A Randomized, Controlled Trial of Doxycycline in the Treatment of Acute Bronchitis

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Acute bronchitis is a common reason for visits to primary care physicians and a commonly given reason for antibiotic treatment. However, evidence regarding the efficacy of antibiotics for this syndrome is lacking. In a randomized trial, a one-week course of a frequently used antibiotic, doxycycline, was compared with one week of placebo in 74 otherwise healthy adults with acute bronchitis.

The doxycycline group fared no better than the placebo group for all 13 outcomes measured, including duration of cough, clinical improvement at one week, return visits for unresolved symptoms, days away from work, and subjective ratings of cough severity, sleep loss, diminished activity and overall well-being.

Doxycycline is not beneficial in the treatment of acute bronchitis in otherwise healthy adults.

Acute bronchitis is a clinical syndrome characterized by cough and sputum production, accompanied by upper respiratory tract and systemic manifestations of infection. It is a common illness, consistently ranking as one of the most frequently made diagnoses by primary care physicians.[1-5]

Acute bronchitis is believed to be caused by infection of the bronchi and often occurs in persons with no underlying lung disease. It can be induced in volunteers who inhale rhinovirus[6] and is sometimes associated with evidence of respiratory syncytial virus, rhinovirus, parainfluenza virus, influenza virus, adenovirus, and enterovirus infection.[7-9] Five to 10 percent of bronchitis cases in college students,[10,11] young airmen,[12] and patients in a prepaid health plan[13] were associated with laboratory evidence of mycoplasma infection.

Although many believe that acute bronchitis is solely a viral disease, others believe that bacterial superinfection is common. Potentially pathogenic bacteria can be cultured from the sputum or pharynx of many acute bronchitis patients,[14] but the distribution of organisms is not strikingly different from oropharyngeal flora of normal persons.[15-17] Unfortunately, there is no inexpensive, safe, and effective method for accurately establishing the causal agent of acute bronchitis in clinical practice. Acute bronchitis has, therefore, been considered a clinical diagnosis without specific regard to the type of infectious agent.

Antibiotic use for acute bronchitis is common but is not supported by evidence of efficacy. In

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a survey of 44 rural medical practices in New England, bronchitis was the second most common diagnosis resulting in antibiotic treatment; about 70 percent of episodes of bronchitis were treated with antibiotics.[18] Likewise, a survey conducted by the author demonstrated that Missouri primary care physicians prescribe antibiotics for about 75 percent of their patients with acute bronchitis. Several clinical trials have compared one antibiotic with another in the treatment of acute bronchitis,[14,19,20] but only one controlled trial comparing antibiotic treatment with placebo was found in an extensive literature review. Stott and West compared doxycycline with placebo in patients with cough and purulent sputum of less than seven days' duration.[21] No benefit was found with antibiotic treatment. Despite this finding, the use of antibiotics in the management of acute bronchitis is widespread.

It is important to clarify further the role of antibiotics in this common syndrome and to confirm or deny their value. The efficacy of doxycycline was chosen for study because of that drug's convenient dosing schedule, low incidence of side effects, and spectrum of activity against common respiratory pathogens, and because tetracycline drugs are frequently used for acute bronchitis.

This study differs somewhat from that of Stott and West. They enrolled only patients with purulent sputum who were ill for less than one week, excluded patients with rhonchi, and followed patients for only two weeks. A pilot study indicated that only one half of patients with this syndrome resolved their cough within two weeks. Furthermore, a questionnaire regarding this syndrome and completed by about 100 Missouri primary care physicians revealed that rhonchi or cough of more than one week were criteria frequently used to justify prescription of antibiotics. Many physicians also indicated that white or clear sputum would not deter them from prescribing antibiotics. This information was incorporated in the current study to better test a current standard of practice for this syndrome.

Methods

Selection of Subjects

The study was conducted at two family medical care centers associated with the University of Missouri Hospitals and Clinics. Data collection was begun in September 1981 and completed in February 1983.

Patients were referred to the investigator at the discretion of the primary provider who made the diagnosis of acute bronchitis. The investigator then interviewed and examined the patient to determine eligibility. Those included in the study were persons aged 21 to 65 years who gave informed consent, had cough and sputum production as prominent complaints, and had concurrent upper respiratory tract infection, rhonchi, or history of fever. Patients were excluded if there were contraindications to doxycycline, underlying heart or lung disease including asthma and chronic bronchitis (cough productive of sputum on most days for at least three months of the year for more than two years), antibiotic use in the prior ten days, temperature above 39.5° C, history of pneumonia in the preceding six months, signs of consolidation on chest examination, recent inhalation of irritating dusts or fumes, or signs or symptoms of sinus infection. Laboratory tests and roentgenograms were done at the discretion of the primary provider and were not a routine part of the study.

