Rate of Concurrent Otitis Media in Upper Respiratory Tract Infections With Specific Viruses

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Objective: To estimate the coincidence of new otitis media (OM) for first nasopharyngeal detections of the more common viruses by polymerase chain reaction (PCR). New OM episodes are usually coincident with a viral upper respiratory tract infection (vURTI), but there are conflicting data regarding the association between specific viruses and OM.

Design: Longitudinal (October-March), prospective follow-up of children for coldlike illness (CLI) by diary, middle ear status by pneumatic otoscopy, and vURTI by PCR.

Setting: Academic medical centers.

Participants: A total of 102 families with at least 2 children aged between 1 and 5 years (213 children; mean [SD] age, 3.7 [1.5] years; 110 male; and 176 white) were recruited from the local communities at 2 study sites by advertisement.

Main Outcome Measures: New OM and CLI episodes and nasopharyngeal virus detections.

Results: A total of 176 children (81%) had isolated PCR detection of at least 1 virus. The OM coincidence rates were 62 of 144 (44%) for rhinovirus, 15 of 27 (56%) for respiratory syncytial virus, 8 of 11 (73%) and 1 of 5 (20%) for influenza A and B, respectively, 6 of 12 (50%) for adenovirus, 7 of 18 (39%) for coronavirus, and 4 of 11 (36%) for parainfluenza virus detections ($P = .37$). For rhinovirus, new OM occurred in 50% of children with and 32% without a concurrent CLI ($P = .15$), and OM risk was predicted by OM and breastfeeding histories and by daily environment outside the home.

Conclusions: New OM was associated with nasopharyngeal detection of all assayed viruses irrespective of the presence or absence of a concurrent CLI. Differences among viruses were noted, but statistical significance was not achieved, possibly because of the low power associated with the small number of nonrhinovirus detections.

OM-vURTI coincidence in children, the literature is inconsistent with respect to the relative importance of the different vURTIs.2,8,12,16,19-22 However, because most interventions that are potentially useful in preventing new OM during a vURTI are virus specific, unbiased estimates of virus-specific OM risk are needed.1,8 This study addresses that need using a longitudinal format with high-density assessments for detection of OM, CLI, and nasopharyngeal virus in a large group of unselected children. The null hypothesis tested is that the new OM coincidence rate of a vURTI is not virus specific. Acceptance or rejection of this hypothesis is important for developing rational strategies to prevent that complication.

METHODS

The data for this report were abstracted from those available for the first 4 years of an ongoing, 5-year study designed to characterize the causal relationships among vURTIs, CLIs, and OM in young children. The protocol was approved by the institutional review boards at the University of Pittsburgh and the University of Virginia. Families at 2 study sites (Pittsburgh, Pennsylvania, and Charlottesville, Virginia) with 2 children aged between 1 and 3 years were recruited for participation by advertisement. Exclusion criteria included the presence in either child of a serious medical condition, a medical condition that predisposes to persistent OM, a nonintact or structurally abnormal tympanic membrane, a preexisting sensorineural hearing loss, or an inability to cooperate sufficiently with the examination and test procedures. After affirmation of willingness to participate and acquisition of written informed consent, families were entered into the study in October with an anticipated follow-up through April of that year and were reimbursed for participation. The study subjects included the 2 index children and any older siblings younger than 10 years who provided assent.

The data for this report consist of demographic information for each child (age, sex, and race), information on selected OM risk factors (history of OM, frequent colds, breastfeeding, and exposure to tobacco smoke and the child’s daily environment) for a subset of children (those enrolled at the Pittsburgh site in years 1-4 and at the Charlottesville site in years 2-4),23 the longitudinal daily assignments of the presence or absence of a CLI day as recorded by a parent and weekly assignments of the presence or absence of OM as assessed by bilateral pneumatic otoscopy performed by validated study personnel. These data were supplemented with virus detections by polymerase chain reaction (PCR) assay of nasal secretions collected from the children during a parent-identified CLI episode in the child or in an enrolled sibling, at the onset of a new OM episode (either unilateral or bilateral, asymptomatic or symptomatic) in the child or in a sibling, and at random times during illness-free periods. Not all samples during these designated target periods could be collected because some children refused at times to cooperate with the requisite procedures, and this was especially true when free nasal secretions were absent.

For each subject, parent-recorded CLI days were coded as longitudinal strings of 0s (CLI absent) and 1s (CLI present). A CLI episode was defined as 3 or more consecutive days with a parent-reported CLI separated from other episodes by at least 4 days. We did not provide the parents with a definition of a CLI day based on a specific symptom-sign set, and those assignments were made as was typical for each parent’s usual CLI diagnosis in their children.

