

# Viral-Bacterial Synergy in Otitis Media: Implications for Management

Terho Heikkinen, MD\*, and Tasnee Chonmaitree, MD†

## Address

\*Department of Pediatrics, Turku University Hospital, FIN-20520, Turku, Finland.

E-mail: terho.heikkinen@utu.fi

†Department of Pediatrics, Division of Infectious Disease, University of Texas Medical Branch, Galveston, TX, USA.

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Despite the extensive use of broad-spectrum antibiotics, poor clinical response to the treatment of acute otitis media is common. Evidence derived from numerous studies during the past two decades supports a crucial role for respiratory viruses in the etiology and pathogenesis of acute otitis media, and recent studies indicate that viruses may also have a profound adverse effect on the resolution of this disease. Viruses seem to interact with bacteria and enhance the local inflammatory process in the middle ear. Effective adjuvant therapies are needed to improve outcome in children with otitis media. Increasing knowledge of the role of viruses, viral-bacterial interaction, and host inflammatory mechanisms in otitis media may lead to major improvements in the management of this disease.

## Introduction

Acute otitis media (AOM) is a major health care problem of childhood and the most common reason for outpatient antibiotic therapy in children in the United States and many other parts of the world. Wang *et al.* [1] analyzed computerized databases for physician visits and antibiotic prescriptions for different respiratory infections in preschool children in Canada. AOM accounted for 33% of all physician visits and 39% of all antibiotic prescriptions in children younger than 5 years of age.

Although AOM is usually considered a bacterial infection and is therefore treated with antibiotics, there is convincing evidence that respiratory viruses play a crucial role in the etiopathogenesis of this disease [2]. AOM usually occurs in conjunction with a viral upper respiratory infection (URI) and in the vast majority of cases can be clearly regarded as a complication of a viral URI. Koivunen *et al.* [3] recently corroborated earlier findings about the temporal development of AOM in the course of URI. Of 250 episodes of AOM in children, the incidence was highest

during days 2 through 5 after the onset of respiratory symptoms. The distinctive role of URI in the development of AOM was also demonstrated by Daly *et al.* [4], who followed 596 infants from birth to age 6 months. Respiratory tract infection was the most important predictor for early AOM, indisputably outweighing other risk factors (*eg*, day-care attendance). The strongest evidence for the decisive role of viruses in the etiopathogenesis of AOM is, however, provided by direct intervention trials investigating the efficacy of viral vaccination in the prevention of AOM. Studies with influenza vaccine have demonstrated that prevention of the preceding viral URI is an effective way to prevent the development of AOM as a complication [5,6,7••].

Although the close association between URI and AOM is well established, the detection rates of respiratory viruses in nasopharyngeal specimens from children with AOM have usually ranged from 30% to 50% [2]. In previous studies, detection of respiratory viruses has been based on virus culture and/or viral antigen detection methods, and it is obvious that limitations in these techniques have resulted in underdetection of viruses in the specimens. The recent development of polymerase chain reaction (PCR)-based assays for several respiratory viruses may substantially increase the rates of viral detection in nasopharyngeal specimens [8•,9]. Pitkäranta *et al.* [10•] studied 92 children with AOM using PCR for detection of rhinovirus, respiratory syncytial virus (RSV), and coronavirus and found at least one of these viruses in the nasopharyngeal aspirates from 62% of the children. In a recent study from the University of Turku, Finland, we searched for viruses in nasopharyngeal aspirates with rapid antigen detection for RSV, influenza virus, parainfluenza virus, and adenovirus and with PCR for rhinovirus, enterovirus, and coronavirus. By these methods, viral infection could be documented in 90% of 67 children with AOM (A. Ruohola *et al.*, Unpublished data).

## Pathogenesis

Dysfunction of the eustachian tube is generally considered the most important factor in the pathogenesis of AOM. Numerous studies in both animals and humans have provided strong evidence of a causal role for respiratory viruses in the disruption of normal eustachian tube function [2]. One plausible mechanism by which viruses may cause eustachian tube dysfunction is that viruses are known to induce the release of cytokines and other inflam-

**Table 1. Detection of viruses in middle-ear fluids by culture or antigen detection methods in children with acute otitis media between 1982 and 1996**

