The Treatment of Acute Bronchitis With Trimethoprim and Sulfamethoxazole

Peter Franks, MD, and J. Arthur Gleiner, MD
Rochester, New York

Sixty-seven previously healthy patients with acute bronchitis were randomized and treated with either a fixed dose of trimethoprim and sulfamethoxazole or placebo for seven days. All outcomes examined showed a trend favoring the use of antibiotic, with statistically significant differences for cough, night cough, mean temperature, and use of antihistamines or decongestants. Night cough occurred on 84 percent of nights in the control group vs 56 percent in the antibiotic group ($P = .003$). Cough occurred on 99 percent of days for patients in the control group vs 93 percent of days for patients in the antibiotic group ($P = .05$). Mean temperature over the seven nights was 37.3° C in the control group vs 36.9° C in the antibiotic group ($P = .004$). The use of antihistamines and decongestants was reduced from 32 percent of days in the control group to 6 percent of days in the antibiotic group ($P = .005$). Patients in the antibiotic group worked 73 percent of days vs 55 percent of days for patients in the control group, which was significant when patients were stratified by the appearance of their sputum on Gram stain ($P = .006$). Smoking history was not found to help predict the response to antibiotic therapy.

Acute bronchitis in previously healthy adults is a frequently encountered problem in general medical practice. Acute bronchitis is usually defined clinically, based on history and physical examination, as acute cough with sputum in the absence of pneumonia. Antibiotics are often prescribed empirically, usually without laboratory confirmation of pathogenesis. Despite the wealth of data demonstrating the usefulness of antibiotics in treatment of acute exacerbations of chronic bronchitis, there are few data to support the routine use of antibiotics in acute bronchitis. Most studies that have purported to demonstrate the effect of antibiotics have compared two or more antibiotics without placebo control.[1-10] Data from these studies do not clearly support preference for any single agent and shed no light on whether there is any benefit of antibiotic compared with placebo. The only placebo-controlled study[11] showed doxycycline to be no more effective than placebo in reducing the duration of cough, sputum production, or time lost from work. Since antibiotic therapy carries actual and potential costs to the patient, it is essential to demonstrate that the routine use of antibiotics for this illness is justified.

Several antibiotics are reasonable choices for treatment of acute bronchitis based on their in vitro activities and evidence of clinical safety.[12-15] The combination of trimethoprim and sulfamethoxazole was studied because of theoretical advantages over other commonly used antibiotics.[15-18] These advantages include excellent absorption, achievement of tissue and sputum levels equal to

From the Department of Preventive, Family, and Rehabilitation Medicine, and the Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York. Requests for reprints should be addressed to Dr. Peter Franks, The Family Medicine Program, 885 South Avenue, Rochester, NY 14620.

or greater than serum levels, and peak sputum levels in excess of the minimal inhibitory concentrations for common bacterial pathogens implicated in acute bronchitis. In addition, trimethoprim and sulfamethoxazole are relatively safe and well tolerated and have a convenient dosage schedule. A double-blind placebo-controlled study of the effectiveness of using trimethoprim and sulfamethoxazole to treat the clinical syndrome of acute bronchitis was, therefore, undertaken.

The major hypothesis was that patients treated with trimethoprim and sulfamethoxazole would have a shorter duration of illness as measured by cough, sputum production, fever, and general sense of well-being. Because it was anticipated that the admission criteria would not differentiate between subjects with bacterial bronchitis and those with viral etiologies, a second hypothesis was that performing sputum Gram stains would allow a more accurate prediction of subjects who would benefit from antibiotic therapy.