Bilateral pneumatic otoscopy on enrolled children was scheduled at approximately weekly intervals at an in-home visit (Pittsburgh) or at a study clinic visit (Charlottesville). At each observation time, both ears were examined by a validated otoscopist and classified as to the presence or absence of OM based on ratings of the tympanic membrane with respect to visibility, condition, position, appearance, color, vascularity, light reflex, and mobility. A positive diagnosis for OM was made when middle ear effusion (with or without air-fluid level) was observed irrespective of the presence or absence of concurrent signs of middle ear infection. Acute OM was diagnosed by the presence of OM with concurrent signs of middle ear infection including parental report of ear pulling, otalgia, irritability, and fussiness and otoscopic signs of erythema and/or white opacification (other than from scarring) of the tympanic membrane, bulging or fullness of the tympanic membrane, or otorrhea from a perforation of a previously intact tympanic membrane. Otitis media with effusion (OME) was assigned to OM episodes without concurrent signs of infection. Episodes of AOM but not OME were treated empirically with antibiotics. Because otoscopy was not necessarily performed at a time when the child first presented with otologic symptoms (the children were seen and treated by their primary care physician for most illnesses), subclassification of OM for this report was biased toward OME assignment.

Otoscopic data were coded for the left and right ears as OME present or absent (0 = absent; 1 = present), and AOM present or absent (0 = absent; 2 = present). Between otoscopic assessments, daily OM assignment for each ear was made based on the previous 7 days with the preceding and subsequent days considered. A new OM episode was defined as a sequence of 1s preceded and followed by a sequence of 0s, and an episode of AOM was defined as a newly introduced string of 2s, irrespective of preceding and subsequent observations. In the analysis, the child was considered to be the unit of measure, and either new unilateral or bilateral OM episodes were assigned as a new OM episode.

The technique for collecting nasal secretions from the children and the methods and protocols for storage and transport of the specimens to the virology laboratory were previously described.24 Samples were assayed in batches for PCR detection of adenovirus, coronavirus, influenza virus A and B, paramyxovirus, rhinovirus (picornavirus), and respiratory syncytial virus (RSV) using a protocol adapted from the commercially available Hexaplex procedure (Prodesse Inc, Waukesha, Wisconsin) as described in previous publications.6 Each viral species was assigned a numeric code, and the temporal distribution for these codes was overlaid onto the sequence strings for CLI and new OM episodes. Detections of the same virus within a 20-day period and without an intermittent observation of a different virus or “no detectable virus” were linked as a single virus detection. To avoid bias associated with multiple same-virus detections, the data analyses were based on the concurrence in each child of OM for the first detection of each assayed virus in isolation (ie, disregarding assays with multiple identified viruses).

The data map (longitudinal sequence strings for CLI, OM, and virus detections) was read from entry to termination of each child’s participation, and the first detection of each assayed virus in isolation was identified. Associated new CLI and new OM episodes were assigned if the episode duration embedded the detection or occurred within 7 days after or 3 days before the virus detection. For the first detection of each virus in each child, the presence or absence of a new OM episode and of the OM subtype was assigned based on those criteria. Data for OM episodes of long durations and with multiple, nonidentical virus detections at different times were not included in the calculation of OM coincidence. For each virus, the OM coincidence rate of a first virus detection was calculated as the sum.
RESULTS

The data for 213 children (176 white and 110 male) were available for analysis. These children ranged in age from 1.0 to 8.6 years (mean [SD] age, 3.7 [1.5] years); 63, 54, 60, and 36 different children were studied in years 1 through 4, respectively. Of these, 176 (81%) had at least 1 detection of an assayed virus; 114, 51, 6, 1, and 4 children had at least 1 detection of 1, 2, 3, 4, and 5, respectively, of the assayed viruses. For each virus, the Table reports the number of persons with at least 1 detection, the number of first detections that were included in the calculation of OM coincidence rate, the number of associated new OM episodes, the number assigned to AOM, and the OM coincidence rate with 95% confidence intervals.

At least 1 rhinovirus detection occurred in 70% of enrolled subjects, and new OM was coincident in 44% of the first detections. The other viruses were detected in less than 13% of the subjects, and the new OM coincidence rate varied from a low of 20% for influenza B virus to a high of 73% for influenza A virus detections. The difference in the OM coincidence rate among these viruses was not statistically significant ($\chi^2 = 6.5; P = .37$). However, the low detection frequency for most viruses greatly constrained the power of the statistical test. Nonetheless, with the exception of parainfluenza type 1 for which only 2 detections were observed, new OM episodes were coincident with the detection of all assayed virus species in the nose and/or nasopharynx.