Study	Patients, <i>n</i>	Virus-positive cases, %	
		Total	Virus alone
Klein <i>et al.</i> [22]	53	25	15
Sarkkinen <i>et al.</i> [23]	84	8	NA
Sarkkinen <i>et al.</i> [24]	137	18	7
Chonmaitree <i>et al.</i> [25]	84	20	2
Arola <i>et al.</i> [26]	143	11	6
Arola <i>et al.</i> [27]	88	19	NA
Chonmaitree <i>et al.</i> [28]	58	19	0
Chonmaitree <i>et al.</i> [29]	271	24	6
Chonmaitree <i>et al.</i> [30]	106	18	5
Total	1024	19	6

NA—not available.

matory mediators from target cells in the nasopharynx [11,12]. After intranasal challenge, many of these mediators have been shown to provoke eustachian tube dysfunction [13]. In a recent study of adult volunteers, Fritz *et al.* [14] reported that nasal lavage fluid levels of interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , interferon- $\gamma$ , and IL-10 increased in response to influenza virus infection, and the levels correlated significantly with the magnitude and time course of the symptoms. The host-response mechanisms triggered by a viral infection are, however, extremely complex, involving a network of factors that affect each other in a time-dependent manner. Patel *et al.* [15•] showed that the production of IL-8 by respiratory epithelial cells during an RSV infection was primarily regulated by IL-1 $\alpha$ . Further, IL-1 $\beta$  and TNF- $\alpha$  induced the synthesis of IL-8 at 24 hours but partially inhibited the synthesis of this cytokine at 48 hours. Another study by the same group demonstrated the existence of a similar autocrine regulation of IL-6 production during RSV infection [16]. Despite the rapidly increasing knowledge of the host inflammatory response during a viral URI, it is likely that many essential factors contributing to the inflammatory processes in the nasopharynx remain to be identified.

Several recent studies have shown that viral infection of the upper respiratory tract may have a substantial impact on the bacterial colonization of the nasopharynx and the adherence of bacteria to epithelial cells [17,18]. Recently, Jiang *et al.* [19] showed that RSV infection significantly enhanced the attachment of nontypeable *Haemophilus influenzae* to human respiratory epithelial cells. They also demonstrated that P5-fimbriae of *H. influenzae* were essential for this increased attachment because no similar effect of RSV infection was observed with P5-fimbriae-deficient mutant strains of *H. influenzae*.

The detailed mechanisms by which bacteria enter the middle ear during AOM are still poorly understood. Some light was shed on this issue by Miyamoto and Bakaletz

[20], who studied the kinetics of ascension of nontypeable *H. influenzae* from the nasopharynx to the middle ear in adenovirus-infected chinchillas. The bacteria entered the middle ear 7 to 10 days after intranasal inoculation. Interestingly, while the bacteria were in the eustachian tube, they preferentially adhered to the mucus instead of the epithelial cells in the eustachian tube.

### Viruses in the Middle-Ear Fluid

The fact that pathogenic bacteria, mainly *Streptococcus pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*, can be isolated from the middle-ear fluid (MEF) in only about 70% of AOM cases [21] has prompted investigators to search for viruses directly in the MEF. During the 1950s and 1960s, when culture was the only available method for virus detection, viruses were rarely found in the MEF. Since the 1980s, improved viral culture techniques and the development of viral antigen detection methods has allowed demonstration of viruses in the MEF in approximately 20% of AOM cases (Table 1) [22–30]. A wide array of viruses has been identified in the MEF, including RSV, influenza and parainfluenza viruses, adenovirus, enterovirus, rhinovirus, cytomegalovirus, rotavirus, and herpes simplex virus.

During recent years, the use of PCR has dramatically increased the rates of virus detection in the MEF. Okamoto *et al.* [31] found RSV genomic sequences in 53% of 44 MEF samples from children with AOM. Pitkäranta *et al.* [10•] used PCR for rhinovirus, RSV, and coronavirus and recovered RNA from at least one of these viruses in the MEF of 48% of 92 children with AOM. In a study by Cone *et al.* [32], DNA from human herpesvirus 6 was detected in 71% of MEFs from 49 children with AOM. These high rates of viral detection have inevitably raised the question of the real significance of these findings. Because of the very high sensitivity of the PCR technique, the question has arisen

whether detection of viruses in the MEF by PCR represents live, replicating viruses with a pathogenetic role in the middle ear or viral materials that have migrated passively from the nasopharynx to the middle ear.

