Viral Otitis Media

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Acute otitis media (AOM) and viral upper respiratory tract infections (URIs) represent the two most common diseases affecting the human population, and account for substantial patient morbidity and health care costs. Epidemiologic and experimental studies suggest that URIs play a causal role in the pathogenesis of AOM. Specifically, viruses can either invade the middle ear (ME) space and invoke an inflammatory response that culminates in ME effusion formation and consequent symptoms, or URIs might cause eustachian-tube dysfunction, resulting in negative ME pressures and subsequent ME effusion (hydrops ex vacuo theory). The events responsible for the inflammatory response of the human ME following viral exposure have not been well characterized. Although many prophylactic and therapeutic interventions have been evaluated for the treatment of AOM, the information on virus-specific interventions is sparse. In this article, the epidemiology, pathogenesis, diagnosis, and management of viral otitis media are reviewed.

Introduction

Viral upper respiratory tract infections (URIs) are the most common diseases affecting the human population and continue to account for significant patient morbidity, mortality, and health care costs annually [1]. Teele *et al.* [2] have shown that by the age of 1 year, more than 60% of children have had at least one episode of acute otitis media (AOM), and by the age of 3 years, more than 40% of children have experienced more than three episodes of AOM. In fact, $3 to $4 billion are spent annually on the medical and surgical treatment of AOM alone [3]. Although antibiotics are the primary treatment for most patients with AOM, a recent meta-analysis demonstrated a relatively modest (13.7%) benefit from this therapy [4]. In addition, ever-growing antibiotic resistance patterns are making therapy for OM significantly more difficult [5]. Concomitant viral infection in cases of AOM has also been proposed as a reason for failure of antibacterial therapy [6]. Moreover, children with hearing loss as a result of prolonged bouts of OM might experience significant problems with speech and language acquisition [7]. There is no question that a better understanding of the pathophysiologic and molecular mechanisms relating viral URIs and AOM will lead to the development of new therapeutic alternatives. Today, a significant number of alternative therapies exist for the treatment of OM. However, the role of these interventions in the setting of viral OM is unclear.

Epidemiology

Epidemiologic studies suggest that a viral URI might precede more than 50% of cases of AOM [8]. Furthermore, Finnish studies have demonstrated a significant correlation between monthly episodes of AOM and the seasonal occurrence of viral URIs [9]. Specific viruses isolated from the upper respiratory tract during episodes of AOM include: influenza (INF) A and B viruses, respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, mumps virus, coronavirus, enteroviruses, and the rhinoviruses (RV), with RSV being the most frequent. Although the reasons for the apparent increased association between RSV-mediated URIs and AOM remains unknown, this finding might be related to the timing of the studies during RSV epidemics or the variation in the sensitivities of methods of viral detection [10,11]. Another potential interpretation is that RSV is more otologically virulent than other viruses [12•].

Pathogenesis

The two most clearly documented factors implicated in the pathogenesis of OM are bacterial infection of the middle ear (ME) space and eustachian-tube (ET) dysfunction. However, clinical and human experimental investigations suggest that the temporal association between viral URIs and episodes of AOM represents a causal relationship. Using either RSV-enriched globulin or inactivated, live, attenuated INF vaccines, significant reductions in the incidence of AOM in selected pediatric populations have been achieved [13–16,17•]. Moreover, in human viral challenge experiments, as many as 20% of individuals infected with one of the common respiratory viruses (INF, RV, or RSV) developed OM following nasal inoculation. In contrast to the epidemiologic findings mentioned, comparative analysis between the various virus-infected groups has shown that INF A infection is significantly more likely to result in OM than are either RSV or RV [18–20]. These studies and others indicate a clear, causal role for viral URIs in the pathogenesis of AOM. There-

fore, a significant impact on the incidence and prevalence of OM could be realized by rational interventions in viral URI pathogenesis as it relates to the formation of OM.