Methods

This study was conducted at the Family Medicine Center of Highland Hospital, a family practice with a patient profile previously found to be representative of the patient population of Rochester, New York.[19] All outpatients who came in for appointments with their usual provider were eligible for the study if they were aged 14 years or older and had a cough productive of sputum for less than 15 days. Patients were excluded from the study if they were pregnant, had a history of sulfa allergy, congestive heart failure, renal failure, or chronic pulmonary disease, or had had any systemic antibiotic within the two weeks prior to enrollment. Patients were also excluded for clinical evidence of pneumonitis or inability to produce a sputum specimen at the time of enrollment. The diagnosis of acute bronchitis therefore rested on clinical grounds, ie, the presence of cough productive of sputum for less than 15 days in the absence of pneumonitis. To keep the methods closely parallel to the treatment of this type of patient in general practice, other laboratory tests were not performed. Informed consent was obtained from eligible patients after the nature of the study was explained, and then a sputum sample was obtained for Gram stain. Major baseline data collected on patients are shown in Table 1. Patients were then randomly assigned to receive trimethoprim and sulfamethoxazole (160/800 mg in a fixed-dose combination) twice daily for seven days or a placebo. The assignment to placebo or active group was done in a double-blind fashion, with the medications having been prepackaged, randomized, and sequentially coded by the manufacturer. The tablets were identical in appearance. The code was broken at the time of data analysis or when the information was required for patient care. Patients were enrolled in the study by their usual family physician, and at the time of enrollment the providers were asked to record any adjunctive therapy recommended to the patient. Providers were also asked to record whether they would have prescribed an antibiotic had the patient not been enrolled in the study.

Each patient was given a form on which to record his or her symptoms during the seven-day course of the study drug. This form consisted of seven identical pages for the patient to make daily records of response to the study medication regarding cough, sputum production, general well-being, fever, return to work, and use of adjunctive therapy. Items to be recorded each day were presence of cough, presence of night cough, frequency of coughing spells (four or more spells per hour scored as 1, one to three spells per hour as 2, more than 10 spells per day but less than one per hour as 3, and fewer than 10 spells per day as 4); amount of cough (more than on day of office visit scored as 1, same as on day of office visit as 2, and less than on day of visit as 3); and temperature, activity level (in bed all day scored as 1, 25 percent of usual level as 2, 50 percent of usual level as 3, 75 percent of usual level as 4, and 100 percent of usual level as 5); for those employed, whether the patient had returned to work; use of adjunctive therapy; and the occurrence of side effects or other new symptoms. Patients were asked to complete all items for seven consecutive days, even if all symptoms resolved or if they had to drop out of the study for some other reason.

A Gram stain of sputum produced at the time of enrollment was examined for each patient and graded on the basis of organisms, polymorphonuclear leukocytes seen, and evidence of contamination. A Gram stain was considered to be "positive" for bacterial infection if more than 20 polymorphonuclear leukocytes per oil field in

Table 1. Baseline Characteristics of Enrolled Patients

Variable	Active Drug (n = 34)	Placebo (n = 33)
Age (mean years)	42	36
History		
Duration of symptoms (mean days)	6	7
Sputum yellow/green	87%	85%
Smoking	43%	60%
Fever (mean °F)	101.9	101.1
Sore throat	75%	68%
Coryza	79%	57%
Dyspnea	26%	46%
Chest pain	54%	42%
Unable to work	45%	62%
Examination		
Temperature (mean °C)	37.1	37.25
Pulse (mean beats/min)	80	73
Pharyngitis	68%	44%
Wheeze/rhonchi	13%	16%
Gram stain positive (see text)	37.5% (n = 32)	30% (n = 30)
Would have treated?	50%	48%

None of the differences were statistically significant (*t* tests for means, chi-square for all others). Gram stains on 5 patients were lost.

at least three fields were seen and if bacteria of no more than two morphological types were seen in the same fields as polymorphonuclear leukocytes. A Gram stain was considered to be contaminated or indeterminate if epithelial cells were also seen in more than three fields. A Gram stain was read as "negative" for bacterial infection in all other instances. All slides were stained, read, and reviewed by one of the authors (JAG).

The data were coded and analyzed by the authors using the SAS computer package.[20] Baseline data were analyzed comparing drug and placebo groups and dropouts from both groups using chi-square tests, Fisher's exact test, and *t* tests as appropriate. For each item in the diary a mean score over the seven days was devised, and the mean scores for the drug and placebo groups were compared using *t* tests. In addition, analysis of variance was used to determine whether there was an interaction between drug effect and history of smoking or between drug effect and Gram stain. Patients who did not complete all seven days of the symptom questionnaire were considered to have remained at the same level of function for each category for the remainder of the seven days as they were on the last day that they completed the form. Multivariate analysis of variance was used to analyze all dependent variables simultaneously, both including dropouts as described above and excluding them.

