Effectiveness of Erythromycin in the Treatment of Acute Bronchitis

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Background. Clinical trials have not shown a consistent benefit of treating bronchitis with antibiotics. Many physicians, however, treat acute bronchitis with antibiotics because of the possibility of *Mycoplasma pneumoniae* or other pathogens. The objectives of this study were to determine the effectiveness of erythromycin treatment in patients with acute bronchitis and to determine whether a newly developed rapid *M pneumoniae* antibody test is useful in predicting which patients will respond to therapy.

Methods. We conducted a randomized, double-blind, placebo-controlled clinical trial at three primary care centers in North Carolina. A convenience sample of 140 patients presenting with acute bronchitis were tested for *M pneumoniae*, 91 of whom were treated with either erythromycin 250 mg four times daily for 10 days or an identical-appearing placebo.

Results. Patients treated with erythromycin missed an average of only 0.81 ± 1.1 days of work compared with 2.16 ± 3.2 days for placebo-treated patients ($P < .02$). There were no significant differences in cough, use of cough medicine, general feeling of well-being, or chest congestion between the erythromycin and placebo groups. Twenty-five percent of the patients tested positive for *M pneumoniae*. There were no differences in response to erythromycin based on whether the patient had a positive test for *M pneumoniae*.

Conclusions. Erythromycin is effective in significantly reducing lost time from work, but it is not effective in reducing cough or other symptoms in patients with acute bronchitis, regardless of the outcome of the *M pneumoniae* antibody test.

Key words. Bronchitis; erythromycin; pneumonia, mycoplasma; treatment outcome.

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Acute bronchitis ranks among the 10 most common illnesses seen in office practice, and its diagnosis and treatment are associated with substantial costs in both time and money.[1-3]

The cause of acute bronchitis is unclear in most cases.[4,5] Epidemiologic studies from various clinical settings document the role of respiratory viruses, including rhinovirus, coronavirus, adenovirus, and influenza virus, in addition to *Mycoplasma pneumoniae*.[6-10] Gram's stain and standard bacterial culture have not been helpful in identifying bacterial causes or predicting which cases might respond to antibiotics,[11-13] and most randomized controlled trials do not show a significant benefit of treating acute bronchitis with antibiotics.[4,11-15]

Mycoplasma pneumoniae causes approximately 20% of cases of community-acquired pneumonia.[16-18] Some epidemiologic evidence suggests that the incidence of *M pneumoniae* bronchitis is 23 times that of mycoplasmal pneumonia.[18] Using retrospective serologic methods, prevalence rates among patients with acute bronchitis have ranged between 5% and 27%.[19-21] Using a newer rapid diagnostic method based on antibody detection and latex agglutination, however, the prevalence was 43% in a study of rural family practice patients.[22]

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The objectives of this study were twofold: (1) to determine the effectiveness of erythromycin treatment in patients with acute bronchitis, and (2) to determine whether a newly developed rapid *M pneumoniae* antibody test is helpful in predicting which patients will respond to erythromycin therapy. The major hypothesis was that erythromycin would be effective in the treatment of unselected patients with acute bronchitis, as exhibited by improvement in cough and measures of general well-being. A second hypothesis was that performing the *M pneumoniae* antibody test would allow a more accurate prediction of who would respond to antibiotic therapy.

Methods

A randomized, prospective, double-blind trial of erythromycin in the treatment of patients with acute bronchitis was performed at three different primary care clinical sites in North Carolina: two family practice centers used for residency training, and one rural family practice. Procedures were standardized for consistency among the sites and approved by the human subjects research committee at each institution.

Subjects were recruited after presenting with symptoms of acute bronchitis to one of the three practice sites. Inclusion criteria included minimum age of 8 years, presence of cough and sputum production, and onset of symptoms within the last 2 weeks. This case definition is similar to the one used in recent clinical trials.[11,14,15] Patients were excluded if they were pregnant, allergic to erythromycin, weighed less than 55 lb, had a history of asthma or chronic obstructive pulmonary disease, had signs of sinusitis, otitis, or pneumonia, or had used systemic antibiotics during the previous 2 weeks. Chest radiographs were not required. Patients were excluded if they had localized crackles or wheezes but could be included if crackles and wheezes were diffuse or intermittent. Informed consent was obtained from all subjects. Subjects underwent a brief standardized history and physical examination, then proceeded to the laboratory for phlebotomy. Serum was obtained and tested for antibodies using the *M pneumoniae* IgG/IgM Antibody Test System (Remel, Inc, Lenexa, Kan); results were usually available in 20 to 50 minutes. The antibody test has a sensitivity of 95.1% and specificity of 86.3%, according to the manufacturer.

All patients with a positive antibody test and one half the patients with a negative antibody test were included in the study and were assigned by random number table in double-blinded fashion to receive either erythromycin 250 mg four times a day for 10 days or a placebo that appeared identical. This procedure was followed because it was anticipated that 33% of the patients would have a positive test for *M pneumoniae*. To conserve resources, one half of the patients with negative tests were randomly excluded from further participation in the study. A power analysis performed before the study determined that at least 120 patients should be tested to detect an improvement of 30% at a power of .80 and $P<.05$ for a four-group comparison.

