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The Common Microbial Causes of Otitis Media with Especial Focus in Saudi Arabia

Mohammad Salem Alshammari, Hamoud Khalid Alshaya, Abdullah Ahmed Alkhalaf, Jamal Ahmed A. Al Marshadi, Ali M. Alshdokhi, Alharbi AbdulAziz Farhan T., Hussain Gadelkarim Ahmed*

College of Medicine, University of Hail, Saudi Arabia

Abstract Otitis media is one of the common medical issues, which frequently faced by pediatricians. All most round 80% of children are probably experience one or more episodes of otitis media before school age. Many etiological factors have been incriminated to the etiology of Acute Otitis Media (AOM). *Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, Staphylococcus aureus, S. pyogenes* are the most common organisms associated with AOM. AOM may happens as a complication of viral upper respiratory tract infection (URI). Although the prevalence rates of OM is gradually decreasing in Saudi Arabia, but still there is a gap regarding the different causes of otitis media, which has high geographical variation. This review discussed the most common microbial agents associated with otitis media with the main focus on: viral and bacterial etiological factors. This review aimed to review the literature regarding the different etiological factors associated with otitis media with especial stress on literature reported from Saudi Arabia in order to help in designing future otitis media prevention and control strategies in Saudi Arabia.

Keywords Otitis media, Microbial causes, Saudi Arabia

1. Introduction

Otitis Media (OM) is a multifaceted disease with numerous diverse causes contributing to its epidemiology. OM is one of the most public childhood infections in children before school age [1] and responsible of a great majority of childhood morbidity [2-5]. OM is classified into a number of disease sub-categories: acute otitis media (AOM), recurrent AOM, OM with effusion (OME) and chronic suppurative OM (CSOM). AOM attends with local and systemic signs and has a fast start [6, 7] and is a leading reason why children are prescribed with antibiotics [8, 9].

It has been estimated that about 20,000 persons die every year from complications related to OM, with the highest death rates in the children below 5 years of age [4]. Persistent or chronic types of the disease can lead to substantial hearing loss and negatively affect learning ability and educational accomplishment [10].

AOM is diagnosed in patients with acute onset, existence of middle ear effusion, physical sign of middle ear inflammation, and symptoms such as pain, irritability, or fever. AOM is commonly a complication of Eustachian tube dysfunction that happens during a viral upper respiratory tract infection (URI) [11].

AOM can be caused by bacteria in 70% to 90% of the cases [12]. Most of AOM cases are resulting from complications of URI with syncytial virus. Other common viruses include: influenza and parainfluenza viruses, rhinoviruses, adenoviruses, and enteroviruses [13]. The most common bacteria causing AOM include *Streptococcus pneumoniae* and *Haemophilus influenzae*, followed by *Moraxella catarrhalis*. *Streptococcus pyogenes* and *Staphylococcus aureus* are found in smaller numbers of cases [14].

It was well established that viral URI have long been revealed to predispose people to bacterial respiratory infections, including otitis media. Latest evidence proposes that *Streptococcus pneumoniae*, which colonize the nasopharynx asymptomatically, can produce changes in the nasopharyngeal environment caused by virus infection by upregulating specific sets of genes involved in biofilm release, dissemination from the nasopharynx to other sites, and protection against the host immune system. Moreover, an understanding of the transcriptional and proteomic changes happening in bacteria throughout transition to infection has directed to detection of novel vaccine targets that are disease-specific and will not disturb asymptomatic colonization. This tactic will escape major alterations in the delicate balance of microorganisms in the respiratory tract microbiome due to eradication of *S. pneumoniae [15]*.

* Corresponding author:
hussaingad1972@yahoo.com (Hussain Gadelkarim Ahmed)
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Information regarding acute otitis media (AOM) etiology is important for developing effective vaccines. Here, bacterial etiology and antimicrobial susceptibility of AOM were determined in young Saudi children. Therefore, the aim of this review was to review the literature regarding the different etiological factors associated with otitis media with especial stress on literature reported from Saudi Arabia (SA) in order to help in designing future otitis media prevention and control strategies in Saudi Arabia.

