Acute Otitis Media With Spontaneous Tympanic Membrane Perforation

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Introduction

Acute otitis media (AOM) is a common disease of infants and young children. In the first three years of life almost all children experience at least one episode of this disease and approximately 50% experience recurrent episodes[1]. AOM is mainly a bacterial disease caused by *Streptococcus pneumoniae*, non-typeable (nt) *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes*[2]. In the majority of cases, even the most severe, the tympanic membrane, although bulges and becomes highly hyperaemic, remains intact. However, in a non-negligible number of children occurs spontaneous tympanic membrane perforation (STMP). The perforation is generally small and is typically located in the anterior-inferior quadrant and limited to the *pars tensa* of the eardrum. STMP causes middle-ear fluid to pass into the external ear canal. Accumulation of a large amount of pus in the middle ear cavity during the first phase of the disease is considered the cause of STMP. This pus exerts pressure on the tympanic membrane blood vessels, causing ischaemia and necrosis of the eardrum and leading to perforation[3]. Because in most cases, SMTP repairs itself spontaneously within few days without any further clinical problems, it is considered a mild AOM complication.

In some recent guidelines for the diagnosis and management of AOM, SMTP is considered a sign of severity indicating systematic antibiotic prescription to prevent further clinical problems[4-6]. On the other hand, STMP accompanying AOM might be considered a benign complication because drainage of pus from the middle ear results in a rapid and marked improvement in symptoms and enables the clinician to prescribe tailored antimicrobial therapy. For this reason, many ear-nose-throat (ENT) specialists for diagnostic reasons in children with an intact tympanic membrane at risk of AOM due to uncommon pathogens or with reduced sensitivity to antimicrobials[7] suggest artificial perforation by means of tympanocentesis. However, AOM with STMP might be a disease with some specific characteristics distinguishing it from uncomplicated AOM. Some studies suggest that AOM with STMP is mainly associated with specific pathogens, though these studies are not conclusive[8-11]. Moreover, its prevention in children with recurrent AOM episodes is significantly more difficult than the prevention of uncomplicated AOM cases[12, 13]. Knowledge of the aetiology, pathogenesis and outcome of AOM with STMP may be useful to better understand the relevance of STMP and plan adequate preventive and therapeutic measures for children, especially for those with recurrent AOM.

Incidence of infectious spontaneous tympanic membrane perforation (STMP)

Although the association of STPM with AOM has been a known clinical problem for centuries, its incidence has never been clearly quantified. Data derived from epidemiological studies carried out to evaluate the incidence, clinical aspects and outcomes of AOM are conflicting in this regard. Older studies reported that STMP occurs in 0% to approximately 30% of AOMs diagnosed in younger children[14-17]. A more recent evaluation carried out in several European countries documented a global incidence of STMP of approximately 7%[18]. However, there were significant differences among countries, ranging from 2.1% of episodes in Italy and 2.2% in the UK to 4.8% in Spain, 6.8% in Germany and 17.2% in Sweden.

Various factors such as age of the studied children, criteria used for AOM diagnosis, use of antibiotics, recording practices and genetic characteristics of the enrolled children can significantly influence the reported incidence of AOM with STMP (**Table 1**).

Table 1. Factors associated with high incidence of acute otitis media (AOM) with spontaneous tympanic membrane perforation (STMP).

Factor
Age <2 years
Stringent criteria used for AOM diagnosis
No use of antimicrobial for AOM management
Being an otitis-prone child
Specific genetic polymorphisms

Pukander[16] and Ingvarsson[17] found that STMP was more common in children less than 2 years of age than in older children, with the incidence gradually declining from 50% to 15% in those older than eight years. Moreover, the highest incidence values were in the studies with the most stringent criteria for AOM diagnosis[15]. When enrolled, children with minor modifications of the tympanic membrane leading to uncertain diagnosis, the incidence of STMP was significantly lower[16]. In addition, early and extensive use of antimicrobials for AOM treatment significantly reduces AOM complications, including STMP incidence[19]. Overestimation of STMP frequency may occur when epidemiological studies include mainly otitis-prone children with histories of previous STMP or patients suffering from an underlying disease that may favour AOM development. Similarly, overestimation is common when studies are mainly based on parents' reporting. In this case, ear discharge due to external otitis could be considered a pathognomonic of AOM with STMP. By contrast, underestimation is possible when AOM with STMP without significant otorrhea is not adequately diagnosed. Finally, the genetic characteristics of the patients may play a role in this regard. In a study evaluating potential associations between variants in genes encoding for factors of innate or adaptive

immunity and the occurrence of recurrent AOM with or without STMP, interleukin (IL)-10 rs1800896TC single nucleotide polymorphism (SNP) and the IL-1α rs6746923A and AG SNPs were significantly more and less common, respectively, among children without a history of STMP than among those who suffered from this complication[20]. However, it has been demonstrated that children suffering from a single episode of AOM with STMP are more prone than children with uncomplicated AOM to experience recurrences. Moreover, they are more prone to develop new episodes with STMP. Berger studied 271 patients up to 13 years old with AOM, among whom 80 (29.5%) had STMP[3]. In the three months following the first episode, 20 (25%) of those with STMP experienced a new AOM episode in comparison with 24 (12.5%) of those without. STMP occurred in 17/20 (85%) of children with previous perforation and in 5/24 (20.8%) of those with previous intact tympanic membrane. Similar findings were reported by Van Cauwenberge *et al*[21]. These authors found that the higher the number of AOM recurrences, the higher the likelihood the STMP might occur. There was only a single episode of AOM accompanied by STMP in 15% of the studied children. The frequency of STMP increased to 29% during the second and third episode of AOM and to 40% in children with 3 or more recurrences.