After enrollment, subjects were instructed on taking the medication and filling out a daily symptom diary using a Likert-type scale. Patients were allowed to use over-the-counter cough and cold medicines at their discretion and were asked to record their use on the daily diary. Subjects were called twice in the next 2 weeks to ensure compliance and to monitor the development of complications. A follow-up visit was scheduled for 14 to 18 days after the initial visit. The symptoms diaries were collected, unused pills were counted and returned, and a brief standardized history and physical examination was performed.

Data were collected from diary entries and by telephone calls. Using chi-square analysis, the treatment group was compared with the placebo group with respect to cough, chest congestion, use of cough medicine, general feeling of well-being, sleep, and amount of normal activities. Dropout rates and side effects were also compared between the two groups. Data were analyzed using logistic regression to determine the effect of other variables in treatment response, such as the presence of *M pneumoniae*, age, smoking status, purulence of sputum, and presence of abnormal physical examination findings.

Results

One hundred forty patients were screened and tested for *M pneumoniae*. Ninety-one were randomized to receive erythromycin or placebo. The average age of participants was 37 years. Sixty-five percent of the patients were female, 47% were nonwhite, and 35% were smokers. Initial characteristics of patients assigned to treatment and control groups are shown in the Table.

Patients treated with erythromycin missed an average of 0.81 ± 1.1 (SD) days of work, compared with 2.16 ± 3.2 (SD) days missed among patients treated with placebo ($P<.02$). This relationship was maintained when controlled for *M pneumoniae* serology status (Figure).

Patients' self-reported coughing frequency did not improve significantly faster in erythromycin-treated patients as compared with controls. Similarly, there were no significant differences in the use of cough medicine, general feeling of well-being, or chest congestion between the groups. Using logistic regression analysis, responses to erythromycin and placebo treatment did not differ

Table. Initial Characteristics of Erythromycin and Placebo Groups

Characteristic	Erythromycin Group, % (n=49)	Placebo Group, % (n=42)
Age (mean years±SD)	36 ± 13.0	38.2 ± 14.5
Sex (female)	67.3	64.3
Race (nonwhite)*	57.1	38.0
Smoking	31.2	38.1
Cough (mean number of days ±SD)	88.8 ± 7.6	7.7 ± 1.6
Purulent sputum	85.4	83.3
History of headache	44.9	53.7
History of fever	40.8	55.0
Initial temperature (>99.5° F)	8.1	12.2
Abnormal lung examination†	38.8	55.0
Tender anterior cervical nodes	16.3	27.5
Pharyngeal erythema	38.8	45.0

*$P < .05$.
†*Any diffuse or intermittent rales, rhonchi, or wheezing.*
SD denotes standard deviation.

based on age, race, sex, fever, smoking status, or presence of purulent sputum.

According to the initial antibody test, 25% of patients screened were positive for *M pneumoniae*. Among those enrolled, there were no significant differences between patients testing positive and those testing negative based on age, smoking status, fever, purulence of sputum, or other factors.

Fifteen percent of patients taking placebo and 36% of those taking erythromycin reported side effects or problems with the medicine at the first follow-up phone call between days 3 and 5 ($P<.04$). The most common problem was gastrointestinal upset, which was present in 26% of erythromycin patients and 5% of placebo patients ($P<.01$). Seventy-four percent of all patients returned for follow-up and pill counts (79% of the erythromycin group and 67% of controls). Of those who returned, 94% had taken one half or more of the medication.

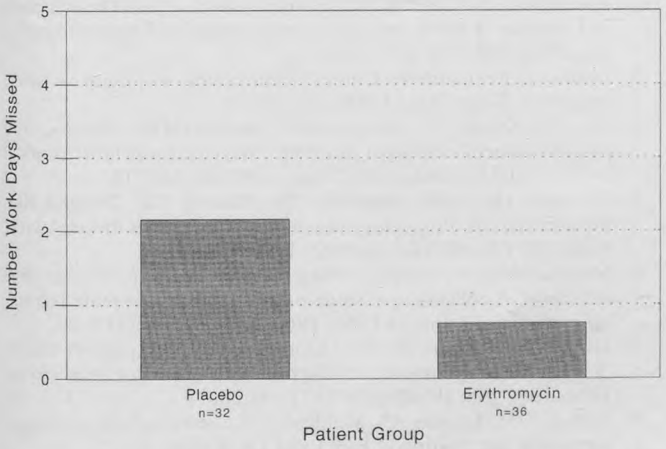

Figure. Average number of workdays missed, as reported by patients on follow-up visit.

