Azithromycin Prophylaxis during a Hospital Outbreak of *Mycoplasma pneumoniae* Pneumonia

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Outbreaks of *Mycoplasma pneumoniae* (MP) in closed communities can have a high attack rate and can last several months. Azithromycin chemoprophylaxis has not been evaluated as a means of limiting transmission. This randomized, double-blinded placebo-controlled trial of azithromycin was conducted among asymptomatic hospital employees during an MP outbreak. Oropharyngeal swabs were obtained for detection of MP by polymerase chain reaction, and questionnaires were administered to assess clinical illness. Of the 147 employees who were enrolled, 73 received azithromycin and 74 received placebo. Carriage was similar within and between groups at weeks 1 and 6 (9.6% vs. 6.7% and 10.3% vs. 13.2%, respectively). Four episodes of clinically significant respiratory illness occurred in the azithromycin group versus 16 episodes in the placebo group (protective efficacy, 75%; 95% confidence interval, 28%–91%). Use of azithromycin prophylaxis in asymptomatic persons during an MP outbreak in a closed setting may be of value in reducing clinical illness.

*Mycoplasma pneumoniae* is a common cause of respiratory infections in adults and school-age children, causing ~15%–20% of all community-acquired pneumonia [1, 2]. Clinical expression of the illness can range from nonspecific flulike symptoms, such as a dry cough, fevers, and myalgias, to nonpulmonary signs and symptoms, such as rashes, ataxia, and encephalitis [3–5].

In closed communities, such as long-term residential facilities, military bases, religious communities, and hospitals, *M. pneumoniae* outbreaks can last several months and can have attack rates as high as 25% [6–11]. Although mortality is low, these outbreaks can cause significant morbidity. Outbreak control can be challenging because of the difficulties in diagnosis and the long incubation period. Current recommendations for control of outbreaks of *M. pneumoniae* illness in closed communities are limited to cohorting of patients who become symptomatic and using respiratory droplet precautions [12]. Even with proper implementation of these measures, however, outbreaks may persist. Previous studies on the effect of antibiotic prophylaxis in an outbreak setting have shown some promising results [7–10], but these trials were limited by poor compliance with the medication [9, 10], faulty observational design [7, 9], or depletion of susceptible persons [7–10]. Azithromycin, a new, long-acting macrolide antibiotic with decreased side effects, has been shown to reduce carriage of *M. pneumoniae* and clinical illness; however, no placebo-controlled trials of azithromycin prophylaxis have been conducted in outbreak settings. We report the first double-blinded, randomized, placebo-controlled trial of azithromycin prophylaxis for the control of mycoplasma infections.

Subjects and Methods

Background

In early August 1999, an infection control nurse in a state psychiatric hospital reported a cluster of pneumonia cases of unknown etiology among residents of the facility to the state health department and the Respiratory Diseases Branch (RDB) at the Centers for Disease Control and Prevention (CDC). Of 257 residents, 28 (11%) had a radiographic diagnosis of pneumonia. The first case had been diagnosed in early June, and new cases were occurring at the time of contact with the RDB. There had also been anecdotal reports of illness among the staff. Nasopharyngeal swabs from 8 residents yielded no evidence of viral pathogens; however, 9 of 11 oropharyngeal (OP) swabs tested at the CDC were positive by polymerase chain reaction (PCR) analysis for *M. pneumoniae*.

Once the outbreak was recognized, the hospital implemented standard infection control practices, including strict respiratory droplet precautions, cohorting of ill patients, and education of the
employees regarding the illness and presenting symptoms. The CDC was invited by the hospital and state department of health to assist in an investigation of the outbreak and to conduct a study of azithromycin prophylaxis among asymptomatic persons.

