Reducing the Frequency of Acute Otitis Media by Individualized Care

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Objective: We sought to determine if use of more stringent diagnostic criteria for acute otitis media (AOM) than currently advocated by the American Academy of Pediatrics, tympanostentesis and pathogen-specific antibiotic treatment (individualized care) would result in reducing the incidence of recurrent AOM and consequent tympanostomy tube surgery.

Methods: A 5-year longitudinal, prospective study in Rochester, NY, was conducted from July 2006 to July 2011 involving 254 individualized cared children. When this individualized care group developed symptoms of AOM, strict diagnostic criteria were applied and a tympanocentesis was performed. Pathogen resistance to empiric high-dose amoxicillin/clavulanate (80 mg/kg of amoxicillin component) caused a change in antibiotic to an optimized choice. Legacy controls (n = 208) were diagnosed with the same diagnostic criteria by the same physicians as the individualized care group and received the same empiric amoxicillin/clavulanate (80 mg/kg of amoxicillin component) but no tympanocentesis or change in antibiotic. Community control children (n = 1020) were diagnosed according to current American Academy of Pediatrics guidelines and treated with high-dose amoxicillin (80 mg/kg) without tympanocentesis as guideline recommended.

Results: 5.9% of children of the individualized care group compared with 14.4% of Legacy controls and 27.3% of community controls became otitis prone, defined as 3 episodes of AOM within a 6-month time span or 4 AOM episodes within a 12-month time span (P < 0.0001). 2.4% of the individualized care group compared with 6.3% of Legacy controls, and 14.8% of community controls received tympanostomy tubes (P < 0.0001).

Conclusions: Individualized care of AOM significantly reduces the frequency of AOM and tympanostomy tube surgery. Use of strict diagnostic criteria for AOM and empiric antibiotic treatment using evidence-based knowledge of circulating otopathogens and their antimicrobial susceptibility profile also produces improved outcomes.

Key Words: otitis prone, acute otitis media, tympanostomy tubes, tympanocentesis, amoxicillin, amoxicillin/clavulanate


Otitis media is the most common pediatric malady, after the common cold, diagnosed among children in the U.S., and insertion of tympanostomy (pressure equalizing) tubes is the most common surgical procedure performed in children, after circumcision. Antimicrobials are recommended for treatment of acute otitis media (AOM), and their use for AOM is a standard of therapy. Current practice guidelines of the American Academy of Pediatrics (AAP) endorse an escalation to broader spectrum antimicrobials for AOM treatment failure and recurrent AOM. Guidelines also endorse the insertion of tympanostomy tubes for children who have recurrent AOM or prolonged otitis media with effusion. The recommendations have been made for tympanostomy tube insertion because of concern that repetitive infection or prolonged middle ear fluid might result in sequelae.

The otitis prone (OP) condition in children has been described to occur when a child experiences 3 episodes of AOM in 6 months or 4 episodes in 12 months. Nearly all children who reach that frequency of AOM are 6 to 30 months of age. Prior studies suggest that about 30% of children meet the OP definition. In 2006, we began a longitudinal, prospective study of AOM in children age 6 to 30 months to better understand the immune response of children to otopathogens, and impact of individualized care on the frequency of recurrent AOM and the rate of tympanostomy tube surgery. Here we describe the outcomes of children receiving individualized care with respect to meeting an OP definition and undergoing tympanostomy tube surgery. Outcomes were compared with 2 age-matched control groups of children.

METHODS

General Design

This report includes longitudinal data for the 5-year time span July 2006 to July 2011 from children enrolled in a prospective study supported by the National Institutes of Deafness and Communication Disorders. Healthy, individualized care children, hereafter referred to as the intervention group, were children without previous episodes of AOM, enrolled at 6 months of age from a single middle class, suburban sociodemographic pediatric practice in Rochester, NY (Legacy Pediatrics). The children in the intervention group were seen for each AOM episode until 30 months of age. Exclusion criteria were children greater than 6 months old at time of enrollment, history of AOM prior to 6 months of age and any immunocompromised or anatomical defect that would make the child prone to AOM. The University of Rochester Medical Center and Rochester General Hospital Institutional Review Boards approved this study.

