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Comparative Randomized Trial of Azithromycin Versus Erythromycin and Amoxicillin for Treatment of Community-Acquired Pneumonia in Children

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Summary. Our objective was to compare the clinical efficacy of azithromycin vs. erythromycin and amoxicillin in the treatment of presumed bacterial community-acquired pneumonia in ambulatory children, and to evaluate the etiologies of these illnesses. One hundred and ten children, aged 1 month to 14 years, were enrolled between January 1996–January 1999. Children were distributed into two groups according to clinical and radiological patterns: classic or atypical pneumonia. Patients with classic pneumonia were randomly assigned to receive oral amoxicillin 75 mg/kg/day for 7 days, or azithromycin 10 mg/kg/day for 3 days; patients with atypical pneumonia received azithromycin 10 mg/kg/day for 3 days, or erythromycin 50 mg/kg/day for 14 days. Chest X-ray, clinical, and laboratory parameters were obtained on enrollment. Clinic visits were performed on days 3, 7, and 14, and chest X-ray follow-up on days 7 and 14. Microbiological diagnosis of classic pathogens was based on blood and bronchial secretion cultures. The diagnosis of atypical pathogens *C. pneumoniae*, *C. trachomatis*, and *M. pneumoniae* was based on PCR and serologic tests.

Forty-seven children met the criteria for classic pneumonia (23 children received azithromycin, and 24 received amoxicillin), and 59 children had atypical pneumonia (33 children were treated with azithromycin, and 26 with erythromycin). Demographic characteristics at enrollment were similar between children with classic pneumonia treated with azithromycin and erythromycin and children treated with azithromycin and erythromycin for atypical pneumonia. However, on day 7, children with classic pneumonia who received azithromycin normalized their chest X-ray more often than those who received amoxicillin (81.0% vs. 60.9%, respectively, $P = 0.009$). The same was true for children with atypical pneumonia; their chest X-rays had normalized by day 14 (100% in those with azithromycin vs. 81% in those with erythromycin, $P = 0.059$). Also, children with atypical pneumonia treated with azithromycin had earlier cessation of cough than children treated with erythromycin (3.6 ± 1.9 vs. 5.5 ± 3.6 days respectively, $P = 0.02$). There were only three children with side effects (mild diarrhea, all in the erythromycin group). Etiological agents were identified in 41% of children.

In conclusion, azithromycin is an effective therapeutic option for the treatment of community-acquired classic and atypical pneumonia in children. **Pediatr Pulmonol. 2003; 35:91–98.**

Key words: azithromycin; community-acquired pneumonia; children; erythromycin; amoxicillin.

INTRODUCTION

Bacterial pneumonia is a frequent occurrence worldwide. In Chile, acute lower respiratory tract infections account for nearly 31% of the pediatric outpatient visits to health centers annually, with 2% of these for pneumonia.[1] However, on a seasonal basis these figures double. Therefore, the effort to find a drug which is effective, is easy to administer, and has a low profile of side effects is justified. Azithromycin is an antibiotic belonging to the azalide subclass of macrolide antibiotics, which has a wide therapeutic spectrum and presents pharmacokinetic advantages. It is stable at gastric pH, is absorbed rapidly when given orally, has a rather long half-life of 11–14 hr,

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reaches a high concentration in macrophages, neutrophils, and monocytes, and has a wide tissue distribution from where it is released very slowly.[2] In spite of relatively low plasma concentrations in lung tissue and sputum, it reaches higher concentrations than are typically needed to inhibit the majority of respiratory pathogens for at least 7 days after the last dose.[2] Azithromycin is effective against *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, and atypical bacteria such as *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, and *Chlamydia pneumoniae*.[2–4] This antimicrobial agent can be used in a single 10 mg/kg daily dose for 3 days, which constitutes a clear advantage over conventional treatment with other macrolides and betalactams.[3]

The aims of our study were to test the clinical efficacy of a 3-day course of azithromycin in the treatment of community-acquired pneumonia in children and to determine the microbiologic etiologies involved.