**Outbreak Investigation**

We conducted an epidemiologic investigation among the residents and staff at the hospital to better characterize the outbreak. A 3-tiered case definition was used for mycoplasma-like illness (MLI). A case of definite outbreak-associated MLI was defined as a radiographically confirmed pneumonia or a positive PCR result for *M. pneumoniae*, along with symptoms of respiratory infection, occurring after 15 May 1999, in a resident of the hospital; a probable case of MLI was defined as respiratory illness with cough, fever, and myalgias; and a possible case of MLI was defined as illness with 2 of the 3 symptoms present (cough, fever, or myalgias). Symptom logs were placed at the nursing station on each ward, education sessions were held for the staff, and the staff was asked to contact the infection control nurse if a resident met the case definition of a possible MLI. Active surveillance for cases among the patients continued through 15 November 1999, ~6 weeks after the last documented MLI. Hospital charts and chest radiographs were reviewed for all residents identified to have respiratory symptoms. OP swabs for PCR analysis were obtained from all patients identified to have probable or possible MLI after mid-August.

A survey was distributed to all employees on the payroll of the facility. A second survey was administered to nonresponders. The survey requested information on basic demographics, type of work, history of personal illness, and illness among family members occurring after 15 May 1999. Illness in employees was categorized only as probable or possible cases of MLI, because of the inability of collecting reliable diagnostic information. Information on illness among the employees is limited to the period preceding the survey administration, 15 May 1999 to 1 September 1999.

**Azithromycin Chemoprophylaxis Study among Employees**

The ongoing outbreak of *M. pneumoniae* infection among patients and staff provided the opportunity to assess the impact of azithromycin in a controlled manner. We conducted a randomized, double-blinded placebo-controlled trial of azithromycin treatment among the employees to determine whether azithromycin could reduce carriage and transmission of *M. pneumoniae* as well as prevent development of severe clinical illness. The study was performed among the employees of the institution rather than the patients because of concerns that not all of the patients at this facility for persons with psychiatric and developmental disabilities would be capable of giving informed consent. The study began on 23 August 1999 and was completed on 7 October 1999.

The study participants were randomized to receive either 5 days of azithromycin (500 mg on day 1 and 250 mg on days 2–5) or an identical-appearing placebo. Enrollees were screened for the following exclusion criteria: receipt of antibiotics in the 4 weeks before enrollment; allergy to macrolide antibiotics; and receipt of medications that can interact with azithromycin, such as dilantin, phenobarbital, ergotamine, dihydroergotamine, triazolam, theophylline, and digoxin. Participants were also excluded if they had a history of any known liver or kidney disease or an arrhythmia. Because it is unknown whether azithromycin has an effect on the fetus, women who reported that they were pregnant or might become pregnant during the study were also excluded.

Carriage of *M. pneumoniae* throughout the study was assessed by PCR analysis of OP swabs obtained at enrollment, week 1, and week 6. The length of the study, 6 weeks, was selected to encompass 2 incubation periods of *M. pneumoniae* (2–3 weeks). Clinical illness was assessed by administration of 5 questionnaires regarding intercurrent illness over the 6 weeks of the study. A clinically significant respiratory illness was defined as a respiratory illness that developed after enrollment in the study, resulted in a visit to a physician, and was treated with an antibiotic. Employees who became ill were requested to submit throat swabs for *M. pneumoniae* testing.

**Sample size.** Using the parameters α = .05 for a 1-tailed comparison and β = .20, a baseline carriage rate of 25% [7, 10, 11], a spontaneous resolution of carriage in the placebo group of 10%, an eradication rate of 75% in the treatment group, and a dropout rate of 10%, we determined that 75 people were needed in both the treatment and the control groups. The estimate of a 75% eradication rate in the treatment group was conservative. Although Feikin et al. [7] were able to look at only a small number of colonized persons who were treated with a macrolide antibiotic, 100% (7/7) were not colonized 2 weeks after treatment.

**Laboratory methods.** OP swabs were obtained by 2 of the principal investigators (T.B.H. and M.G.), using a Dacron swab. The OP swabs were placed immediately into SP4 medium [13] and were agitated for 1 min to dislodge any *M. pneumoniae* present. The swab was then discarded, and the inoculum was placed on dry ice and was shipped overnight to the CDC. The samples were stored at ~70°C until thawed for analysis.