2. Epidemiology of Otitis Media in Saudi Arabia

Up to date there is no pan national study featured the disease in Saudi Arabia. However, there are some studies conducted in certain regions of Saudi Arabia. The first study in this context conducted in Dammam (SA) to assess the epidemiology of hearing loss for children at school age. About 7.12% of the children were found with hearing impairment of whom 92.98% had conductive, 3.5% mixed and 3.5% sensor neural deafness. The study concluded that OM was the prime cause of compromised hearing [16]. In An epidemiological survey conducted in Riyadh (SA), 6421 children clinically examined. Hearing defect was identified in 7.7% of the children [17, 18]. Another epidemiological surveyed 9540 children for chronic suppurative otitis media, found that 1.3% of the children experienced chronic suppurative otitis media, and 9 with cholesteatoma [19]. Also AOM was identified in 1.05% of the children. Younger children (<40 years) had higher incidence rates than relatively older (8-12 years). Males had significantly ($P < 0.01$) higher rate of AOM than females.

The prevalence of AOM in the children from the different provinces varied, being higher in those from the Southern and Central regions. Also it was detected that the prevalence of AOM was higher among children whose parents were cousins compared with non-relative parents ($P > 0.001$). Those with poor socio-economic status indicated bigger rate particularly those living in the Southern part with poor or insufficient health services facilities. AOM was significantly associated with hearing impairment ($P < 0.00001$) [20]. In a study curried out in Riyadh (SA) to evaluate the prevalence of hearing loss and to find out its diverse types. Out of 2574 children 45 children were diagnosed with hearing impairment (84.4% conductive and 15.6% sensori-neural), with a total prevalence of 1.75% (95% C.I.: 1.25, 2.25). The majority of cases were females (71.1%), of school age (80.0%), with conductive deafness (84.4%). More than one-half of cases had bilateral deafness (55.6%) of mild degree (57.8%). As for conductive deafness, OM with effusion rated first as a cause of deafness (34.9%), followed by wax and chronic otitis media (23.3% each), while traumatic perforated drum came last (2.3%). Sensorineural deafness constituted 16.2% of all cases [21].

3. Diagnosis of Otitis Media

The serious concerns of imprecise diagnosis of AOM have directed to a call for greater education concerning the diagnostic confidence of AOM [22]. It is necessary to properly detect children with AOM, but the diagnosis is often challenging [23, 24]. Whereas children with AOM typically present with clinical symptoms of fever, ear pain, and irritability, these symptoms are broad-based and often overlap with OME and viral upper respiratory infection [25, 26]. Proficient skills in pediatric otoscopy is critical for performing a precise diagnosis of AOM as the complaint is confirmed by the detection of an effusion and acute inflammatory alterations in the middle ear. Diagnostic doubt due to an inadequacy of pediatric otoscopy skills has led to an over-diagnosis of AOM, which gave rise to an increased incidence of antimicrobial resistance and higher healthcare costs due to needless antibiotic prescriptions and surgical referrals [24]. Moreover the use of combed culture and polymerase chain reaction results, H. influenzae and S. pneumoniae may be involved in 70% and 43% of clinically problematic bacterial acute otitis media episodes, correspondingly [27].

4. Viral Related Otitis Media

It was well established that AOM usually happens during URI, even in the absence of nasopharyngeal bacterial colonization [28]. It is now approved that AOM is a bacterial complication of viral UR), however, viruses alone can cause AOM. The high incidence of AOM results from the extremely high burden of viral URIs. About 35% of URI episodes are complicated by AOM, taking place mostly within the first week of URI beginning [29, 30].

Influenza virus is a major health care burden and is associated with significant morbidity and mortality. Influenza viruses are significant human respiratory pathogens that cause both seasonal, endemic infections and periodic, unpredictable pandemics. Even though individuals of all ages are infected, the highest prevalence is in school-age children; ultimate severity is in infants and the elderly. Influenza A and B viruses are the most common causes of influenza-like illness, but other pathogens (Influenza C, Parainfluenza virus) also cause illness [31, 28].

Though certain types of the lately discovered respiratory viruses (e.g., *Coronaviruses* of the Severe Acute Respiratory Syndrome, *SARS*, and the Middle East Respiratory Syndrome, *MERS*) have owned a lot of publicity [32], common respiratory viruses still have unusually extra influence on the global human health.

Various respiratory viruses are of hundreds of diverse serotypes; these viruses can cause the common cold, or URI. *Rhinoviruses* and *coronaviruses* (229E, OC43 and NL63) are the most common causes of URI. Other virus groups that also cause URI may have distinctive characteristics, for

example, *respiratory syncytial virus (RSV)* is the principal cause for severe bronchiolitis demanding hospitalization among neonates and infants; influenza viruses cause annually epidemics with potentially severe respiratory symptoms and problems; and parainfluenza viruses are commonly associated with acute laryngitis. Comparatively new respiratory viruses such as *human bocaviruses* and *metapneumoviruses h*ave also been revealed to cause URI and AOM in children [33-35]. Though human *bocavirus type 1* causes primarily respiratory infections, virus shedding can exist in the nasopharynx for an extended period; thus the whole impact of this virus in respiratory infections is still vague [34, 35].

