Erythromycin in the Treatment of Acute Bronchitis in a Community Practice

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To assess the efficacy of erythromycin in treating acute bronchitis, 52 adults were enrolled in a randomized trial comparing a one-week course of erythromycin with placebo. Among smokers, no difference in outcome was noted. Among nonsmokers, trends favored more rapid resolution of key symptoms in the erythromycin group, but these trends did not generally achieve statistical significance. These results suggest a trial with a larger sample size.

Acute bronchitis may be characterized as an acute inflammation of the tracheobronchial tree marked by cough and sputum production, with a clear chest radiograph and no evidence of extrapulmonary involvement.[1] A frequently made diagnosis in family practice,[2] this illness has recently received some attention with regard to its therapy. While most textbooks advocate a symptomatic treatment approach, antibiotic use is widespread.[3,4] Studies employing doxycycline, amoxicillin, and trimethroprim-sulfamethoxazole (TMP-SMX) combinations have been reported with variable results. Indeed, two studies using doxycycline showed no advantage to its use,[5,6] while another recent report noted some advantage to the use of TMP-SMX.[7] Review of prescribing habits in several practices has shown erythromycin to be prescribed frequently for acute bronchitis. This report presents the results of a randomized double-blind prospective trial comparing patient response to erythromycin with patient response to placebo in the treatment of acute bronchitis in smokers and in nonsmokers.

METHODS

The Fairfax Family Practice Center, located in the suburban Washington, DC, area, serves as a model office for the Department of Family Practice, Medical College of Virginia. Its 12,000-patient population is primarily white, middle class, and well educated. Residents provide approximately 85 percent of patient care.

Patients were recruited from August 1, 1983, through June 20, 1984, based on the following criteria: (1) clinical evidence of acute bronchitis of two weeks' or less duration, (2) no other primary sites of infection (sinusitis, otitis media, etc), (3) age 18 through 65 years, (4) no previous hypersensitivity to macrolide antibiotics, (5) no evidence of underlying pulmonary or hepatic disease, (6) no current pregnancy, (7) no current use of theophylline compounds, and (8) no recent antibiotic use.

Acute bronchitis was defined as a lower respiratory tract infection of two weeks' or less duration with sputum production and no evidence of pneumonia clinically or on chest radiograph. Fifty-two patients volunteered and were accepted into the study.

The study population was defined in relation to the larger group of practice patients with this disease entity. To assess disease prevalence and to generate a population group for demographic purposes, charts of all patients with the diagnosis of acute bronchitis recorded during the study period were reviewed. One hundred nineteen patients were identified who met the study criteria but had not entered the study.

After examination by a physician and informed consent, each participant had a chest radiograph taken (reviewed by a radiologist), and when possible, produced a sputum sample for Gram stain and culture. Gram stains were reviewed by the physician and the investigators and rated as purulent if there were more than five white cells (WBC) per high-power field (HPF) under oil-immersion lens. Cultures were sent to

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TABLE 1. CHARACTERISTICS OF STUDY POPULATION COMPARED WITH NONPARTICIPANT FAIRFAX FAMILY PRACTICE CENTER POPULATION WITH ACUTE BRONCHITIS

	Study Group (n=50)	Population with Bronchitis (n=119) Not in Study Group
Mean age (years)*	32.2	35.3
Sex (% female)*	50.0	66.4
Smokers (%)**	46.0	29.4

**No significant difference at the .05 level*
***Fischer's exact test yielded an observed significance level of .005*

a local commercial laboratory for processing and interpretation.

Each participant then received (on a random basis) a numbered, sealed bottle containing 21 tablets of either placebo or erythromycin base as 333 mg enteric-coated tablets (E-Mycin, Upjohn Company, Kalamazoo, Michigan) to be taken three times daily. Each participant also received a form to keep a daily record of symptoms. Each symptom was scored as 1 if resolved, 2 if improved, 3 if unchanged, and 4 if worse. The symptoms under inquiry were cough, sputum production, fever, headache, rhinorrhea, chest discomfort, earache, sore throat, disability for work, feeling ill, and nausea. Participants were reexamined on the eighth day of their participation, and log sheets and bottles with any remaining pills were collected at that time. Physicians recorded their impression of the participant's response.

Data were assessed based on analysis of patient-reported symptom scores for each day in the study. Mean daily scores for each symptom on each day of the study were computed, and the mean number of days until improvement (symptom scored 1 or 2) for each symptom was calculated. Both *t* tests and Wilcoxon tests were performed to analyze comparisons. Because the study group contained a disproportionate number of smokers when compared with all patients with bronchitis, all results were stratified by smoking status as well as by drug received, producing the following groups: nonsmokers receiving erythromycin, smokers receiving erythromycin, nonsmokers receiving placebo, and smokers receiving placebo.

