize the nasopharynx such as *Streptococcus mitis*, the transferred gene were incorporated into their own DNA resulting in all β -lactam antimicrobials including penicillin having a decreased binding affinity by the penicillin-binding proteins (PBPs). Moreover, several other mechanisms for antibiotics resistance have been identified such as increased drug efflux, target mutations, decreased bacterial permeability, and reduced penetration of the antibiotics to the target sites [23, 24].

The emergence of penicillin resistant strains globally poses therapeutic problems. As an alternative, Macrolides such as azithromycin or clindamycin that generally considered a good alternative for β -lactam antibiotics were used widely for treatment of respiratory tract infections, however, recent data revealed an increasing prevalence of macrolide-resistant *S. pneumoniae* in various parts of the world [25, 26]. The ability of pneumococcal strains to acquire resistance genes such as *erm* gene, which codes for a ribosomal methylase that confer a significant resistance against macrolides as well as *mef* gene, which codes for a macrolide efflux pump are two main mechanisms of resistance [27]. In addition, *S. pneumoniae* can also acquire resistance gene from gram-negative

bacteria such as *Escherichia coli*, *Klebsiella* spp., and *Haemophilus* spp. by natural transformation. Similarly, pneumococcal strains can acquire *pbp* gene mosaics (involving *pbp1a* and *pbp2*) by transformation which confer resistance to extended spectrum cephalosporins and amoxicillin [28, 29].

To date, pneumococcal strains revealed resistance to more than three separate classes of antibiotics, hence, they are considered to be multidrug resistant [15]. Unfortunately, the prevalence of antibiotics-resistant *S. pneumoniae* in the nasopharynx of children increases the risk of resistant strains that cause pneumococcal infection. Multiple factors potentially involved in emerging and spreading multidrug-resistant *S. pneumoniae* (MDR-SP), but prior excessive and improper use of antibiotics, day care attendance, young age as well as horizontal gene transfer are the most frequently identified risk features [14, 17].

Compared to adults, the immune systems of the infants take time to fully develop. Data about the resistance rates in young infants (especially six month or less) are relatively rare for this age group, therefore, knowledge is essential for determining the proper antibiotics against AOM. In current study we aimed to determine the antibiotic resistance patterns of *S. pneumoniae* as the most frequently isolated bacterial strain.

Patients and Methods

Infants six months of age or less from both gender who were diagnosed with AOM by an Ear-Nose-and-Throat (ENT) specialist visited outpatient clinics in Erbil city from January 17, 2021 to August 25, 2021 were enrolled in the study.

Consents were taken from the parents for participation in the study. Swabs from ear discharges (unilateral or bilateral) were collected by a sterile swab under aseptic precautions and inoculated on blood agar (Oxoid), MacConkey agar (Himedia), manitol agar (Himedia) and Sabouraud dextrose agar (Oxoid). All agar plates were incubated at 37°C for 24-48 hours and were examined after 24 and 48 hours. Plates showing no growth with 48 hours (within) were recorded as negative cultures. The isolates were identified according to colonies morphology, Gram’s stain reaction and standard biochemical reactions that routinely are used in microbiological diagnostic laboratories. The antibiotic susceptibility pattern for *S. pneumoniae* isolates against Amoxicillin, Amoxicillin + Clavulanic acid, Ampicillin, Penicillin G, Cefalothin, Cefalexin, Ceftriaxone, Cefotaxime, Imipenem, Meropenem, Tetracycline, Doxycycline, Ciprofloxacin, Azithromycin, Erythromycin, Clindamycin, Gentamycin, Trimethoprim-Sulfamethoxazole, Chloramphenicol, Vancomycin (Oxoid, UK) was evaluated according to the guidelines of Clinical and Laboratory Standards Institute (CLSI) 2015[30].

Inclusion Criteria

Infants at age six months or younger from both gender, who were diagnosed with unilateral or bilateral AOM by an Ear-Nose-and-Throat (ENT) specialist that need

antibiotics were enrolled in the study.

Exclusion Criteria

Infants who had known immunologic disorders, and those does not need antibiotics, and who had received antibiotic treatment within four weeks and, were excluded from the current study.

Statistical analysis

In the current study, most of the data were presented as a percentage by using excel program depending on the percentage calculation equations.

Results

The total number of infants with AOM was 148 infants, males were 87 patients (58.8%) and female were 61 patients (41.2%) Table (1). From these patients, 168 samples were obtained for culture, pure cultures were 96 (64.9%) and mixed infections were recorded in 20 (13.5%) of patients, while 32 (21.6%) of cultured samples were sterile Table (2). Positive bacterial cultures were obtained in 116 patients (78%), *S. pneumoniae* was the leading one, (40%) followed by *Staphylococcus aureus* (31%), *Pseudomonas aeruginosa* (11%), *Esherichia coli* (7%), *Klebsiella pneumoniae* (5%), *Proteus mirabilis* (4%) and *Candida albicans* (2%). In General, the frequency of the isolated microorganisms from infants with otitis media in male (65%) were higher than female (35%) Table (3).