The percentages of all associated OM episodes classified as AOM were 8%, 33%, 38%, 17%, 29%, and 75% for rhinovirus, RSV, influenza A virus, adenovirus, coronavirus, and parainfluenza virus, respectively. Pairwise comparisons of these percentages with rhinovirus were statistically significant for RSV ($P = .02$) and parainfluenza virus ($P = .005$) but was not significant for the other viruses (Fisher exact test).

The large number of isolated rhinovirus detections allowed for a comparison of OM coincidence between virus detections with and without a concurrent CLI. Of the 134 detections with data for both OM and CLI, 32 (24%) were not associated with either CLI or OM, 18 (13%) were associated with OM without CLI, 42 (31%) were associated with CLI without OM, and 42 (31%) were associated with both OM and CLI. Thus, for rhinovirus detections, 42 of 84 (50%) with and 18 of 50 (32%) without a concurrent CLI were associated with new OM (Fisher exact test, $P = .15$). For this subset, the OM risk of rhinovirus detection was 45% and of rhinovirus CLI was 50%.

When the demographic variables (age, sex, and race), OM history (yes or no), frequent cold history (yes or no), breast feeding history (yes or no), exposure to tobacco smoke (yes or no), and daily environment (day care, school, or home with mother and/or father) were entered into a logistic regression equation to predict rhinovirus-associated CLIs ($n = 121$), only race (white > black; odds ratio, 0.31; $P = .03$) and parainfluenza history (present > absent; odds ratio, 2.6; $P = .03$), daily environment (out of home > home with mother and/or father; OR, 2.4; $P = .03$) and breastfeeding history (present > absent history; odds ratio, 3.7; $P = .02$) were identified as predictors. When these variables and CLI presence or absence were entered into the equation to predict rhinovirus-associated OM episodes, history of OM (present > absent; odds ratio, 2.6; $P = .03$), daily environment (out of home > home with mother and/or father; OR, 2.4; $P = .03$) and breastfeeding history (present > absent history; odds ratio, 3.7; $P = .02$) were identified as predictors. When these variables were entered into a stepwise regression equation to predict the frequency of OM episodes associated with

<table>
<thead>
<tr>
<th>Virus</th>
<th>Total No. of Persons With Virus Detection</th>
<th>Analyzable, No.</th>
<th>OM (AOM$^-$), No.</th>
<th>OM Coincidence Rate (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>151</td>
<td>140</td>
<td>62 (5)</td>
<td>0.44 (0.36-0.53)</td>
</tr>
<tr>
<td>RSV</td>
<td>27</td>
<td>27</td>
<td>15 (5)</td>
<td>0.56 (0.35-0.75)</td>
</tr>
<tr>
<td>Influenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>11</td>
<td>11</td>
<td>8 (3)</td>
<td>0.73 (0.39-0.94)</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>5</td>
<td>1 (0)</td>
<td>0.20 (0.01-0.72)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>12</td>
<td>12</td>
<td>6 (1)</td>
<td>0.50 (0.21-0.79)</td>
</tr>
<tr>
<td>Coronavirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>229E</td>
<td>2</td>
<td>2</td>
<td>1 (1)</td>
<td>0.50 (NA)</td>
</tr>
<tr>
<td>OC43</td>
<td>17</td>
<td>16</td>
<td>6 (1)</td>
<td>0.38 (0.15-0.65)</td>
</tr>
<tr>
<td>All</td>
<td>19</td>
<td>18</td>
<td>7 (2)</td>
<td>0.39 (0.17-0.64)</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0 (0)</td>
<td>0.00 (NA)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>7</td>
<td>3 (2)</td>
<td>0.43 (0.10-0.82)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1 (1)</td>
<td>0.50 (NA)</td>
</tr>
<tr>
<td>All</td>
<td>11</td>
<td>11</td>
<td>4 (3)</td>
<td>0.36 (0.11-0.69)</td>
</tr>
</tbody>
</table>

Abbreviations: AOM, acute otitis media; NA, not applicable; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.
any first virus detection for each subject (n = 137), history of OM (present > absent [P = .009]), daily environment (out of home > home with mother and/or father [P = .03]), and breastfeeding history (present > absent history [P < .001]) were again identified as significant predictors.