RESULTS

Fifty-two patients received erythromycin or placebo, and 50 patients completed the study. One participant did not return for follow-up, and one patient withdrew from the study after one day. The study group contained a disproportionate number of smokers, and this difference was statistically significant (Table 1). This population also tended to be younger and more frequently were male compared with nonparticipants; however, these differences were not statistically significant. Most nonparticipants did receive antibiotics (85.8 percent), and the majority were prescribed erythromycin (78 percent). Fewer than 30 percent of eligible patients chose to enter the study, and physicians frequently noted in the chart that patients who opted not to participate in the study stated a strong preference to receive antibiotics.

TABLE 2. CHARACTERISTICS OF STUDY PATIENTS

	Erythromycin (n=26)	Placebo (n=24)
Mean age (years)	32.0	32.5
Sex (% female)	57.7	41.7
Smokers (%)	50.0	41.7

Twenty-seven participants received erythromycin, while 25 received placebo; one from each group withdrew. There were no significant differences between the two groups in age, sex, or smoking status, or in symptom characteristics at entry to study (Table 2). Productive cough, as an entry criterion, was present in all patients. The next most frequent symptoms were chest discomfort (80 percent), rhinorrhea (68 percent), and sore throat (60 percent). Fever and earache were much less common. Most patients reported feeling ill, and the majority noted a decreased ability to work. (Neither of these symptoms was precisely defined.) Other than pharyngeal inflammation, positive physical findings were uncommon. Nausea was reported at least once during the study by five patients taking erythromycin and nine receiving placebo.

Twenty-nine participants were able to produce sputum samples at study entry (56 percent). These were all cultured, yielding normal respiratory flora in all but two cases, one of which grew Hemophilus influenzae, the other Streptococcus pneumoniae. Gram staining was performed on 23 samples, 17 of which contained greater than 5 WBC/HPF. No viral studies were done.

The 140 statistical comparisons of mean daily symptom scores for the four analysis groups yielded 10 statistically significant differences, 6 favoring erythromycin, and 4 favoring placebo. At the .05 level one would expect seven statistically significant differences based on chance alone. All of the differences favoring erythromycin occurred in the nonsmoker group, and all of the differences favoring placebo occurred in the smoker group.

Nonsmokers receiving erythromycin generally tended to report lower scores for cough, sputum production, headache, and chest discomfort. Scores were statistically significantly lower for the erythromycin

group on days 3, 5, and 6 for cough, day 3 for sputum production, day 5 for headache, and day 6 for chest discomfort. There also was a trend favoring nonsmokers taking erythromycin in the "able to work" category on days 2 and 4 ($P < .10$), but this trend did not reach statistical significance. In no case did nonsmokers receiving placebo record significantly lower scores than those receiving erythromycin. The analysis of mean number of days until improvement also consistently favored the erythromycin group among nonsmokers, but the difference reached statistical significance only for sore throat. Figure 1 displays a trend for nonsmokers receiving erythromycin toward more rapid improvement in cough, sputum production, and work disability.

Among smokers, statistically significant differences favored placebo on day 1 for headache and on days 1, 2, and 3 for chest discomfort. Unlike the nonsmoker group, however, these differences were not part of any consistent trend. The analysis of mean number of days until improvement for smokers showed no significant differences between the treatment groups and suggested no consistent trend.

The physicians' assessments of outcome showed a tendency toward better outcomes in the erythromycin group as a whole, but that trend was not statistically significant. (Eighty-one percent receiving erythromycin resolved or improved vs 58 percent receiving placebo resolved or improved.) An intriguing fact is that 10 of the 22 patients who were judged resolved were in the nonsmoker receiving erythromycin group; however, this finding is not statistically significant given the small cell sizes. Nonsmokers who received erythromycin tended to fare better than their placebo-receiving counterparts (10 of 13 resolved vs 6 of 14 resolved, respectively), although this trend did not achieve statistical significance. In contrast, smokers showed little difference in the physician assessment between the erythromycin (3 of 13 resolved) and placebo (3 of 10 resolved) groups.

