Azithromycin Therapy in Hospitalized Infants with Acute Bronchiolitis is Not Associated with Better Clinical Outcomes: A Randomized, Double-Blinded, and Placebo-Controlled Clinical Trial

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Objective To test the hypothesis that azithromycin reduces the length of hospitalization and oxygen requirement in infants with acute viral bronchiolitis (AB).

Study design We performed a randomized, double-blinded, placebo-controlled trial in southern Brazil, from 2009 to 2011. Infants (<12 months of age) hospitalized with AB were recruited in 2 hospitals. Patients were randomized to receive either azithromycin or placebo, administered orally, for 7 days. At enrollment, clinical data were recorded and nasopharyngeal samples were collected for viral identification through immunofluorescence. Main outcomes were duration of oxygen requirement and length of hospitalization.

Results One hundred eighty-four patients were included in the study (azithromycin 88 subjects, placebo 96 subjects). Baseline clinical characteristics and viral identification were not different between the groups studied. A virus was detected in 112 (63%) patients, and of those, 92% were positive for respiratory syncytial virus. The use of azithromycin did not reduce the median number of days of either hospitalization \( (P = .28) \) or oxygen requirement \( (P = .47) \).

Conclusions Azithromycin did not improve major clinical outcomes in a large sample of hospitalized infants with AB, even when restricting the findings to those with positive respiratory syncytial virus samples. Azithromycin therapy should not be given for AB because it provides no benefit and overuse increases overall antibiotic resistance. (J Pediatr 2012;161:1104-8).

See related article, p 1097

Acute viral bronchiolitis (AB) is the most common lower respiratory tract illness among infants. It is characterized by acute inflammation, edema, and increased mucus production after an acute viral infection. The management of AB has been, for the past decades, almost exclusively supportive, with oxygen supplementation, adequate hydration, and ventilatory support for severe cases.¹ Despite the extensive research to find effective therapies, clinical trials did not show interventions with relevant clinical impact on AB.¹

Macrolides have a well-established antibacterial effect,² covering a wide spectrum of agents, including intracellular pathogens, such as Mycoplasma pneumoniae and Chlamydia pneumoniae. In the past years, an additional anti-inflammatory property has been associated with macrolide use³⁻⁵; more recently, 1 experimental study has linked macrolides with a specific antiviral effect⁶ against rhinovirus.

Recent clinical trials have reported that some macrolides had a beneficial effect in the treatment of inflammatory lung diseases, such as cystic fibrosis and asthma.⁴,⁷ Macrolides seem to inhibit interleukin (IL)-6 and IL-8 production and to reduce overall neutrophilic inflammation.⁸ Because AB is characterized by a strong neutrophilic airway response,⁹,¹⁰ some small trials have used this rationale to test the efficacy of macrolides in this illness. In 1 study of hospitalized infants with moderate to severe AB, clarithromycin significantly reduced length of stay in hospital (LOS).¹¹ Contrarily, in another trial, azithromycin was not effective for respiratory syncytial virus (RSV) infection in young infants.¹² These contrasting findings may be related to differences in methodology and small sample sizes.

In the present study, we tested the hypothesis that a 7-day course of azithromycin reduces the LOS and oxygen requirement in a large recruited population of infants with AB.
Methods

This study is a randomized, double-blinded, placebo-controlled trial. Infants with a clinical diagnosis of AB were recruited from the pediatric emergency departments or hospital wards of 2 large, tertiary hospitals, in Porto Alegre, Brazil. Patients were randomized to receive either azithromycin or placebo, administered orally, once daily, for 7 days. Clinical data were recorded and nasopharyngeal samples for viral identification were collected at enrollment. All subjects were followed until discharge.

A diagnosis of AB was confirmed if children were: (1) aged 12 months or younger and admitted with a clinical diagnosis of AB (prodromal viral symptoms, with a first episode of wheezing/crackles, and tachypnea); and (2) recruited within 48 hours of hospitalization and had a maximum of 72 hours of a history of lower respiratory tract clinical manifestations (wheeze and/or respiratory distress). Main exclusion criteria were: (1) any contraindication for oral macrolide therapy; (2) prescription of macrolide therapy by the attending physician due to clinical and radiologic features consistent with a diagnosis of Chlamydia sp or Bordetella pertussis respiratory infection; (3) having a chronic cardiopulmonary disorder, congenital or acquired immunodeficiency, or neuromuscular disease; and (4) history of prematurity or other neonatal complications.

