Acute Tonsillopharyngitis Associated with Atypical Bacterial Infection in Children: Natural History and Impact of Macrolide Therapy

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This study evaluated the natural history of acute tonsillopharyngitis associated with atypical bacterial infections, showing that Mycoplasma pneumoniae and Chlamydia pneumoniae organisms are frequently found in children with acute tonsillopharyngitis. The study also demonstrated, for what we believe to be the first time, that, unless adequately treated, acute tonsillopharyngitis associated with infection with M. pneumoniae and C. pneumoniae may have a negative outcome with a high risk of recurrence of respiratory illness.

It has recently been demonstrated that nonstreptococcal acute tonsillopharyngitis (AT) seems to be associated with Mycoplasma pneumoniae and Chlamydia pneumoniae infection [1–7]. The aim of the present study was to evaluate the natural history of AT associated with atypical bacterial infection, the tendency of such AT to recur spontaneously, and the effect of macrolide treatment on the early and late outcome of AT.

**Study population and follow-up.** The study was conducted at the primary care center of the Institute of Pediatrics of Milan University (Milan, Italy). All patients who were between 6 months and 14 years of age and who attended our outpatient clinic from 1 February 2002 to 1 March 2003 because of AT were enrolled in the study. AT was defined by evidence of inflammation of the uvula and pharynx or tonsils in the presence of fever, sore throat, or dysphagia, but without any signs or symptoms of lower respiratory tract infection [8]. The criteria for exclusion from the study included presence of severe concomitant diseases, receipt of systemic antibiotic treatment during the 48 h preceding study entry, and either receipt of azithromycin during the week preceding study entry or receipt of intramuscular benzathine penicillin G during the month preceding study entry. The study protocol was approved by the institutional review board of the University of Milan, and written, informed consent was obtained from the parents or legal guardians of all study participants.

At enrollment, data on the demographic characteristics and medical history of the children were systematically recorded using standardized written questionnaires [3, 4]. After a complete physical examination was performed, laboratory samples, including acute-phase serum samples for the assay of antibodies to M. pneumoniae and C. pneumoniae and nasopharyngeal aspirates for the detection of M. pneumoniae and C. pneumoniae DNA, were obtained from all of the patients. A rapid test and throat culture were performed to detect Streptococcus pyogenes, and the children for whom test results were positive were excluded from the study.

The only investigator who was responsible for randomization (S.E.) ensured that the enrolled children were blindly randomized, by means of a computerized list, to receive either azithromycin (10 mg/kg/day for 3 days for 3 successive weeks) given together with symptomatic therapy (acetaminophen, 10 mg/kg per dose) or symptomatic therapy alone. Each child’s caregiver was asked to return to the study center immediately if the child experienced persistent, recurrent, or worsening signs and symptoms, and the caregivers were instructed not to inform the examining physician whether the child had received azithromycin or not. On the basis of clinical findings, the respiratory illnesses of these children were classified into 2 disease groups, each of which was further divided into 3 subgroups: (1) upper respiratory tract infections, including AT (sore throat and evidence of inflammation of the uvula and pharynx or tonsils in the presence of fever), rhinosinusitis (persistent rhinorrhea for >10 days), and croup (inspiratory stridor, cough, and hoarseness due to an obstruction in the laryngeal region); and (2) lower respiratory tract infections, including acute bronchitis (cough and/or rhonchi with normal findings on a chest radiograph), wheezing (cough and/or dyspnea with expiratory rales and/or wheezes unrelated to any known specific sensitization, with normal findings on a chest radiograph), and pneumonia (fever, cough, tachypnea, and decreased breath sounds or localized rales, with a positive finding on a chest radiograph) [9].
For children with these respiratory illnesses, the prescribing of antibiotics that are active against atypical bacteria (i.e., macrolides, tetracyclines, and quinolones) was not allowed.

The medical history, general physical condition, and clinical symptoms of each patient were blindly reevaluated by 1 investigator (S.B.) 4–6 weeks after enrollment. At the same time, a second serum sample was obtained to assay *M. pneumoniae* and *C. pneumoniae* antibody titers in the convalescent phase. Also during this visit, the investigator responsible for randomization evaluated patient compliance (defined as the patient having taken at least 90% of the prescribed doses) by quantifying the unused medication, confirming with the parent or guardian that the patient had taken the medication as instructed, and then checking the dosing diary.

At the time of the second study visit, the patients were scheduled to return for 2 additional visits (on median postenrollment day ± SE, 90 ± 15 and 180 ± 15), at which times their clinical signs and symptoms would be assessed by the same investigator (S.B.), who did not know whether the patients had received azithromycin or not. Again, each patient’s caregiver was asked to return to the study center whenever the child developed symptoms of respiratory tract illness. The prescription of antibiotics active against atypical bacteria also was not allowed for these patients.

