# Randomized Placebo-Controlled Trials of Antibiotics for Acute Bronchitis: A Critical Review of the Literature

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*Background.* Acute bronchitis is a common clinical problem that causes considerable morbidity and presents both diagnostic and treatment dilemmas for the physician. An evaluation of all published randomized controlled trials of antibiotics in the treatment of acute bronchitis was conducted to (1) quantitatively assess methodologic rigor, (2) determine if effectiveness of antimicrobial therapy is known, and (3) analyze strengths and weaknesses of randomized controlled trials in family practice settings.

*Methods.* A scoring system for the evaluation of randomized controlled trials was adapted for this study. Four raters, who were blinded to which journals published the studies and the type of antibiotic used in each study, assessed the six randomized clinical trials for treatment of bronchitis identified through a literature search. The trials were rated according to criteria that measured internal validity.

*Results.* Scores for internal validity ranged from 65.5 to 102.5 points with a maximum possible score of 120 points (54.6% to 85.4%). The two trials with the highest scores assessed doxycycline and showed no benefit from use of this antibiotic. Single trials that studied erythromycin and trimethoprim-sulfamethoxazole showed improvement in outcome from use of these drugs; however, of the six trials, these two studies ranked fourth and fifth for internal validity. Low scores resulted from small sample size, possible contamination with other treatment measures, and poor assessment of subjects' compliance with antibiotic regimen.

*Conclusions.* An evaluation of the current literature does not support antibiotic treatment for acute bronchitis. Further studies of this common illness are indicated. It is hoped that this critical review of randomized control trials will prove useful in the planning of future studies, in placing greater emphasis on methodologic rigor, and in giving greater consideration to the practical constraints of research in the family practice setting.

*Key words.* Antibiotics; bronchitis; clinical trials; outcome assessment. (*J Fam Pract 1993; 36:507-512*)

Antibiotic therapy for acute bronchitis is one of many controversial issues in family medicine amenable to study through a randomized controlled trial. Studies that have examined this common medical problem have yielded conflicting results.[1-6] The purpose of this paper is to (1) examine the findings of randomized controlled trials of antibiotic treatment for acute bronchitis on the basis of trial methodology, (2) determine whether the effectiveness of antibiotic treatment of acute bronchitis is known, and (3) analyze both the strengths of, and difficulties inherent in, conducting randomized controlled trials in family practice settings.

## Methods

To identify *all* randomized placebo-controlled trials of antibiotic therapy for acute bronchitis that had been

Table 1. Characteristics and Conclusions of Six Clinical Trials of Antibiotics for Acute Bronchitis

| Reports of Trials* | Study Antibiotic | Sample Size | Major End Points | Conclusions | Internal Validity % Maximum Attainable Score† |
|---|---|---|---|---|---|
| 1. Howie and Clark, 1970 | Dimethylchlortetracycline, 300 mg p.o. bid × 5 days | 829 | Duration of cough, purulent sputum, nasal discharge, and loss of work days | NB | 54.6 |
| 2. Stott and West, 1976 | Doxycycline, 200 mg p.o. on day 1, then 100 mg × 9 days | 212 | Duration of cough, sputum, running nose, malaise, and time off from work | NB | 81.3 |
| 3. Franks and Gleiner, 1984 | Trimethoprim-sulfamethoxazole | 67 | Frequency and duration of cough, temperature, use of adjunctive therapy, and return to work | AS | 70.0 |
| 4. Williamson, 1984 | Doxycycline, 100 mg p.o. bid × 3 days, then od × 4 days | 74 | Duration of cough, number of return visits, days off from work | NB | 85.4 |
| 5. Brickfield et al, 1986 | Erythromycin, 333 mg p.o. tid × 7 days | 52 | Daily symptom scores for cough, sputum production, headache, chest discomfort, malaise, work disability | NB (Nonsignificant trend favoring symptom reduction in nonsmokers) | 76.7 |
| 6. Dunlay et al, 1987 | Erythromycin, 333 mg p.o. tid × 10 days | 63 | Daily symptom scores for cough, sputum, production, congestion, sore throat, malaise, disability | AS | 76.3 |

*A number was assigned to each trial for use of relating text to table; also trial number corresponds with reference number.
†Maximum attainable internal validity score = 120.
AS denotes antibiotic superior; NB, no (antibiotic) benefit.

published in the English language, the medical literature from 1980 through 1992 was searched (manually and by computer) using *Index Medicus, Family Medicine Literature Index, Family Medicine Research,* and *Current Canadian Index*. In addition, the bibliographic sections of the studies found were examined for further references, and a *Science Citation Index* search was conducted using these authors' names. By these methods, a total of six published randomized placebo-controlled trials of antibiotic therapy for acute bronchitis were identified (Table 1).