Table (1): Distribution of AOM according to the gender

Sex	No. of case	Percentage
Male	87	58.8
Female	61	41.2
Total	148	100%

Table (2): Microbial isolates from infants with otitis media

Type	No. of case	Percentage
Monomicrobial (Pure culture)	96	64.9
Polymicrobial (Mixed culture)	20	13.5
No growth (Sterile)	32	21.6
Total	148	100

Table (3): Frequency of isolated microorganisms from infants with otitis media

Total positive bacterial cultures = 168				
Bacteria	No.	%	Gender	
			Male (%)	Female (%)
<i>Streptococcus pneumoniae</i>	68	40	46 (68)	22 (32)
<i>Staphylococcus aureus</i>	52	31	39 (75)	13 (25)
<i>Pseudomonas aeruginosa</i>	19	11	10 (53)	9 (47)
<i>Esherichia coli</i>	11	7	4 (36)	7 (64)
<i>Klebsiella pneumoniae</i>	9	5	7 (78)	2 (22)
<i>Proteus mirabilis</i>	6	4	3 (50)	3 (50)
<i>Candida albicans</i>	3	2	1 (33)	2 (67)
			Total	
			110 (65)	58 (35)

Among the 148 AOM patients studied, 29 (20%) were bilateral while unilateral AOM were recorded in 40 patients (27%) of right ear and in 79 patients (53%) of left ear Table (4).

Out of 116 culture- positive cases, 51 (44%) infants were bottle feed and 84 (72%) infants who exposed to cigarette smoke at home Table (5).

Table (4): Distribution of patients based according to side affected

Ear	Frequency	Percentage (%)
Right	40	27
Left	79	53
Bilateral	29	20
Total	148	100

Table (5): Frequency distribution of study population according to risk factors for AOM

No. of culture-positive cases = 116		
Ear	Frequency	Percentage (%)
Bottle feeding	51	44
Passive smoking	84	72

As *S. pneumoniae* was comprised the most frequent pathogen in the selected age, current study has been focused on analyzing the antibiotic resistance of this bacterium. All the 68 *S. pneumoniae* isolates were screened for their antibiotic susceptibility toward different classes of antibiotics. The antibiotic susceptibility testing showed imipenem and vancomycin as the most effective drugs (100%) followed by, chloramphenicol (96%), meropenem (91%), gentamycin (82%), doxycycline (74%). More than half (57%) of

S. pneumoniae isolates were sensitive to both azithromycin and tetracycline azithromycin. On the other hand, *S. pneumoniae* isolates showed highest resistance rate against Penicillin and Erythromycin (100%), followed by cefalothin (90%), trimethoprim-sulfamethxaone (88%), cefalexin and clindamycin (82%) and cefotaxime (78%) (Table-6). In current study, *S. pneumoniae* isolates showed resistance to more than three separate classes of antibiotics, multidrug resistant was present in 42 of the 68 (64.7%).

Table (6): Susceptibility patterns of *S. pneumoniae* isolates to various antibiotics

Classes of Antibacterial drugs	Tested antibiotics (Concentrations)	Antibiotic generations	Total isolates (n= 68)			
			Resistant		Sensitive	
			No.	%	No.	%
Beta-Lactams	Amoxicillin (10 µg)	3 rd	42	62	26	38
	Amoxicillin + Clavulanic acid (20/10 µg)	4 th	38	56	30	44
	Ampicillin (10 µg)	3 rd	33	49	35	51
	Penicillin G (10 units)	1 st	68	100	0	0
	Cefalothin (30 µg)	2 nd	61	90	7	10
	Cefalexin (30 µg)	3 rd	56	82	12	18
	Ceftriaxone (30 µg)	3 rd	46	68	22	32
	Cefotaxime (30 µg)	NCG	53	78	15	22
	Imipenem (10 µg)	NCG	0	0	68	100
	Meropenem (10 µg)		6	9	62	91
Tetracycline	Tetracycline (30 µg)	NCG	29	43	39	57
	Doxycycline (30 µg)	2 nd	18	26	50	74
Fluoroquinolones	Ciprofloxacin (5 µg)	2 nd	34	50	34	50
Macrolides antibiotics	Azithromycin (15 µg)	2 nd	43	63	25	57
	Erythromycin (15 µg)	NCG	68	100	0	0
	Clindamycin (2 µg)	NCG	56	82	12	18
Aminoglycosides	Gentamycin (10 µg)	NCG	12	18	56	82
Sulfonamides	Trimethoprim-Sulfamethxaone (1.25/ 23.75 µg)	NCG	60	88	8	12
Phenicol	Chloramphenicol (30 µg)	NCG	3	5	65	96
Glycopeptide	Vancomycin (30 µg)	NCG	0	0	68	100