MATERIALS AND METHODS

Patients and Specimens

From January 1, 1996 to January 1, 1999, 110 children aged 1 month to 14 years, with a clinical diagnosis radiologically confirmed of presumably bacterial community-acquired pneumonia, eligible for treatment with oral antibiotics and without signs of respiratory insufficiency, were enrolled in the study at the Pediatric Pulmonary Section, Exequiel Gonzales Cortes Children's Hospital, Santiago, Chile. Written consent for participation in the study was obtained from the parents or legal guardians. The Children's Hospital Ethics Committee approved the study. Exclusion criteria included the following: history or evidence of chronic pathology of any organ system, chronic pulmonary disease, history of prematurity, treatment with any antibiotics within 5 days prior to enrollment, or known hypersensitivity to β-lactam antibiotics or macrolides. Due to the guidelines of the Chilean Ministry of Health, patients less than 3 months of age with pneumonia were hospitalized, but the entrance criteria and medical management were identical to those of the older children in the study.

ABBREVIATIONS

ESR	Erythrocyte sedimentation rate
IFD	Direct immunofluorescence
IFI	Indirect immunofluorescence
NPA	Nasopharyngeal aspirates
NS	Not significant
PBS	Phosphate-buffered saline
PCR	Polymerase chain reaction
SD	Standard deviation
2SP	0.2 M sucrose phosphate transport medium

The investigators (R.K. and L.R.) divided the study population into two groups according to clinical and radiological patterns. One group included those children who presented with signs of classic bacterial pneumonia, with high fever and chest findings of crackles or signs of consolidation, and chest X-rays with segmental, alveolar, or lobar consolidation. The second group included patients with atypical pneumonia, with prominent and frequently paroxysmal cough, variable fever, few clinical signs of consolidation, crackles and wheezing, and chest X-rays with a mixed alveolar-interstitial pattern. Patients from the classic pneumonia group were randomly assigned to receive oral amoxicillin 75 mg/kg/day in three divided doses for 7 days, or azithromycin 10 mg/kg once daily for 3 days, whereas patients in the atypical pneumonia group were randomly assigned to receive oral azithromycin 10 mg/kg once daily for 3 days, or erythromycin 50 mg/kg/day in three divided doses for 14 days. The dose of amoxicillin used in the study was high in order to cover moderate penicillin-resistant *S. pneumoniae*.

On the day of enrollment, routine laboratory tests (i.e., white blood cell and differential counts, erythrocyte sedimentation rate (ESR), and C-reactive protein) and a chest-X-ray were performed in each child. Likewise, samples for blood culture, acute phase serum, and respiratory specimens for bacterial and viral studies were obtained on admission. Respiratory specimens consisted of both nasopharyngeal aspirates (NPA) and bronchial secretions. NPAs were collected with a mucus extractor and divided into three equal parts. One portion was mixed with phosphate-buffered saline (PBS) and used for respiratory virus detection by indirect immunofluorescence. The second portion was also mixed with PBS and used for the detection of *B. pertussis* by direct immunofluorescence. The third portion was inoculated into 2 ml of 0.2-M sucrose phosphate transport medium (2SP) and used for *U. realyticum* and *M. pneumoniae* cultures, and for polymerase chain reaction (PCR) assays. Bronchial secretions were obtained with a mucus extractor after cough induction. This specimen was used for routine aerobic microbiological culture.

After study entry, each child was evaluated at three clinic visits, on study days 3, 7, and 14. A chest X-ray was done in each child on study days 7 and 14. All chest X-rays done on study days 7 and 14 were seen by the same blind radiologist, who was not familiar with the patients' clinical history and treatment group. In order to evaluate the response to treatment in the classic pneumonia group, we calculated the proportion of children without fever on day 3 and/or improvement of more than 75% of radiographic baseline findings on study day 7. In the atypical pneumonia group, response to treatment was based on number of days with cough, and/or improvement of more than 75% of radiographic baseline findings on study day 14.