A scoring form (Table 2) for the quantitative analysis of randomized controlled trials was devised by the authors. Similar forms have previously been published in the medical literature.[7] A total of 35 criteria were selected by the authors as being of importance to the design and validity of randomized controlled trials. Thirty of the criteria (2 to 4 and 9 to 35 in Table 2) addressed the internal validity of a study, which is concerned with the avoidance of drawing false-positive or false-negative conclusions about causal hypotheses.[8] Accordingly, these items were considered to be of fundamental importance to a study's results, and were used to assess each trial's methodology. The other criteria referred to external validity or ethical considerations. For each criterion, a score

of 1 was given if it was completely met, 0.5 if partially met, and 0 if unmet. The highest possible total score for each study was 30.

All identifying information was removed from each study prior to distribution to the four reviewers to ensure that they would be blind to the authorship, publication, location, and year of the trial. Two of the reviewers (P.O. and M.M.) were practicing physicians and faculty members, and two (K.S. and A.M.) were epidemiologists pursuing postgraduate degrees in community health. The trials were rated independently by each reviewer and then discussed in conference. On those occasions in which a consensus could not be reached, each reviewer scored as he or she believed was most appropriate. The postconference scores were analyzed for interrater agreement using the Kappa statistic.[9]

## Results

Only six published placebo-controlled randomized clinical trials of antibiotic therapy for the treatment of acute bronchitis were identified through a complete English language literature search (Table 1). All six trials were

Table 2. Checklist for Review of Randomized Controlled Trial of Antibiotic versus Placebo in the Treatment of Acute Bronchitis

Definition of Population
 1. Recruitment process described?
 *2. Confounders and method of minimizing their effect described (must include smoking or prognostically stratify on smoking)?
 *3. Exclusion criteria described (include chronic obstructive lung disease)?
 *4. Disease is precisely defined?
Ethics
 5. Signed informed consent obtained?
Numbers of Patients Eligible, Reject Log
 6. Numbers eligible and rejected given: reasons for rejection given?
 7. Numbers who participated and reasons for refusals?
 8. Demographics of eligibles, rejects and refusals?
Withdrawals After Randomization
 *9. Number of withdrawals:
 *10. Reasons for withdrawals?
 *11. Withdrawals balanced between control and treatment groups?
 *12. Not more than 30% withdrawals in either group?
Therapeutic Intervention
 *13. Intervention clinically relevant, appropriate?
 *14. Intervention described sufficiently to replicate?
 *15. Co-interventions balanced?
Contamination
 *16. Contamination is addressed?
Placebo Control Regimen
 *17. Placebo and treatment appear and taste the same?
Randomization
 *18. Randomization is blinded?

 *19. Method of randomization acceptable (random number table of computer generated)?
Blinding of Patients and Treatment Team
 *20. Patients blind to assignment?
 *21. Treatment team blind?
 *22. Blinding to results maintained over study for both groups?
Adequate Sample Size
 *23. Sample size calculated to detect specified differences (alpha and beta appropriate)?
Testing of Randomization
 *24. Distribution of prognostic indicators assessed by treatment group?
Compliance
 *25. Tested by objective method?
Outcomes
 *26. Major outcomes clinically appropriate?
 *27. Reliability of major outcomes reported?
 *28. Major outcomes measured equally in both groups?
 *29. Major outcomes are appropriate, reliable and measured equally in both groups?
Side Effects
 *30. Side effects reported?
 *31. Side effects compared between both groups?
Analysis
 *32. Appropriate statistical tests used?
 *33. P values reported for significance tests?
 *34. Significance reported by confidence intervals?
 *35. Withdrawals analyzed appropriately?

*Indicates criteria related to internal validity.
Adapted from Chalmers TC, Smith H Jr, Blackburn B, Silverman B, Schroeder B, Reitman D, Ambroz A. A method for assessing the quality of a randomized control trial. Controlled Clinical Trials 1981; 2:31–49. Used with permission of the publisher, Elsevier Science Publishing.

conducted in family practice outpatient settings and involved the testing of one of four commonly used antibiotics. Four trials (1, 2, 4, 5) demonstrated no statistically significant difference in outcomes achieved by administering dimethylchlortetracycline, doxycycline, or erythromycin as compared with placebo. The remaining two trials (3 and 6) demonstrated significant superiority of antibiotic over placebo therapy. Compared to placebo, Franks et al[3] found that patients treated with trimethoprim-sulfamethoxazole had significantly fewer subjective complaints of night cough and fever, and were less likely to use antihistamine or decongestant adjunctive medication. Analysis did not show a benefit for subgroups stratified by smoking history. Dunlay et al[6] demonstrated that erythromycin-treated patients were significantly more likely than those given placebo to have lower subjective symptom severity scales for sputum production, "cold" symptoms and "general health," less frequent use of adjunctive medications, and fewer reports of purulent sputum and abnormal lung examinations documented at the 2-week follow-up visit.