Two control groups were identified using the same inclusion and exclusion criteria as the intervention group, and their demographic data collected for matching to the individualized care cases. “Legacy controls” were identified from the same recruitment site as the intervention group. These children all received primary care at the same site as the intervention group, with the same physician investigators (validated otoscopy) and J.R.C.) making the diagnosis of AOM using the same criteria as the intervention group and were empirically treated for AOM in the same manner as the intervention group (see below). Legacy controls were children whose parents declined to participate in the longitudinal, prospective study wherein consent was provided to perform tympanocentesis for all cases of AOM. They were matched for age and length of follow-up as possible. “Community controls” were identified from a community-based private pediatric practice that participated in the longitudinal, prospective study by referral of...
children to the physician investigators conducting the study (M.E.P and J.R.C.). That practice had a very similar sociodemographic profile as the intervention/Legacy controls site. Community controls were matched to the intervention group for age and length of follow-up as possible. The pediatricians of community controls diagnosed AOM according to the AAP definition after training in general pediatrics at US training programs. The community pediatricians were not validated otoscopists because none had undergone special training, as previously described.

Definitions

In the intervention group and Legacy controls, children with acute onset of symptoms compatible with the diagnosis of AOM were diagnosed with AOM using pneumatic otoscopy with a strict requirement for: (1) tympanic membrane (TM) bulging or fullness; (2) cloudy or purulent effusion behind the TM or the TM was completely opacified; and (3) TM mobility reduced or absent.

For all intervention group cases and both Legacy and community control group cases, an AOM event was considered a new event if the child presented with an AOM 14 days after a preceding AOM. AOM treatment failure (AOMTF) was defined by the persistence of symptoms and signs of AOM beyond 48 hours after the start of antibiotic treatment or before 14 days had passed because diagnosis resulting in a change in antibiotic therapy. The OP condition was defined in this study by 3 separate episodes of AOM in a 6-month time span or 4 separate episodes in a 12-month time span. The children were seen in a follow-up examination 3 weeks after the initial diagnosis of AOM to assure that symptoms had resolved and the TM was no longer full or bulging (intervention group and Legacy controls) or the medical record stated that the examination was normal (community controls). Residual middle ear fluid (MEF) was considered a normal finding at the follow-up visit for cases and controls. For AOMTF among the intervention group cases, the TM was still bulging and a repeat tympanocentesis produced MEF and additional antibiotic treatment was necessary.

Tympanocentesis

MEF for culture was obtained as previously described.

Treatment Regimen

Intervention group children were empirically treated with amoxicillin/clavulanate at a dose of 80 mg/kg/day of amoxicillin divided twice daily for a 5-day regimen regardless of age. The authors (M.E.P and J.R.C.) treat AOM with short-course antibiotic treatment unless the child had an antibiotic within the prior 30 days. If the MEF grew Streptococcus pneumoniae (Spn) that was penicillin sensitive or intermediate, the child continued on amoxicillin/clavulanate. If the MEF grew Spn that was penicillin resistant, the child was treated with ceftriaxone once daily, every other day for 3 doses at 50 mg/kg/dose regardless of penicillin allergy status. If the MEF grew Haemophilus influenzae (NTHi) or Moraxella catarrhalis (M.cat), the child was contained on amoxicillin-clavulanate. An exception occurred if an Spn was isolated that expressed a serotype 19A capsule. If the strain had a minimum inhibitory concentration of >4 mcg/mL to ceftriaxone and was expressed a serotype 19A capsule. If the strain had a minimum inhibitory concentration of >4 mcg/mL to ceftriaxone and was susceptible to levofoxacin, then levofoxacin was prescribed at a dose of 20 mg/kg/day divided twice daily for 10 days. Culture and sensitivity results were available within 48–72 hours for the intervention group cases of AOM. Legacy controls were empirically treated with amoxicillin/clavulanate at a dose of 80 mg/kg/day of amoxicillin divided twice daily for a 5-day regimen unless the child had antibiotics within the prior 30 days or had AOMTF. In those circumstances, the child was treated with 3 doses of ceftriaxone (50 mg/kg/dose) per AAP recommendations.

Community controls were treated with high-dose amoxicillin (80 mg/kg/day divided twice daily) for 10 days as first-line therapy and 10 days high-dose amoxicillin/clavulanate for AOMTF and recurrent AOM episodes per AAP recommendations. Heptavalent pneumococcal conjugate vaccine was given to nearly all subjects until April 2010 when the 13-valent pneumococcal conjugate vaccine became available and was given to nearly all thereafter.