Microbiology

Bronchial secretions were spread onto two glass slides for Gram staining, and then inoculated on 5% sheep blood agar and chocolate agar. Each agar plate was streaked into four quadrants to obtain semiquantitative counts of organisms. Plates were incubated at 35°C in 5% CO_2 and examined after 24 hr of incubation. If no growth occurred, plates were reincubated for additional 24 hr. Gram-stained slides were microscopically examined for quality assessment and for identification of predominant organism. Specimens were considered adequate if the ratio of polymorphonuclear to epithelial cells per low-power (10×) field was greater than 20. Quantitative cultures ($>10^5$ colonies/mL) were evaluated in combination with Gram stain results. Isolates were identified by using standard microbiologic methods.[5] For diagnosis of *B. pertussis*, bronchial specimens were inoculated onto Regan-Lowe charcoal agar (Oxoid), and were also spread onto a glass slide for direct immunofluorescence (IFD) staining. Agar plates were incubated at 35°C in a moist chamber for 7 days, and were discarded if negative.[5] For blood cultures, 5–10 mL of blood were obtained and immediately inoculated in a 1:10 ratio into each of two bottles of tripticase soy broth (Difco) containing 0.025% sodium polyanethol sulfonate. Bottles were incubated aerobically at 35°C and read once daily for 7 days to detect positive cultures. Terminal subcultures on blood and chocolate agar were performed on negative bottles on day 7. For isolation of *U. urealyticum*, specimens in 2SP were decimally diluted into urea broth (U9) and inoculated on A7 agar plates.[6] Broth media were incubated aerobically at 35°C for 5 days and examined daily for evidence of an alkaline pH change. A7 plates were incubated at 35°C in 5% CO_2 for 5 days and examined microscopically for colonies. *U. urealyticum* was identified on the basis of their urea metabolism and by the characteristic colony appearance.[7] For *M. pneumoniae* recovery, specimens in 2SP were inoculated into a Hayflick biphasic medium and incubated aerobically at 35°C for 6 weeks.[8] Subcultures to Hayflick agar plates were made after 15 days incubation and when color began to change. Plates were incubated in a moist chamber with 5% CO_2 at 35°C, examined microscopically for colonies weekly, and discarded after 1 month if no growth occurred. *M. pneumoniae* was identified by the appearance of colonies and acid production from glucose. Suspect colonies were confirmed as *M. pneumoniae* by hemadsorption in the presence of washed 1% suspension of group O human erythrocytes in PBS.[9]

Serology

Serum samples were tested for IgG antibodies to *C. pneumoniae* by indirect immunofluorescence (IFI), using elementary bodies of *C. pneumoniae* AR-39 (Washington Research Foundation, Seattle, WA) as antigens. The procedure was described elsewhere.[10] The presence of IgM antibodies to *C. trachomatis* was measured by IFI by using elementary bodies of E and L2 strains of *C. trachomatis* (Washington Research Foundation) as antigens.[11] According to the criteria of Schachter et al.,[12] an IgM titer of >1:32 was considered positive. An IFI test (Zeus, Israel), and a μ-capture enzyme-linked immunosorbent assay (ELISA) (Savyon, Israel) were used to test patient sera for IgM antibodies to *M. pneumoniae* according to the manufacturer's instructions. Sera with absorbance values equal to or greater than the cutoff value of +10% were considered positive in the ELISA test. An antibody titer ≥1:16 on a single first serum specimen was considered positive by IFI.