## Interrater Agreement

Interrater agreement as measured by Kappa score ranged from 0.675 to 0.940. These values were statistically sig-

nificant, with magnitudes indicating moderate to excellent interrater reliability.

## Assessment of Studies

For each trial the reviewer's scores for internal validity were summed. These totals are represented as percentages of the maximum attainable score in Table 1. The two highest scores for internal validity were from trials testing doxycycline (2 and 4); they reported no antibiotic benefit. The third and fourth highest scores for internal validity were from trials testing erythromycin; one reported no antibiotic benefit but showed a trend toward antibiotic superiority (trial 5), while the other (trial 6) showed significant antibiotic superiority. The trial using trimethoprim-sulphamethoxazole (trial 3) ranked fifth in its score of internal validity; this study reported antibiotic superiority over placebo. The trial testing dimethylchlortetracycline (trial 1), which showed no antibiotic benefit, ranked lowest for internal validity.

## Combined Percentage Scores

By combining the points scored by all 6 studies for each internal validity item, we were able to consider the

Table 3. Percentage of Internal Validity Criteria Met by All Six Papers

| Internal Validity Criteria | Overall Score,*<br>% |
|---|---|
| Testing of randomization | 100 |
| Blinding | 97 |
| Definition of population | 84 |
| Withdrawals | 83 |
| Side effects | 78 |
| Statistical analysis | 76 |
| Therapeutic interventions | 74 |
| Outcomes | 73 |
| Randomization | 68 |
| Sample size | 50 |
| Placebos | 46 |
| Compliance | 42 |
| Contamination | 2 |

*Scores assigned by each author for their criteria in all 6 trials were summed, averaged, and expressed as a percentage of the total possible attainable score.

strengths and weaknesses of these family practice setting randomized controlled trials. The combined score, as a percentage of total attainable score, obtained for internal validity-related categories of criteria is given in Table 3. Approximately three quarters of the criteria for internal validity were met by the trials as a group.

Of the criteria assessed, appropriate randomization, blinding of observer and subject, and attainment of adequate sample size are the most critical to the internal validity of a study.[10] Although the average score for blinding was high (97%), lower average scores were seen for randomization (68%) and sample size (50%). All the trials except that by Howie and Clark[1] were double-blinded, with blinding maintained over the course of the study. By contrast, the only trial reporting an acceptable blinded randomization method (random number table or computer-generated numbers) was the study by Williamson.[4] This latter study was also the only one that demonstrated predetermination of an adequate sample size. Two other studies[3,6] were also considered to have an adequate sample size as they demonstrated antibiotic superiority, but there was no indication that sample size had been calculated to take into account type II error if the results had not been significant.

Of the remaining criteria, an average score of >75% was obtained for testing of randomization, defining of the population, handling of withdrawals, description of side effects, and statistical analysis. Criteria that did not score well included the description of the placebo regimen, compliance, and contamination. In most of the trials, the placebo regimen was not described sufficiently in order to determine whether blinding could have been maintained. Only the studies by Dunlay et al[6] and by Scott and West[2] measured compliance, and none of the studies adequately assessed the possibility of contamination caused by self-prescribed or externally prescribed curative efforts.

## Outcome Criteria

Because our scoring system accepted any reasonable and consistent array of outcome measures, it does not reflect the variability of types of outcomes used in these studies. Most studies used both objective and subjective measures. These included duration of individual symptoms, time off from work, and repeat visits to the physician. Multiple outcomes were used in most. Alpha values were not usually adjusted for multiple comparisons. No two studies used exactly the same outcomes. A clinical index combining various symptoms was used in only two studies: Brickfield et al[5] and Dunlay et al.[6]

## Discussion

In the National Ambulatory Care Survey (1989),[11] acute bronchitis was the ninth most common outpatient illness seen by physicians in the United States. Costs resulting from physician visits and antibiotic therapy at that time were estimated at 200 to 300 million US dollars per year. In addition to direct medical costs, acute bronchitis leads to significant work absenteeism and lost productivity.

The present study performed quantitative analyses of published randomized controlled trials that addressed the question of whether antibiotic therapy was effective in the treatment of acute bronchitis. Only six such studies were identified. Publication bias is possible, as negative trials are less likely to be published, and data from trials that showed no antibiotic benefit may have been inadvertently excluded. However, unpublished literature can be difficult to locate, and has not undergone peer review.