A sample size of 36 subjects per group was calculated[22] as sufficient to detect a 30 percent reduction in cough duration with $\alpha < .05$ and $\beta < .20$.

Design

Patients referred to the study were given a spoken and written explanation of the trial and its potential risks; a consent form was signed if the patient agreed to the conditions of the study. Subjects were then sequentially assigned a trial number previously allocated to either placebo or doxycycline by use of a random numbers table. The trial was double-blind, with neither investigator nor subject aware of the identity of the assigned medication.

Data were collected at the patient's first visit for acute bronchitis, at a seven- to ten-day follow-up interview, and at weekly intervals by telephone until the syndrome was resolved. The standardized protocol used included age, sex, smoking history, duration of cough, character of sputum, respiratory and systemic symptoms, vital signs, and physical examination findings.

Each subject was instructed in the use of antipyretics, fluids, rest, and nonprescription cough

medications. After an explanation of potential risks and benefits, some patients requested and were given a prescription for a codeine-containing antitussive medication.

Each subject received a one-week course of therapy consisting of eight trial drug capsules, with instructions to take three doses at 12-hour intervals over the first 24 hours, then one dose daily thereafter. Capsules were to be taken with milk or food. The capsules appeared to be identical but contained either placebo or 100 mg of doxycycline.

Subjects were also given a symptom diary and asked to rate the following characteristics on a ten-point scale each day for seven days: general sense of well-being, bother of cough, interruption of sleep by cough, and limitation of activity, as well as presence or absence of a feverish feeling, the color of the sputum, and the number of doses of codeine-containing antitussive medicine taken.

Patients were then seen seven to ten days later by the investigator, who ranked clinical improvement on a five-point scale and recorded information about clinical response, drug side effects, use of antitussives, and work absence during the trial period. If patients in either group were not much improved at the follow-up visit, they were given the option of receiving an antibiotic prescription without breaking the code. Some patients, therefore, received two courses of antibiotic therapy.

Weekly telephone calls to estimate the duration of the illness were then made until the acute bronchitis syndrome was completely resolved. A chart review was also done to detect complications over the subsequent two months.

A chart review of 18 patients with acute bronchitis seen during the study period and fitting the selection criteria but not referred to the trial was performed to assess potential selection bias.

Data Analysis

Outcome variables included duration of cough, days absent from work, complications, clinical impression at follow-up visit, doses of antitussive medication, feverish days, days of purulent sputum, perceived need for antibiotic at the follow-up visit, unscheduled return visits, severity of cough, loss of sleep from cough, activity level, and overall sense of well-being. Statistical analysis was accomplished with the chi-square and *t* test (one-sided).

To assess whether doxycycline might have greater efficacy in some subgroups, the outcome variables were also compared after stratification by various combinations of entry characteristics and by scores on a composite severity index. This index score was created by assigning one point to each of the following entry characteristics: smoking history, cough of more than ten days' duration, production of yellow or green sputum, temperature of 38° C or greater, and rhonchi on lung examination. These points were added to create a severity index score ranging from 0 to 5.

Results

Seventy-four patients were enrolled in the trial: 39 in the doxycycline group, and 35 in the placebo group. Sixty-nine patients provided adequate data for analysis. Data from one subject with exercise-induced asthma were excluded, two patients were dropped after three days at their request, and data were incomplete for two other subjects who did not return for the follow-up appointment and who could not be reached by telephone.

The patients entered in the trial were compared with patients seen in the practices during the study period who fit the inclusion criteria but who were not referred to the study. The nonparticipant group was similar to the participant group for all characteristics measured.

The placebo and doxycycline groups were nearly identical with respect to pertinent demographic and clinical entry characteristics (Table 1). Outcome characteristics of the two groups are displayed in Tables 2 and 3 and in Figures 1 and 2.