Polymerase Chain Reaction (PCR)

Specimens for PCR were collected into 2 mL of 0.2 M sucrose phosphate transport medium (2SP). Specimens were transported to the laboratory on ice and stored at −70°C until use. For the PCR, 200 μL of each specimen were centrifuged at 13,000 rpm for 30 min. The pellet was suspended in 100 μl of lysis buffer containing 10 mM. Tris-HCl (pH 8.5), 50 mM KCl, 2 mM $MgCl_2$, 1% Triton X-100 (Sigma, St. Louis, MO), and 200 μg/mL proteinase K (Gibco BRL, US). The samples were incubated for 60 min at 60°C, heated for 15 min at 94°C, and quickly cooled on ice. PCR products were purified by extraction with phenol-chloroform-isoamylalcohol and chloroform-isoamylalcohol successively, and collected by ethanol precipitation.[13] Amplification of DNA by PCR was performed for the following organisms, as described elsewhere:[13] *M. pneumoniae*, *C. pneumoniae*, and *C. trachomatis*. Oligonucleotide primers were synthesized according to published gene sequences.[14–16] The products of PCR were analyzed by 1.5% agarose gel electrophoresis and ethidium bromide staining.

Statistical Analysis

To evaluate differences between groups, the chi-square test was used for categorical variables, and Student's *t*-test for continuous variables. Statistical significance was defined by a two-sided α level of 0.05.

RESULTS

Of the 110 enrolled patients, 4 children developed serious pneumonia in the first 12 hr of enrollment and were excluded from the study (3 had atypical pneumonia, were less than 2 month of age, and belonged to erythromycin group, and the other had classic pneumonia, was 3 years of age, and was in the amoxicillin group). The remaining 106 children completed the study.

The mean age of the 106 children was 4.9 years, and 53 were male. Forty-seven children met the criteria for classic

TABLE 1—Demographic Characteristics of Children at Admission With Community-Acquired Pneumonia[1]

	Atypical pneumonia (N = 59)	Classic pneumonia (n = 47)	*P* values
Age (months)	59.8 ± 52.9	58.8 ± 47.1	NS
Gender ratio (male/female)	1.3	1.2	NS
Duration of symptoms (days)	8.1 ± 5.8	3.6 ± 2.4	<0.0001
White blood cell count (per mm^3)	13,121 ± 8,070	17,500 ± 9,147	0.008
% immature cells	9.1 ± 8.6	17.9 ± 14.2	0.0004
% neutrophils	46.1 ± 19.1	54.0 ± 15.8	0.026
ESR (mm/hr)	45.0 ± 33.2	76.9 ± 34.1	<0.0001
C-reactive protein (mg/L)	49.2 ± 61.9	156.0 ± 117.1	<0.00001
Temperature (°C)	37.3 ± 0.8	38.5 ± 0.9	<0.0001

[1]Mean ± SD; ESR, erythrocyte sedimentation rate; NS, not significant.

pneumonia, and 59 for atypical pneumonia. Demographic characteristics of the two groups are shown in Table 1. Children with classic pneumonia had significantly fewer days of symptoms than those with atypical pneumonia (3.6 ± 2.4 days vs. 8.1 ± 5.8 days, respectively, $P < 0.0001$). Also, the children with classic pneumonia had a significantly higher temperature on admission than those with atypical pneumonia (38.5 ± 0.9°C vs. 37.3 ± 0.8°C, respectively, $P < 0.0001$, Table 1).

Based on Chilean Ministry of Health rules, children with pneumonia and younger than 3 months of age were hospitalized; these were 10 children in the atypical pneumonia group (3 with azithromycin and 7 with erythromycin, $P = 0.09$). Those children with classic pneumonia had a significantly higher erythrocyte sedimentation rate, C-reactive protein, white blood cells count, % of immature cells, and % of neutrophils than children with atypical pneumonia (Table 1).