The mechanisms whereby viral URIs result in ME inflammation (*ie*, OM) and effusion formation have not been well characterized. Respiratory viruses can directly invade the ME cleft, resulting in inflammation. Viruses can also disrupt normal ET-ME physiology and immune function, thereby predisposing the ME to secondary bacterial or viral infection or sterile effusion formation by unknown mechanisms (*ie*, hydrops ex vacuo theory).

Substantial evidence supports the theory that viral infection of the ME space plays a role in the pathogenesis of OM. Viruses can invade the ME as either a sole pathogen or as a coinfectious agent with bacteria and, rarely, with other viruses. Viruses have been identified in the effusions of patients with AOM. For example, Ruuskanen *et al.* [9] summarized the results of 15 studies using either standard culture techniques or virus-specific antigen detection methods. In these studies, which were performed between 1955 and 1988, 10% (n = 1221; range 0 to 55%) of ME effusions were positive for, at least, one of the respiratory viruses during episodes of AOM. More recent studies using modern viral culture techniques or virus-specific ELISA (enzyme-linked immunosorbent assay) have demonstrated significantly higher rates (17%) of viral detection (n = 591; range 7% to 32%) [10].

The most recent studies, using molecular biologic techniques, have demonstrated a substantially greater incidence of viral presence in ME effusions. In these studies, reverse transcriptase–polymerase-chain reaction (RT-PCR) has been used as a highly sensitive technique for identifying pathogen-specific genomic sequences in approximately 50% of ME effusions [11,21•]. In an INF A human challenge experiment in Pittsburgh, RT-PCR was used to identify INF A RNA (and *Streptococcus pneumoniae* DNA) in the ME effusion of a subject with culture-negative AOM [18]. This study clearly demonstrated that INF virus was present in the ME space at some time prior to myringotomy. Similar RT-PCR findings for bacterial positivity have indicated active, ongoing infection rather than persistence of archival genomic material [22]. Clearly, these findings for viral ME infections must be corroborated. However, such results support the fact that viruses can directly invade the ME space in some cases of AOM.

Many studies also support the concept that viral URIs can alter normal ET-ME physiology. This outcome might also be an important event in the initiation of AOM. During naturally occurring URIs, abnormal ME pressures and ET dysfunction have been documented using standard testing protocols [23]. To further study the effects of viruses on the ET-ME system, human and animal experimental systems were developed. In humans, intranasal inoculation of healthy adult volunteers with RV type 39, RV Hanks, INF A, or RSV can reliably result in ET-opening failure, abnormal ME pressures, and AOM [18,19,24,25]. The temporal pattern of the observed otologic consequences (*ie*, ET obstruction > ME underpressure > OM) suggests a causal mechanism. That is, viral URIs disrupt normal ET-opening function, which results in ME underpressures, and subsequent ME effusion formation. Because the ME is essentially a noncollapsible gas pocket, ME underpressures are thought to predispose to effusion formation by either aspiration of infectious nasopharyngeal secretions through the ET, with consequent exudation (*ie*, inflammation) or underpressure-induced transudation (*ie*, hydrops ex vacuo theory).

The studies discussed earlier document the responses of the human ET-ME system to viral challenge. In contrast, investigating the effects of viral URIs on the ET-ME system of animals provides the opportunity to study specific factors while controlling for many of the confounding variables inherent in human investigations. Invasive methodologies not applicable to the human experimental system might also be used to elucidate the cause and effect relationships more clearly in animal models.