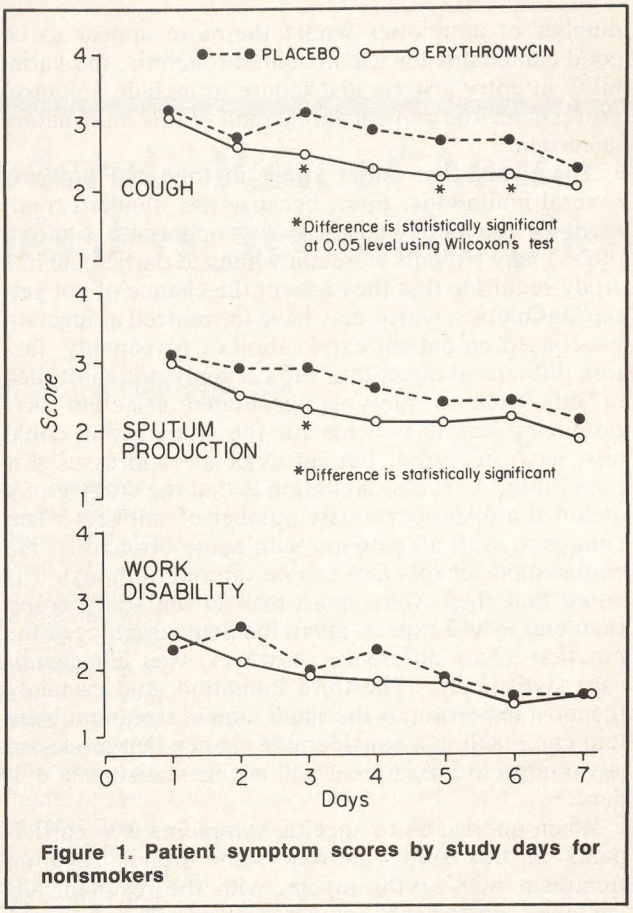

Figure 1. Patient symptom scores by study days for nonsmokers

DISCUSSION

Acute bronchitis is a self-limiting disease that from a theoretical standpoint does not require antibiotic intervention.[1] The use of antibiotics in this entity is nonetheless a widespread practice.[3,4] Few trials have compared the use of antibiotics with placebo, so that scientific justification for the use of antibiotics is scant.

Antibiotic use has been reported in a number of previous studies, but comparison is hampered by differences in entry criteria. Stott and West[5] compared a course of ten days of doxycycline to placebo in 207 patients with productive cough of up to one week's duration and normal findings on chest examination. They found no advantage to tetracycline and recommended against its use. Williamson[6] compared doxycycline to placebo and also found no advantage for the treated group. Franks and Gleiner[7] recently reported results of a comparison between TMP-SMX and placebo; a number of advantages were found for the group receiving antibiotics. That group performed better in duration of night cough, fever, and use of symptomatic measures. They found smoking history not to be helpful in predicting outcome.

Several trials comparing two antibiotics have been reported. Carroll et al[8] and Cooper et al[9] have compared TMP-SMX with amoxicillin in five-day regimens and found both to be effective. Chest roentgenograms, however, were not done routinely, and inclusion criteria required positive findings on lung examination. How well patients would have responded in this setting with no antibiotic treatment is unanswerable in these trials. Murphy et al[10] compared amoxicillin with lymecycline and also noted a good response in both groups; however, in this study entry criteria were not clearly stated. Pekkanen and Josefsson[11] compared two regimens of different enteric-coated erythromycin bases in a ten-day course, documenting good tolerances of the drug and clinical response rates similar to those reported here at reassessment. While a

number of antibiotics would therefore appear to be good candidates for use in acute bronchitis, the variability in entry criteria and failure to include a control group make the clinical application of this information uncertain.

The population under study in this trial presents several limitations. First, because the standard treatment for productive cough in the community is antibiotics, many patients were not willing to participate in a study requiring that they accept the chance of not getting antibiotics, which may have introduced a selection bias based on patient expectation or personality, factors difficult to quantitate and certainly not controlled in this trial. A physician-generated selection bias producing less ill patients for the study group could also have occurred, but no evidence addresses this possibility. A second limitation is that the study group included a disproportionate number of smokers when compared with all patients with acute bronchitis. No explanation for this fact can be offered, although it is noted that there were more men in the study group than one would expect, given the demographics of the practice. (This difference, however, was not significant statistically.) The third limitation, and certainly the most important, is the small sample size, a problem that can result in a considerable chance that moderate advantages to a treatment will not be statistically evident.[12]

When queried as to specific symptoms, the participants in this study showed some trends favoring treatment with erythromycin, with the resultant advantages prominent among nonsmokers. A trend toward more rapid improvement, as reflected by lower mean daily scores and by shorter mean number of days until improvement, was noted by nonsmokers receiving erythromycin for cough, sputum production, headache, chest discomfort, and work disability. In this study, smokers derived no benefit from erythromycin therapy when compared with smokers receiving placebo.

Improvements reported by patients coincided with physician assessment of participants. The data suggest that based on criteria physicians employ, recovery was to some extent a function of smoking status. When further broken down, a consistent trend emerged wherein nonsmokers receiving erythromycin showed the best clinical response, while smokers less frequently experienced resolution of the disease, regardless of antibiotic status. The majority of patients in both groups were judged to show at least some improvement, highlighting the benign nature of this illness. Both physicians' and patients' reports consistently showed trends favoring the nonsmoker receiving erythromycin group, trends that did not reach statistical significance.

Important features of this study included the universal chest roentgenograms and the sputum cultures. The chest films excluded the possibility of clinically occult cases of pneumonitis contaminating the study group. The sputum cultures grew pathogens in only two cases; whether this represented problems in collection, preservation, or transportation of specimens is unknown. Viral or mycoplasmal organisms may have been the etiologic agent in a large percentage of cases. This aspect of the study highlights the need for better characterization of the causes of acute bronchitis.

The very consistent trends favoring the erythromycin-treated group of nonsmokers suggest the need to address smoking status carefully in all future studies. Shortening the mean time to symptom improvement by one day or returning a patient to work one day sooner would certainly be clinically significant outcomes of a bronchitis treatment, and results of this order are here suggested but not statistically proven for nonsmokers. The results of this study argue strongly for new trials with larger sample sizes, if possible with a study population more amenable to withholding of antibiotics.

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