Among the 47 children with classic pneumonia, 23 received azithromycin and 24 amoxicillin (Table 2). There were no significant differences between the groups of children who received azithromycin vs. amoxicillin in terms of clinical baseline findings or laboratory characteristics or severity of abnormalities in chest X-ray at admission. The clinical response on days 3, 7, and 14 was also similar in children treated with azithromycin vs. amoxicillin (Table 3). The total number of days with fever (>38.0°C) were 1.7 ± 1.1 (mean ± SD) in the azithromycin group vs. 2.0 ± 1.3 in the amoxicillin group ($P = 0.34$), and the total number of days with cough were 8.1 ± 5.6 vs.

TABLE 2—Demographic and Historical Characteristics of Children at Admission With Classic Community-Acquired Pneumonia by Treatment Group[1]

	Azithromycin (n = 23)	Amoxicillin (n = 24)	*P* values
Age (months)[2]	64.1 ± 44.0	53.6 ± 50.3	NS
Gender ratio (male/female)	0.8	1.2	NS
Duration of symptoms (days)[2]	3.6 ± 2.3	3.7 ± 2.6	NS
History of respiratory disease[3]			
None (%)	26.1	33.3	NS
Wheezing (%)	73.9	58.3	NS
Previous pneumonia (%)	0.0	4.2	NS
Previous hospitalization (%)	0.0	4.2	NS
At admission			
White blood cell count (per mm^3)[2]	17,823 ± 10,500	17,204 ± 7,945	NS
% immature cells[2]	17.7 ± 14.2	18.0 ± 14.6	NS
% neutrophils[2]	53.1 ± 14.4	54.8 ± 17.2	NS
ESR (mm/hr)[2]	76.8 ± 32.5	77.1 ± 36.2	NS
C-reactive protein (mg/L)[2]	152.4 ± 129.6	159.5 ± 106.5	NS
Chest X-ray[4]	21.7	16.7	NS
% fever (>38.0°C)	60.9	79.2	NS
Rales/crackles (%)	87.0	100.0	NS

[1]ESR, erythrocyte sedimentation rate; NS, not significant.
[2]Mean ± SD.
[3]Percentages may exceed 100%, since patients can have more than one condition.
[4]Chest X-ray, % of chest X-rays with multilobar alterations (segmental, alveolar, or lobar filling pattern).

TABLE 3—Comparison (in Percent) Between Azithromycin vs. Amoxicillin in Children With Classic Community-Acquired Pneumonia[1]

	Azithromycin (n = 23)	Amoxicillin (n = 24)	*P* values
On 3 days of treatment			
Fever (>38.0°C)	8.7%	12.5%	NS
Use of accessory respiratory muscle	4.3%	4.2%	NS
Rales/crackles	87.0%	83.3%	NS
On 7 days of treatment			
Fever (>38.0°C)	0.0%	0.0%	NS
Use of accessory respiratory muscle	0.0%	0.0%	NS
Rales/crackles	13.0%	16.7%	NS
X-ray >75% of improved	81.0%	60.9%	0.009
On 14 days of treatment			
Fever (>38.0°C)	0.0%	0.0%	NS
Use of accessory respiratory muscle	0.0%	0.0%	NS
Rales/crackles	4.3%	0.0%	NS
X-ray >75% improved	100.0%	100.0%	NS

[1]NS, not significant.

6.8 ± 4.7, respectively ($P = 0.58$). However, on day 7, more children in the azithromycin group had a normal chest X-ray than in the erythromycin group (81.0% vs. 60.9%, respectively, $P = 0.009$).