However, there a lack of literature denotes the relationship between OM and viruses among Saudi children. The available data denotes the epidemiology of viruses among adults particularly influenza viruses. In a survey conducted among pilgrims as they arrived in Jeddah (SA) for Hajj, the prevalence of any respiratory-virus infection was 14.5% (12.5% among arriving pilgrims and 14.8% among departing pilgrims). The highest viruses identified (both groups combined) were *rhinovirus-enterovirus* (N = 414, 12.9%), *coronaviruses* (N = 27, 0.8%), *respiratory syncytial virus* (N = 8, 0.2%), and *influenza A virus* (N = 8, 0.2%) comprising pandemic *influenza A (H1N1*) (N = 3, 0.1%). The prevalence of pandemic *influenza A (H1N1)* was 0.2% (N = 1) among arriving pilgrims and 0.1% (N = 2) among departing pilgrims [36, 37]. Another recent study examined 300 patients with influenza-like clinical presentation during the period January 2015 – January 2016 in King Khalid Hospital, Saudi Arabia. Approximately 18% were diagnosed with *H1N1 virus* infection; their age ranged from 7 months to 85 years, with a mean age of 25 years. Among them, 34 (63%) were males and 20 (37%) were females [38].

5. Bacterial Related Otitis Media

Nasopharyngeal colonization is an essential starting step in the pathogenesis of AOM. *Streptococcus pneumoniae (Spn), Haemophilus influenzae (*NTHi*), and Moraxella catarrhalis* colonize the nasopharynx and are the three most common AOM pathogens [39]. In initial studies after introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in the US, strains of *Spn* conveying capsular types included in PCV7 were found to be less often from the Nasopharyngeal [40-42], as causes of AOM [43], and aggressive pneumococcal disease [44]. The success of PCV7 in dropping aggressive pneumococcal disease and pneumococcal AOM has developed strong and undeniable [45-47].

NTHi arose as the most common AOM isolate after introduction of conjugated heptavalent pneumococcal vaccine (PCV7) in children <2 years of age [48]. The virtual withdrawal of vaccine serotypes in S pneumoniae carriage has happened in young children, with quick replacement with penicillin-non-susceptible non-vaccine serotypes, mainly 19A and 35B. Excluding the age group at highest risk, preceding prognosticators of carriage, such as child care presence and the attendance of young siblings, have not been altered [49]. There have been inconsistent reports on an increase in nasopharyngeal colonization by *Staphylococcus aureus. In a study* examined nasopharyngeal carriage of *Streptococcus pneumoniae* and *Staphylococcus aureus* among infants and young children with AOM in a country where usage of PCV7 has been increasingly employed. Among 1783 children joined, 60.8% carried *S. pneumoniae*, and 9% carried *S. aureus.* Among *S. pneumoniae* carriers, the rate of *S. aureus* carriage was 8.4%, compared with 9.9% among *S. pneumoniae* non-carriers. The rate of *S. pneumoniae* carriage in the PCV7-vaccinated population was lower (59.8%) than that witnessed in the non-vaccinated population (66.2%; P<.04). In contrast, in young children (age, <2 years) with AOM, it was suggested that the *S. aureus* carriage rate is not exaggerated by PCV7 immunization (9.0% in vaccinated children vs. 8.7% in non-vaccinated children). Moreover, in children aged >1 year, the booster dose brings a sharp decline in the carriage of vaccine serotypes of *S. pneumoniae*, deprived of any alteration in *S. aureus* carriage [50]. An upsurge in *S. aureus* colonization is a concerning likelihood in light of the growing prevalence of severe community-acquired methicillin resistant *Staphylococcus aureu*s infections. Methicillin-resistant Staphylococcus aureus (MRSA) is nowadays a well-known community pathogen in many countries worldwide. Community-acquired MRSA (CA-MRSA) infections have altered numerous aspects of staphylococcal infections in children comprising the epidemiology, clinical manifestations, laboratory approach, antibiotic management, and prevention. [51].

Most reports from Saudi Arabia in this context dealt with epidemiology of OM rather than investigation of the etiological causes. However, some studies investigated the bacterial related OM. In one study 336 clinically significant *S. pneumoniae* isolates were collected from different laboratories in Riyadh (SA). Most of these isolates were from pulmonary and OM (68.2%), and 31.8% were extra-pulmonary (blood and CSF). Of the 336 isolates, 44.6% were susceptible to penicillin, and 55.4% were penicillin non-susceptible (35.7% were intermediate and 19.7% were fully resistant) [52].