Etiology of acute otitis media with spontaneous tympanic membrane perforation

The same four pathogens that are considered the etiologic agents of uncomplicated AOM can be found in the external ear canal of patients with STMP. However, the question remains whether STMP occurs because some ear pathogens are more aggressive than others or because STMP is a complication independent of the pathogen that causes AOM (**Table 2**).

Table 2. Etiologic agents related with an increased risk of acute otitis media with spontaneous tympanic membrane perforation

Etiologic agent
Streptococcus pneumoniae infection due to invasive pneumococcal strains
Infections due to *Streptococcus pyogenes*
Co-infections with pathogens including non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*
Biofilm production due to non-typeable *Haemophilus influenza*

The evidence seems particularly significant for *S. pyogenes* and *S. pneumoniae*, although the evaluation of the final results of some studies is complicated by several factors. The first is the widespread use of the pneumococcal conjugate vaccines (PCVs) that, after inclusion in the immunization schedule of infants and young children in most countries, have caused worldwide changes in the circulation of *S. pneumoniae* and the frequency with which all the AOM pathogens

cause this disease. Ben-Shimol *et al*. carried out a prospective population-based study in southern Israel in which all AOM episodes submitted for middle ear fluid (MEF) culture in children <3 years from 2004 through 2015 were included.[22]. The incidence of AOM cases due to *S. pneumoniae,* non typable *(*nt) *H. influenzae, M. catarrhalis* and *S. pyogenes* and those that were culture-negative was calculated in the period before the introduction of PCVs and that occurred after the heptavalent PCV (PCV-7) vaccine and the thirteen-valent vaccine (PC-V13) were available. Both pneumococcal and non-pneumococcal AOM episodes, including those in which more than one pathogen was cultured, declined substantially following sequential PCV-7/PCV-13 introduction. The reduction in non-pneumococcal episodes was ascribed by these authors to early prevention of AOM episodes, resulting in a lower rate of complex, often non-pneumococcal AOM[22]. The second factor is the reduced number of studies in which the aetiologies of uncomplicated and complicated AOMs have been evaluated simultaneously. Tympanocentesis is not routinely recommended for ethical reasons[6], and most recent studies of AOM aetiology have included only cases with STMP[23,24]. This practice precludes any possibility of comparing the two types of AOM.

Streptococcus pyogenes

The available data on *S. pyogenes* indicate that this pathogen is more common in AOM complicated by STMP than in uncomplicated cases. Segal *et al*. studied 11,311 episodes of AOM, including both uncomplicated (the great majority) and complicated cases, and found that *S. pyogenes* could be identified in the MEF in only 3.1% of the cases compared to 47.9%, 43.2% and 4.1% of nt-*H. influenzae*, *S. pneumoniae* and *M. catarrhalis*, respectively[25]. However, the clinical features of *S. pyogenes* AOM were significantly different and generally more severe than those of AOM caused by other pathogens, suggesting that *S. pyogenes* might cause faster and more significant damage to the tympanic membrane. Episodes of *S. pyogenes* AOM occurred mainly with STMP and were accompanied by high fever and other systemic findings, such as upper - and lower -respiratory infections. Similar results were reported by Leibovitz *et al*. in a study in which 5,247 culture-positive patients with AOM were enrolled[10]. In the 822 children with STMP, *S. pyogenes* was found in a significantly greater proportion than in those without (47/822, 5.7%, vs 44/4425, 1%, $p<0.01$). Further confirmation of the role of *S. pyogenes* in causing STMP is given by the data collected by Grevers *et al*.[8] with a study carried out in Germany (*S. pyogenes* in 17/5 of othorrea samples) and by Marchisio *et al*.[9] with a retrospective evaluation performed in Italy.

Streptococcus pneumoniae

The real importance of *S. pneumoniae* as direct cause of STMP is difficult to ascertain. However, Palmu *et al*., in a study performed before the introduction of PCVs, reported that initial episodes of AOM with STMP were mainly due to this pathogen[11]. Bacterial cultures of the STMP samples revealed a higher proportion of pneumococci (35%) and lower proportions of *M. catarrhalis* (3%) and mixed cultures (3%) than did the other MEF cultures. However, pre-existing perforations that suggest recurrent diseases[26] were more likely to contain nt-*H. influenzae* (30%) and mixed pathogens (18%) and were less likely to be culture negative