The chinchilla (*Chinchilla laniger*) has been used extensively to study the role of viral URIs in the pathogenesis of AOM [26–29]. Collectively, this group of studies indicates that intranasal inoculation of the chinchilla with either INF A or adenovirus can result in: 1) impairment of both ME pressure maintenance (*ie*, ventilatory function) and clearance functions of the ET; 2) potentiation of AOM formation when co-inoculated with bacteria (either *S. pneumoniae* or *Hemophilus influenzae*); and 3) similar histopathologic changes in the ET and ME, which correlate with the functional impairments observed. Interestingly, in a finding similar to a previous human study, ascension of both adenovirus and nontypeable *H. influenzae* through the ET to the ME was reported following intranasal inoculation [18,30]. A similar synergistic relationship could not be documented for coinfection with adenovirus type 1 and *Moraxella catarrhalis* using the same chinchilla model [31]. Using an intrabullar inoculation model, Chung *et al.* [27] demonstrated that INF A exposure results in morphologic damage to the mucosal epithelium, capillary engorgement, subepithelial hemorrhage, tissue edema, and inflammatory cell infiltration. In that study, neutrophils were the earliest cells to enter the ME following inoculation.

Investigators have noted that in cases of bacterial and viral coinfection, OM is more severe, less responsive to antibiotics, and associated with a longer duration of effusion [8]. Explanations for these findings include viral effect on neutrophil function, local reactions interfering with antibiotic concentrations, and the induction of inflammatory mediators with enhancement of the degree of inflammation [32]. The mechanisms of these interactions might be nonspecific, but in some cases appear to be pathogen specific. The association between INF A and pneumonia secondary to *S. pneumoniae* has long been recognized. This association has also been demonstrated in experimental OM, as previously described [18]. The tendency of these two pathogens to cause coinfection might, in part, be explained by the changes in the binding capacity of nasopharyngeal and ET

epithelial cells [33]. Hirano *et al.* [34] recently recognized changes in lectin-binding properties of murine nasopharyngeal mucosa in mice inoculated with INF A. Cultures from the nasopharynx of these mice suggested that alteration in the glycoconjugate structure lining the nasopharyngeal mucosa is associated with a reduction in bacterial clearance. These studies demonstrate a method by which a virus enhances the pathogenicity of a specific bacteria rather than simply enhancing a nonspecific inflammatory response.

Diagnosis

The diagnosis of URIs and AOM is routine practice for most clinicians. However, determining the specific pathogen causing an episode of OM is challenging, if not impossible at times. When clinically indicated, myringotomy and culture can be performed. Although this might be practical in some cases of bacterial AOM resistant to therapy, most laboratories are not equipped to perform timely identification of viral pathogens. Given the paucity of antiviral therapies available to the clinician, identification of viral pathogens is not currently a clinical issue. However, as effective antivirals are developed, the rapid identification of the viral pathogen responsible for a URI and/or AOM will become necessary.

Management

Given our lack of ability to distinguish between an episode of viral OM and bacterial OM, the management remains empiric. The discussion of the management can be separated into the prophylaxis of AOM and the treatment of AOM.

Prophylaxis

The prophylaxis of viral OM essentially implies either prevention of AOM as a complication of URI or prophylaxis of URI itself. Prophylaxis of recurrent AOM with antibiotic therapy has been extensively studied. Although these studies are not limited to cases of viral URI, given the association between URI and AOM, some conclusions can be inferred. In 13 randomized, placebo-controlled trials, antibiotic prophylaxis reduced the incidence of AOM by 0.12 episodes per patient-month [35]. Given the rising incidence of antibiotic resistance and the modest benefit observed with prophylaxis, it seems prudent to limit antibiotic prophylaxis to high-risk individuals. High-risk individuals include patients who are very young, immunocompromised, at risk for suppurative or systemic complications, or those with craniofacial growth abnormalities. Patients with cochlear implants and recurrent AOM should also be considered for prophylaxis.

Other systemic medications used for treatment of URIs include antihistamines, decongestants, nonsteroidal anti-inflammatory drugs, vitamin C, and glucocorticoids. Although some of these agents have been found to improve symptoms, their efficacy in preventing the development of OM has not been determined [36]. Zinc used as either lozenges or as nasal spray has recently received a great deal of attention in the marketplace. The use of zinc for the treatment of URI has been studied extensively, and results are inconclusive. Zinc has not been shown to decrease the severity or duration of the symptoms of the common cold, and its effect on the incidence of associated OM is not clear [37].