DNA extraction was performed by using the QIAamp DNA kit (Qiagen) according to the “body fluids” protocol, with the following modification of the manufacturer’s instructions: after 600 µL of the sample was thawed and was centrifuged for 20 min at 23,100 g. 400 µL of the supernatant was discarded, and the pellet was resuspended in the remaining 200 µL before the extraction protocol was begun.

For PCR analysis, we designed primers targeted to the ATPase gene of *M. pneumoniae* (TQMpneuA and TQMpneuB; Biotechnology Core Facility, CDC) [14]. TaqMan PCR procedures were strictly controlled by the use of specific probes to avoid false-positive reactions, and a customized internal positive control (IPC) was used to monitor inhibition. The IPC was engineered so that it was amplified by use of the same primer set, but it was differentiated from the target DNA by unique probes to the IPC and to the target DNA. All other reagents used in the PCR reaction were from the TaqMan PCR Core Reagent Kit (PE Applied Biosystems). The primer and probe concentrations were 0.3 µM for primer pneuA, 0.9 µM for primer pneuB, 100 nM for the tetrachloro-6-carboxyfluorescein–labeled IPC probe, and 150 nM for the 6-carboxyfluorescein–labeled target probe. Other reaction conditions were 0.5 U of Amplerase UNG and 0.625 U of AmpliTaq Gold (both from PE Applied Biosystems) and 50 copies of IPC. Five microliters of sample DNA preparation was added, to yield a final volume of 25 µL. Because we have found inhibition of the PCR reaction to be a concern, we set up 3 separate reactions for each sample tested, each of which contained 5 µL of the following
Figure 1. Mycoplasma-like illness (MLI) among residents at State Hospital A by week of onset, 1999. □. Definite cases of MLI; ■. possible cases of MLI.

Statistical Analysis

Data were entered, verified, and edited by use of Epi Info, Version 6 (CDC) [15]. An intent-to-treat analysis was performed, to determine the efficacy of azithromycin in preventing clinically significant respiratory illness. The χ² and Fisher exact tests were used for comparisons of proportions, and the Wilcoxon rank sum test was used for comparisons of medians between the 2 groups [15]. We used standard methods to calculate the number of persons it was necessary to treat to prevent a case of clinically significant respiratory illness [16]. Multivariable analysis and the Kaplan-Meier life-table were used to evaluate the protective effect of azithromycin over the 6 weeks of the study. The log-rank test was used in the Kaplan-Meier analysis to assess for statistical significance between the azithromycin and the placebo groups [17]. For all statistical comparisons, P < .05 was considered to be significant.

Results

Outbreak investigation. We identified 60 cases of MLI among the 257 residents in the facility, of which 41 were definite cases and 19 possible cases. The overall attack rate of MLI was 23.3% (60/257). Because of the use of radiographs and PCR testing, all residents who met the probable case definition also met the definition for a definite case. Of the 41 persons with definite cases, 23 were PCR positive for *M. pneumoniae*, and 30 had radiographic evidence of a patchy bilateral or unilateral infiltrate. The index patient was a resident who was admitted from the community at the end of May and developed symptoms at the beginning of June. There were 3 waves of cases during the outbreak, and cases continued to occur until the beginning of October (figure 1).

Surveys were completed by 372 (84%) of the 440 employees at the institution, of whom 124 reported some form of respiratory illness: 39 (31.4%) had probable cases of MLI, and 43 (34.6%) had possible cases. The overall MLI attack rate among employees was 22% (82/372) and was similar between employees and residents (P = .70). The earliest cases preceded the admission of the index resident case, and employee cases were continuing at the time of the survey. When compared with employees with little patient contact, employees who spent a majority of their work time in contact with the patients were significantly more likely to report an MLI (table 1). Illness was associated with increasing time spent with patients.