No significant differences between the two groups were found for duration of cough, doses of antitussive medication, feverish days, or days of purulent sputum. Patients in the placebo group missed fewer days of work than those in the doxycycline group (0.6 days vs 1.5 days, $P = .03$). Three patients in the placebo group and four patients in the treatment group made unscheduled return visits because of unresolved cough; clinical evaluation revealed no evidence of pneumonia, and all seven patients experienced resolution of cough within two weeks of the unscheduled visit. Four patients in the placebo group and eight patients in the doxycycline group requested and received an antibiotic prescription at the follow-up visit. No patient was hospitalized and no signifi-

Table 1. Comparability of Groups at Entry

Characteristic	Placebo Group (n = 35)	Doxycycline Group (n = 39)
Mean age (yr)	35	32
Sex (men/women)	12/23	17/22
Cigarette smoker (%)	34	31
Cough, mean duration (d)	10.4	8.0
Purulent sputum (%)	84	92
Mean temperature at visit (°C)	36.7	36.9
Rhonchi on examination (%)	27	27
Cough medicine prescribed (%)	42	46
Mean severity index score	1.9	1.7

Table 2. Outcome Variables—Control vs Treatment Groups

Characteristic	Placebo Group (n = 32)	Doxycycline Group (n = 37)	P
Work absence, days during trial	0.6	1.5	.03
Cough duration (d)	18.2	20.1	.50
Doses of antitussive	5.0	4.7	.85
Feverish days during trial	1.2	1.4	.71
Days of purulent sputum	3.3	3.5	.65
Antibiotics at follow-up visit (%)	12	24	.19
Unscheduled return visits (%)	9	13	.69

cant complications were noted during the trial or during a chart review. These outcomes are summarized in Table 2.

Figure 1 displays graphically the mean symptom diary scores for four self-rated variables on each of seven days. There were no statistically significant differences in overall sense of well-being, interruption of sleep, bothersomeness of cough, or limitation of activity for any day and no trends are noted.

The curves in Figure 2 represent the time course of cough resolution for the two groups. The time of resolution was similar in the two groups; about 45 percent of the subjects were still coughing two weeks after entering the trial and about 25 percent were still coughing after three weeks.

Table 3. Clinical Evaluation at Follow-Up Visit

Clinical Evaluation	Placebo Group (n = 32) Percentage	Doxycycline Group (n = 37) Percentage
Worse	0	0
Same	3	6
A little better	30	35
Much better	67	56
Well	0	3
($\chi^2 = 2.0$, $df = 4$, P = .57)		

The distribution of clinical improvement ratings at the seven- to ten-day follow-up visit is similar for the two groups and is demonstrated in Table 3. A chi-square analysis showed no statistical difference for these distributions.

Several subgroups of patients were analyzed to assess the effect of doxycycline on patients prone to more severe disease. These subgroups included individuals with cough of more than ten days' duration at entry, those aged over 35 years, those who were cigarette smokers, those with rhonchi on chest examination, those with purulent sputum, and those with a severity index score of 3 or greater. The doxycycline subgroups fared no better than the control subgroups on any of the outcome parameters.

Presumed side effects of treatment, including nausea, vomiting, skin rash, and vaginitis, were more common in the doxycycline group. The differences were not statistically significant, however.

One might question whether the lack of effect in the treatment group might be due to inadequate sample size. A standard formula[22] was used to calculate β for two outcome variables—cough duration and clinical evaluation at one week. The likelihood of missing a clinical effect as great as a 20 percent difference was very low (power > 0.8).

Discussion

The trial was designed to test the use of doxycycline in the clinically defined syndrome

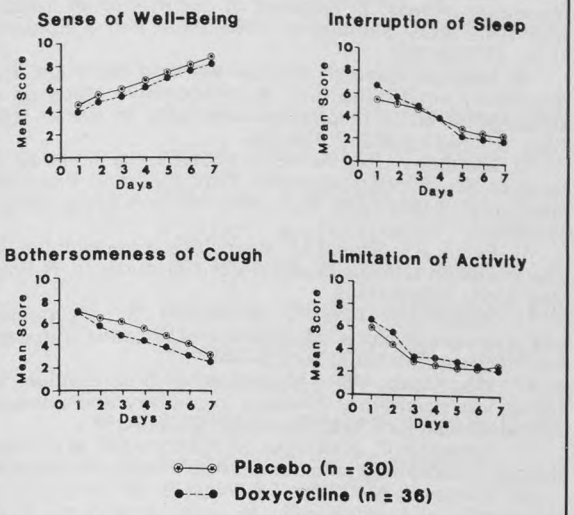

Figure 1. Mean score from symptom diary (vertical axis) vs day of trial (horizontal axis) for each of four self-assessed variables. P > .05 for all differences

