Antibiotics in Acute Bronchitis: A Meta-analysis

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PURPOSE: Most patients with acute bronchitis who seek medical care are treated with antibiotics, although the effectiveness of this intervention is uncertain. We performed a meta-analysis of randomized, controlled trials to estimate the effectiveness of antibiotics in the treatment of acute bronchitis.

SUBJECTS AND METHODS: English-language studies published January 1966 to April 1998 were retrieved using MEDLINE, bibliographies, and consultation with experts. Only randomized trials that enrolled otherwise healthy patients with a diagnosis of acute bronchitis, used an antibiotic in the treatment group and a placebo in the control group, and provided sufficient data to calculate an effect size were included.

RESULTS: We identified eight randomized controlled trials that satisfied all inclusion criteria. These studies used one of three antibiotics (erythromycin, doxycycline, trimethoprim/sulfamethoxazole). The use of antibiotics decreased the duration of cough and sputum production by approximately one-half day (summary effect size 0.21; 95% CI, 0.05 to 0.36). For specific symptoms, there were nonsignificant trends favoring the use of antibiotics: a decrease of 0.4 days of purulent sputum (95% CI, −0.1 to 0.8), a decrease of 0.5 days of cough (95% CI, −0.1 to 1.1), and a decrease of 0.3 days lost from work (95% CI, −0.6 to 1.1).

CONCLUSION: This meta-analysis suggests a small benefit from the use of the antibiotics erythromycin, doxycycline, or trimethoprim/sulfamethoxazole in the treatment of acute bronchitis in otherwise healthy patients. As this small benefit must be weighed against the risk of side effects and the societal cost of increasing antibiotic resistance, we believe that the use of antibiotics is not justified in these patients. **Am J Med. 1999;107: 62– 67.** ©1999 by Excerpta Medica, Inc.

Acute bronchitis is a common clinical disorder characterized by the acute onset of cough and sputum production in a patient with no history of chronic pulmonary disease and no evidence of pneumonia or sinusitis. This definition excludes patients with acute exacerbation of underlying pulmonary disorders, in whom a previous meta-analysis found that antibiotic use led to a small, statistically significant benefit (1). The effectiveness of antibiotics in patients with acute bronchitis remains uncertain, although the disorder is the tenth most common diagnosis seen by physicians in the United States, accounting for 10 million office visits annually (2).

The etiology of acute bronchitis is unclear. Most studies have identified viruses (adenovirus, rhinovirus, coronavirus, influenza, parainfluenza, respiratory syncytial virus, and coxsackievirus) as the cause in the majority of patients (3–14). Atypical bacteria, including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species, have been reported to cause 5% to 25% of cases of acute bronchitis (15–17), and typical bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Branhamella catarrhalis*) have been recovered from the sputum in 7% to 44% of patients (8,18,19). However, the importance of positive bacterial cultures from sputum is not known, because many of these pathogens are part of the oropharyngeal flora (3,9,20–22). Recent evidence suggests that some bronchitis in adults may be caused by *Bordetella pertussis* and *parapertussis*, which are better known for their role in causing whooping cough in children (23).

The majority of patients diagnosed with acute bronchitis in the United States are treated with antibiotics (24–27). In a nationwide survey of >1,500 physicians, Gonzales et al (25) found that two-thirds of patients without underlying lung disease who were diagnosed with acute bronchitis were treated with antibiotics. In another survey, 75% of children with a diagnosis of acute bronchitis were given a prescription for antibiotics (26).

Although antibiotics are often used in the treatment of acute bronchitis, their efficacy is uncertain. Clinical trials examining this issue have yielded conflicting results (28–37), and qualitative reviews are similarly inconclusive (7,9,17,38,39). Widespread antibiotic use carries a substantial cost, puts patients at risk for medication side effects, and promotes antibiotic resistance.

To clarify the optimal treatment of this disorder, we performed a meta-analysis to determine whether antibiotics were beneficial in patients with acute bronchitis. Using explicit inclusion and exclusion criteria and accepted quantitative methods (40–42), a meta-analysis provides summary estimates of effectiveness that may clarify the disparate results of previous trials (43).

METHODS

Literature Review

The literature review began with a computerized MEDLINE search using the subheading "bronchitis, drug

therapy" and the term "xs acute disease," and included English-language articles published between January 1966 and April 1998. The reference lists of all retrieved articles were scanned, and experts were consulted to identify potential trials not identified in the MEDLINE search.