The two doxycycline studies (2 and 4 on Table 1) that achieved high scores for internal validity (81% to 85%) showed no antibiotic benefit. Therefore this antibiotic cannot be recommended in the therapy of acute bronchitis, and it would be a poor choice for future studies. Of the two erythromycin trials, one (trial 5) showed no significant antibiotic benefit (though a trend among nonsmokers was present), and the other (trial 6)

showed antibiotic superiority over placebo (Table 1). However, fewer (76%) criteria for internal validity were met in these trials. Trimethoprim-sulfamethoxazole was found to be superior to placebo (trial 3), and dimethyl-chlortetracycline was of no benefit (trial 1) (Table 1); however, even fewer (55% to 70%) internal validity criteria were met in these studies.

The difficulties encountered in family practice research were apparent in our review of these six randomized controlled trials. The definition of disease may be problematic. Furthermore, there are no firm objective diagnostic tests for diseases like bronchitis. Randomized trials in family practice must conform to these constraints if their results are to be generalizable to the practice setting. Thus, in the study of acute bronchitis, the exclusion of other conditions, such as sinusitis and pneumonia, may be difficult, and investigations such as radiography may be neither available nor practical for these patients.

The difficulty of developing diagnostic criteria is compounded by the fact that it may not be possible clinically to reliably distinguish between acute bronchitis of viral and bacterial etiology.[12,13] Both viral and bacterial pathogens may result in purulent sputum.[12] A sputum culture revealing a predominant respiratory pathogen by Gram stain and culture is helpful only if the specimen is uncontaminated by upper airway secretions, cultured promptly, and obtained from patients without pulmonary or systemic disease predisposing them to bacterial colonization of the respiratory tract.[14] Most laboratories do not routinely culture sputum for certain pathogens such as Mycoplasma pneumoniae or Chlamydia pneumoniae. In addition, the delay in receiving culture and sensitivity results may pose a problem for family practitioners who must make therapeutic decisions in the interim.

Reliance on a clinical definition of disease, however, will inevitably allow for occasional false-positive and false-negative diagnoses. To be as consistent as possible in diagnoses in which multiple clinicians are involved, work should be based on reliable clinical diagnostic criteria, which would ensure similarity of patients enrolled and make comparison between studies and generalization of the results to other patient populations possible.

In using clinical definitions of this condition, diagnostic ascertainment bias may occur.[10] For example, if cases of sinusitis or pneumonia caused by bacterial infection were inadvertently included in the studies, positive responses to antibiotic therapy may favor significant outcomes for the antibiotic arm of the trials. Thus clinical criteria for diagnosis should attempt to eliminate these cases from inclusion in future studies, or stratify these data before randomization according to the probability of a study subject having one of these conditions (eg, fever, purulent rhinitis, or postnasal discharge).

Difficulties also arise because of the variety of measures used to determine antibiotic effectiveness. Work needs to be done on the development of clinical indices that incorporate the many outcomes reported and can be used in the family practice setting.

Enrolling sufficient numbers of patients in a clinical trial may be problematic,[15] whether in a family practice or hospital setting; physicians may not be willing to randomize patients who they believe require active therapy. Another unavoidable problem in family practice research is dealing with contamination, co-interventions, and losses to follow-up in these settings that are not encountered to the same degree in hospital studies, in which a greater degree of control may be exerted over the trial subjects and conditions.

For unselected patients with acute bronchitis, the value of antibiotic therapy remains unclear.[16] The studies reviewed in this paper suggest possible benefit for treatment with erythromycin or trimethoprim-sulfamethoxazole. The use of tetracycline or doxycycline is not recommended in this population. In the minority of cases in which particular bacterial pathogens are identified, such as Mycoplasma pneumoniae or Bordetella pertussis, specific antibiotic therapy is indicated. However, treatment for the majority of patients is largely symptomatic, aimed at the control of cough. Primary prevention must be emphasized, with increased immunization efforts against selected agents such as influenza and pertussis, and the reduction of risk factors such as cigarette smoking.

Future trials of erythromycin or trimethoprim-sulfamethoxazole in the therapy of acute bronchitis are indicated. Emphasis should be placed on methodology in order to meet those criteria most fundamental to internal validity. Other questions regarding this condition may also be amenable to research in the family practice setting. These include, among others, the role of expectorants or cough suppressants in the management of cough, the influence of stress in host response, and the importance of environmental risk factors in the pathogenesis of this condition.

There are compelling reasons for encouraging family physicians to conduct randomized controlled trials in routine outpatient settings. Such trials, if properly conducted, can yield results that are useful, important, and applicable to common therapeutic dilemmas. Critical reviews of randomized clinical trials through the use of a scoring system allow evaluation of the study results and enable the planning of future trials. They are also an excellent teaching tool. It is hoped that they will be validated and prove to be useful in family practice through an emphasis on methodologic rigor despite the

practical constraints of research in the outpatient setting. Many important therapeutic questions remain unanswered; it is therefore urgent that quality research in family practice settings be promoted and encouraged.

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