*NCG: No Classified Generation

Discussion

AOM is a common infection, particularly in infants and children occur multiple times during the first few years of life. AOM is caused by a virus or by bacteria and rarely fungi [2, 5]. In terms of gender, there was a predominance of male (58.8%) compared with female (41.2%) infants with AOM which was agreed with several previous studies [31, 32]. However, Stangerup [33] and Zhang [34] have shown that no gender differences were found in the incidence of AOM. Indeed, gender is a significant epidemiological factor for several diseases and most of the previous studies suggest male gender as a risk factor for AOM and even for recurrent AOM especially at first year of life [35], however the reasons for this sex predominance are not well known and has not been extensively studied, one possible explanation of the observed differences could be related to an inadequate IgG2 antibody production, or a delayed maturation of IgG2 in male [36].

In the present study, bottle-fed children had higher odds of AOM than breast-fed. Indeed, the effects of breast-feeding on the incidence of otitis are thoroughly investigated. Contrary to reports from some authors, Albert [37] and Vytautas [38] who found that breastfeeding was associated with a lower risk of AOM in children especially the first six months of life. The protective effect of the human milk related to the immunological properties that provide specific antibodies against AOM [13].

The data in the current study showed that infants of smoker parents are at increased risk of AOM. Although numerous studies have reported such association in children, either

due to increasing the rate of carriage and colonization of *S. pneumoniae* for the reason that tobacco smoke decreases mucociliary clearance by respiratory epithelium potentially facilitating bacterial adhesion and colonization [39], or depressing the local immune function as well as increasing the ability of bacterial adherence to host epithelium cells of the respiratory system [40, 41], other studies achieved by Roger [42], Liisa [43] and Kilpi [44] have not documented these findings.

Based on results from present study, *S. pneumoniae* was the most prevalent aerobic bacteria isolated from the infants with AOM, which accounted for 40% (68/168) of all strains. This is in agreement with earlier study conducted by Waheeb; et al., reported that *S. pneumoniae* was the predominant agent [45]. In contrast other studies show *Staphylococcus aureus* [46], *Pseudomonas aeruginosa* [47], and *Haemophilus influenzae* [48]. Variation in the frequency rates of these pathogens possibly related to the different laboratory procedures used to identify bacteria, aerobic or anaerobic conditions, season, age group, vaccination status against different pathogenic bacteria and different health care programs in various geographical locations.

S.pneumoniae is among the largest drivers of antibiotic use particularly in young children. Data about the resistance rates of *S pneumoniae* in young infants (six month or less) are relatively rare and Knowledge is essential for determining the proper antibiotics against AOM. *S. pneumoniae* isolates from infants with AOM showed a significant resistance rate to penicillin and erythromycin followed by cefalothin,

trimethoprim-sulfamethoxazole, cefalexin and clindamycin (82%). These findings are almost in accordance with previous studies conducted in Taiwan [49], Canada [50], and Iran [51], however the exact rates slightly changed depending on geographic region and age group.

More than half of *S. pneumoniae* isolates were resistance to ceftriaxone and cefotaxime. These results appear to be in line with what has been reported by Aza and Katan [52]. In contrast to our result and according to Iliyasu et al. study from Nigeria [53], ceftriaxone and cefotaxime were highly recommended due to their highly effective activity.

Among the tested antibiotics in the current study, imipenem and vancomycin showed an excellent activity against all *S. pneumoniae* isolates. Interestingly, most of those isolates that showed resistance against vancomycin and imipenem were also resistance to penicillin. Similarly, previous studies reported by Chinwendu [54], Seyed [55], Abdulrahman [56], Aza and Katan [52], revealed 100% resistance against *S. pneumoniae*.

Meropenem, chloramphenicol, gentamycin and doxycycline were also found to be effective in present study and can be considered a drug of choice in the treatment of otitis media caused by *S. pneumoniae*, however the overuse of meropenem should be discouraged, to reduce the potential for the emergence of resistant strains.

The antimicrobial resistance test in present study indicates the emergence of a multidrug resistance (i.e., non-susceptibility to three or more antibiotic classes) pattern among *S. pneumoniae* isolates and most of the isolate

revealed co-resistance to penicillin, erythromycin, clindamycin, and tetracycline. Multidrug resistance was present in 42 of the 68 (64.7%). Furthermore, the increase of multidrug resistance in *S. pneumoniae* isolates makes the treatment of these infections even more difficult.

