A Placebo-Controlled, Double-Blind Trial of Erythromycin in Adults With Acute Bronchitis

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Sixty-three otherwise healthy adults with acute productive cough and no clinical evidence of pneumonia were randomized to receive a ten-day course of erythromycin or placebo. Fifty-seven of these patients returned completed symptom diaries or returned for a two-week follow-up visit. Patients treated with erythromycin reported a more rapid improvement in subjective ratings of cold symptoms, general health, sputum production, and a mean symptom score. Fewer patients in the erythromycin group required cough or cold medications or were congested by day 10 ($P < .05$). The treatment group was also less likely to have purulent sputum (9 percent vs 36 percent, $P < .05$) and abnormal lung examinations (0 percent vs 29 percent, $P < .01$) at a two-week follow-up visit. These results support the use of erythromycin in acute bronchitis.

Acute bronchitis is generally defined as the presence of acute productive cough in patients without underlying lung disease who have no clinical evidence of pneumonia. Acute bronchitis ranks among the ten most frequent office diagnoses.[1,2] It has been estimated that approximately 12 million physician visits are made each year for this illness at a cost of $200 million to $300 million.[3]

Despite the frequency of acute bronchitis, its treatment remains controversial. It is generally agreed that antibiotics are indicated in acute exacerbations of chronic bronchitis. Antibiotics are not generally recommended for acute bronchitis, however, because it is usually considered to be a viral illness.[4] In spite of these recommendations, antibiotics are frequently prescribed.[3,5]

The use of antibiotics in the treatment of acute bronchitis has not been fully evaluated, and the few well-controlled clinical trials have yielded conflicting results.[5–8] A double-blind, placebo-controlled trial was undertaken to determine whether treatment with erythromycin prevents complications or results in more rapid resolution of symptoms. Erythromycin was chosen because it achieves excellent penetration into sputum and is effective against most common respiratory pathogens.[9]

Submitted, revised, February 18, 1987.

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METHODS

The University of Michigan Family Practice Center is located in a small town in a semirural area. Patients are predominantly white and are mainly from lower and middle socioeconomic backgrounds. Family practice residents, physician faculty, and a physician assistant provide care.

Patients were eligible for the study if they were 18 years of age or older and were experiencing a productive cough. They were excluded for any of the following: pregnancy, erythromycin allergy, chronic lung disease including asthma or chronic obstructive pulmonary disease, treatment with a systemic antibiotic in the past two weeks, or clinical evidence of an infection usually treated with an antibiotic such as pneumonia or sinusitis. No radiographic or laboratory studies were required for entry into the study.

After determining eligibility and obtaining informed consent, the patient's primary care physician recorded certain demographic and clinical characteristics, performed a limited physical examination, and visually examined a sputum sample for purulence. Patients were then given the next in a numbered sequence of medication bottles containing a ten-day course of either an enteric-coated erythromycin base (E-mycin, [UpJohn] 333 mg three times a day, the recommended dose for respiratory infections) or an identical-looking placebo. The medication bottles were randomized in blocks of eight by the manufacturer, and neither the patient, the physician, nor

TABLE 1. PATIENT CHARACTERISTICS AT THE TIME OF ENTRY INTO THE STUDY

Patient Characteristics	Placebo (n = 31)	Erythromycin (n = 32)
Patient history		
Male (%)	42	41
Average age (years)	44	43
Smokers (%)	42	34
Duration of cough (days)	7.2	7.1
Duration of sputum production (days)	5.4	6.2
Purulent sputum (%)	84	81
Physical examination		
Temperature > 100.5°F (38°C) (%)	3	0
Abnormal lung examination (%)	19	16
Produced sputum sample (%)	26	35
Produced purulent sputum (%)	13	25

the investigators were aware of their true contents. The physician who enrolled the patient was free to prescribe or recommend any cough or cold preparation.