Topical medications such as nasal decongesants and intranasal steroids likewise have not been shown to decrease the incidence of URI-associated AOM. In a recent clinical trial, Ruohola *et al.* [38] studied 210 children with URI. The children were randomized to receive either intranasal fluticasone or placebo. AOM occurred in 38% of children treated with fluticasone and 28% of children who received placebo. The difference was not statistically significant. Interestingly, when the cause of the URI was determined to be RV, administration of fluticasone was associated with a statistically significant increase in the incidence of AOM.

Prophylaxis of URI and AOM with vaccination has been studied during the past decade. The INF vaccine has been shown to reduce the incidence of OM in selected populations. Heikkinen *et al.* [14] vaccinated 187 day-care center children with standard, inactive INF vaccine and compared results in these children with those in a control group of children who had not received the vaccine. INF was diagnosed in 3% of the of the vaccinated group and 16% of controls. During the INF epidemic, 60% of the vaccinated group developed OM compared with 67% of the controls. The overall incidence of OM associated with INF A was reduced by 83% in the vaccinated group. The total number of children diagnosed with OM in the vaccinated group was 18.7%, compared with 29.4% in the control subjects. Therefore, the administration of the INF vaccine resulted in a 36% reduction in the incidence of AOM from all causes. Clements *et al.* [15] vaccinated children aged 6 to 30 months and found a 32% reduction in the incidence of AOM during the INF season and a 28% reduction in the incidence of serous OM. More recently, Marchisio *et al.* [39] performed a single-blinded, prospective, randomized, controlled trial that demonstrated a 43.7% reduction in episodes of AOM in children vaccinated with the inactivated, virosomal subunit INF vaccine. In other clinical trials, the live, attenuated intranasal INF vaccine has been shown to reduce the incidence of febrile AOM by 30% [16,17•]. No difference was seen in the incidence of afebrile AOM. The attenuated vaccine has some advantages in that it generates a broader immune response with greater longevity. However, if vaccines are not sufficiently attenuated, a greater incidence of side effects can be expected. The study group consisted of only children with recurrent AOM.

The preliminary results from these trials using INF vaccines are encouraging, and the next logical step would be to investigate vaccines against other viruses. Currently, both live and subunit RSV vaccines are under investigation [40]. These vaccines have not been shown to offer protection against lower airway disease in children, and their efficacy against OM has not been investigated.

Passive immunity with high doses of RSV immunoglobulin appears to have a significant impact on preventing both RSV– and non-RSV–related AOM in high-risk populations [13]. A major drawback of passive immunization is the high cost associated with the monthly injections. More research must done in this area to reduce the substantial morbidity associated with RSV infections of both the upper and lower respiratory tracts. Currently, this intervention should be limited to high-risk patients.

Parainfluenza virus types 1, 2, and 3 are a third class of viruses causing OM. Currently, two vaccines against type 3 have been tested in infants and have been found to be safe and immunogenic. However, data to support their efficacy in reducing URI and OM is lacking [41]. Antiviral therapy for rhinovirus infections has been undergoing extensive research, with several drugs emerging. Pirodavir is a capsid-binding, anti-picornaviral drug with activity against human rotavirus (HRV). Pirodavir has been shown to reduce the frequency of abnormal ME pressures only when used prophylactically [42]. The role of this drug in prophylactic therapy of URIs is unclear.

The use of recombinant interferon in the treatment of URI has been studied, and results demonstrate some benefit with respect to the otologic complications of HRV infection [43]. When given within 36 hours of infection, interferon therapy was associated with early resolution of ET function and reduced viral shedding. More recently, several agents tested seem to have some benefit in experimental HRV or coxsackievirus infection. These include receptor-decoy soluble intracellular adhesion molecule-1 (sICAM-1), the anti-picornavirus capsid-binder pleconaril, and HRV3C protease inhibitor [44]. More extensive investigation is needed to determine the safety and efficacy of these agents.