Microbiology

MEF samples were processed for bacterial culture as described previously.

Molecular Biology

When MEF samples were negative by culture, the fluid was tested by multiplex polymerase chain reaction to detect nonviable otopathogens as previously described.

Statistics

Despite best efforts, observation times for subjects without an AOM episode were not constant, and differed significantly between groups. Since variable exposure times may introduce bias in comparisons of episode rate, the Cox proportional hazards model, which controls for variable exposure times, was used. The analysis resulted in estimates of hazard ratios, interpretable as the ratio of episode rates between groups. The Cox proportional hazards model was applied separately to comparisons of the intervention/Legacy controls and the intervention/community controls. To rule out the possibility that any group difference was attributable to confounding due to heterogeneous risk factor distributions, all available risk factors were separately included in the regression model to detect any influence on episode rates. Kaplan–Meier survival curve estimates were used for nonparametric comparisons of event-free (OP development or pressure equalizer tube insertion) functions, with differences in survival curves assessed using a log-rank test. The Cochran–Armitage trend test was used to detect increasing or decreasing trends of proportion differences with respect to an ordinal variable. Otherwise, differences in proportions were tested using Fisher’s exact test.

For the results presented in Table 1, 17 subjects were excluded from the intervention group because they withdrew from the study with <6 months follow-up and 25 subjects were excluded because they were recruited from the community control practice where AOM diagnosis was made by that control group’s standard.

RESULTS

Description of the Cohorts

There were 254 children in the intervention group, 208 in the Legacy control group and 1020 in the community control group. The majority of the children were Caucasian, male, breast fed, had no family history of AOM, had no tobacco smoke exposure in the home, did not attend day care (in the intervention and Legacy control group), were health-insured and were up to date with either the 7- or 13-valent pneumococcal conjugate vaccine (PCV7 or PCV13) vaccinations (Table 2).

Otopathogens and Antibiotic Treatment

Table 1 shows the AOM episode numbers for the intervention, Legacy control and community control groups. There were 0.9, 1.0 and 1.8 AOM episodes/subject in the intervention, Legacy controls and community controls, respectively. There were no significant differences between the intervention and Legacy controls in this analysis that focused on any AOM event occurring within
TABLE 1. Distribution of AOM Episodes for the Intervention Group and the Legacy and Community Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group N = 212</th>
<th>Legacy Controls N = 208</th>
<th>Community Controls N = 1020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of AOM</td>
<td>186</td>
<td>203</td>
<td>1817</td>
</tr>
<tr>
<td>No. (%) of subjects with any AOM episodes</td>
<td>91 (43%)#,#,#</td>
<td>102 (49%)#,#,#</td>
<td>704 (69%)#,#,#</td>
</tr>
<tr>
<td>No. (%) of subjects with 1 AOM episode</td>
<td>43 (20%)#,#,#,#</td>
<td>51 (25%)#,#,#,#</td>
<td>175 (17%)#,#,#,#</td>
</tr>
<tr>
<td>No. (%) of subjects with 2 AOM episodes</td>
<td>24 (11%)#,#,#,#</td>
<td>22 (11%)#,#,#,#</td>
<td>146 (29%)#,#,#,#</td>
</tr>
<tr>
<td>No. (%) of subjects with 3 AOM episodes</td>
<td>13 (6%)#,#,#,#</td>
<td>13 (6%)#,#,#,#</td>
<td>182 (18%)#,#,#,#</td>
</tr>
<tr>
<td>No. (%) of subjects with 4 or more AOM episodes</td>
<td>11 (5%)#,#,#,#</td>
<td>16 (8%)#,#,#,#</td>
<td>204 (20%)#,#,#,#</td>
</tr>
</tbody>
</table>

The odds ratio for AOM episode (at least 1) between the Legacy and intervention groups was 2.30 (1.56, 3.41) P < 0.0001 and between the community and intervention groups was 3.98 (2.98, 5.38) P < 0.0001. To determine if the differences in proportions depended on the number of episodes, the Cochran–Armitage test was used. This tests specifically for dependencies of proportion differences in the form of increasing or decreasing trends with respect to the number of AOM episodes (Agresti 2002). No such trend was found between the intervention and Legacy groups, but was found between the community and intervention groups, so that differences in proportions between these groups was positively associated with the number of AOM episodes.