The results for the present study demonstrate temporal coincidences among CLI expression, new OM, and virus detection in the upper respiratory tract at rates consistent with those previously reported.9,10,21 While the observed relationships are associative, past studies of experimental vURTIs in adult human volunteers provide strong evidence for causality with vURTIs precipitating both CLI expression and otologic complications.2,3 As expected, most of the children (71%) had at least 1 rhinovirus detection, but the detection rates for the other assayed viruses were much lower, varying between 5% and 13%. This distribution is consistent with the results of studies focusing on the viral cause of CLIs with sampling over the typical CLI season.21

For rhinovirus, not all detections were associated with a CLI, and a CLI was not a prerequisite for OM development. While the OM coincidence rate was higher for CLI rhinovirus detections, this was not significant. Otologic complications in the absence of CLIs were previously reported for experimental vURTIs in adults22 and for natural vURTIs in children.23 These data suggest that the pathways activated during a vURTI leading to OM and to the symptoms and/or signs representing a CLI are somewhat independent.

An analysis of the possible predictors of CLI expression and new OM during rhinovirus detection showed that children identified by their parents as being white predicted CLI expression, while a positive history of OM, a positive history of breastfeeding, and a daily environment outside of the home predicted OM risk. The effect of OM history and daily environment on OM risk is consistent with previous reports, but the effect of breastfeeding is directionally opposed to that of past studies.23 It should be noted that previous studies of OM “risk factors” did not condition the enumerated OM events on virus presence (or, more weakly, on CLIs) as was done here for rhinovirus (and all viruses). These comparative results suggest that breastfeeding may be protective against vURTIs but not against OM once virus infection is established; that negative OM history is protective against OM during established virus infections; and that daily environment at home with the mother and/or father protects against vURTIs and OM during established vURTIs.

In the present study, nasopharyngeal secretion samples were collected for virus assay in all enrolled siblings on the detection of OM (irrespective of concurrent otologic symptoms and/or signs) in any sibling, on the detection of a CLI in any sibling, and at random times throughout the typical CLI season. The rate of concurrent new OM varied from a low of 20% for influenza A, and the rate of OM episodes assigned to AOM was different among viruses, varying from a low of 8% for rhinovirus to a high of 75% for parainfluenza virus. Notably, OM was coincident with detection of all viruses assayed, but the differences among viruses in that rate did not achieve statistical significance. The latter may have resulted from low power, given the small sample sizes for nonrhinovirus detections and the uncontrolled differences in OM risk factors among the subpopulations with specific virus detections.

Past studies reported an excess OM risk for RSV infections vis-à-vis infection with other viruses,7,8,12,19-21 but our results show that if a difference exists, its magnitude is small. Some of those studies were biased by design factors that included dependence on otologic signs and/or symptoms for OM identification (restricting the identified OM episodes to AOM, which our data show to be virus specific), the source population (eg, children in a hospital, where viruses that cause more serious complications such as RSV and influenza A would be overrepresented), and study season (eg, seasonal epidemics where viruses circulating at the time of sampling would be overrepresented). Reports that estimated coincidence rates from virus detections in the middle ear are especially vulnerable to these biases because the denominator for rate calculations (number infected with the virus in the population) is not known.

In conclusion, our null hypothesis that there are no differences in the new OM coincidence rates for different viruses could not be rejected. Overall, the OM coincidence rate for virus detection was 0.43. For most viruses, the 95% confidence interval placed on the OM rates was large, but for rhinovirus that interval was much smaller (0.36-0.53). Rhinovirus is the most common virus infection in children and, unlike some of the other viruses, children can be reinfected with a different strain of the virus in the same season. Combined with our data, these observations suggest that most new OM episodes are coincident with a rhinovirus vURT. Because of the large number of rhinovirus stains, it is unlikely that a vaccine will be developed any time soon, and the effectiveness of the limited number of antipicornavirus agents (eg, interferon, pleconaril) available has not been evaluated with respect to preventing OM. A generalized approach to preventing OM episodes associated with a vURT should target those events responsible for interpersonal virus transmission with the goal of preventing vURTIs in the at-risk population.

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Author Contributions: Dr Doyle had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Alper, Winther, and Doyle. Acquisition of data: Winther, Mandel, and Hendley. Analysis and interpretation of data: Alper, Winther, Mandel, and Doyle. Drafting of the manuscript: Alper, Mandel, and Doyle. Critical revision of the manuscript for important intellectual content: Alper, Winther, Mandel, Hendley, and Doyle. Statistical analysis: Doyle. Obtained funding: Doyle.

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REFERENCES