Several medications are currently available that show activity against INF A. In a randomized, double-blinded, placebo-controlled study of rimantadine consisting of 105 patients, rimantidine administered 48 hours after inoculation had a beneficial effect for virus shedding, symptom load, and sinus pain [45]. However, rimantadine had no effect on otologic complications. The neuraminidase inhibitors zanamavir and oseltamivir have also been studied, with more encouraging results. When given early in the course of disease, both drugs have been shown to reduce otologic manifestations of INF infection [46,47].

Surgical prophylaxis of recurrent AOM consists of tympanostomy tube placement with or without adenoidectomy. Prospective, randomized trials investigating the efficacy of tympanostomy tube placement have shown that tubes decrease the total time spent with OM as well at the morbidity of the episodes of OM when compared with placebo [48]. Adenoidectomy has been shown to decrease the incidence and duration of AOM and, therefore, should play a role in prophylaxis [49]. However, the risks of adenoidectomy limit its use to more severely affected patients—that is, those patients of appropriate age who have failed primary tympanostomy tube placement, and those patients categorized as high-risk, as described earlier. In general, surgical prophylaxis of AOM is reserved for those patients who fail medical therapy, or those patients categorized as high-risk. Given the encouraging results from clinical trials with the INF vaccine, vaccination should be considered during the appropriate season in children who have significant recurrent AOM but do not meet criteria for surgical prophylaxis. Both surgical and medical prophylaxis should be considered when indicated for high-risk patients.

Treatment

Because clinicians do not have the ability to rapidly determine the etiology of each case of AOM, treatment of all cases of AOM is empiric. Currently, there is no viral-specific therapy available; therefore, a discussion of the treatment of viral AOM essentially relies on information derived from the treatment of all cases of AOM. The goals of treatment of AOM include symptomatic relief, prevention of complications, and clearance of effusion with normalization of hearing. In general, therapeutic decisions should be made on an individual basis, with high-risk patients requiring more aggressive intervention. Any treatment of AOM must be evaluated against the natural history of the disease. Placebo-treated, nonsevere OM demonstrates a spontaneous resolution of pain and fever by 4 to 7 days in up to 88% of children [50]. Clinical resolution of all signs and symptoms occurs in 73% of children by 7 to 14 days. The only exception is ME fluid, with 47% clearing fluid by 2 weeks, 60% by 1 month, and 75% by 3 months. Given this high rate of spontaneous resolution, it is difficult to demonstrate the efficacy of interventions in cases of AOM without studies involving very large numbers of patients.

The current standard treatment for AOM, at least in the United States, is a course of antibiotics and analgesics. Placebo-controlled clinical trials demonstrate significant symptom relief using antibiotics at 2 to 7 days, with a 13% improvement in complete clinical resolution [51,52]. It should be noted that these trials exclude high-risk children. The dramatic decrease in incidence of suppurative complications since the advent of antibiotics lends additional support of the theory that antibiotics play a major role in AOM. Given that pain is a major component of the morbidity of AOM, analgesic therapy seems to be beneficial.

The use of systemic and topical steroids has been extensively studied in the setting of OM effusion (OME), but there are few data concerning their use in AOM. The use of steroids, both intranasal and systemic, in the setting of OME is controversial. A recent review of clinical trials concluded that although steroids alone or in combination with an antibiotic might lead to a more rapid resolution of OME in the short-term, there is no evidence of a long-term benefit [53]. More trials are necessary to determine the role of steroids in AOM; however, the risks of systemic steroids would probably outweigh any benefit that might be obtained over antibiotics alone. The use of systemic decongesants and antihistamines

for the treatment of AOM has been extensively studied, and there appears to be no benefit for the use of these medications in this setting [54].