Recent data from studies at the University of Texas, Galveston provide additional evidence of the active role of at least some viruses in the pathogenesis of AOM [33••]. Heikkinen *et al.* [33••] determined the prevalence of various respiratory viruses in the MEF of 456 children with AOM. The specific viral cause of the URI could be determined in 41% of the cases. In children with AOM during a documented RSV infection, the same virus could be detected in the MEF in 74% of cases. The relative prevalence of RSV in the MEF was significantly higher than that of parainfluenza (52%) or influenza viruses (42%), which in turn were found significantly more often in the MEF than were enteroviruses (11%) or adenoviruses (4%). This study has two major implications. First, the results indicate that RSV has a particularly strong ability to invade the middle ear. Second, the different relative prevalences of the viruses in the MEF suggest that while some viruses may indeed enter the middle ear passively along with nasal secretions, others actively invade the middle ear and may contribute to the inflammatory process in the middle-ear mucosa. If all viruses found in the MEF were only "innocent bystanders" without any active role, they should be detected in the MEF at roughly equal rates during different viral infections. In this study, the relative importance of rhinoviruses could not be determined because the incidence of rhinovirus infections was too low for a meaningful analysis [33••]. However, a study by Pitkäranta *et al.* [10•], who used PCR to detect viruses in the MEF, suggested that the prevalence of rhinoviruses in the MEF may be similar to that of RSV.

In about two thirds of cases in which virus has been detected in the MEF by culture or antigen detection methods, bacteria have also been isolated (Table 1). Interestingly, *S. pneumoniae* was cultured significantly more often in MEFs containing influenza viruses than in those containing RSV or parainfluenza viruses [33••]. Overall, mixed viral-bacterial infections represent approximately 15% of all cases of AOM. Current estimates of either sole viral or mixed viral-bacterial AOM may not, however, represent the true occurrence of viruses in the middle ear because it is obvious that underdetection of viruses is still common. Further, it has also been suggested that the bacteriologic techniques routinely used are not sensitive enough for full detection of bacteria in the MEF [34]. Therefore, it is possible that with the increasing availability of the more sensitive techniques for detection of both viruses and bacteria, our current concept of the relative distribution of viral and/or bacterial causes of AOM will be transformed in the near future [8•,9,34,35].

### Role of Viruses in Treatment Failure

Despite proper antibiotic treatment of AOM in children, poor clinical response is a frequent phenomenon. This

often results in a change in the antibiotic or even the use of several courses of different antibiotics for the same episode because physicians assume that the cause of the failure is bacterial resistance to the antibiotic used. It has been shown, however, that resistant bacteria account for only a small proportion (about 20%) of these cases [36]. During the past decade, much attention has been focused on the potential role of viruses in treatment failure. Although viruses are often found in the MEF, the importance of this finding has been questioned because viral replication in the human middle-ear epithelium during AOM has not been demonstrated. Nevertheless, the results of clinical studies from Texas and Finland strongly suggest that viruses play a significant role in the outcome of otitis media.

In a study of the effect of viruses on the outcome of AOM, MEF samples were obtained from 58 children before and 2 to 4 days after initiation of antibiotic treatment [28]. Although the bacteria in the MEF were susceptible to the antibiotic used, bacteriologic failure at the second tympanocentesis was observed in 33% of the children who had both bacteria and virus in the initial MEF compared with 3% of children with only bacteria in the MEF. The effect of viruses on the outcome of otitis media was further supported by a subsequent larger study of 271 children [29]. In this study, otitis media persisted in a significantly higher proportion of children with combined viral and bacterial infection than in those with bacteria alone in the MEF. Arola *et al.* [27] studied 22 children with AOM who had failed to improve after 2 days of antibiotic therapy. Bacteria were found in the MEF in only four of these children, and only one isolate was resistant to the antibiotic used. Viruses were detected in the MEF of 32% of these children compared with 15% of children in a comparison group with newly diagnosed, untreated AOM. Whether different viruses have a varying impact on the clinical outcome of otitis media is not known, but Sung *et al.* [37] suggested that rhinoviruses may be more commonly associated with bacteriologic failure than are other respiratory viruses.

The mechanisms by which the presence of viruses in the middle ear might interfere with the resolution of otitis media are still unclear. Some respiratory viruses, particularly influenza viruses, are known to have a suppressive effect on polymorphonuclear leukocyte function [38], potentially resulting in delayed clearance of bacteria from the middle ear. Another hypothesis is that viral infection of the middle-ear epithelium causes local inflammation that interferes with the penetration of antibiotics into the middle ear, resulting in lower concentrations of antibiotics. Although some data are available to support this theory [39,40], additional studies are needed.