The patient completed the first page of a symptom diary during the initial visit and was instructed to complete a subsequent page at the end of each of the next nine days. Each page of the diary contained two sections of questions about the patient's symptoms. In the first section the patient rated five symptoms (day cough, night cough, sputum amount, congestion, and general health) on a scale of 1 to 5 with 5 representing maximum severity. Scores from all five scales were later averaged to calculate the symptom mean. In the second section the patient indicated the presence or absence of seven symptoms (day cough, night cough, sputum production, congestion, sore throat, felt poor, and unable to work or carry out daily routine). Other questions in the diary evaluated compliance with the study medication, side effects, smoking habits, and the use of cough or cold medications for symptomatic relief.

Patients were called twice during the ten-day study period to monitor compliance and check for the development of complications. A follow-up visit with one of the investigators was scheduled for approximately 14 days after the initial visit. At the follow-up visit clinical characteristics were again elicited, a limited physical examination was performed, the sputum was visually inspected, and any unused pills were returned and counted.

The chi-square test was used for statistical analysis of discrete data. Fisher's exact test was used instead of chi-square when the expected number in any cell was less than five. Diary means on days 2 to 10 were compared using covariance analysis adjusting for the ratings on day 1.

RESULTS

Sixty-three patients were enrolled in the study from November 1983 to April 1984, and from November 1984 to May 1985. There were no statistically significant differences between the patients enrolled in 1983 to 1984 and those in 1984 to 1985 or between the placebo (n = 31) and erythromycin (n = 32) groups at the initial visit (Table 1). Eighty-three percent of all patients reported purulent sputum and 32 percent produced a sputum sample. Only one patient was febrile. Seventeen percent of the patients had abnormal lung examinations, mostly scattered rhonchi or wheezes. No patients had lung examinations suggestive of pneumonia, and the abnormal findings were evenly distributed between the placebo and erythromycin groups.

Six patients, one treated with erythromycin and five with placebo, did not return their diaries or come back for their follow-up examinations. An additional nine patients stopped taking their medication during the ten-day period. Four of these, all treated with erythromycin, discontinued their medication because of gastrointestinal side effects. The other five (three erythromycin, two placebo) had various reasons for stopping their medication such as "forgot" and "didn't help." These nine patients provided partial data sets because they either returned incomplete diaries or came back for follow-up visits. The data were analyzed with (n = 57) and without (n = 48) these partial data sets, with equivalent results. Neither those patients who were lost to follow-up nor those patients who discontinued their medication were different from the overall patient group in any of the entry characteristics noted in Table 1.

Data from the 48 patients with complete data sets are presented. Compliance among these patients was equal in the placebo and erythromycin groups as measured by the number of pills returned at the follow-up visit and by responses in the diaries to questions about pills taken daily. Forty-five of these 48 patients returned for their follow-up visit.

Each of the five symptom severity scales from section 1 of the patient diaries, as well as the calculated symptom mean, showed more rapid improvement in the erythromycin group than in the placebo group. This difference was statistically significant at the .05 level or greater for most days from day 6 to 10 for three of the scales (sputum production, cold symptoms, and general health) and for the symptom mean (Figure 1). The differences were not statistically significant for the day and night cough scales

(not displayed). Smoker (n = 14) and nonsmoker (n = 34) symptom severity scores were not statistically different on any day.

The results for day 10 from section 2 of the diaries are listed in Table 2. Fewer patients treated with erythromycin reported each of the symptoms, and this difference was significant at the .05 level for congestion. These differences were not present on day 1.

The percentage of patients who took cough and cold medications for symptomatic relief is shown in Table 3. Fewer patients in the erythromycin group took cough and cold medications from days 5 to 10, and this difference was significant at the .05 level on day 10. Although the cough medicines prescribed were not standardized, approximately the same proportion of patients in both groups received medication containing codeine.

The results of the two-week follow-up visit are shown in Table 4. Fewer patients treated with erythromycin reported purulent sputum (9 percent vs 36 percent, $P < .05$) and fewer had abnormal lung examinations (0 percent vs 29 percent, $P < .01$).