# P = 0.24; # P < 0.0001; # P = 0.35; # P = 0.28; # P = 0.01; # P = 0.88; # P = 0.28; # P = 1.00; # P < 0.0001; # P < 0.0001; # P < 0.0001.

TABLE 2. Study Population Demographics

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group N = 254</th>
<th>Legacy Controls N = 208</th>
<th>Community Controls N = 1020</th>
<th>Fishers Exact P Value Intervention vs. Legacy Controls</th>
<th>Fishers Exact P Value Intervention vs. Community Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>130 (51)</td>
<td>116 (56)</td>
<td>530 (52)</td>
<td>P = 0.30</td>
<td>P = 0.73</td>
</tr>
<tr>
<td>Male</td>
<td>124 (49)</td>
<td>92 (44)</td>
<td>490 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>175 (69)</td>
<td>183 (88)</td>
<td>796 (78)</td>
<td>P &lt; 0.0001</td>
<td>P = 0.004</td>
</tr>
<tr>
<td>Other</td>
<td>79 (31)</td>
<td>25 (12)</td>
<td>224 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast-feeding ever</td>
<td>137 (54)</td>
<td>150 (72)</td>
<td>490 (48)</td>
<td>P &lt; 0.0001</td>
<td>P = 0.12</td>
</tr>
<tr>
<td>Breast-feeding never</td>
<td>117 (46)</td>
<td>58 (28)</td>
<td>530 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history AOM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>117 (46)</td>
<td>96 (46)</td>
<td>490 (48)</td>
<td>P = 1.0</td>
<td>P = 0.53</td>
</tr>
<tr>
<td>No</td>
<td>137 (54)</td>
<td>112 (54)</td>
<td>530 (52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38 (15)</td>
<td>21 (10)</td>
<td>153 (15)</td>
<td>P = 0.12</td>
<td>P = 0.92</td>
</tr>
<tr>
<td>No</td>
<td>216 (85)</td>
<td>187 (90)</td>
<td>867 (85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daycare</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-home based</td>
<td>64 (25)</td>
<td>37 (18)</td>
<td>408 (40)</td>
<td>P = 0.004</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Center based</td>
<td>58 (15)</td>
<td>19 (9)</td>
<td>122 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>152 (60)</td>
<td>152 (73)</td>
<td>490 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV7/13 up to date</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>251 (99)</td>
<td>206 (99)</td>
<td>969 (95)</td>
<td>P = 0.63</td>
<td>P = 0.003</td>
</tr>
<tr>
<td>No</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>51 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

the 6 to 30 months age range of study children, without time con- striction for 3 events in 6 months or 4 events in 12 months (the OP definition we used). Both the intervention and Legacy control group both had significantly fewer AOM events compared with the community controls (P < 0.0001 for both). Similarly the intervention and Legacy control group had significantly fewer third AOMs (P < 0.0001 for both) and 4 or more AOMs (P < 0.0001 for both).

Table 3 shows the otopathogen distribution for the AOM episodes. Spn and NTHi were the most commonly isolated otopathogens for all episodes of AOM. Multiple otopathogens were isolated from AOM#1 episodes: 2 Spn + Mcat, 1 Spn + NTHi and 1 NTHi + Mcat; AOM#2 episodes: 2 Spn + Mcat, 1 Spn + NTHi and 2 NTHi + Mcat; AOM#3 episodes: 1 Spn + Mcat and 1 Spn and NTHi; AOM #4 episodes: 2 Spn + Mcat and 1 NTHi + Mcat and AOM#6 episodes: 1 Spn + NTHi. Eighteen tympanocenteses had no growth, but polymerase chain reaction methods identified DNA of Spn and/or NTHi and/or Mcat for 12 (67%) of the 18 leaving 8 MEFs that were both culture and polymerase chain reaction negative.

Based upon MEF culture results, there were 17 (19% of the total AOM infections) changes from the empiric antibiotic choice (no changes were made when 34 MEF had no growth on culture). Fourteen of the changes were due to antibiotic resistance; 2 children were changed from amoxicillin-clavulanate to ceftriaxone due to penicillin resistant Spn isolates; 12 children had Spn 19A isolates that were resistant to both penicillin and ceftriaxone[11] and the child’s antibiotic was changed to levofloxacin. Three children were changed to cefixime due to intolerance of amoxicillin-clavulanate and isolation of NTHi.