Short-term (1-month) and long-term (6-month) clinical responses to treatment were evaluated on the basis of criteria reported elsewhere [4]. For short-term evaluation, a clinical cure was defined as complete resolution of the acute signs and symptoms of AT present at enrollment, without the reappearance of any clinical signs or symptoms of respiratory tract infection after the initial clinical cure. For the long-term evaluation, a clinical cure was defined as the absence of new episodes of AT, with no diagnosis of any other kind of upper or lower respiratory tract infection being made during the study period.

**Evaluation of atypical bacterial infections** Each acute-phase and convalescent-phase serum sample was tested, after absorption, for IgM and IgG antibodies against *M. pneumoniae*, by use of ELISA (Pantec), and for IgM, IgA, and IgG antibodies against *C. pneumoniae*, by use of microimmunofluorescence (Labsystems), as described elsewhere [3, 4, 7, 10]. The nasopharyngeal aspirates were evaluated for the presence of *M. pneumoniae* and *C. pneumoniae* DNA by use of validated nested PCR [3, 4, 7, 10]. Acute infection with *M. pneumoniae* and *C. pneumoniae* was diagnosed on the basis of previously established criteria [3, 4, 7, 10].

**Statistical analysis.** *P* < .05 was considered to be statistically significant for all of the statistical tests. The parametric data were compared using analysis of variance with terms for treatment and tests for multiple comparisons. The Kruskal-Wallis test was used when the data were nonparametric or were not normally distributed. The categoric data were analyzed us-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Children receiving Azm and symptomatic therapy&lt;sup&gt;a&lt;/sup&gt; (n = 44)</th>
<th>Children receiving symptomatic therapy&lt;sup&gt;a&lt;/sup&gt; only (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>3.8 (0.6–14)</td>
<td>4.1 (0.6–14)</td>
</tr>
<tr>
<td>Male</td>
<td>27 (61.4)</td>
<td>54 (60.7)</td>
</tr>
<tr>
<td>Breastfed for &gt;3 months</td>
<td>25 (56.8)</td>
<td>52 (58.4)</td>
</tr>
<tr>
<td>Attending day care or school</td>
<td>39 (88.6)</td>
<td>79 (88.8)</td>
</tr>
<tr>
<td>Exposed to passive smoke</td>
<td>14 (31.8)</td>
<td>27 (30.3)</td>
</tr>
<tr>
<td>History of allergies</td>
<td>3 (6.8)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Previously received vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate vaccine</td>
<td>1 (2.3)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>3 (6.8)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Family members living together, median (range)</td>
<td>4 (2–8)</td>
<td>4 (3–7)</td>
</tr>
<tr>
<td>Siblings, median (range)</td>
<td>1 (0–4)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>Respiratory tract infections during the previous 6 months,&lt;sup&gt;b&lt;/sup&gt; median (range)</td>
<td>3 (1–6)</td>
<td>3 (1–7)</td>
</tr>
<tr>
<td>Antibiotic courses received during the previous 6 months,&lt;sup&gt;b&lt;/sup&gt; median (range)</td>
<td>2 (0–5)</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>Hospitalizations during the previous 6 months,&lt;sup&gt;b&lt;/sup&gt; median (range)</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. There was no significant difference between the patient groups. Azm, azithromycin.

<sup>a</sup> Symptomatic therapy involved acetaminophen.

<sup>b</sup> Before study enrollment.
Table 2. Short-term (1-month) and long-term (6-month) outcomes for children with acute tonsillopharyngitis.