Inclusion criteria consisted of the following: randomized trials using an antibiotic in the treatment group and a placebo in the control group; subjects with acute bronchitis, no history of chronic lung disease, and pneumonia excluded by chest radiograph or clinical exam; therapy for at least 5 days; and the presentation of sufficient data to calculate the difference in efficacy between the treatment and the placebo as a continuous variable. Studies were excluded if they were nonexperimental in design or if they compared one antibiotic with another without a placebo arm.

For each study, two authors independently abstracted the author, journal title, year of publication, sample size, average age of subjects, antibiotic regimen used, major outcome measure(s), and the inclusion and exclusion criteria. Discrepancies in the abstracted data were resolved by consensus.

Analysis

The eight eligible studies did not use a common outcome measure. When several outcomes were available from one study, we chose "days of sputum production" as the main outcome, because this symptom is most characteristic of the disease (4). For studies that did not include the outcome "days of sputum production," we chose the outcome in the study that was the most clinically similar (sputum production score, cough amount score). We transformed each outcome into units of standard deviation, thus giving a comparable effect size for different outcomes. The study-specific effect size was the difference in the mean outcome for the antibiotic and placebo groups, divided by the pooled standard deviation of the outcome measure in that study. The summary effect size across studies was calculated as a weighted average of the study-specific effect sizes, with weights equal to the inverse of the estimated variance. The significance of the summary effect size, standardized by its estimated variance, was assessed by comparing it with the standard normal distribution. A test for heterogeneity was calculated by comparing the weighted average of the squared differences between summary and study-specific effect sizes with an appropriate X^2 distribution, with the same weights being used. These calculations used standard formulas (44), which assume that the outcomes are normally distributed and the sample sizes are approximately equal in the antibiotic and placebo groups.

We also calculated summary mean differences for all outcomes reported by four or more studies. The summary measure was the weighted average of the difference between the antibiotic and placebo groups in the mean

Table 1. Reasons for Exclusion of Reports Retrieved from Literature Search

Reason for Exclusion	Number of Reports
Not original data	74
No control group	87
Main intervention was not antibiotic therapy	16
Patients with COPD were included	11
Main intervention was prophylaxis	1
Subjects had another infectious disorder (sinusitis, bronchiolitis)	4
Insufficient data presented	2
Total excluded	195

COPD = chronic obstructive pulmonary disease.

outcome measure for each study. Weights were given by the inverse of the variance of each mean difference, estimated using the pooled standard deviation for each study. Tests of the significance of the observed summary mean differences and of heterogeneity were also performed (44).

We examined the potential for publication bias using the correlation between the number of subjects and the effect size in each study. If small studies with negative results were less likely to be published, then the correlation between number of subjects and effect size would be large. If there was not any publication bias, then there should not be a significant correlation between the number of subjects and the effect size.

RESULTS

Our search identified 203 reports, including 10 randomized, placebo-controlled trials of antibiotics for the treatment of acute bronchitis (28–37). Two (28,31) of these studies had to be excluded because insufficient data were presented in the original articles, and attempts to retrieve the necessary data from the authors were unsuccessful. The remaining eight trials, all of which used one of three antibiotics (erythromycin, doxycycline, trimethoprim/sulfamethoxazole), were included in the meta-analysis. Reasons for exclusion are listed in Table 1. The characteristics of the 10 randomized controlled trials, including the two that were excluded because of insufficient data, are shown in Table 2.

The overall summary effect size was 0.21 (95% CI, 0.05 to 0.36) indicating a small (about one-fifth of a standard deviation), statistically significant benefit from the use of antibiotics (Figure), equivalent to approximately one half day less of cough and sputum production.

Three outcomes were reported by at least four studies (Table 3). Although each of these results favor antibiotics, none was statistically significant. For days of purulent

