Acute Mastoiditis in the Pneumococcal Conjugate Vaccine Era

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Following the introduction of the 7- and 13-valent pneumococcal conjugate vaccines, we observed an inverse relationship between the increasing rate of immunized children and the proportion of middle ear fluid cultures collected during acute mastoiditis episodes that tested positive for Streptococcus pneumoniae among a subset of children 0 to 6 years old who had initially presented with severe acute otitis media and had bacterial cultures collected during tympanocentesis or from spontaneous otorrhea.

Acute mastoiditis (AM) is a suppurative complication of acute otitis media (AOM), which often requires hospitalization and intravenous antibiotics and sometimes requires surgery. The most common otopathogen in AM is Streptococcus pneumoniae (1). In an attempt to control the impact of pneumococcal diseases, pneumococcal conjugate vaccines (PCVs) were gradually implemented in many countries during the past decade. In Israel, PCV7 was formally introduced into the national immunization program in July 2009 and was replaced by PCV13 in November 2010 (2). Both vaccines were or are, respectively, given at 2, 4, and 12 months of age. This change in the vaccination regimen allowed us to study the dynamics of AM incidence and bacteriology in a subset of children with AOM throughout a short time frame, from the pre-PCV7 era to the post-PCV13 era.

This study was approved by the Edith Wolfson Medical Center’s ethics review board. We retrospectively identified children 0 to 6 years of age who presented to the pediatric emergency room from 1 January 2008 through 31 December 2013 with severe AOM, defined as an AOM episode which either required tympanocentesis, due to a lack of clinical improvement after ≥48 h of antibiotic therapy, or presented with spontaneous otorrhea. In these children, we identified AM episodes (International Classification of Diseases code 383.0X). The AM diagnosis was based on clinical findings (postauricular tenderness, erythema or swelling, protruding auricle, palpable/ﬂuctuating mass) and systemic signs (fever, lethargy, irritability, poor feeding, diarrhea). Children with previous ear surgery, immune deﬁciencies, and congenital malformations of the ear, nasopharynx, or palate were excluded from the study. In all eligible children, middle ear ﬂuid (MEF) cultures were collected either during tympanocentesis with the use of a sterile flocked swab or from spontaneous otorrhea, from which pus was collected by swabbing the external ear meatus. Samples were processed for conventional cultures at the Edith Wolfson Medical Center’s microbiology laboratory. MEF cultures that tested positive for external ear canal saprophytes were excluded.

The PCV status for each AM episode was obtained from records at the Mother and Child Health Clinics, where all childhood vaccines are given in Israel. Each child was categorized according to his or her vaccination status at his or her AM presentation as either “unimmunized” if no dose of PCV immunization had been given or “any PCV7/PCV13 immunized” if ≥1 dose of PCV7/PCV13 had been given. Any child who had received both the PCV7 and the PCV13 immunizations during the transition period between these 2 vaccines was categorized as “any PCV13 immunized,” due to the broader coverage of the newer PCV13.

Statistical analysis was performed per AM episode (not per patient) using SPSS 17.0 software. Contingency table analysis for comparing rates between unmatched samples was performed using the chi-square test or Fisher’s exact test, as appropriate.

A total of 279 children 0 to 6 years of age contributed 295 severe AOM episodes (16 children contributed 2 AOM episodes each). Of these children, 57 presented with 58 AM episodes (1 boy contributed 2 AM episodes), which resulted in an incidence rate of 1 AM episode/5 severe AOM episodes in our study population.

Table 1 displays the demographic and bacterial data of AM episodes in our study years. Boys and children <2 years of age insigniﬁcantly contributed more AM episodes (37 [64%] and 38 [66%]; P = 0.4 and 0.9, respectively). AM developed despite adequate antibiotic therapy in 29 (50%) episodes. In these instances, oral antibiotics (mostly amoxicillin) and a combination of oral antibiotics and otic antibiotic solution treatments were administered for 24 (85%) and 4 (15%) episodes, respectively. The rest of the AM episodes (27 [50%]) presented in an abrupt, sudden manner, and no antibiotics had been given prior to admission. All of the patients were hospitalized and treated with intravenous antibiotic therapy for 7 to 10 days. The most common systemic antibiotics were cefuroxime and ceftriaxone, administered for 32 (55%) and 23 (40%) episodes, respectively.

In 3 (5%) AM episodes, advanced complications included internal jugular vein thrombosis (n = 1), epidural abscess (n = 1), and sepsis (n = 1). Of the 55 (95%) blood cultures which were collected during hospitalization of the patients, only one culture grew S. pneumoniae, which also grew in the MEF culture from that child. All 3 (5%) cerebrospinal fluid cultures were negative. Surgical interventions were performed for 6 (10%) AM episodes; ventilating tubes were inserted during all of these episodes, and mastoidectomy was performed during 5 episodes.

In all of the AM episodes, MEF cultures were obtained; 21 (36%) were positive. When comparing data from 2008 to 2011 with those from 2012 to 2013, there were fewer negative MEF cultures, and there was a lower rate of AM patients previously
treated with antibiotics \((P = 0.04)\). One single bacterial species grew in 19 (90%) of the specimens, and multiple bacteria grew in 2 (10%) of the specimens. \(S. pneumoniae\) and \(Haemophilus influenzae\) were cultured as single organisms in 16 (76%) and 2 (10%) specimens, respectively. In addition, \(S. pneumoniae\) grew in 2 other polymicrobial cultures with other bacteria, whereas \(H. influenzae\) grew in 1 polymicrobial culture. The proportion of \(S. pneumoniae\) in AM cultures declined from 2010. In 2012, only 1 MEF culture, from a 20-month-old boy who was not adequately immunized with PCV13 and presented with 2 AM episodes which were not treated with antibiotics prior to his presentation, grew \(S. pneumoniae\). There was no growth of \(S. pneumoniae\) in MEF cultures in 2013.