Results

A total of 67 patients were enrolled. There were no significant differences between the antibiotic and placebo groups at the time of enrollment (Table 1).

Thirteen patients did not return their symptom forms—4 in the placebo group and 9 in the antibiotic group (see Appendix for detailed information on these patients). Patients who did not return their forms were significantly more likely to have a positive Gram stain ($P = .02$, Fisher's exact test). Of the 4 patients taking placebo who dropped out of the study, 3 had a positive Gram stain and 1

Table 2. Mean Outcomes Over Seven Days of Study

Variable	Active Drug (n*)		Placebo (n*)		P**
Cough	93%	(25)	99%	(29)	.05
Night cough	56%	(25)	84%	(29)	.003
Cough frequency†	2.6	(24)	2.35	(29)	.18
Cough amount†	2.4	(24)	2.2	(28)	.19
Temperature (°C)	36.9	(23)	37.3	(22)	.004
Activity level†	3.6	(24)	3.4	(29)	.29
Return to work	74%	(19)	60%	(29)	.09
Expectorant/antitussive	32%	(25)	42%	(29)	.17
Analgesic/antipyretic	40%	(25)	48%	(29)	.27
Antihistamine/decongestant	6%	(25)	29%	(29)	.005

*n = Number of patients responding
**t* Test, one-tail probability
†See text for explanation of scoring

patient's Gram stain was lost. Of the 9 patients who dropped out of the antibiotic group, 5 had positive Gram stains, 3 had negative Gram stains, and 1 patient's Gram stain was lost. There were no other significant differences between those who returned their forms and those who did not in any of the variables recorded at the time of enrollment. Four patients discontinued their medication before the end of seven days because of side effects (headaches and nausea), 1 in the placebo group and 3 on antibiotics. Two patients discontinued their medication because they felt completely well (1 in the placebo and 1 in the antibiotic group). Two patients withdrew from the study and stopped medication because of increased symptoms, 1 in the antibiotic and 1 in the placebo group.

Of the seven possible days for patients to have continued coughing, a mean of 99 percent of the placebo group and 93 percent of the antibiotic group recorded a cough ($P = .05$, t test, one tail). Of the remaining ten variables, all showed a trend favoring the antibiotic group. For three of these variables, the difference between antibiotic and placebo groups was statistically significant (Table 2). Patients on antibiotics showed a statistically significant difference in presence of night cough, fever, and use of antihistamine or decongestant adjunctive therapy. Analysis of variance did not show any benefit for subgroups stratified by history of smoking. The use of analysis of variance to stratify for the Gram stain findings showed, however, that patients in the antibiotic group were significantly more likely to have returned to work by the end of the study (Table 3); that is, although overall the antibiotic did not show a statistically significant benefit, when the results were stratified by Gram stain, a statistically significant benefit emerged. No other result was affected by the results of the Gram stain. The multivariate test of all dependent variables for the hypothesis of no overall drug effect revealed a statistically significant benefit ($P = .008$, two-tailed test). When the analysis was repeated excluding all patients with incomplete forms, the statistical outcome was unchanged.

Discussion

This study was designed to evaluate the effectiveness of trimethoprim and sulfamethoxazole in acute bronchitis diagnosed by history and physical examination. Other studies that have evaluated this problem have been inconclusive. In particular, prior studies have been flawed by use of antibiotics that are bacteriostatic rather than bactericidal and by lack of demonstration that the agent used achieved adequate levels in tissue and sputum. No attempt was made in prior studies to perform multivariate analysis. Although the positive results in this study may have been biased by

Table 3. Mean Number (Percentage) of Days Worked

	Placebo No. (%)	Antibiotic No. (%)
Gram Stain		
Positive	6 (36)	6 (55)
Negative	9 (68)	11 (84)
Analysis of Variance		
Drug effect	P = .006, 1-tail	
Gram stain effect	P = .013, 1-tail	
Interaction between drug and Gram stain effect	P = .23, 2-tail	

the inclusion of patients with syndromes known to be responsive to antibiotics, such as pneumonia, the intent of the study was to investigate a syndrome, usually defined clinically. Thus the results may be generalized to the clinical situation where the same bias occurs; that is, further tests such as chest x-ray films are not routinely obtained.