Table 2. Randomized Trials of Antibiotics in Acute Bronchitis

First Author, Year (reference)	No. of Subjects	Antibiotic	Main Outcome Measure	Study Result (95% CI)*	Standardized Effect Size (95% CI)†
Howie, 1970 (31)	836	Demethyl-chlortetracycline	Average days of purulent spit	0.3‡	Not available‡
Stott, 1976 (33)	207	Doxycycline	Days of yellow spit	0.6 (−0.2 to 1.4)	0.20 (−0.08 to 0.48)
Franks, 1984 (30)	54	Trimethoprim/sulfamethoxazole	Cough amount score	0.2 (−0.2 to 0.6)§	0.25 (−0.30 to 0.79)
Williamson, 1984 (34)	69	Doxycycline	Days of purulent sputum	−0.2 (−1.2 to 0.8)	−0.09 (−0.57 to 0.38)
Brickfield, 1986 (28)	50	Erythromycin	Sputum production score	0.2‡¶	Not available‡
Dunlay, 1987 (29)	45	Erythromycin	Sputum production score on day 10	0.5 (0.1 to 0.9)#	0.80 (0.20 to 1.41)
Scherl, 1987 (32)	31	Doxycycline	Days of sputum	1.9 (−0.2 to 4.0)	0.64 (−0.08 to 1.36)
Verheij, 1994 (35)	140	Doxycycline	Days of productive cough	0.5 (−0.4 to 1.4)	0.18 (−0.15 to 0.52)
Hueston, 1994 (36)	23	Erythromycin	Days of productive cough	−0.4 (−2.4 to 1.6)	−0.21 (−1.14 to 0.72)
King, 1996 (37)	91	Erythromycin	Days of sputum production	0.7 (−1.3 to 2.7)	0.14 (−0.27 to 0.55)

* Result is the mean in the antibiotic group minus the mean in the placebo group for the main outcome measure. A positive result indicates a benefit from antibiotics. A negative result indicates a benefit from placebo.

† Effect size is the difference between the mean outcome in the antibiotic and placebo groups divided by the pooled standard deviation.

‡ These studies did not provide data that allowed calculation of a confidence interval or a continuous outcome measure, and therefore could not be included in the overall summary effect size.

§ Cough amount score was a patient-reported score on a severity scale of 1 to 3.

¶ Sputum production score was a patient-reported score on a severity scale of 1 to 4.

Sputum production score was a patient-reported score on a severity scale of 1 to 5.

CI = confidence interval.

sputum, the summary mean difference was 0.4 (95% CI, −0.1 to 0.8); the mean difference was 0.5 (95% CI, −0.1 to 1.1) for days of cough and 0.3 (95% CI, −0.6 to 1.1) for
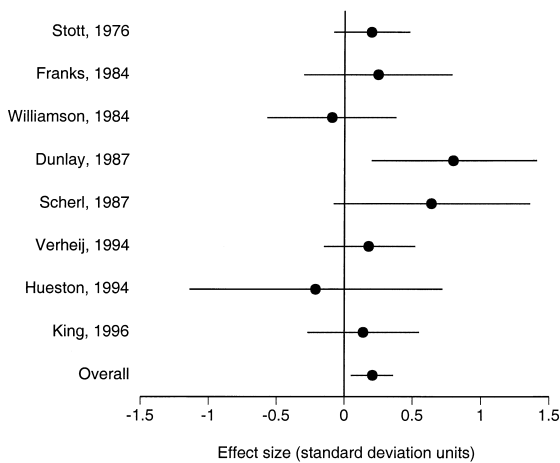
days lost from work. The effect of antibiotic treatment on days lost from work was very small, and unlike days of cough and sputum production, did not approach statistical significance.

A test for heterogeneity was not significant for the overall summary effect size ($P = 0.37$) or for days of sputum production ($P = 0.50$), suggesting that these results are homogenous and can be combined. A test for heterogeneity was significant for the summary mean difference for days lost from work ($P = 0.03$) and days of cough

Figure. Effect sizes and summary overall estimate. Effect size is the difference between the mean outcome in the antibiotic and placebo groups divided by the pooled standard deviation. Horizontal lines denote 95% confidence intervals. Dots represent point estimates.

Table 3. Summary Mean Differences between Antibiotic and Placebo Groups

Outcome Measure (reference)	Summary Mean Difference (95% CI)*
Days of purulent sputum (6 trials) (32–37)	0.4 days (−0.1–0.8)
Days of cough (4 trials) (32–35)	0.5 days (−0.1–1.1)†
Time off work (6 trials) (32–37)	0.3 days (−0.6–1.1)†

* Summary mean difference is the weighted average of the difference between the antibiotic and placebo groups in the mean outcome measure for each study.

† A test of heterogeneity was statistically significant.

CI = confidence interval.

($P = 0.05$), suggesting that these outcomes may have been derived from studies that used different methods. There was no correlation between study size and overall effect size ($r = -0.13$, $P = 0.75$).