<table>
<thead>
<tr>
<th>Outcome, type of infection, and clinical response</th>
<th>Children receiving Azm and symptomatic therapy</th>
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</tr>
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<tbody>
<tr>
<td><strong>Short term</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical bacteria</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Clinical success</td>
<td>20 (100.0)</td>
<td>31 (91.2)</td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>No atypical bacteria</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Clinical success</td>
<td>22 (91.7)</td>
<td>51 (92.7)</td>
</tr>
<tr>
<td>Failure</td>
<td>2 (8.3)</td>
<td>4 (7.3)</td>
</tr>
<tr>
<td>All</td>
<td>44</td>
<td>89</td>
</tr>
<tr>
<td>Clinical success</td>
<td>42 (95.5)</td>
<td>82 (92.1)</td>
</tr>
<tr>
<td>Failure</td>
<td>2 (4.5)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td><strong>Long term</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical bacteria</td>
<td>20</td>
<td>34</td>
</tr>
<tr>
<td>Clinical success</td>
<td>13 (65.0)</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td>Failure</td>
<td>7 (35.0)</td>
<td>25 (73.5)</td>
</tr>
<tr>
<td>Only 1 respiratory infection</td>
<td>2 (10.0)</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>&gt;1 respiratory infection</td>
<td>5 (25.0)</td>
<td>22 (64.7)</td>
</tr>
<tr>
<td>&gt;1 LRTI</td>
<td>3 (15.0)</td>
<td>21 (61.8)</td>
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<tr>
<td>No atypical bacteria</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Clinical success</td>
<td>14 (58.3)</td>
<td>27 (49.1)</td>
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<tr>
<td>Failure</td>
<td>10 (41.7)</td>
<td>28 (50.9)</td>
</tr>
<tr>
<td>Only 1 respiratory infection</td>
<td>6 (25.0)</td>
<td>21 (38.2)</td>
</tr>
<tr>
<td>&gt;1 respiratory infection</td>
<td>4 (16.7)</td>
<td>7 (12.7)</td>
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<tr>
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<td>36 (40.4)</td>
</tr>
<tr>
<td>Failure</td>
<td>17 (38.6)</td>
<td>53 (59.6)</td>
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<td>8 (18.2)</td>
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**NOTE.** Data are no. or no. (%) of patients. Azm, azithromycin; LRTI, lower respiratory tract infection.

**Long term**

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Results. A total of 133 patients who were 6 months to 14 years of age (81 patients were male; median patient age, 4.0 years) were enrolled in the study. Table 1 presents the demographic and clinical characteristics of the study patients at baseline.

The serologic and PCR findings for 54 patients (40.6%) confirmed the presence of an acute atypical bacterial infection, which occurred significantly more frequently among patients aged $\geq$3 years (39 [53.4%] of 73 patients) than among those aged <3 years (15 [25.0%] of 60 patients) ($P = .001$). Acute infection with *M. pneumoniae* was serologically determined in 36 (85.7%) of the 42 subjects infected with this pathogen alone, and it was confirmed by PCR in 6 subjects (14.3%). Acute *C. pneumoniae* infection was serologically determined in 10 (90.9%) of the 11 patients infected with this pathogen alone and was confirmed by PCR in 5 (50.0%) of these 10 patients. Two children showed evidence of acute mixed infection with *M. pneumoniae* and *C. pneumoniae*: acute *M. pneumoniae* infection was serologically determined in both patients, and *M. pneumoniae* DNA was detected in 1 patient (50.0%); acute *C. pneumoniae* infection was serologically determined in both patients and was confirmed by PCR in 1 patient (50.0%).
Table 2 shows short- and long-term outcomes of AT, according to the therapy prescribed at enrollment. In the short term, there was no significant difference between children with or without atypical bacterial infection. In the long term, clinical cures were significantly more frequent among patients who received azithromycin than among those who were treated with symptomatic therapy alone (P < .05). All of these findings were similar, regardless of the age of the children (<3 years vs. ≥3 years of age).

Discussion. The results of the present study show that *M. pneumoniae* and *C. pneumoniae* infections are frequently observed in children with AT. The results also demonstrate, for what we believe to be the first time, that unless these infections are adequately treated, they may have a negative outcome, with the risk of recurrence of respiratory illness also involving the lower respiratory tract being significantly higher than that observed for children with AT with no evidence of *M. pneumoniae* and *C. pneumoniae* infections. Although the sample size was quite limited and nasopharyngeal aspirates were not obtained during every episode of respiratory illness that occurred during follow-up, the similar characteristics of the study patients treated with azithromycin and those treated with symptomatic therapy only support the casual distribution of atypical bacteria in our population and the role of such bacteria in increasing the risk of recurrence of respiratory illness in children with AT.

On the basis of our previous experience [10, 11], azithromycin was administered for 3 days during each of 3 successive weeks, a treatment period that is considered long enough to ensure clinical cure [12]. The fact that, during follow-up, the children did not receive any other drug that is active against atypical bacteria makes it possible to exclude any interference with the original infection with *M. pneumoniae* and *C. pneumoniae*. Moreover, demonstration that azithromycin was not effective in children with AT in the absence of atypical bacteria infection and that its administration significantly reduced recurrences of respiratory illness and lower respiratory tract infections only in the children with acute infection with *M. pneumoniae* and *C. pneumoniae* supports the role of these pathogens in the development of AT.

In conclusion, our findings indicate that atypical bacterial infections in children with AT seem to be associated with an increased risk of additional recurrences of respiratory illness also involving the lower respiratory tract that can be substantially reduced by prolonged macrolide treatment. If confirmed in larger study populations, these data suggest the need for reanalysis of the diagnostic and therapeutic approach to AT, to distinguish the cases associated with atypical bacteria infection and to treat them with appropriate antibiotic therapy.

Acknowledgments

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Potential conflicts of interest. All authors: no conflicts.

References