No infectious or respiratory complications occurred in any patients for whom follow-up data were obtained (n = 57). In addition, there were no reported complications in the six patients who were lost to follow-up, several of whom were later contacted by telephone.

DISCUSSION

In this study the diagnosis of acute bronchitis was based on history and physical examination alone, an approach consistent with standard clinical practice, although it may have resulted in the inclusion of a few patients with undetected pneumonia or sinusitis. Adding radiographs or sputum studies to the entry criteria may have enhanced specificity; however, these studies are expensive and are not generally performed in the evaluation of acute bronchitis.

The 63 patients enrolled in the study represented approximately 20 percent of the patients diagnosed with acute bronchitis during the study period. This low enrollment rate is probably due to the belief of many patients (and their physicians) that antibiotics are a proven remedy for acute bronchitis, rather than the introduction of any systematic bias. In fact, a chart review that was conducted after the first bronchitis season showed that patients enrolled in the study were similar in age and sex, and had findings on examination for temperature, the presence of purulent sputum, and lung abnormalities similar to those of a random sample of patients who were not enrolled.

The results of the study indicate that adults with acute bronchitis recover more rapidly when treated with eryth-

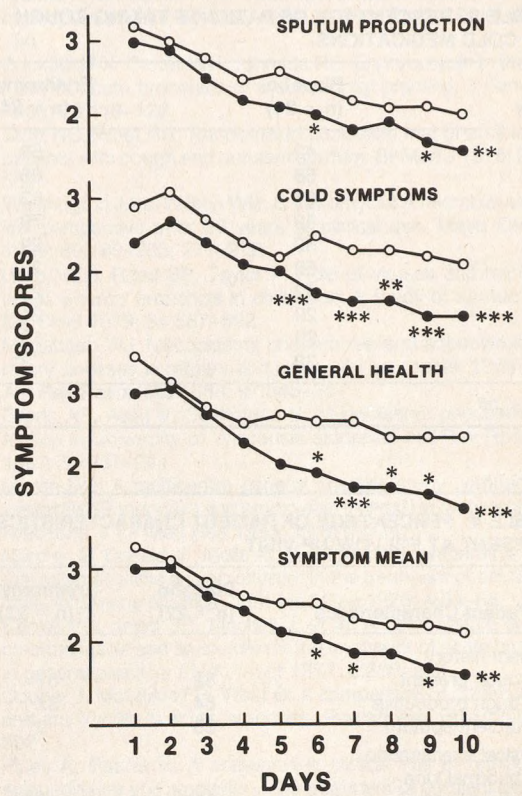

Figure 1. Mean symptom scores for patients treated with placebo (open circles, n = 24) and erythromycin (closed circles, n = 24 on days 1 through 9, n = 21 on day 10). *P < .05 **P < .01 ***P < .005

TABLE 2. PERCENTAGE OF PATIENTS WITH SYMPTOMS PRESENT ON DAY 10

Symptom	Placebo (n = 24)	Erythromycin (n = 21)
Day cough	67	62
Night cough	58	33
Productive cough	71	48
Congestion	75	38*
Sore throat	25	5
Felt poor	30**	14
Unable to work or carry out daily routine	13**	5***

* $P < .05$
** $n = 23$
*** $n = 20$

TABLE 3. PERCENTAGE OF PATIENTS TAKING COUGH OR COLD MEDICATIONS

Day	Placebo (n = 24)	Erythromycin (n = 24)
1	42	63
2	58	88
3	67	63
4	63	79
5	50	29
6	50	33
7	42	25
8	29	21
9	29	13
10	38	3*

* $P < .05$

TABLE 4. PERCENTAGE OF PATIENT CHARACTERISTICS PRESENT AT FOLLOW-UP VISIT

Patient Characteristics	Placebo (n = 22)	Erythromycin (n = 23)
Patient history		
Cough present	82	61
Cough productive	64	57
Purulent sputum	36	9*
Physical examination		
Abnormal lung examination	29**	0***
Produced sputum sample	24**	14**
Produced purulent sputum	10**	0**

* $P < .05$
** $n = 21$
*** $P < .01$

romycin. Statistically significant differences favoring the erythromycin group were found in most of the symptom severity scales on days 6 to 10, after the antibiotic had taken effect. In addition, by the end of the study fewer patients treated with erythromycin noted the presence of congestion or purulent sputum, required medications for symptomatic relief, or had abnormal lung examinations.