Azithromycin chemoprophylaxis study. Of the 196 employees who expressed interest in participating in the study, 147 were eligible and enrolled: 73 in the azithromycin group and 74 in the placebo group. Of the 47 employees who were excluded from the study, 26 had taken antibiotics in the previous 4 weeks, 12 reported taking medications that interacted with azithromycin, 3 reported allergies to macrolide antibiotics, 3 had medical conditions that did not allow them to participate, 2 were pregnant, 1 had MLI symptoms at enrollment, and 1 person would not be able to complete the study because of vacation. There were no differences between the azithromycin- and placebo-treated groups with respect to age, sex, amount of patient contact, or illness in family members (table 2).

Side effects and adverse events. Four (5%) participants in the azithromycin group did not complete their medication regimen because of allergic reactions such as facial swelling, itchy
throat, and hives. All 4 completed the course of OP swabs and questionnaires according to their original assignment and remained in the analysis. Other adverse events, all of which were diarrhea, occurred equally between the groups (6 in the azithromycin-treated group and 5 in the placebo group). Five people in each group were lost to follow-up, leaving 68 in the azithromycin group and 69 in the placebo group for analysis.

**OP carriage of M. pneumoniae.** M. pneumoniae carriage at enrollment was 9.6% and 6.7% in the azithromycin and placebo groups, respectively ($P = .53$; table 3). Carriage was similar within and between groups at weeks 0, 1, and 6. Of 7 persons in the azithromycin group who were colonized with *M. pneumoniae* at enrollment, carriage had been eradicated by day 7; however, 2 had reacquired carriage of *M. pneumoniae* by day 42 of the study. Of 5 persons in the placebo group who were carriers of *M. pneumoniae* at enrollment, carriage had been eradicated in 3 by day 7, and the other 2 individuals were still carriers at day 42. Although requested to do so as part of the study design, no ill employees returned for throat swab collection at the time of their illness.

**Clinical illness among study participants.** Four episodes of clinically significant respiratory illness occurred in the azithromycin group versus 16 episodes in the placebo group (protective efficacy, 75%; 95% confidence interval [CI], 28%–91%). Most cases of clinically significant respiratory illness in persons who received azithromycin occurred during the last weeks of the study, whereas respiratory illness among persons who received placebo was reported continually throughout the study (figure 2). To prevent 1 case of clinically significant respiratory illness, 6 persons would need to be treated with azithromycin (95% CI, 3–30). The probability of the azithromycin-treated group remaining free of clinically significant respiratory illness remained higher than that of the placebo group throughout the study period ($P = .004$, log-rank test).

**Discussion**

This is the first randomized, placebo-controlled study of azithromycin for control of an outbreak of *M. pneumoniae* infections in a closed setting, and, similar to the findings of uncontrolled studies, we were able to demonstrate a reduction in illness with minimal drug side effects in those receiving azithromycin. Although azithromycin prophylaxis did not significantly affect carriage of *M. pneumoniae* in this study, there was a large difference between groups in the development of clinically significant respiratory illness. The protective effect was seen 1 week after treatment and lasted through the fifth week of the study.

A number of earlier studies have shown that chemoprophylaxis for *M. pneumoniae* in a closed setting may be effective in reducing illness, but these studies have been limited. Jensen et al. [9] demonstrated a reduction in symptoms but not serologic conversion in those receiving oxytetracycline versus placebo in a hospital setting. Feikin et al. [7] showed that azithromycin, when administered to all persons early in an outbreak of *M. pneumoniae* infections at a military academy, dramatically reduced the *M. pneumoniae* carriage rate. Klausner et al. [8] conducted an observational study in a hospital setting that compared sequentially no intervention, cohorting of sick persons, and cohorting of sick persons plus azithromycin prophylaxis for asymptomatic persons. They showed that treatment of all residents with azithromycin reduced the secondary attack rate of *M. pneumoniae* illness. Ackelsberg [11] also demonstrated, in a closed religious community, that treatment of asymptomatic persons could decrease expression of clinical illness. With the exception of the study by Jensen et al. [9], there were no control groups in these studies, and it is possible that the outbreaks had already extended

### Table 1. Attack rate of mycoplasmalike illness by self-reported amount of patient contact among employees at State Hospital A during an outbreak of *Mycoplasma pneumoniae* infection in a psychiatric facility.