Discussion

Although standard reference texts do not recommend routine use of antibiotics,[5,23,24] primary care physicians treat 70% to 93% of all episodes of acute bronchitis with antibiotics.[14,25,26] Most randomized controlled trials of antibiotics have yielded negative results, while a few have shown a small benefit from antibiotic therapy.[4] The rationale for the current study is rooted in evidence that *M pneumoniae* is one of the leading treatable causes of acute bronchitis, and that a rapid diagnostic kit to detect the presence of antibodies to *M pneumoniae* was recently developed. In an earlier study by King and Muncie,[22] 43% of outpatients with respiratory symptoms were positive for *M pneumoniae*, and 63% of those with scattered wheezes or rhonchi were positive.

The current study partially supports our primary hypothesis that erythromycin is effective in the treatment of unselected patients with acute bronchitis, as evidenced by treated patients missing fewer workdays. There was, however, no significant improvement in symptoms among patients taking erythromycin. The finding that patients treated with erythromycin miss significantly fewer workdays gives some support for the current practice by many primary care physicians of prescribing this antibiotic for acute bronchitis. Returning to work may be a surrogate for improved health status that is more valid than assessing individual symptoms. There may be other systemic symptoms besides cough and chest congestion that make untreated patients miss more work. The effect of erythromycin on individual symptoms was small and did not reach statistical significance.

The findings of this study did not support our secondary hypothesis regarding *M pneumoniae*. The presence of a positive test for *M pneumoniae* did not identify those who would most benefit from erythromycin: patients testing negative also improved and returned to work sooner. One possible explanation is that the positive predictive value (PPV) is not sufficient to identify those who would benefit. Assuming accuracy in the test sensitivity and specificity (95.1% and 86.3%, respectively) provided by the manufacturer and a prevalence of 25% for *M pneumoniae* among patients with acute bronchitis (range of previous studies, 5% to 43%),[19-22] the PPV would be 69.8%.[27] This would indicate misclassification of almost one third of the patients testing positive in the study and would reduce the chance to show a difference in the response to therapy of patients testing positive and those testing negative to *M pneumoniae*. The improvement seen in patients treated with erythromycin may be attributable to treatment of other susceptible organisms, such as *Chlamydia pneumoniae*. *C pneumoniae* may cause 3%

to 10% of acute bronchitis; rates of up to 22% have been seen in epidemics.[28–30]

Further, use of cold and cough medications may have affected the patients' reporting of symptoms, thereby masking the ability of the antibody test to predict who would have fewer symptoms while being treated with erythromycin. Also, recent evidence suggests that bronchodilators may reduce symptoms in patients with acute bronchitis[31]; however, such medications were used by only 12 patients in the current study.

Erythromycin's beneficial effects on patients with acute bronchitis may be mediated through nonantibiotic effects. Erythromycin can inhibit the excretion of caffeine and theophylline, prolonging their effects and enhancing their bronchodilator properties.[32] In addition, erythromycin may reduce bronchial hyper-responsiveness through direct anti-inflammatory action.[33]

Previous controlled trials have yielded mixed results regarding the effectiveness of antibiotics in acute bronchitis. Stott and West[13] found no benefits of doxycycline over placebo in patients with cough and purulent sputum of less than 7 days' duration. Williamson[14] also showed no benefit, despite adequate statistical power, and found no clinical indicators that could predict which patients might be helped by doxycycline. Franks and Gleiner,[11] however, showed marginal improvement in clinical outcome with use of trimethoprim/sulfamethoxazole. Brickfield[12] showed a trend toward improvement with erythromycin in 22 patients with acute bronchitis, but the results did not achieve statistical significance. Dunlay and colleagues[15] reported significant clinical improvement using erythromycin in 45 subjects. This is the most encouraging trial to date in support of the use of antibiotics for acute bronchitis, but the investigators concluded that further research is needed to determine which patients will benefit most from antibiotics.

Limitations of the current study include an insufficient number of patients to do multiple subgroup analyses. This may explain why this and previous studies have been unable to determine whether certain selected patients may benefit from antibiotics. Treating unselected patients may "dilute" a treatment effect. In addition, only 74% of patients returned for follow-up, despite telephone calls to increase compliance. The study was limited to one geographic area and may not be generalizable to other areas, especially if the prevalence of *M pneumoniae* and *C pneumoniae* is found to be geographically variable. Insufficient serum was available to do extensive secondary testing for confirmation of *M pneumoniae* antibody test results.

Future studies should employ a validated health status measure to further evaluate functional status and ability to return to work. Future studies should also evaluate newer macrolide antibiotics because of their advantages over erythromycin, ie, less gastrointestinal upset, shorter duration of therapy, and broader spectrum antibiotic coverage.[34]

The results of the current study add evidence to the findings by Dunlay and colleagues[15] that antibiotic treatment of patients who have acute bronchitis may be beneficial. The finding of a 25% prevalence of *M pneumoniae* in the current study, along with previous evidence of the presence of *C pneumoniae* in 3% to 22% of cases, suggests that some patients may have treatable acute bronchitis. Treatment helps patients miss fewer workdays and it also helps patients feel better somewhat sooner. The role of testing for *M pneumoniae* using the antibody test is currently unclear; however, the antibody test may be helpful in determining appropriate treatment when patients are not responding to initial therapy.

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