Conclusions

Viral organisms clearly play a major role in the pathogenesis of OM. The cellular virus–host interactions that ultimately lead to OM are not well characterized. Sophisticated methods to identify viral elements are available, and in the future might be clinically applicable for the treatment of URI and AOM. Until these methods are available, the use of specific antiviral medications will be limited. The use of vaccination in the prophylaxis of AOM shows great promise, and more work needs to be performed both in the laboratory to develop more effective vaccines, and in the clinic to determine the role of currently available vaccines.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wald ER, Guerra N, Byers C: **Upper respiratory tract infections in young children: duration of and frequency of complications.** *Pediatrics* 1991, **87:**129–133.
2. Teele DW, Klein JO, Rosner B: **Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study.** *J Infect Dis* 1989, **160:**83–94.
3. Stool SE, Field M: **The impact of otitis media.** *Pediatr Infect Dis J* 1989, **8:**S11–S14.
4. Rosenfeld RM, Vertrees JE, Carr J, *et al.*: **Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from thirty-three randomized trials.** *J Pediatr* 1994, **124:**355–367.
5. Dowell SF, Butler JC, Giebink GS, *et al.*: **Acute otitis media: management and surveillance in an era of pneumococcal resistance: a report from the Drug-Resistant Streptococcus Pneumoniae Therapeutic Working Group.** *Pediatr Infect Dis J* 1999, **18:**1–9.
6. Patel JA, Reisner B, Vizirinia N, *et al.*: **Bacteriologic failure of amoxicillin-clavulanate in treatment of acute otitis media caused by nontypeable Haemophilus influenzae.** *J Pediatr* 1995, **126:**799–806.
7. Bluestone CD, Klein JO: **Intratemporal complications and sequelae of otitis media.** In *Pediatric Otolaryngology.* Edited by Bluestone CD, Stool S. Philadelphia: WB Saunders; 1990:489–494.
8. Arola M, Ziegler T, Ruuskanen O, *et al.*: **Rhinovirus in acute otitis media.** *J Pediatr* 1988, **113:**693–695.
9. Ruuskanen O, Arola M, Putto-Laurila A, *et al.*: **Acute otitis media and respiratory virus infections.** *Pediatr Infect Dis J* 1989, **8:**94–99.
10. Ruuskanen O, Heikkinen T: **Otitis media: etiology and diagnosis.** *Pediatr Infect Dis J* 1994, **13:**S23–S261.
11. Vesa S, Kleemola M, BlomQvist S, *et al.*: **Epidemiology of documented viral respiratory infections and acute otitis media in a cohort of children followed from two to twenty-four months of age.** *Pediatr Infec Dis J* 2001, **20:**574–581.
12. • Heikkinen T, Thint M, Chonmaitree T: **Prevalence of various respiratory viruses in the middle ear during acute otitis media.** *N Engl J Med* 1999, **340:**260–264.

Detection of respiratory viruses in AOM using modern techniques.

13. Simoes EA, Groothuis JR, Tristram DA, *et al.*: **Respiratory syncytial virus-enriched globulin for the prevention of acute otitis media in high-risk children.** *J Pediatr* 1996, **129:**214–219.
14. Heikkinen T, Ruuskanen O, Waris M, *et al.*: **Influenza vaccination in the prevention of acute otitis media in children.** *Am J Dis Child* 1991, **145:**445–448.
15. Clements DA, Langdon L, Bland C, *et al.*: **Influenza A vaccine decreases the incidence of otitis media in 6- to 30- month-old children in day care.** *Arch Pediatr Adolesc Med* 1995, **149:**1113–1117.
16. Belshe RB, Mendelman PM, Treanor J, *et al.*: **The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children.** *N Engl J Med* 1998, **338:**1405–1412.
17. • Belshe RB, Gruber WC: **Prevention of otitis media in children with live attenuated vaccine given intranasally.** *Pediatr Infect Dis J* 2000, **19:**S66–S71.

Multicenter clinical trial using live, attenuated influenza vaccine for prevention of OM.