(16%). These findings indicate that the first episodes of AOM with STMP are due mainly to this pathogen, and other bacteria, alone or in combination, are only associated with STMP later, in association with recurrent episodes. On the other hand, several studies have shown that *S. pneumoniae* is an extremely common cause of early AOM[11, 27, 28], and many cases are particularly severe because they are associated with significant increase of inflammatory markers and high fever, intense otalgia, and, rarely, bacteraemia[29-32]. Early severe pneumococcal AOM is caused by the most aggressive serotypes, most of which were included in PCVs. The mucosal damage they cause may favour infections by bacteria with lower pathogenicity, such as the less invasive pneumococcal serotypes and nt-*H. influenzae*.[33] Mixed infection due to the pneumococcal serotypes most commonly carried by healthy subjects in association with nt-*H. influenzae* alone or in combination with other pathogens were significantly more common in older children with bilateral AOM, recurrent episodes, and previous tympanocentesis. By contrast, cases due to single *S. pneumoniae* infections were associated with serotypes shown to have higher pathogenicity. The type of damage caused by the invasive pneumococcal serotypes and whether STMP can occur as a consequence of this damage are presently unsolved problems.

Non-typeable *Haemophilus influenzae and Moraxella catarrhalis*

Data suggesting a direct relationship between ear infection with pathogens other than *S. pyogenes* and *S. pneumoniae* and the development of AOM with STMP are lacking. However, there is evidence of dominance of nt-*H. influenzae* in ear discharge from Indigenous Australian children with AOM with STMP[34]. Similar findings were reported by Grevers *et al*.[8], who found that nt-*H. influenzae* was the most common aetiologic agent both in the group of patients with STMP and in the group of children who underwent tympanocentesis (18% and 13% of samples, respectively). Generally, non-pneumococcal AOMs develop in older children than those due to *S. pneumoniae* or, if they are diagnosed during infancy, they occur after a first severe pneumococcal AOM. The main pathogens associated with these AOM episodes are nt-*H.influenzae* alone or a mixture of ear pathogens. However, co-infections between these pathogens and *M. catarrhalis* or *S. pyogenes* can also be detected, particularly when molecular methods of bacterial identification are used[24,35].

The Italian study

In our most recent study we aimed to evaluate the etiologic role of the most common bacterial pathogens associated with acute otitis media (AOM) in children with AOM and spontaneous tympanic membrane perforation (STMP). Between May 1, 2015 and April 30, 2016, 177 children, 6 months to 7 years old, with AOM complicated by STMP within 12 hours were prospectively enrolled. Middle ear fluid (MEF) was tested by real-time polymerase chain reaction for *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, *Streptococcus pyogenes*, *Moraxella catarrhalis* and *Staphylococcus aureus*. Among the 177 children with AOM and STMP, 92/100 (92.0%) of those with recurrent AOM and 13/77 (16.9%) without recurrent AOM had recurrent STMP ($p<0.001$). A single pathogen was identified in 70 (39.5%) MEF samples, whereas 2, 3, and 4 bac-

teria were detected in 54 (30.5%), 20 (11.3%), and 7 (4.0%) cases, respectively. Nontypable *H. influenzae* was the most common and was identified in 90 children (50.8%), followed by *M. catarrhalis* (62 cases, 35.0%) and *S. pneumoniae* (48 cases, 27.1%). Nontypable *H. influenzae* was the most frequent pathogen in children with coinfections. Children with coinfections, including nontypeable *H. influenzae,* had significantly more frequent recurrent AOM (adjusted odds ratio 6.609, 95% confidence interval 1.243-39.096, p=0.03). Recurrent AOM episodes appear to be associated with an increased risk of AOM with STMP. In AOM with STMP, the aetiology seems different from that commonly found in uncomplicated AOM, with nontypeable *H. influenzae* detected at a high frequency, especially in children with recurrent STMP and often in association with other pathogens.

Biofilm

The main driver of the role played by nt-*H. influenzae* and other pathogens in the determination of recurrent AOM and treatment failures seems to be their ability to form a biofilm in the middle ear. All ear pathogens are capable to form biofilm, although data for the biofilm-forming phenotype of nt-*H. influenzae* are more extensive, while those for *S. pneumoniae* and *M. catarrhalis* are evolving. Clinical isolates of nt-*H. influenzae* are able to form a well-developed biofilm in the middle ear of a chinchilla host within 5 days after direct challenge of the middle-ear cavity[36]. Biofilms are detectable in the middle ear of children with recurrent AOM and persist even after treatment during clinical remission[36].Together with the physical barrier provided by the matrix, all these functional modifications explain why bacteria within the biofilm have increased resistance to the humoral and cellular mechanisms of host immunity and to antibiotics[36]. Moreover, these changes favour persistence of bacteria in the site of the infection even after treatment, resulting in recurrences and possibly in chronic disease. It is not known whether synergies between specific pathogens can led to STMP. Further evidence is needed to explain why, despite numerous recurrences, many children never experience STMP, whereas others with similar characteristics develop STMP in association with several new AOM episodes.

Conclusion

Recurrent AOM episodes appear to be associated with an increased risk of AOM with STMP. In AOM with STMP, the aetiology seems different from that commonly found in uncomplicated AOM, with nontypeable *H. influenzae* detected at a high frequency, especially in children with recurrent STMP and often in association with other pathogens.

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