Perhaps the most plausible explanation for the adverse effect of viruses on the outcome of otitis media is provided by studies demonstrating that viruses increase the production of cytokines and inflammatory mediators in the middle ear. Numerous inflammatory mediators (*eg*, IL-1 $\beta$ , IL-2, IL-6, IL-8, TNF, histamine, leukotrienes, prostaglan-

dins) have been detected in the MEF of patients with otitis media [41–43]. In a study of 248 children with AOM [44], histamine concentrations in the MEF were higher in those with evidence of concurrent viral infection than in those without and bacteria and viruses appeared to have an additive effect on the histamine content in the MEF. Further, 3 to 5 days of antibiotic treatment did not decrease the histamine concentrations, and the pretreatment levels tended to be higher in children with persistent otitis media than in those who had a good response to treatment. In another study [30], the concentrations of leukotriene B4 (LTB4) and IL-8 were measured in 271 MEF samples from 106 children. The highest concentrations of these mediators were found in MEFs containing both bacteria and virus. In five children who had bilateral AOM and similar bacterial findings in both ears, LTB4 and IL-8 levels were higher in the ear that contained virus than in the contralateral ear. High concentrations of LTB4 at the time of AOM diagnosis and initiation of antibiotic treatment were associated with an increased rate of treatment failure. Antibiotic treatment had no effect on the levels of these mediators. Similarly, in a study of two chemokines, macrophage inflammatory protein-1 $\alpha$  and monocyte chemoattractant protein-1 (which are considered histamine-releasing factors), higher concentrations of these substances were found in MEF samples containing both bacteria and virus than in samples with bacteria alone [45].

### Management Implications

Our increasing knowledge of the role of viruses and the detailed inflammatory mechanisms in the middle ear during AOM may have a substantial impact on the management of this disease in the future. Considering the rapidly increasing antimicrobial resistance of bacteria and the frequently observed poor clinical response to antibiotic treatment, it is clear that effective adjuvant therapies are needed to improve outcome. Various inflammatory mediators, whether induced by bacteria, viruses, or both, appear to play a prominent role in the enhancement or prolongation of the inflammatory process in the middle ear. Because these mediators cannot be controlled by antibiotics, it is understandable that the inflammatory process in the middle ear may persist long after the elimination of the bacteria.

Previous trials have failed to demonstrate any efficacy of antihistamines, decongestants, or prostaglandin inhibitors for the treatment of otitis media. Recently, Ruohola *et al.* [46•] investigated the efficacy of oral steroid treatment as adjuvant therapy in AOM. In children with AOM draining through tympanostomy tubes, a 3-day course of prednisolone combined with standard antibiotic treatment significantly shortened the duration of otorrhea compared with antibiotic treatment alone. Whether short-term use of

steroids early in the course of AOM would also improve the outcome of AOM in children with intact tympanic membranes remains to be determined.

In addition to suppression of the inflammatory process in the middle ear, the role of specific antiviral treatments may come into consideration in the future. The recently developed neuraminidase inhibitors zanamivir and oseltamivir are well tolerated, safe, and effective against influenza A and B infections in adults and older children, but no data are available on the use of these drugs in young children [47]. Another new antiviral agent with theoretic potential for use in otitis media is pleconaril, which is effective against enteroviruses and most clinically important serotypes of rhinoviruses (Hayden *et al.*, Paper presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 1999). However, even though antivirals were shown to be effective adjuvant treatments of otitis media, their successful use in clinical situations would require the availability of easy, rapid, and accurate methods to determine the specific viral cause of the infection.

Because approximately one third of AOM cases have no proven bacterial cause, withholding antibiotic treatment in nonbacterial AOM might be safe and would reduce unnecessary use of antibiotics. Previous studies have shown that serum levels of C-reactive protein and IL-6 are significantly higher in bacterial than in nonbacterial AOM [48,49]. Because of substantial overlap, however, neither of these markers is a reliable screening test for clinical purposes.

### Conclusions

Rather than being a simple bacterial infection that is effectively treated with antibiotics, otitis media is a very complex disease. The etiopathogenesis of AOM involves viruses, bacteria, and a large network of other factors that affect each other in a time-dependent manner. Respiratory viruses play a crucial role in initiating the whole cascade of events that ultimately lead to the development of AOM. In the middle ear, viruses seem to interact with bacteria and enhance the local inflammatory process, which in turn may significantly impair the outcome of the disease. It is obvious that effective adjuvant treatments for otitis media are needed. The development of new innovative strategies for management of this disease will require further research into respiratory viruses, viral-bacterial interaction, and the host immune and inflammatory response during otitis media.

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