18. Buchman CA, Doyle WJ, Skoner DP, *et al.*: **Influenza A virus–induced acute otitis media.** *J Infect Dis* 1995, **172:**1348–1351.
19. Buchman CA, Doyle WJ, Skoner D, *et al.*: **Comparison of the nasal and otologic responses following intranasal challenge with influenza A virus and rhinovirus type 39.** In *Recent Advances in Otitis Media.* Edited by Lim DJ, Bluestone CD, Casselbrant M, et al. Hamilton Ontario: BC Decker; 1996: 431–433.
20. Buchman CA, Doyle WJ, Pilcher O, *et al.*: **Nasal and otologic effects of experimental respiratory syncytial virus infection in adults.** *Am J Otolaryngol* 2002, **23:**70–75.
21. • Chonmaitree T: **Viral and bacterial interaction in acute otitis media.** *Pediatr Infect Dis J* 2000, **19:**S24–S30.

Review of the role of viruses and bacteria in AOM.

22. Rayner MG, Zhang Y, Gorry MC, *et al.*: **Evidence of bacterial metabolic activity in culture-negative otitis media with effusion.** *JAMA* 1998, **279:**296–299.
23. Winther B, Hayden FG, Arruda E: **Viral respiratory infection in schoolchildren: effects on middle-ear pressure.** *Pediatrics* 2002, **109:**826–832.
24. Alper CM, Doyle WJ, Skoner DP, *et al.*: **Prechallenge antibodies moderate disease expression in adults experimentally exposed to rhinovirus strain hanks.** *Clin Infect Dis* 1998, **27:**119–128.
25. Doyle WJ, Alper CM, Buchman CA, *et al.*: **Illness and otologic changes during upper respiratory virus infection.** *Laryngoscope* 1999, **109:**324–328.
26. Bakaletz LO, Daniels RL, Lim DJ: **Modeling adenovirus type 1-induced otitis media in the chinchilla: effect on ciliary activity and fluid transport function of eustachian tube mucosal epithelium.** *J Infect Dis* 1993, **168:**865–872.
27. Chung MH, Griffith SR, Park KH, *et al.*: **Cytological and histological changes in the middle ear after inoculation of influenza A virus.** *Acta Otolaryngol (Stockh)* 1993, **113:**81–87.
28. Park KH, Bakaletz LO, Coticchia J, *et al.*: **Effect of influenza A virus infection on ciliary activity and dye transport function in the chinchilla ET.** *Ann Otol Rhinol Laryngol* 1993, **102:**551–553.
29. Suzuki K, Bakaletz LO: **Synergistic effect of adenovirus type 1 and nontypeable Haemophilus influenzae in a chinchilla model of experimental otitis media.** *Infect Immun* 1994, **62:**1710–1718.
30. Miyamoto N, Bakaletz LO: **Kinetics of the ascension of NTHi from the nasopharynx to the middle ear coincident with adenovirus-induced compromise in the chinchilla.** *Microb Pathog* 1997, **23:**119–126.
31. Bakaletz LO, Murwin DM, Billy JM: **Adenovirus serotype 1 does not act synergistically with *Moraxella* (*Branhamella*) *catarrhalis* to induce otitis media in the chinchilla.** *Infect Immun* 1995, **63:**4188–4190.
32. Chonmaitree T, Henrickson KJ: **Detection of respiratory viruses in the middle ear fluids of children with acute otitis media by multiplex reverse transcription-polymerase chain reaction assay.** *Pediatr Infect Dis J* 2000, **19:**258–260.