It is not clear which pathogens are being treated by erythromycin. One recent study found Streptococcus pneumoniae and Hemophilus influenzae in only two of 29 sputum samples from adults with acute bronchitis.[7] No pathogenic bacteria were found in the other 27 samples, a finding consistent with the results of an earlier study that showed bacterial pathogens to be found rarely in children with bronchitis.[10] Another potential pathogen is mycoplasma. Evidence of mycoplasma infection has been found in 10 to 20 percent of university students with acute bronchitis.[11,12] Although not addressed in the current study, the microbiologic aspects of acute bronchitis define an area that warrants further investigation.

Although several studies of acute bronchitis compare one antibiotic with another,[13–18] there are only four double-blind studies comparing antibiotics with placebo. One of these studies showed more rapid improvement in patients treated with trimethoprim-sulfamethoxazole.[6] Patients who received the antibiotic had more rapid resolution of their symptoms and missed fewer days of work. Another study of erythromycin in acute bronchitis showed a positive antibiotic effect in a group of 27 nonsmokers.[7] The study reported here showed a more rapid reduction of symptoms in the erythromycin group regardless of smoking status, and the larger sample size (n = 63) enabled greater statistical significance to be achieved in several of the measurements.

That the two remaining studies used doxycycline and did not show an antibiotic effect[5,8] may be due to differences in the antibiotics or in the study protocols. One doxycycline study treated patients for only seven days.[5] In the study reported here, much of the antibiotic effect was seen on days 8 to 10, and this late improvement would have been missed. The other doxycycline study excluded patients who had symptoms for greater than one week or who had abnormal lung examinations.[8] By using more restrictive eligibility criteria, this study may have selected patients who were less ill and therefore more likely to have viral infections.

Despite the more rapid improvement in the erythromycin group, 61 percent continued to have some cough at the two-week follow-up visit. This finding was also noted in another study, which followed patients until their symptoms had completely resolved.[5] One half of these patients coughed for two weeks, and one quarter were still coughing after three weeks. These persistent symptoms indicate that the infectious process is not the only cause of cough in acute bronchitis. Patients who continue to cough may have developed the heightened airway reactivity of postinfectious bronchitis.[19] Alternatively, some patients diagnosed with acute bronchitis may actually have asthma.[20] Patients with either postinfectious bronchitis or asthma would benefit from bronchodilators.

It is becoming clear that acute bronchitis may have several causes. Some patients respond to antibiotics, some to bronchodilators, and some to cough suppressants. Further research is needed to help the physician identify which patients will respond to which therapy. A first step might be to study a group of patients with pulmonary function tests, radiographs, and sputum studies. Results from such a study would help clarify the role of infection and bronchoconstriction in acute bronchitis.

The decision to prescribe antibiotics in acute bronchitis involves weighing the potential risks and benefits. On the one hand, studies that follow patients for prolonged pe-

riods of time show that patients eventually recover whether treated with an antibiotic or not.[5,8] The development of pneumonia or other complications has not been reported.[5–8] The expense and potential side effects of antibiotics must also be considered. Thirteen percent of the patients in the current study who were treated with erythromycin discontinued the medication because of gastrointestinal side effects.

On the other hand, patients treated with erythromycin did recover more quickly than patients treated with placebo. These results are also consistent with those of a previous study of erythromycin in acute bronchitis.[7] Certainly further research is needed to try to separate those patients who will benefit from antibiotics from those who will not. At the present time, however, these results support the use of erythromycin in acute bronchitis.

Acknowledgment

The Upjohn Company, Kalamazoo, Michigan, provided the erythromycin and placebo used in this study.

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