The PCV status was retrieved for all the children. In 2008, none of the children was immunized with PCV, whereas in at least 90% of the AM episodes in 2011 to 2013, the children had been immunized with PCV7/PCV13, as shown in Fig. 1A. The dynamics of MEF bacteriology from AM episodes, by PCV status, are shown in Fig. 1B. Any-prior-PCV13-immunized children with AM had a significantly lower proportion of \(S. pneumoniae\)-positive MEF cultures, compared with unimmunized children or any-PCV7-immunized children \((P = 0.03\) and 0.04, respectively).

Here, we show that following the introduction of PCV7 and, more prominently, the introduction of PCV13, the proportion of \(S. pneumoniae\)-positive MEF cultures from AM episodes significantly decreased.

To date, data on the effect of PCV13 on AOM and AM are limited. A recent insurance claim study from the United States showed that the AM incidence rate had already decreased shortly before the introduction of PCV13 \((3)\). A steeper decline was observed in 2010 (introduction year) and 2011 (first U.S. postmarket year), almost in parallel to the similar downward trend in rates of AOM visits. In a different U.S. study, mastoiditis cases, which have been especially associated with serotype 19A isolates (covered by PCV13 but not by PCV7), had the greatest percent decrease in 2011, compared with the 3 years preceding the introduction of PCV13 \((4)\).

Due to the short interval between the introductions of PCV7 and PCV13, the impact of PCV13 on PCV7-immunized children was not as dramatic as that of PCV7-immunized children. However, in the second postintroduction year, the proportion of \(S. pneumoniae\)-positive MEF cultures continued to decrease, indicating that the vaccine is effective in preventing AM in both PCV7- and PCV13-immunized children.

### Table 1: Demographic and Bacterial Data from Acute Mastoiditis Episodes Among Children 0 to 6 Years of Age, by Study Year

<table>
<thead>
<tr>
<th>Variable</th>
<th>2008 (67)</th>
<th>2009b (48)</th>
<th>2010c (53)</th>
<th>2011 (49)</th>
<th>2012 (39)</th>
<th>2013 (39)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of AM episodes (% of eligible AOM episodes)</td>
<td>12 (18)</td>
<td>7 (15)</td>
<td>8 (15)</td>
<td>12 (25)</td>
<td>12 (31)d</td>
<td>7 (18)</td>
<td>58</td>
</tr>
<tr>
<td>Boys (no. [%])</td>
<td>10 (83)</td>
<td>4 (58)</td>
<td>6 (75)</td>
<td>4 (33)</td>
<td>11 (92)</td>
<td>2 (28)</td>
<td>37 (64)</td>
</tr>
<tr>
<td>Age &lt;2 yr (no. [%])</td>
<td>6 (50)</td>
<td>2 (28)</td>
<td>6 (75)</td>
<td>9 (75)</td>
<td>10 (83)</td>
<td>5 (72)</td>
<td>38 (66)</td>
</tr>
<tr>
<td>Previously treated with antibiotics (no. [%])</td>
<td>4 (33)</td>
<td>4 (58)</td>
<td>4 (50)</td>
<td>5 (42)</td>
<td>8 (75)</td>
<td>4 (58)</td>
<td>29 (50)</td>
</tr>
<tr>
<td>Patients undergoing surgical intervention (no. [%])</td>
<td>2 (17)</td>
<td>0 (0)</td>
<td>4 (50)</td>
<td>2 (17)</td>
<td>2 (17)</td>
<td>3 (42)</td>
<td>13 (22)</td>
</tr>
</tbody>
</table>

a 58.
b Formal PCV7 introduction year.
c PCV13 introduction year.
d One patient presented with 2 separate AM episodes.
e Surgical interventions were ventilating tube insertions and mastoidectomies. A ventilating tube was inserted during all mastoidectomies.

FIG 1 (A) PCV status in the study population, by year. PCV status was determined at acute mastoiditis presentation. Any PCV immunized, children who had received at least 1 dose of PCV7/PCV13; unimmunized, children who had not been PCV immunized. (B) Otopathogen distribution in MEF cultures from acute mastoiditis episodes, by PCV status. Mc, Moraxella catarrhalis; NTHi, nontypeable Haemophilus influenzae; Sp, Streptococcus pneumoniae. There was a significant reduction in positive \(S. pneumoniae\)-positive MEF cultures in acute mastoiditis cases in PCV13-immunized children (15%), compared with unimmunized children (41%) and PCV7-immunized children (50%) \((P = 0.03\) and 0.04, respectively).
and PCV13 in Israel (spaced only 14 months), we were not able to witness any AM time trends after PCV7 introduction, as reported elsewhere (5–9). While some studies reported decreased AM rates after the introduction of PCV7 (7,10), others found no change or even an increase (11).

This study’s main strengths are in the reporting of MEF cultures, not relying on nasopharyngeal cultures, and knowledge of the exact PCV status for each child at his or her AM presentation. Therefore, we believe that our results truly reflect these children’s tympanomastoid cavity colonization status during their AM episode(s). Limitations of our study include the small number of patients and the lack of serotype identification. Although our results may not be generalizable to all AOM patients, we believe that they are valid and show for the first time that AM incidence and bacteriology changed after the introduction of PCV13. Further studies are warranted to monitor all-cause and pneumococcal AM in the post-PCV13 era.

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REFERENCES