

Acute Otitis Media Is Not a Pure Bacterial Disease

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(See the article by Ruohola et al. on pages 1417–22)

Acute otitis media (AOM) is one of the most common diseases seen in the pediatric practice. It has generally been considered a bacterial disease, with *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and/or *Moraxella catarrhalis* as the major causes. Therefore, the disease has generally been treated with antibiotic, making AOM the leading cause of antibiotic prescription in the United States and contributing to the emergence of antibiotic-resistant bacteria.

Microbiological studies of AOM have traditionally been performed by bacterial culture of the middle ear fluid (MEF) specimens obtained by needle aspiration. Although bacterial pathogens have been isolated in the majority of cases, cultures have still yielded negative results for pathogenic bacteria in ~12%–35% of cases [1]. Studies using more-sensitive culture techniques and PCR have shown increasing bacterial yield [2, 3]. Although *Mycoplasma* and *Chlamydia* species have been detected infrequently [4–6], presence of respiratory viruses in MEF samples obtained from children with AOM has become evident with the more-sensitive de-

tection techniques used [7–9]. Even with the effort to identify more viruses in MEF in recent studies, 15%–25% of MEF samples still contain no identifiable pathogen. The major reasons for failure in detection of pathogens in MEF have been limited volume of MEF and limited availability of sensitive detection methods for a broad spectrum of microbial pathogens, especially viruses.

In this issue of *Clinical Infectious Diseases*, investigators from 3 European countries have combined efforts to identify bacteria and viruses in MEF specimens obtained from 79 children with acute ear infection and drainage through tympanostomy tubes [10]. Attempts were made to detect a broad range of bacteria and viruses known to be associated with respiratory infections and/or AOM. Bacterial detection methods included routine culture, multiplex PCR (*H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, and *Alloiococcus otitidis*), and broad-range PCR. Viral detection methods included viral culture, viral antigen detection (respiratory syncytial virus, adenovirus, influenza viruses A and B, and parainfluenza virus types 1–3), and PCR (rhinovirus, enterovirus, and coronavirus 229E and OC-40). In addition, PCR was performed on selected samples for respiratory syncytial virus and influenza A and B viruses, human metapneumovirus, adenovirus, parainfluenza virus types 1–4, coronavirus NL63, and human bocavirus, a newly recognized respiratory virus in the Parvoviridae family. The re-

sults showed bacteria and/or viruses in 96% of cases and both bacteria and viruses together in 66% of cases.

A few aspects of this study deserve particular consideration. First, the study population did not have intact tympanic membranes. However, otorrhea appeared acutely <48 h before study entry, implicating AOM in children with indwelling tympanostomy tubes; it is reasonable to assume that the microbiology of AOM in children with intact tympanic membranes would be similar. Second, bacterial and/or viral nucleic acids, as opposed to live bacteria and/or viruses, were detected in MEF specimens in this study. There has been ample evidence of live bacteria and viruses in MEF, and animal models have shown the ability of either bacteria, viruses, or combined bacteria and viruses to induce AOM [9, 11–13]. Last, results of virus typing showed a relatively high detection of picornaviruses (41% overall, with 20% rhinovirus, 11% nontypeable picornavirus, and 10% enterovirus) and relatively low detection of respiratory syncytial virus (14%). This may be explained by the following: the age of the children (median age, 21 months) is older than the peak age incidence of AOM (6–18 months); the study may have been performed during a low-activity respiratory syncytial virus season; and varying sensitivity of PCR assays for each virus may also affect the detection rate of various viruses. Additional studies with a larger number of children at the peak age inci-

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dence of AOM are needed to compare the relative importance of each respiratory virus in AOM.

Despite the issues mentioned above, this study provides valid important messages. By using sensitive techniques to detect a broad range of pathogens, bacteria and/or viruses can be detected in almost all cases. Next, any virus that causes respiratory infection, including newly recognized viruses such as bocavirus, can be detected in the MEF of patients with AOM. Finally, bacterial and viral coinfection occurs in approximately two-thirds of all cases.

The results of this study confirm what was previously believed: that AOM is generally associated with bacterial and/or viral infection and that diagnostic methods generally used were not adequate to detect most of the possible pathogens. More important, combined bacterial and viral infections are very common, accounting for the majority of cases. This latter concept has 2 major clinical implications: results of antibiotic treatment of AOM may not be as expected when the disease is not a pure bacterial infection, and the concept may also apply to other respiratory diseases, such as sinusitis and pneumonia, in both adults and children.

If AOM is a bacterial disease, appropriate antibiotic is indicated. However, in the majority of cases when AOM is not a “pure” bacterial disease, response to antibiotic treatment can only be partial. Indeed, results of antibiotic treatment for AOM have varied from very effective to indifferent. Failure of antibiotic treatment in some cases of AOM could be attributed to such factors as inappropriate antibiotic, resistant bacteria, or biofilm formation [14]. Nevertheless, viruses are not the “innocent bystanders” in the middle ear. In AOM cases for which both bacteria and viruses were detected in the MEF, results of antibiotic treatment were impaired compared with results of treatment of AOM associated with bacteria alone [13, 15]. Studies have shown that viruses have

contributed to poor treatment outcome by increasing middle ear inflammation (as evidenced by increased levels of inflammatory mediators) [16, 17], decreasing neutrophil function [18], and decreasing antibiotic penetration into the middle ear [19].

This knowledge about the combined nature of bacterial and viral infections in AOM should remind us of possible unpredictable results of antibiotic treatment in AOM. Recent trends of treatment of AOM have relied less on antibiotic, because many patients with AOM recover spontaneously without antibiotic treatment. This has led to the recent recommendation from the American Academy of Pediatrics and the American Academy of Family Physicians to withhold antibiotic treatment in mild and selected AOM cases [20]. For severe AOM cases for which antibiotic is indicated, viral coinfection could lead to clinical failure even when appropriate antibiotic has sterilized the MEF. When one keeps in mind the possibility of combined bacterial and viral infections in AOM, expectations for antibiotic treatment of AOM will be more realistic, and a failed course of antibiotic treatment may not be promptly blamed on antibiotic-resistant bacteria, leading to continuous changes in antibiotic regimens. Watchful waiting after a treatment course may also become an alternative. Because antiviral drugs are not available to treat upper respiratory tract infection (except for influenza) in children, and because viral diagnosis is not generally performed, the use of antiviral drugs cannot be recommended for treatment of AOM at this time.

It has long been known that many bacterial diseases of the upper and lower respiratory tract, such as sinusitis and pneumonia, are preceded by viral infection. Viruses impair host defense, including neutrophil function, and create the milieu to promote infection of the respiratory tract by pathogenic bacteria, which mainly colonize the nasopharynx. Increased bacterial attachment to epithelial cells and in-

creased colonization of bacteria have been shown to result from viral infection [21–23]. Similar to AOM, it is possible that the virus can also enter sites such as paranasal sinuses and lungs, causing combined bacterial and viral infection. Effects of antibiotic treatment in “pure” bacterial versus combined bacterial and viral sinusitis and pneumonia deserve further study.

In conclusion, evidence to date suggests that AOM is not a pure bacterial disease in majority of cases. Antibiotic treatment may not result in optimal outcome in these cases because viral coinfection may enhance the degree of inflammation and impair the efficacy of antibiotic treatment. The concept of combined bacterial and viral infection may also apply to other bacterial diseases of the respiratory tract, such as sinusitis and pneumonia. Further studies are required to determine the effect of combined bacterial and viral infections of the respiratory tract in adults and children.

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