Among the 59 children with atypical pneumonia, 33 received azithromycin and 26 erythromycin (Table 4). There were no significant differences in terms of clinical baseline and laboratory characteristics and chest X-ray abnormalities at admission between children treated with azithromycin vs. erythromycin. The total number of days with fever (>38.0°C) were 1.0 ± 1.5 (mean $\pm$ SD) in the azithromycin group vs. 0.6 ± 0.9 in the erythromycin group ($P = 0.36$). The clinical response between the treatment groups on days 3, 7, and 14 were also similiar (Table 5). However, those children who received azithromycin had an earlier cessation of cough than children treated with erythromycin (3.6 ± 1.9 vs. 5.5 ± 3.6 days, respectively, $P = 0.02$). Moreover, on day 14, more children in the azithromycin group achieved greater than 75% improvement of their radiographic baseline findings

TABLE 4—Demographic and Historical Characteristics of Children at Admission With Atypical Community-Acquired Pneumonia by Treatment Group[1]

	Azithromycin (N = 33)	Erythromycin (n = 26)	*P* values
Age (months)[2]	62.6 ± 53.6	56.2 ± 52.8	NS
Gender ratio (male/female)	0.9	1.2	NS
Duration of symptoms (days)[2]	8.6 ± 6.4	7.5 ± 5.0	NS
History of respiratory diseases[3]			
None (%)	24.2	50.0	0.08
Wheezing (%)	67.7	44.0	NS
Previous pneumonia (%)	21.2	19.2	NS
Previous hospitalization (%)	9.1	7.7	NS
At admission			
White blood cell count (per mm^3)[2]	$12{,}672 \pm 6{,}170$	$13{,}692 \pm 10{,}088$	NS
% immature cells[2]	9.2 ± 8.0	9.1 ± 6.3	NS
% neutrophils[2]	48.2 ± 17.3	43.4 ± 21.1	NS
ESR (mm/hr)[2]	47.82 ± 35.34	41.39 ± 30.64	NS
C-reactive protein (mg/L)[2]	61.1 ± 36.6	34.12 ± 30.68	NS
Chest X-ray[4]	42.4	57.7	NS
% fever (>38.0°C)	78.8	84.6	NS
Wheezing (%)	24.2	34.6	NS
Rales/crackles (%)	87.9	80.8	NS

[1]ESR, erythrocyte sedimentation rate; NS, not significant.
[2]Mean $\pm$ SD.
[3]Percentages may exceed 100% since patients can have more than one condition.
[4]Chest X-ray, % of chest X-rays with multilobar alterations (mixed alveolar-interstitial pattern).

TABLE 5—Comparison (in Percent) Between Azithromycin vs. Erythromycin in Children With Atypical Community Acquired Pneumonia[1]

	Azithromycin (n = 33)	Erythromycin (n = 26)	*P* values
On 3 days of treatment			
Fever (>38.0°C)	6.1%	4.0%	NS
Wheezing	27.3%	48.0%	NS
Rales/crackles	57.6%	64.0%	NS
On 7 days of treatment			
Fever (>38.0°C)	0.0%	0.0%	NS
Wheezing	25.8%	28.0%	NS
Rales/crackles	0.0%	4.0%	NS
X-ray >75% improved	61.5%	46.7%	NS
On 14 days of treatment			
Fever (>38.0°C)	0.0%	0.0%	NS
Wheezing	3.6%	7.7%	NS
Rales/crackles	0.0%	0.0%	NS
X-ray >75% improved	100.0%	81.0%	0.059

[1]NS, not significant.

than those in the erythromycin group (100% vs. 81% respectively, $P = 0.059$). Three children in the erythromycin group developed mild diarrhea in their first 24 hr of treatment, but it was not necessary to suspend the drug.