In study from SA, 142 patients had OM with effusion, and 58 had chronic OM but without effusion. All of them were *Bacteroides* species. The antimicrobial susceptibility pattern of the isolates showed a 100% sensitivity of the *Bacteroides* isolates to metronidazole and chloramphenicol and a high level of resistance to commonly used systemic antibiotics. Fungal infection of the middle ear was found in 6.5% of the isolates [53]. Between June 2009 and May 2011, 66 children were enrolled. S. pneumoniae was detected in 6 episodes and non-typeable *H. influenzae* (NTHi) in 8 episodes. Moreover, Staphylococcus aureus, which is an uncommon cause of AOM, was detected in 17 episodes. Pneumococcal serotypes were 7F (n=2), 23F (n=2), 19F (n=1) and 15F (n=1).

Susceptibility to cefotaxime was observed in all pneumococcal and *H. influenzae* isolates, to cefuroxime in 4/6 pneumococcal and 8/8 *H. influenzae* isolates, and to penicillin in 5/6 pneumococcal isolates [54].

6. Management

For OM prevention and treatment, particularly AOM, the knowledge on the importance of microbial causing agent with the related clinical indications is very crucial. As AOM is not a pure bacterial illness, the respiratory viruses commonly induce co-infection several bacterial types. In 80-90% of the cases of AOM, bacterial pathogens can be isolated from middle ear fluid, mostly with the three oto-pathogens separately or in combination. Moreover, respiratory viruses were detected in 20-70% of the cases with AOM using conventional and molecular diagnostic methods. As viral infection is self-limited, antibiotics are the only treatment available for AOM [28]. Therefore, many cases of AOM may not need antibiotics (pure viral) or sometimes the middle ear exudate containing bacteria (e.g. pus) may drain via the Eustachian tubes once their function returns to normal.

Depending on the latest clinical trials for which strict criteria for AOM diagnosis were applied [55, 56], the American Academy of Pediatrics has updated the clinical practice guideline on diagnosis and treatment of AOM in 2013 [24]. Primary antibiotic therapy is now endorsed only in infants and children with severe symptoms of AOM or if they attend with oto-rrhea, seemingly with rupture of the tympanic membrane. Children with non-severe symptoms, including those younger than 2 years of age with unilateral AOM, may be perceived without antibiotic primarily. For prevention determinations, the general objective is to decrease or prevent nasopharyngeal colonization of bacterial oto-pathogens, and prevent young children from having viral URI. Whereas the significance of decreasing environmental risks cannot be over stressed, the usage of bacterial and viral vaccines will probably create a significant influence. The licensure of the existing pneumococcal vaccine (PCV-13) in 2010 in the US, with a wider coverage for 6 extra serotypes, has more condensed OM-related healthcare practice [57].

Prevention of viral URI is complicated because of the diversity of several respiratory virus types that are connected to URI. Nonetheless, development has been made through the use of influenza vaccines, the only available respiratory virus vaccines to date. Since early 1990's, investigators have shown that trivalent, inactivated influenza vaccines and later, live-attenuated influenza vaccine have successfully banned AOM during influenza seasons [58, 59]. The vaccines work through preventing influenza infection and influenza-related AOM. The greater influenza activity in the season, the greater probability the 'good-matched' vaccines will be more active in preventing influenza and influenza-related AOM when compared to controls. Moreover, there has been studies on prevention of AOM by early treatment of influenza in children, which indicated that treatment with oral oseltamivir significantly abridged newfangled AOM in young children with laboratory-established influenza infection [60]. Prevention of AOM over the application of respiratory viral vaccines has a likely to be extra effective with the accessibility of vaccines against for more mutual AOM-related viruses with such as RSV. On the other hand, despite decades of RSV vaccine investigation, no RSV vaccine has been established to phase III clinical trials to date. However, any upcoming development to be made concerning vaccination against common respiratory viruses will have an influence on plummeting the liability of AOM.

7. Conclusions

OM may be responsible of many cases of hearing loss among children particularly in Saudi Arabia. The crucial improvement of audiological facilities in schools and primary health centers, is needed. Evidence-based guidelines to detect, screen, and manage OM, particularly AOM may emerge as a future strategy to prevent hearing loss in Saudi Arabia. As many of respiratory viruses play significant part in the pathogenesis and interact with bacteria during AOM, Effective prevention of the disease may depend on prevention of nasopharyngeal bacterial colonization, as well as declining of viral URI prevalence through introduction strict prevention strategies including vaccinations, public awareness and hygiene measures.

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