In the final analysis, an assessment of the usefulness of trimethoprim and sulfamethoxazole in acute bronchitis must take into account many factors with relatively soft end points. A strict cost-benefit analysis is useful, but provides only limited information to the clinician faced with the immediate problem of an ill patient in his office who is insisting that an antibiotic be prescribed. These data provide support for the use of trimethoprim and sulfamethoxazole in the treatment of patients with acute bronchitis because of the clinically important and statistically significant benefits that were associated with the use of trimethoprim and sulfamethoxazole in patients with acute cough who produced sputum in the office. This benefit appears to be independent of prior smoking history or of Gram stain findings in the sputum. It was hypothesized that a more accurate prediction could be made on the outcome of trimethoprim and sulfamethoxazole therapy by looking at the sputum Gram stains. There are several possible reasons that outcome appeared to be relatively independent of Gram stain. Gram stains are subject to possible method errors such as inadequate or improper collection of specimens, sampling errors in preparing or viewing the slides, and inappropriate criteria for judgment of the results of the slide. No evidence of inconsistent reading of the slides was found. It remains possible that specimens did not reflect the clinical status of the patient, however, and in the office setting there does not appear to be a reliable way to circumvent this problem.

In view of the earlier return to work of patients who were treated with trimethoprim and sulfamethoxazole, it is probable that treatment is cost effective considering the low cost and morbidity involved in therapy. However, no formal cost analysis was performed. Since acute bronchitis is a self-limited condition with a favorable outcome in the overwhelming majority of patients, and since there is some hazard to using antibiotics, this issue warrants further investigation.

The problem of statistically analyzing multiple outcomes is complex and unresolved. The use of multiple outcomes is desirable to allow adequate evaluation of response in situations where all of the end points are relatively "soft." There are multiple ways to aggregate data to simplify the presentation. Rather than developing a scoring system to combine all results into a synthesized outcome, it was decided to present the results as shown in Table 2 to allow the reader to fashion his or her own interpretation. The probability of four results significant at a level of $P < .05$ in a series of 29 independent tests is $P = .05$.[21] The probability of 11 independent tests all having a trend in the same direction is $P < .001$. The tests reported here, however, are not independent, since some of the outcomes are correlated. The multivariate test result that takes account of the correlation between the outcome variables is compatible with these results. The multivariate test assigns equal weight to each outcome variable that is undesirable on clinical grounds.

These results differ from those of Stott and West,[11] who found no benefit from the use of doxycycline in the treatment of patients similar to those reported here. The differences found may reflect antibiotics used, difference in patient populations (since patients in that study were not required to produce sputum prior to enrollment), or inadequate discriminatory power in study design, since a nonsignificant trend in favor of doxycycline was found in that study.

Although these data are incomplete, no evidence that a bias was introduced to explain the results was found. To explain the results on the basis of systematic bias, one would have to hy-

pothesize either that patients taking trimethoprim and sulfamethoxazole who dropped out did much worse than those who remained in the study, or that those who took placebo and dropped out fared much better. These hypotheses seem equally unlikely in that although patients who dropped out were more likely to have positive Gram stains, there was no evidence that within the group who dropped out those who were taking trimethoprim and sulfamethoxazole were significantly more ill as judged by any of the baseline parameters.

The results of this study support the use of trimethoprim and sulfamethoxazole in patients with cough and sputum production who have no clinical evidence of pneumonitis and no contraindications to this medication. The routine use of Gram stain in this group of patients is not recommended, since the use of this test does not improve the clinician's ability to predict response to antibiotic therapy with trimethoprim and sulfamethoxazole.

Acknowledgment

The trimethoprim and sulfamethoxazole used in this study were provided by Hoffmann-La Roche, Inc.