Infants were randomized (simple/unrestricted randomization) to receive either a daily oral dose of azithromycin (10 mg/kg/d) or an equivalent volume of placebo for 7 days. Medication was administered within 72 hours of initial clinical symptoms and a blinded study team member supervised this intervention.

A standardized form was used to collect clinical information of the patients included in the trial. All infants were managed according to protocols routinely used by the pediatric staff in both hospitals. Infants enrolled in the study could receive additional therapies (other than macrolides) prescribed by the attending pediatricians, and these were recorded for the analysis. Assessment of clinical data included signs of severity at admission (respiratory rate and accessory muscle use), use of medications (bronchodilator, corticosteroids, and antibiotic therapy), site of admission, LOS, measurements of oxyhemoglobin saturation, and levels of oxygen requirement (and number of days of use).

Viral Identification

A nasopharyngeal sample for respiratory viruses was collected from each patient at enrollment. Direct immunofluorescence (Respiratory Virus Panel; Biotrin, Dublin, Ireland) was used to detect adenovirus, parainfluenza (1, 2, and 3), influenza (A and B), and RSV.

Outcome Measures

Primary outcomes were: (1) LOS for AB; and (2) duration of supplemental oxygen required. Patients’ discharge was decided when infants showed oxyhemoglobin saturation consistently at ≥94% saturation in room air and oral feeding was established for at least 6 hours. Other variables analyzed were: (1) antibiotic use; (2) bronchodilators use; and (3) admission to the pediatric intensive care unit. We also analyzed clinical outcomes in the following subgroups: (1) age of ≤3 months; (2) identification of respiratory viruses; and (3) positive for RSV.

Statistical Analyses

To detect a reduction in LOS of 1 day (SD 2 days), based on data from the study of Tahan et al,11 allowing for a 2-sided 5% significance level and a power of 80%, a sample size of 63 patients per group would be required (http://www.stat.ubc.ca/~rollin/stats/ssize). Considering that analysis based on age and viral identification was a secondary aim, the researchers aimed to enroll between 180 and 200 infants. The authors have considered that benefits of <1 day (24 hours) of LOS would not be relevant to have an impact on clinical practice.

The primary outcomes (LOS and duration of supplemental oxygen requirement) were compared between groups by use of Mann-Whitney tests, considering that outcome variables failed in the tests for normality. Kaplan-Meier curves were used to assess the effect of azithromycin on LOS.

The protocol has been approved by the Human Research Ethics Committees of both participating institutions, and the study was registered in the Brazilian Clinical Trials Registry (No. RBR-257ZBC), which is a joint project of the Brazilian Ministry of Health and the Pan-American Health Organization (http://www.ec.gov.br).

Results

During the study period, 189 infants were evaluated for eligibility in the clinical trial (109 from Hospital São Lucas/Pontificia Universidade Católica do Rio Grande do Sul, and 80 from Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul). Four patients were excluded and 1 patient was lost through follow-up (Figure 1). Baseline characteristics of the studied patients are shown in Table 1. There were no differences in baseline characteristics between the intervention and the control groups, except for respiratory rate, which was higher in the placebo group. From the 184 patients included, 176 nasal samples were collected for viral etiology tests, before randomization. Of the total samples collected, 64.4% (112 of 176) were positive for at least 1 virus. Of these, RSV was the most common (n = 104, 92.8%), followed by influenza and parainfluenza. The proportion of infants positive for respiratory viruses or specifically for RSV infection did not differ between the groups studied.

LOS (primary outcome) was not different between placebo and treated groups, nor was the time of oxygen supplementation. Kaplan-Meier curves for probability of discharge from hospital showed no significant difference between the groups (Figure 2). Subgroup analysis for age and specific
viral diagnosis showed no significant differences (Table II). There was no beneficial effect by treatment group in patients who had RSV infection or among infants with AB who were stratified by age (with a cut-off at 3 months of age) (Table II). Results for other secondary outcomes, such as antibiotic or bronchodilator prescriptions, also did not show significant differences between placebo and active groups.