Incidence of Otitis Prone Cases

Figure 1 shows the OP-free rates of children in the intervention, Legacy control and community control groups from July 2006 to July 2011. In the intervention cohort, the cumulative frequency of meeting the OP definition within the study window of 6 to 30 months was 5.9% (15 of 254 children) compared with 14.4% (30 of 208) of Legacy controls and 27.3% (278 of 1020) of community controls (P < 0.0001). The Cox ratio of meeting the OP definition comparing the intervention group to Legacy controls was 1.85 (95% confidence interval [CI] = 0.98, 3.50), P = 0.053. When we repeated this estimate, stratifying by daycare, the hazard ratio was 2.79 (95% CI = 1.01, 7.74), P = 0.044. Using a contingency
analysis based on occurrence during the study period the difference between intervention group and Legacy control children was 2.68 (95% CI = 1.35, 5.53), \( P = 0.002 \). The Cox ratio of meeting the OP definition comparing the intervention group with community controls was 3.78 (95% CI = 2.23, 6.43), \( P < 0.0001 \).

Incidence of Tympanostomy Tube Surgery

Figure 2 shows the percentage of children who underwent tympanostomy tube surgery in the intervention, Legacy control and community control groups. In the intervention group, the cumulative frequency of undergoing tympanostomy tube surgery was 2.4% (6 of 254 children) compared with 6.3% (13 of 208) Legacy controls and 14.8% (151 of 1020) community control children (\( P < 0.0001 \)). The Cox ratio of undergoing tympanostomy tube surgery comparing the intervention group to Legacy controls was 1.95 (95% CI = 0.72, 5.24), \( P = 0.17 \). When we repeated this estimate, stratifying by daycare, the Cox ratio was 4.91 (95% CI = 0.057, 42.11), \( P = 0.14 \). Using a contingency analysis based on occurrence during the study period the difference between intervention group and Legacy controls was 2.75 (95% CI = 0.95, 8.99), \( P = 0.056 \). The Cox ratio of undergoing tympanostomy tube surgery comparing the intervention group to community controls was 4.70 (95% CI = 2.04, 10.80), \( P < 0.0001 \).

Influence of Risk Factors and Respiratory Season

A significant difference in frequency between the intervention and Legacy controls was found for race (Caucasian versus other), breast-feeding (ever versus never) and attendance in day care (attended versus not) (Table 2). Hazard ratios for daycare/no daycare comparisons were significantly >1 for AOM and tympanostomy tube insertion episode rates within the intervention group and both Legacy control and community control groups, whereas breast-feeding had no such effect. Regarding race, the OP rates for non-Caucasians were too low to further examine any treatment group/race interaction. The influence of day care on the Cox ratios for the intervention group/Legacy controls comparisons was noted above.

Two demographic variables, gender and PCV7 or PCV13 (up to date), were significantly different for the intervention group and community controls. PCV7/PCV13 differed significantly in proportion (only 3 subjects were not PCV7/PCV13 up to date in the intervention group). Within the community controls, the Cox ratio for a PCV/no PCV comparison was 2.91 (\( P = 0.018 \)) for AOM rates and 3.73 (\( P = 0.064 \)) for tympanostomy tube insertion rates. When PCV7/PCV13 was introduced as a covariate in the intervention group/community controls comparison model,

**TABLE 3. Otopathogen Distribution for AOM Episodes in the Intervention Group**

<table>
<thead>
<tr>
<th>Otopathogen</th>
<th>AOM #1 n = 43</th>
<th>AOM #2 n = 24</th>
<th>AOM #3 n = 13</th>
<th>AOM #4 n = 5</th>
<th>AOM #5 n = 4</th>
<th>AOM #6 n = 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No growth*</td>
<td>N = 9 (22%)</td>
<td>N = 4 (17%)</td>
<td>N = 2 (15%)</td>
<td>N = 2 (40%)</td>
<td>N = 1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>N = 10 (44%)</td>
<td>N = 10 (42%)</td>
<td>N = 8 (62%)</td>
<td>N = 3 (60%)</td>
<td>N = 1 (25%)</td>
<td>N = 1 (50%)</td>
</tr>
<tr>
<td>Nontypeable Haemophilus influenzae</td>
<td>N = 13 (30%)</td>
<td>N = 11 (46%)</td>
<td>N = 3 (23%)</td>
<td>N = 1 (20%)</td>
<td>N = 2 (50%)</td>
<td>N = 2 (100%)</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>N = 6 (15%)</td>
<td>N = 4 (17%)</td>
<td>N = 2 (15%)</td>
<td>N = 3 (60%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Polymerase chain reaction was performed on no growth MEF. Streptococcus pneumoniae (Spn), Nontypeable Haemophilus influenzae (NTHi), or Moraxella catarrhalis (Mcat) DNA was identified in 7 (77%) of 9 middle ear fluids in AOM #1 (2 Spn, 7 NTHi, 1 Mcat), 2 (50%) of 4 in AOM #2 (1 Spn, 1 NTHi, 1 Mcat), 1 (50%) of 2 in AOM #3 (2 NTHi, 1 Mcat), 1 (50%) of 2 in AOM #4 (1 NTHi) and 1 (100%) of 1 in AOM #5 (1 Mcat).