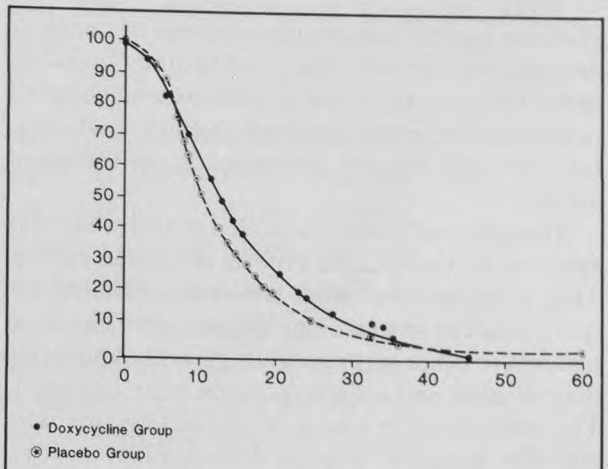

Figure 2. Time course of the resolution of cough: percentage with unresolved cough (vertical axis) vs day of trial (horizontal axis)

of acute bronchitis, with the diagnosis made in the way physicians generally make it. One might question the decision not to perform diagnostic tests in the study patients; several reasons led to this decision. Laboratory tests and chest roentgenograms are not routinely done in clinical practice. Sputum cultures and Gram stains are expensive and cumbersome and may not accurately identify organisms in the middle and lower respiratory tract.[23] Direct sampling for cultures from the lower respiratory tract is not justifiable in this self-limited disease. Virologic studies are expensive and not generally available and cannot be performed within a clinically useful length of time. Mycoplasma is associated with perhaps 5 to 10 percent of acute bronchitis episodes in young adults,[10-13] but probably with a much lower frequency in older adults.[24] Cold agglutinin titers can be done rapidly in an attempt to identify mycoplasma infections, but false-positive and false-negative tests are common[11,25] and the utility of cold agglutinin titers has not been tested in this disease. Chest roentgenograms for patients with acute cough very rarely result in changes in management or outcome.[26] It is, thus, unlikely that any currently available laboratory technique provides valuable diagnostic and therapeutic information in a cost-effective, safe, accurate manner.

Doxycycline was chosen for this trial because of its convenient dosing schedule, its favorable bioavailability,[27] its ability to penetrate the respiratory tract[28,29] and its spectrum of activity against common respiratory pathogens. Streptococcus pneumoniae, Hemophilus influenzae, and mycoplasma are the organisms most often believed to be treatable etiologic agents, and these organisms are sensitive to doxycycline at the respiratory tract levels achieved with the dosage used.[29,30] It must be emphasized, however, that there is no compelling evidence to implicate these specific agents.

Though not a primary objective of this study, the subjects enrolled in both groups provided an unusual opportunity to observe the natural history of acute bronchitis. Several clinical points of relevance emerged. The duration of the illness was much greater than anticipated. Nearly one half of the subjects coughed for two weeks or more after seeing the physician; 25 percent were still coughing after three weeks. Although bothersome symptoms steadily ameliorated over the first few days, only one person was back to normal after one week. There were no important complications or hospitalizations, and no patient was observed to develop pneumonia. Acute bronchitis thus seems to be a troublesome, prolonged illness with a happy ending.

The findings of this study are consistent with those of Stott and West, who compared doxycycline to placebo in the syndrome of cough and purulent sputum and found no benefit to treatment with the antibiotic.[21] Their study included only patients with symptoms of less than seven days'

duration and did not include duration of cough as an outcome variable. The present study found no benefit from doxycycline in patients with cough of more than ten days' duration at entry, and duration of cough was not shortened in the treatment group.

The group of patients enrolled in this study was selected by the specific criteria described earlier. They were recruited from university-affiliated primary care centers and may or may not differ from patients in other settings. Patients with underlying lung disease and elderly persons were excluded. The analysis of a group of nonparticipants who met the selection criteria demonstrated no evidence of selection bias. The randomization procedure produced two groups with nearly identical entry characteristics. It seems reasonable to conclude that these findings are generalizable to other settings.

Primary care physicians are frequently confronted by the patient with a bothersome, productive cough accompanied by upper respiratory tract infection. Often such patients are treated with antibiotics in hopes that any bacterial component of the infection can be minimized. No benefit was found with antibiotic treatment during an extensive evaluation of outcome variables. No trends favoring doxycycline use were noted even in the "sicker" groups, and no clinical parameters were able to define subgroups that benefited from doxycycline. The common clinical practice of prescribing antibiotics for patients with acute bronchitis is not supported by this study.

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