**Discussion**

The present study demonstrated that treatment with azithromycin for 7 days did not alter the clinical course of AB. Importantly, our clinical trial used adequate methodology and power to answer the question of whether infants with a first virally triggered episode of wheezing benefit from the use of macrolide therapy at the time of the acute event. This finding is important considering that there is an international trend regarding the effect of macrolides in AB with the inclusion of a proper sample size. It also is possible that differences in bioavailability, pharmacokinetic properties, or intrinsic immunomodulatory effects between azithromycin and clarithromycin may explain different results. Although clinical trials with murine models have demonstrated anti-inflammatory (in vivo) and antiviral effects (in vitro) of macrolides in animals infected with parainfluenza and rhinovirus.4,17

Two previous studies have tested macrolides in AB. Tahvan et al11 have shown that in hospitalized infants with moderate to severe AB, a 3-week intervention with clarithromycin significantly reduced LOS and oxygen requirement. However, only 21 patients were included in the study. This study also presented a relevant mistake in the statistical analysis of the main outcome (LOS), which was discussed previously in a letter to the editor.18 In contrast, a study by Kneyber et al12 showed that infants and young children with RSV lower respiratory tract disease did not benefit from routine treatment with macrolides. The authors estimated an appropriate study with a sample size of 100 patients, but the trial was interrupted when only 71 patients were included; thus, a type II error cannot be ruled out.12 Therefore, in our study, we believe that we have answered this question more properly, with a negative result regarding the effect of macrolides in AB with the inclusion of a proper sample size. It also is possible that differences in bioavailability, pharmacokinetic properties, or intrinsic immunomodulatory effects between azithromycin and clarithromycin may explain different results. Although clinical trials have shown the same antimicrobial efficacy,19,20 one study that investigated pharmacokinetics of these drugs showed that clarithromycin has higher concentrations in epithelial lung and alveolar cells.21

Recent studies showed that viral respiratory infections in infants induce different cytokine inflammatory responses.22,23 However, when we analyzed the subgroup of 104 subjects who had RSV-positive AB, we did not observe any significant difference between the active and the placebo groups for the main outcomes (ie, LOS and days in use of supplemental oxygen). Interestingly, Laham et al22 suggested that different viruses might cause disease via different mechanisms or share a common mechanism that is distinct from immune activation. Our study was designed with a clinical practical purpose: to evaluate whether macrolide treatment in AB could have any significant clinical impact, regardless of the viral etiology.
Nevertheless, antibiotics, especially macrolides, are still of no benefit among young infants hospitalized with acute bronchiolitis. Kozyrskyj et al. documented that dispensing rates for macrolides in children with wheezing increased 15-fold between 1996 and 2000. This is consistent with reported increases in the use of these antibiotics across Canada and the United States, after their introduction on the market in the 1990s. A facilitating factor for this overprescription in many countries is that macrolides are well tolerated, safe, and easy to use in the pediatric age group. Other studies of antibiotic utilization also have reported significant macrolide use in patients with exacerbations of wheezing. Chlamydia sp and Mycoplasma pneumoniae have been identified in children with acute episodes of wheezing, but neither the role of these organisms in precipitating wheezing in AB nor an effect of treatment is known. Infection by atypical bacteria probably is less common (~10% of cases) in infants with AB. Hence, in AB, atypical bacterial infection should not be a frequent clinical indication for the prescription of macrolides.

Considering the published data indicating overuse of macrolides among preschool-aged children and the perception that this finding is not restricted to a few geographic areas but is worldwide, the results of our study reinforce that health professionals should be concerned with both the inadequate indication in infants with AB and inducing increased antimicrobial resistance in young children. This problem of overprescription might be even more relevant in developing countries, as is the case for the population we have studied.

Some limitations of our study should be acknowledged here. First, it is known that the treatment of infants with AB varies depending on hospital protocols and, lately, it depends on a subjective decision by the attending pediatrician, as occurred in this study. However, the percentage of patients in whom bronchodilators or antibiotics were prescribed was similar in the azithromycin and the placebo group, thus reducing the possible confounding factor by treatment differences. Second, inflammatory markers such as ILs or cellular counts in the respiratory secretions were not measured, but even a positive association between inflammatory markers and macrolide use would not be clinically relevant based in our negative findings. Last, we did not test our samples for other respiratory infections, such as Chlamydia sp, M pneumoniae, Bordetella pertussis, and rhinovirus. In AB, rhinovirus is commonly detected. Hence, we cannot rule out that in our study a beneficial effect of macrolides could be found in cases of AB caused solely by rhinovirus. A recent publication has shown that co-detection of viruses with B pertussis was present in 8.5% of <6-month-old infants with bronchiolitis. Depending on the frequency of B pertussis or atypical bacteria, different responses to macrolides may be observed in subgroups of infants with AB, which was not the main objective of our study.