Table 6 shows the frequency of microbiologic etiologic agents. For the whole population, 53 causal bacterial pathogens were identified in 44/106 (41%) children. Etiologic agents were identified in close proportions among children with atypical pneumonia as in those with classic pneumonia (57.6% vs. 40.4%, respectively, $P = 0.08$). *M. pneumoniae* was the most common pathogen found (31/106, 29.2%), either as single agent (25 cases) or in association with other pathogens (6 cases). The next most common agent was *S. pneumoniae*, which was isolated in 7 (6.6%) cases. *M. pneumoniae* was significantly more prevalent in the atypical pneumonia group than in the classic pneumonia group; conversely, *Streptococcus pneumoniae* was isolated only in children with classic pneumonia (Table 6). *H. influenzae* and *B. pertussis* were diagnosed each in 4 (3.8%) children. *C. pneumoniae* was detected in 3 (2.8%) patients, *C. trachomatis* in 2 (1.9%) infants less than 3 months old, and *M. catarrhalis* in 2 (1.9%). Eight out of 106 (7.5%) children had more than one pathogen isolated: in 7 cases two bacterial pathogens, and in 1 case, three. Etiologic agents of ''atypical pneumonia'' were found in 9/47 (19%) patients with clinical classic pneumonia. Conversely, ''classical pneumonia bacteria'' were detected in 3/59 (5%) of children in the clinical atypical pneumonia group.

Twenty-four of 56 (42.9%) patients with an identified etiologic agent received azithromycin, and those bacterial isolates corresponded to *M. pneumoniae*, *S. pneumoniae*, *C. pneumoniae*, and *H. influenzae*. Thus, due to random distribution, children with *C. trachomatis*-positive, *M. catarrhalis*-positive, or *B. pertussis*-positive isolates did not receive azithromycin. In 28/31 cases with *M. pneumoniae*, serologic diagnosis was confirmed by PCR. Three out of 7 cases of *S. pneumoniae* were identified from blood culture, and 4 from sputum culture. All cases with *C. trachomatis* and *C. pneumoniae* were diagnosed by PCR and serology (Table 7).

DISCUSSION

The results of this study indicate that azithromycin given for 3 days was as effective as amoxicillin or erythromycin for treatment of classic and atypical community-acquired pneumonia in pediatric patients. However, children with classic pneumonia who received azithromycin normalized their chest X-ray on day 7 significantly more often than those treated with amoxicillin. The same was true for atypical pneumonia: children on azithromycin therapy had a trend toward greater improvement in their chest X-ray on day 14 than those treated with

TABLE 6—Etiological Agents Identified in Children With Community-Acquired Pneumonia by Group[1]

	Atypical pneumonia (n = 59)		Classic pneumonia (n = 47)	
Agent	Azithromycin (n = 33)	Erythromycin (n = 26)	Azithromycin (n = 23)	Amoxicillin (n = 24)
*M. pneumoniae**	12	11	5	3
*S. pneumoniae***	0	0	4	3
C. trachomatis	0	2	0	0
C. pneumoniae	1	1	1	0
H. influenzae	1	1	0	2
B. pertussis	0	4	0	0
M. catarrhalis	0	1	0	1

[1]Numbers did not end up at the same total, as a patient can have more than one agent. Viruses and *U. urealyticum* were not included in the analysis.
*$P = 0.037$.
**$P = 0.001$ between children with atypical vs. classic pneumonia as a group.

TABLE 7— Microbiological Test for Etiological Agents Identified in Children With Community-Acquired Pneumonia[1]

		Bronchial secretion			Serum		
Agent	Blood Culture	Culture	PCR	IFD	IFI (IgM)	IFI (IgG)	ELISA (IgM)
M. pneumoniae (n = 31)		19	28		31		31
S. pneumoniae (n = 7)	3	4					
C. trachomatis (n = 2)			2		2		
C. pneumoniae (n = 3)			3			3	
H. influenzae (n = 4)		4					
B. pertussis (n = 4)				4			
M. catarrhalis (n = 2)		2					

[1]Numbers did not add to the same total because an agent can be identified with more than one microbiological method. Viruses and *U. urealyticum* were not included in the analysis. IFD, direct immunofluorescence; IFI, indirect immunofluorescence; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

erythromycin. In children with atypical pneumonia, azithromycin was also significantly more effective than erythromycin in reducing cough. Moreover, azithromycin therapy had no side effects, in contrast to erythromycin.