Conclusions

The present study revealed that *S. pneumoniae* was the dominant isolates in infants aged six months and less with otitis media. Most of the isolates showed high levels resistance to routinely used antibiotics. However, imipenem, vancomycin and chloramphenicol, gentamicin and fluoroquinolones, have highest activity against all the isolated bacteria. Penicillin, erythromycin and cefalothin should no longer be recommended as the first choice in the empirical therapy to treat pneumococcal infection. Over half (64.7%) of the identified isolates were classified as multidrug resistant. Increase in the number of multi-drug resistance strains is a matter of concern as it will increase the economic and health burden for the children.

Recommendations

The high resistance levels against AOM disease in infants found in the Erbil city of Iraq are alarming. The fact that AOM is among the largest drivers of antibiotic use in children, can lead to the development of antibiotic resistance strains in countries where the antibiotics widely used. Therefore, patterns prior treatment has paramount importance for better management of otitis media and drug-resistant infections.

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Conflict of interest: Nil

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نمط مقاومة المضادات الحيوية للمكورات الرئوية في الرضع الذين تقل أعمارهم عن ستة أشهر والمصابين بالتهاب الأذن الوسطى الحاد في مدينة أربيل

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الملخص

خلفية الدراسة: التهاب الأذن الوسطى الحاد هو أحد الاضطرابات الالتهابية الأكثر شيوعًا في الرضع. عدة عوامل مثل الجنس والرضاعة الصناعية و التعرض للتدخين يعتقد أن لها دور في زيادة حدوث التهاب الأذن الوسطى. تعد المكورات الرئوية من أكثر أنواع البكتيريا المسببة لالتهاب الأذن الوسطى عند الرضع في السن السادسة أو أقل. ارتفاع معدل المقاومة البكتيرية بين سلالات المكورات الرئوية ضد المضادات الحيوية وايضا المقاومة للأدوية المتعددة نتج عنها التقليل في الخيارات العلاجية مما شكل تهديدًا كبيرًا للصحة العامة.

اهداف الدراسة: لتحليل أنواع مسببات الأمراض البكتيرية في الرضع الذين تتراوح أعمارهم بين ستة أشهر أو أقل المصابين بالتهاب الأذن الوسطى الحاد وأيضًا تحديد أنماط المقاومة ضد المضادات الحيوية من قبل المكورات الرئوية باعتبارها السلالة البكتيرية الأكثر شيوعًا..

المرضى والطرائق: أجريت الدراسة على ١٤٨ رضيعا بعمر ستة أشهر أو أقل من كلا الجنسين، ٨٧ ذكراً و ٦١ أنثى شخصوا من قبل أخصائي الأنف والأذن والحنجرة باصابتهم بالتهاب الأذن الوسطى الحاد في العيادات الخارجية في مدينة أربيل. تم جمع مسحات الأذن وزرعها. ثم بعد ذلك تم تشخيص العزلات ودراسة مقاومة المكورات الرئوية للمضادات الحيوية .

النتائج: أظهرت الدراسة على ١٤٨ رضيعا مصابا بالتهاب الأذن الوسطى الحاد ان معدل إصابة الذكور أعلى من الإناث وغالبية المصابين هم من الأطفال الذين يرضعون رضاعة صناعية ويتعرضون لدخان السجائر في المنزل. أشارت الدراسة ان المكورات الرئوية هي أكثر شيوعا من بين البكتيريا المعزولة. أظهرت نتيجة دراسة مقاومة ٦٨ من المكورات الرئوية للمضادات الحيوية بأن الإيميبينيم والفانكوميسين والكلورامفينيكول هي من أكثر الأدوية فاعلية ضد البكتيريا المعزولة . من جهة أخرى، أظهرت عزلات المكورات الرئوية مقاومة عالية ضد البنسلين والاريثروميسين والسيفالوثين. لوحظ في الدراسة الحالية ان الغالبية العظمى من المكورات الرئوية أظهرت المقاومة للأدوية المتعددة

الاستنتاجات: الدراسة الحالية شخّصت المكورات الرئوية باعتبارها البكتيريا الأكثر شيوعا في الرضع في سن السادسة أو أقل المصابين بالتهاب الأذن الوسطى الحاد وأظهرت غالبية هذه العزلات نسبة عالية من المقاومة ضد المضادات الحيوية وغالبية هذه العزلات كانت لها صفة المقاومة ضد أدوية متعددة.

الكلمات المفتاحية: التهاب الأذن الوسطى الحاد ، الرضع ، المكورات الرئوية ، المقاومة للأدوية المتعددة

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