33. Tong HH, Grants I, Liu X, *et al.*: **Comparison of alteration of cell surface carbohydrates of the chinchilla tubotympanum and colonial opacity phenotype of *Streptococcus pneumoniae* during experimental pneumococcal otitis media with of without antecedent influenza A virus infection.** *Infect Immun* 2002, **70:**4292–4301.
34. Hirano T, Kurono Y, Ichimiya I, *et al.*: **Effects of influenza A virus on lectin-binding patterns in murine nasopharyngeal mucosa and on bacterial colonization.** *Otolaryngol Head Neck Surg* 1999, **121:**616–621.
35. Williams RL, Chalmers TC, Stange KC, *et al.*: **Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion: a meta-analytic attempt to resolve the brouhaha.** *JAMA* 1993, **270:**1344–1351.
36. Mossad SB: **Treatment of the common cold.** *BMJ* 1998, **317:**33–36.
37. Turner R: **The treatment of rhinovirus infections: progress and potential.** *Antivir Res* 2001, **49:**1–14.
38. Ruohola A, Heikkinen T, Waris M, *et al.*: **Intranasal fluticasone propionate does not prevent acute otitis media during viral upper respiratory infection in children.** *J Allergy Clin Immunol* 2000, **106:**467–471.
39. Marchisio P, Cavagna R, Maspes B, *et al.*: **Efficacy of intranasal virosomal influenza vaccine in the prevention of recurrent acute otitis media in children.** *Clin Infect Dis* 2002, **35:**168–174.
40. Kneyber MC, Kimpen JL: **Current concepts on active immunization against respiratory syncytial virus for infants and young children.** *Pediatr Infect Dis J* 2002, **21:**685–696.
41. Crowe JE: **Immune responses of infants to infection with respiratory viruses and live attenuated respiratory virus candidate vaccines.** *Vaccine* 1998, **16:**1423–1432.
42. Hayden K, Andries K, Janssen PA: **Safety and efficacy of intranasal pirodavir in experimental rhinovirus infection.** *Antimicrob Agents Chemother* 1992, **36:**727–732.
43. Sperber SJ, Doyle WJ, McBride TP, *et al.*: **Otologic effects of interferon beta serine in experimental rhinovirus colds.** *Arch Otolaryngol Head Neck Surg* 1992, **118:**933–936.
44. Hayden FG: **Influenza virus and rhinovirus-related otitis media: potential for antiviral intervention.** *Vaccine* 2000, **19(Suppl1):**S66–S70.
45. Doyle WJ, Skoner DP, Alper CM, *et al.*: **Effect of rimantadine treatment on clinical manifestations and otologic complications in adults experimentally infected with influenza A (H1N1) virus.** *J Infect Dis* 1998, **177:**1260–1265.
46. Walker JB, Hussey EK, Treanor JJ, *et al.*: **Effects of the neuraminidase inhibitor zanamavir on otologic manifestations of experimental human influenza.** *J Infect Dis* 1997, **176:**1417–1422.
47. Whitley RJ, Hayden FG, Reisinger KS, *et al.*: **Oral oseltamivir treatment of influenza in children.** *Pediatr Infect Dis J* 2001, **20:**127–133.
48. Casselbrant ML, Kaleida PH, Rockette HE, *et al.*: **Efficacy of antimicrobial prophylaxis and of tympanostomy tube insertion for prevention of recurrent acute otitis media: results of a randomized clinical trial.** *Pediatr Infect Dis J* 1992, **11:**278–286.
49. Paradise JL, Bluestone CD, Rogers KD, *et al.*: **Efficacy of adenoidectomy for recurrent otitis media in children previously treated with tympanostomy-tube placement: results of parallel randomized and nonrandomized trials.** *JAMA* 1990, **18:263:**2066–2073.
50. Rosenfeld RM: **Natural history of untreated otitis media.** In *Evidence-Based Otitis Media.* Edited by Rosenfeld RM, Bluestone CD. Hamilton, Ontario: BC Decker; 1999:157–177.
51. Rosenfeld RM, Vertrees JE, Carr J, *et al.*: **Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from thirty-three randomized trials.** *J Pediatr* 1994, **124:**355–367.
52. Del Mar C, Glasziou P, Hayem M: **Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis.** *BMJ* 1997, **314:**1526–1529.
53. Butler CC, van Der Voort JH: **Steroids for otitis media with effusion: a systematic review.** *Arch Pediatr Adolesc Med* 2001, **155:**641–647.
54. Flynn CA, Griffin G, Tudiver F: **Decongestants and antihistamines for acute otitis media in children.** *Cochrane Database Syst Rev* 2002, **1:**CD001727.