Our findings are in agreement with two other studies[3,17] which compared the efficacy of a 5-day course of azithromycin vs. 10 days of amoxicililin/clavulanate or erythromycin in the treatment of pediatric pneumonia, and which found a satisfactory and comparable therapeutic outcome among these three antibiotics. To our knowledge, there is only one other study[2] comparing the efficacy of a 3-day course of azithromycin in the treatment of community-acquired lower respiratory tract infections (predominantly pneumonia) in children, with comparable success between azithromycin and a 10-day course of erythromycin; however, those authors reported a higher prevalence of azithromycin side effects than in our study (27% vs. 0%). As we already know, the frequent use of one antibiotic may result in the induction of an antibiotic resistance. For this reason, the use of azithromycin in children with community-acquired pneumonia needs to follow the same precautions as with other antibiotics, and if available, antibiotic resistance patterns in each community can help in selecting the right antibiotic.

Our results highlight the importance of *M. pneumoniae* in pediatric pneumonia, either as sole pathogen or in association with other respiratory agents. Nevertheless, the high incidence of infection by this agent can also be explained by the techniques we used for diagnosis. *M. pneumoniae* diagnosis was based not only on isolation by culture, but also relied on two different serology procedures and on PCR. Other reasons for the high rate of detection of this agent are the age range of our series (mean age, 4.9 years) and regional epidemiological factors. As we know, *M. pneumoniae* infections are found predominantly in children above age 2 years. The importance of *M. pneumoniae* as a cause of pneumonia in our country was previously unknown, since this is the first study assessing prevalence of *M. pneumoniae* infections in children.

In the present study, *S. pneumoniae* was the second most common cause of pneumonia (6 were in children more than 5 years old), and was probably underdiagnosed due to low sensitivity of sputum and blood cultures. The rate of positive blood cultures for *S. pneumoniae* in our study in children with classic pneumonia was 3/47 (6.4%), and was higher than previously reported.[18] There was a low incidence of *H. influenzae* in our study, perhaps as a consequence of the national vaccination plan implemented in Chile since 1996 and/or the low sensitivity of the culture technique. Curiously, all children with *H. influenzae* had more than 5 years old. The isolation of *M. catarrhalis* as a cause of pneumonia in our study is in agreement with the results of another clinical trial.[19] In our study, *M. catarrhalis* was isolated in 2 cases. In one case, it was sole agent in a child with classical pneumonia and amoxicillin treatment, and in the other it case was isolated together with *B. pertussis* (Table 6). *B. pertussis* is not a common cause of pneumonia;[20] 2 of the 4 isolates in our series were associated with other infections; in only 2 children was it the sole agent. All children with *B. pertussis* were less than 5 years old. *C. trachomatis* was detected as a cause of pneumonia in 2 of 12 (17%) infants less than 3 months old. This result is not unexpected, given the relatively low incidence of cervical infection in women in Chile, and which was found to be 4–6% in the last year.[21] We found multimicrobial infections in only 7.5% of children, which is lower than in other studies that reported up 25%.[4,19] Interestingly, only in 19% of our children with a clinical and radiological picture suggesting classic pneumonia were atypical pathogens (e.g., *M. pneumoniae* or *C. pneumoniae*) found. Laboratory findings (white blood cell count, erythrocyte sedimentation rate, C-reactive protein) in these cases were also characteristic for classic pneumonia. *U. urealyticum* was isolated in 3 infants less than 3 months old. They were not included in the results, due to the controversial role of *U. urealyticum* as a cause of pneumonia in term infants.[22] The few viruses isolated (respiratory syncytial virus in

3 cases and adenovirus in 1) were also not considered in the results, since our main purpose was to evaluate the efficacy of azithromycin in the treatment of bacterial pneumonia.

In conclusion, our results suggest that azithromycin is a good therapeutic option for the treatment of community-acquired pneumonia (classic and atypical) in children. It is safe, easy to administer, and effective against all probable respiratory bacterial pathogens in this age group.

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