<table>
<thead>
<tr>
<th>Patient contact, % (n)</th>
<th>Probable cases</th>
<th>Possible cases</th>
<th>All cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Rate, % OR$^b$</td>
<td>No. Rate, % OR$^c$</td>
<td>No. Rate, % OR$^d$</td>
</tr>
<tr>
<td>0–25 (95)</td>
<td>5 5.3 1.0</td>
<td>11 11.5 1.0</td>
<td>16 16.8 1.00</td>
</tr>
<tr>
<td>26–50 (49)</td>
<td>3 6.1 1.17</td>
<td>1 2.0 0.16</td>
<td>4 8.2 0.44</td>
</tr>
<tr>
<td>51–75 (62)</td>
<td>8 12.9 2.67</td>
<td>8 12.9 1.13</td>
<td>16 25.8 1.72</td>
</tr>
<tr>
<td>76–100 (162)</td>
<td>27 16.7 3.6</td>
<td>19 11.7 1.01</td>
<td>46 28.4 1.96</td>
</tr>
<tr>
<td>Total, N = 368</td>
<td>43 16.7 3.6</td>
<td>39 11.7 1.01</td>
<td>82 28.4 1.96</td>
</tr>
</tbody>
</table>

NOTE. OR, odds ratio.

$^a$ Percentage of work time reported to be spent with patients (total no. of patients).

$^b$ $P = .003$, $x^2$ for linear trend.

$^c$ $P = .57$, $x^2$ for linear trend.

$^d$ $P = .007$, $x^2$ for linear trend.

### Table 2. Demographic characteristics of participants enrolled in an azithromycin chemoprophylaxis study during an outbreak of *Mycoplasma pneumoniae* infection in a psychiatric facility.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Azithromycin ($n = 73$)</th>
<th>Placebo ($n = 74$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>51 (69.9)</td>
<td>60 (81.1)</td>
<td>.83</td>
</tr>
<tr>
<td>Median (range) age, years</td>
<td>44 (25–63)</td>
<td>46 (19–64)</td>
<td>.26</td>
</tr>
<tr>
<td>Work involving direct patient contact$^a$</td>
<td>48 (65.8)</td>
<td>47 (63.5)</td>
<td>.78</td>
</tr>
<tr>
<td>Family illness</td>
<td>21 (28.7)</td>
<td>19 (26.7)</td>
<td>.85</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of study participants, unless designated otherwise.

$^a$ Includes physicians, nurses, nursing assistants, and medical aids.
haunted all susceptible persons. Schillinger et al. [10] demonstrated, in a randomized, placebo-controlled trial, that doxycycline reduced the attack rate of *M. pneumoniae*-related illness during a hospital outbreak. The reduction in clinical illness was most significant 2–3 weeks after taking the doxycycline. This study was limited by poor compliance with the 2-week regimen and by the side effects of doxycycline.

Because of the study design, we were unable to show whether azithromycin can shorten an outbreak in a closed setting. Because only half of the staff and none of the patients received azithromycin, it is likely that *M. pneumoniae* continued to circulate within the hospital. To determine whether azithromycin chemoprophylaxis would interrupt the natural course of an outbreak of *M. pneumoniae* infection, multiple outbreaks would have to be randomized to treatment of all persons either with azithromycin or with placebo, which would not be feasible in terms of cost and time.

We were unable to demonstrate a decrease in *M. pneumoniae* carriage. There are a few reasons for this. First, the baseline carriage rate of *M. pneumoniae* among all the study employees at enrollment was 8%. This is a lower baseline carriage rate than those seen in previous studies [7, 10, 11] and was much lower than we expected. The power of the study to detect an effect of azithromycin on carriage of *M. pneumoniae* was only 55%. Second, by treating only a subset of hospital personnel, it is possible that persons whose carriage was eradicated could have been reinfected with *M. pneumoniae* during the study period.