Our results also support previous suggestions that antibiotics are of no benefit among young infants hospitalized with AB. Behrendt et al. found that 25% of hospitalized RSV patients are treated with parenteral antibiotics, even though a secondary or concurrent bacterial infection seldom occurs in hospitalized infants with AB. The international guidelines for the management of AB have advised against the routine use of antibiotics in hospitalized RSV patients. Considering the published data indicating overuse of macrolides among preschool-aged children and the perception that this finding is not restricted to a few geographic areas but is worldwide, the results of our study reinforce that health professionals should be concerned with both the inadequate indication in infants with AB and inducing increased antimicrobial resistance in young children. This problem of overprescription might be even more relevant in developing countries, as is the case for the population we have studied.

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Table II. Primary outcome measurements in patients randomized to treatment with azithromycin or placebo (N = 184)*

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin</th>
<th>Placebo</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>n = 88</td>
<td>n = 96</td>
<td></td>
</tr>
<tr>
<td>LOO2</td>
<td>4.00 (2.00-6.00)</td>
<td>4.00 (3.00-6.00)</td>
<td>.47</td>
</tr>
<tr>
<td>LOS</td>
<td>5.00 (3.00-7.00)</td>
<td>5.00 (3.00-7.00)</td>
<td>.29</td>
</tr>
<tr>
<td>By age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 mo (n = 107)</td>
<td>n = 51</td>
<td>n = 56</td>
<td></td>
</tr>
<tr>
<td>LOO2</td>
<td>4.00 (3.00-7.00)</td>
<td>4.00 (3.00-8.00)</td>
<td>.10</td>
</tr>
<tr>
<td>LOS</td>
<td>6.00 (4.00-7.00)</td>
<td>5.00 (3.00-9.00)</td>
<td>.67</td>
</tr>
<tr>
<td>&gt;3 mo (n = 77)</td>
<td>n = 37</td>
<td>n = 40</td>
<td></td>
</tr>
<tr>
<td>LOO2</td>
<td>3.00 (2.00-5.00)</td>
<td>4.00 (2.00-6.00)</td>
<td>.19</td>
</tr>
<tr>
<td>LOS</td>
<td>3.00 (3.00-6.00)</td>
<td>5.00 (3.00-6.00)</td>
<td>.19</td>
</tr>
<tr>
<td>By virus detection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for virus (n = 112)</td>
<td>n = 52</td>
<td>n = 60</td>
<td></td>
</tr>
<tr>
<td>LOO2</td>
<td>4.00 (3.00-7.00)</td>
<td>5.00 (3.00-7.00)</td>
<td>.44</td>
</tr>
<tr>
<td>LOS</td>
<td>5.00 (3.00-7.00)</td>
<td>5.00 (4.00-8.75)</td>
<td>.41</td>
</tr>
<tr>
<td>Negative for virus (n = 64)</td>
<td>n = 30</td>
<td>n = 34</td>
<td></td>
</tr>
<tr>
<td>LOO2</td>
<td>3.00 (2.00-5.00)</td>
<td>3.00 (2.00-5.00)</td>
<td>.93</td>
</tr>
<tr>
<td>LOS</td>
<td>4.50 (2.75-7.00)</td>
<td>4.00 (3.00-7.00)</td>
<td>.66</td>
</tr>
<tr>
<td>By RSV detection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for RSV (n = 104)</td>
<td>n = 47</td>
<td>n = 57</td>
<td></td>
</tr>
<tr>
<td>LOO2</td>
<td>4.00 (3.00-8.00)</td>
<td>5.00 (3.00-7.00)</td>
<td>.48</td>
</tr>
<tr>
<td>LOS</td>
<td>5.00 (3.00-7.00)</td>
<td>5.00 (4.00-8.50)</td>
<td>.55</td>
</tr>
<tr>
<td>Negative for RSV (n = 72)</td>
<td>n = 36</td>
<td>n = 36</td>
<td></td>
</tr>
<tr>
<td>LOO2</td>
<td>3.00 (2.00-5.00)</td>
<td>3.00 (2.00-5.00)</td>
<td>.64</td>
</tr>
<tr>
<td>LOS</td>
<td>4.00 (3.00-7.00)</td>
<td>4.50 (3.00-6.75)</td>
<td>.70</td>
</tr>
</tbody>
</table>

LOO2: length of oxygen requirement (in days); Sig.: significance level.
*Mean/SD and median/interquartile are both shown for a clear presentation of the variables. Variables were not normally distributed and Mann-Whitney test was used for comparison.
†LOS is given in days.

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References