References

1. Klimek JJ: Use of oral cephalosporins in the treatment of upper and lower respiratory tract infections: An overview. J Int Med Res 8(suppl 1):77, 1980
2. Mogabgab WJ, Pollock B, Beville RB, et al: Treatment of acute bacterial bronchitis and pneumonia with cefaclor. Postgrad Med J 55(suppl 4):62, 1979
3. Brodie NH, McGhie RL, O'Hara H, et al: A double-blind study comparing cefaclor and amoxycillin in the treatment of respiratory tract infections in general practice. Pharmatherapeutica 2:494, 1980
4. Jaffe GV, Grimshaw JJ: Comparative study of cefaclor and amoxycillin in the treatment of respiratory tract infections in general practice. Curr Med Res Opin 6:569, 1980
5. Pines A, Raafat H: A comparative clinical trial of tetroxoprim/sulphadiazine and ampicillin in the treatment of purulent bronchial infections. J Antimicrob Chemother 5(suppl B):201, 1979
6. Lee GS, Kakati R, Mahmoud IA: A comparison of cefaclor and ampicillin in the treatment of respiratory infection in elderly in-patients. Curr Med Res Opin 6:564, 1980
7. Ferber H, Ahrens KH: A short-term study of tetroxoprim/sulphadiazine in the treatment of acute bronchitis and urinary tract infections. J Antimicrob Chemother 5(suppl B):231, 1979
8. Cooper J, McGillion FB, West B: A comparison of cotrimoxazole and amoxycillin in acute bronchitis. Practitioner 220:798, 1978
9. Murphy JE, Donald JF, Molla AL: A single-blind comparative clinical trial of lymecycline and amoxycillin in the treatment of acute bronchitis in general practice. J Int Med Res 4:64, 1976
10. Carroll PG, Krejci SP, Mitchell J, et al: A comparative study of co-trimoxazole and amoxycillin in the treatment of acute bronchitis in general practice. Med J Aust 2:286, 1977
11. Stott NC, West RR: Randomized controlled trial of antibiotics in patients with cough and purulent sputum. Br Med J 2:556, 1976
12. Saginur R, Bartlett JG: Antimicrobial drug susceptibility of respiratory isolates of Hemophilus influenzae from adults. Am Rev Resp Dis 122:61, 1980
13. Ingold A: Sputum and serum levels of amoxycillin in chronic bronchial infections. Br J Dis Chest 69:211, 1973
14. Levin S, Trenholme GM: Use of antibiotics in the outpatient setting. Primary Care 6:3, 1979
15. Wong GA, Pierce TH, Goldstein E, Hoeprich PD: Penetration of antimicrobial agents into bronchial secretions. Am J Med 59:219, 1975
16. Bach MC, Finland M, Gold O, Wilcox C: Susceptibility of recently isolated pathogenic bacteria to trimethoprim and sulfamethoxazole separately and combined. J Infect Dis 128(suppl):S508, 1973
17. Bushby SRM: Trimethoprim-sulfamethoxazole: In vitro microbiological aspects. J Infect Dis 128(suppl):S442, 1973
18. Hansen I, Lykkegaard N, Bertelsen S: Trimethoprim in human saliva, bronchial secretion and lung tissue. Acta Pharmacol Toxicol 32:337, 1973
19. Froom J, Culpepper L, Kirkwood CR, et al: An integrated medical record and data system for primary care: Part 4: Family information. J Fam Pract 5:265, 1977
20. Helwig JT, Council KA (eds): SAS User's Guide: 1979 edition. Raleigh, NC, SAS Institute, 1979
21. Rumke CL: How long is the wait for an uncommon event? J Chronic Dis 35:561, 1982

Appendix

Patients who did not return their diaries are reported. They were followed up by chart review, telephone, and letter.

Trimethoprim and Sulfamethoxazole Group: Two patients had their codes broken within 24 hours—one developed nausea and vomiting with the medication as well as streptococcal pharyngitis requiring penicillin therapy; the other developed otitis media and was continued on trimethoprim-sulfamethoxazole, on which his symptoms resolved; two subsequently reported that they "did OK" but did not follow up; one reported that the medication did not help but did not follow up; no follow-up was available on the remaining four.

Placebo Group: One patient reported getting worse and received care elsewhere, one patient reported not taking the medication because of fear of the side effects, and no follow-up was available on the remaining two.