This study had several additional limitations. The study population may have been exposed to the bacterium and experienced infection before the trial of intervention with azithromycin. We did not do serologic testing for diagnosis of *M. pneumoniae* infection as a way of increasing employee participation in the study. It is possible that asymptomatic infections were occurring, which would reduce the power of the study, since some participants would already have been infected at the beginning of the study.

There was a dramatic difference between the groups in the development of clinically significant respiratory illness. Use of this clinical marker for *M. pneumoniae* infection without diagnostic information may have limited the specificity of the study. Although we intended to collect OP swabs for PCR analysis, ill employees went to their physicians or stayed at home rather than presenting to employee health services. However, the difference in clinical expression of illness between the groups was evident after the first week of the study and appeared to last until the fifth week of the study. This would suggest that azithromycin is useful in suppressing clinical illness in those infected before prophylaxis, as well as in interrupting new transmission for ~3–4 weeks after treatment. Although we are sure that clinically significant respiratory illness was prevented in the azithromycin group, we cannot be sure that the illness prevented was due to *M. pneumoniae*.

An important issue to be considered when deciding on antibiotic prophylaxis is the secondary effects of the drug on other organisms. Although azithromycin is effective against *M. pneumoniae*, there is also some evidence that prophylaxis may select for macrolide-resistant *Streptococcus pneumoniae*. A study by Leach et al. [18] documented that, after administration of 1 dose of azithromycin (20 mg/kg) for the prevention of trachoma, the prevalence of macrolide-resistant *S. pneumoniae* increased from 1.9% to 5.9% . Another study, a trial of azithromycin as chemoprophylaxis for *S. pyogenes* (group A), demonstrated an increase from 2% to 8% in macrolide-resistant *S. pneumoniae* after a 5-day course of azithromycin [19]. The risk of developing resistance must be considered before deciding to institute widespread chemoprophylaxis.

Public health officials may want to consider the use of azithromycin prophylaxis in certain *M. pneumoniae* outbreak settings. Azithromycin prophylaxis may be a very valuable tool for interruption of an outbreak of *M. pneumoniae* in closed settings where populations may be at higher risk for developing more clinically severe disease. In deciding whether to use mass prophylaxis in closed settings, many factors must be considered, including the cost of prophylaxis, allergic reactions, the severity of the illness among the population, development of resistance

### Table 3.
Oropharyngeal carriage of *Mycoplasma pneumoniae* among employees throughout an azithromycin chemoprophylaxis study during an outbreak of *M. pneumoniae* infection in a psychiatric facility.

<table>
<thead>
<tr>
<th>Date</th>
<th>Azithromycin group</th>
<th>Placebo group</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total (%)</td>
<td>no./total (%)</td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>7/73 (9.6)</td>
<td>5/74 (6.7)</td>
<td>.53</td>
</tr>
<tr>
<td>Day 7</td>
<td>5/72 (6.9)</td>
<td>8/74 (10.8)</td>
<td>.41</td>
</tr>
<tr>
<td>Day 42</td>
<td>7/68 (10.3)</td>
<td>9/69 (13.2)</td>
<td>.62</td>
</tr>
</tbody>
</table>

<sup>a</sup> *P* = .76 within the azithromycin-treated group over the study period.

<sup>b</sup> *P* = .45 within the placebo group over the study period.

<sup>c</sup> Azithromycin group vs. placebo group.

![Kaplan-Meier survival curve showing outcome for persons receiving azithromycin prophylaxis during an outbreak of *Mycoplasma pneumoniae*. Solid line, azithromycin-treated group; dotted line, group treated with placebo. *P* = .004, log-rank test.](https://academic.oup.com/jid/article-abstract/183/6/907/2191259)
in other pathogens, and disruption of services to residents and loss of work among the staff.

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**References**