**FIGURE 1.** Kaplan–Meier Estimates of Proportion Developing Otitis Prone State in Months for the 3 Groups.

**FIGURE 2.** Kaplan–Meier Estimates of Proportion Receiving Tympanostomy Tube in Months for the 3 Groups.
the estimate of the Cox ratios were 3.89 ($P < 0.0001$) for AOM rates and 4.83 ($P = 0.0002$) for tympanostomy tube insertion rates. Therefore, controlling for PCV7/PCV13 does not appreciably affect the Cox ratio estimates. The Cox ratios for meeting the definition of OP and undergoing tympanostomy tube surgery were assessed according to respiratory season for each of the 3 cohorts and no significant differences were found.

**DISCUSSION**

This study shows that children strictly diagnosed and treated according to an individualized care approach met the definition of OP, 3 AOM episodes in 6 months or 4 AOM episodes in 12 months, 2.4-fold and 4.6-fold less commonly than Legacy and community controls. Intervention group children underwent tympanostomy tube surgery 2.6-fold and 6.2-fold less commonly than Legacy and community controls. The definition of the OP child was applied for all 3 study cohorts for the entire study time period. In future publications, we will refer to the children in the intervention group who came to meet the OP definition as “stringent OP” to distinguish them as a population of children that we continue to study for differences in innate and adaptive immune responses to recurrent AOM.

We attribute the differences in frequency of the intervention group children becoming defined as OP to 3 possible factors: (1) more accurate diagnosis criteria of AOM due to the requirement for a bulging TM as assessed by validated otoscopists; (2) tympanocentesis to remove as much pus as possible and provide aeration of the middle ear space, along with relief of pain for the child; and (3) empiric antibiotic therapy with agents that have superior activity against the predominant otopathogens in the time frame of the study and modification of therapy based on MEF cultures.

Overdiagnosis clearly contributes to the eventual classification of a child as OP. Recurrent AOM leads to the diagnosis of the OP child and the recommendation for insertion of ear tubes for these children. A more accurate diagnosis of AOM is challenging. Tympanometry and acoustic reflectometry are not useful tools in detecting AOM. Minimal and variable teaching of AOM diagnosis for pediatric residents occurs during medical training. Video otoscopy examinations to assess diagnostic accuracy suggest pediatricians correctly distinguish AOM from otitis media with effusion and a retracted TM about 50% of the time. The best criteria for diagnosis have evolved over the years based on more careful study and confirmation by tympanocentesis. Validated otoscopists undergo training whereby the visual diagnosis with pneumatic otoscopy is confirmed or refuted with tympanocentesis. The minimum accepted criterion standard for validation is 80% accuracy. The validated otoscopists evaluating children in the study population have a documented accuracy >96% based on tympanocentesis confirmation of otopathogens when AOM was diagnosed. Incorporation of intensive otoscopy training to produce more validated otoscopists would go a long way in improving the problem of overdiagnosis of AOM.

The impact of tympanocentesis as performed in the study children on the reduction in recurrent AOM and subsequent tympanostomy tube surgery cannot be separately defined due to our study design. About 10% of the children in the intervention group likely benefited from tympanocentesis because an otopathogen was isolated that was not susceptible to the empirically selected antibiotic started for the child. In comparing the results presented in Table 1 with the results presented in Figure 1, differences were observed between the intervention group and Legacy controls in the latter but not the former analysis. We attribute this difference to a beneficial effect of tympanocentesis in lengthening the interval between AOM episodes such that clustering of events to meet an OP definition occurs less frequently among children who have the procedure done. Not all tympanocenteses are performed in the same manner thus producing mixed results as to the therapeutic value of the procedure. The procedure as performed in this study involved complete evacuation of the middle ear fluid, as possible. Further study will be necessary to clarify this question.

Antimicrobial prescriptions for AOM have been attributed to be a major factor in the emergence of resistance among otopathogens in the United States such that current guidelines endorse withholding antibiotics as an option in select child populations. With the high rate of $\beta$-lactamase producing *NTHi* that cause AOM, the treatment paradigm of intervention/Legacy controls employed amoxicillin-clavulanate as first line therapy. Two recent studies comparing placebo to amoxicillin-clavulanate as therapy showed a clear therapeutic benefit of antibiotics. Given the frequency of $\beta$-lactamase producing organisms and highly penicillin resistant *Spm*, in our study, population amoxicillin (80–100 mg/kg/day) would have been effective in 31% of children. Also amoxicillin is not always consistently absorbed and the probability of achieving the requisite pharmacodynamic exposures for oral $\beta$-lactam regimens is variable. Among the 61 children in this study who developed an AOM due to *Spm*, 12 (20%) children had an episode of infection caused by a serotype 19A strain resistant to penicillin and ceftriaxone but susceptible to levofloxacin, as previously described. Our group has been prospectively monitoring the serotypes of *Spm* that cause AOM since 1995 and published our last update in 2010. Those studies involved the Legacy intervention and control populations as described in this current report. Referral of some children from the community control site to LegacyPediatrics for tympanocentesis commenced in 2006 and the serotypes of *Spm* that cause AOM among children from the community control site have not differed from those isolated from the Legacy site. A report on all the serotypes of *Spm* that caused AOM from our study center and their antibiotic susceptibility for 2008 to 2011 will be published separately (Casey et al, unpublished data).

Rates of ear tube surgery in 2006 to 2011 in Rochester, NY, remained at 10%–12% among children between 6 and 36 months of age in the health-insured population (MVP Insurance, Rochester, NY, personal communication). Tympanostomy tube insertions are not without risk. Although the tubes are in place, otorrhea may develop, leading to otitis externa. After the tubes have been extruded, TM sclerosis, segmental atrophy, retraction pockets, cholesteatoma, persistent perforation and hearing loss may occur. The contribution of tubes versus the disease that preceded the tubes to these sequelae has been studied with differing conclusions.

A referent group for our study might be drawn from the work of Poehling et al involving children in Rochester, NY, who were the same age as the current study during the years 1998 to 2003. The referent group experienced recurrent AOM to meet the definition of OP by age 2 years in 31.8% of children in Rochester, NY (n = 5586) and 30.5% of children in Tennessee (n = 37841). By 2 years of age, tympanostomy tube insertions occurred in 6.2% of children in Rochester, NY, and in 6.6% of children in Tennessee. In another previous study, Thompson et al reported a 25% rate of OP children among those <2 years old from Boston, MA. The frequency of children receiving tympanostomy tubes in Colorado was 13.8% during 1991 to 1992, from a cross-sectional study of the United States was 6.8% during 1991, from a study in Boston, MA, was 10.0% during 1995 to 1996, from a study in Iceland was 30% and a study from Calgary, Canada, was 8.3% during 1997 to 2000.

There are limitations to this study. Although the children were drawn from a prospective cohort, a randomized trial would further validate the result. However, such a trial may be unlikely to occur due to logistics and costs. Our practice is not typical in that both physicians are validated otoscopists (M.E.P. and J.R.C.) and
we perform tympanocentesis routinely for AOM. Improvement in the teaching of otoscopy and tympanocentesis procedure would go a long way to improving the accuracy of AOM diagnosis and the lessen the rates of tympanostomy tube insertions.

In conclusion, this study shows that individualized care consisting of accurate diagnosis TM by validated otoscopyc, use of tympanocentesis and directed antibiotic therapy results in far fewer children becoming classified as OP. As a consequence of the reduction in the diagnosis of recurrent AOM, antibiotic treatment and tympanostomy surgery was used less frequently. The ecological benefit and financial savings from a reduction of recurrent AOM and associated antibiotic therapy and a reduction of tympanostomy tube surgery could be substantial.

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