DISCUSSION

Randomized controlled trials evaluating the efficacy of antibiotics in acute bronchitis have had inconsistent results. Of the eight trials included in our meta-analysis, four showed no benefit from the use of antibiotics (32–34,36), whereas four reported a benefit (29,30,35,37). Part of the discrepancy may be because studies used different outcome measures, some of which are of uncertain clinical importance. For example, the outcome measures in one trial that reported a statistically significant benefit from antibiotics included a reduction in mean temperature from 37.3°C to 36.9°C and a reduction in the use of antihistamines (30).

Because the published trials used several outcome measures, we used the standardized effect size, expressed in units of standard deviation, to quantitate the overall effect of antibiotic therapy. We chose the outcome that is most characteristic of acute bronchitis (days of sputum production) in the six studies where it was available, and we used the most similar outcome in the two other studies (cough amount score, sputum production score). We found a small, statistically significant benefit to the use of antibiotics in patients with acute bronchitis approximately equal to one-fifth of a standard deviation unit. To relate the observed benefit in the summary effect size to clinical variables, we also calculated summary mean differences for all outcomes that were reported by at least four trials (duration of sputum production, duration of cough, and days lost from work), all of which showed small, nonsignificant trends favoring the use of antibiotics. Our meta-analysis suggests that patients with acute bronchitis who are treated with antibiotics have a reduction in the duration of cough and sputum production of approximately one half day.

Our results should be interpreted with caution. As with all meta-analyses, we assumed that the individual trials are sufficiently similar to provide a meaningful summary. The studies did have several important differences. They took place in different geographic locations, used three different antibiotics (erythromycin, doxycycline, trimethoprim/sulfamethoxazole), and were conducted during a 20-year period. However, despite these differences, statistical tests for heterogeneity did not show differences between studies for the main outcome, or for the outcome of sputum production. Although different antibiotics were used, all groups were treated for at least 5 days, and the spectrum of organisms covered by the various antibiotics was similar.

We identified 10 randomized controlled trials in our literature review. Results from two of these trials could not be included because insufficient data were reported (28,31). Both of these trials showed no benefit from the use of antibiotics. Thus, their exclusion tended to bias our results in favor of antibiotics. In addition, the summary effect size may have been overestimated if publication bias made it more likely that studies showing benefit were published, whereas those showing no benefit were not. If there was publication bias, small studies with negative findings should have been unlikely to be published, whereas small studies with positive findings should have been more likely to be published, leading to a correlation between study size and effect size. We found no such correlation.

We used similar methodology to an earlier meta-analysis that examined the effect of antibiotics in patients with acute exacerbations of chronic obstructive pulmonary disease (1). That study reported a summary effect size of 0.22 (95% CI, 0.10 to 0.34), also indicating a small, statistically significant benefit from the use of antibiotics. Patients who were treated with antibiotics had a modest improvement in peak expiratory flow of approximately 11 L/min compared with those treated with placebo. Although the magnitude of benefit from antibiotic treatment in that meta-analysis is similar to that in the current meta-analysis, such a benefit may be more important for a patient with underlying lung disease who has less functional reserve.

The costs of widespread antibiotic use are great for both patients and society. They include prescription costs, medication side effects, and an increase in antibiotic resistance. Several studies have shown that widespread antibiotic use leads to the development of resistant organisms (45–47). Antibiotic use for acute bronchitis constitutes a substantial portion of all antibiotic use in the United States, accounting for 9% of all prescriptions written for children (26). Furthermore, side effects of antibiotics used for acute bronchitis are common, occurring in 10% to 36% of patients (28–31,33,35,37). The practice of routinely giving antibiotics for acute bronchitis encourages patients to expect antibiotics for subsequent episodes (48), which adds to the cycle of medication costs, side effects, and antibiotic resistance. We believe that there should be a clear, substantial benefit to antibiotics to justify these costs.

Some authors have suggested that certain subgroups of patients with acute bronchitis may benefit from antibiotics (9,35,39). In a study of 140 patients randomly assigned to treatment with doxycycline or placebo, Verheij et al (35) reported that doxycycline resulted in clinical benefit among patients older than 55 years and in those who felt ill at study entry. However, approximately 30% of the patients in that study had abnormalities on lung auscultation and therefore may have had conditions such as

pneumonia that would show a large benefit from antibiotic treatment (49). Others have suggested treating patients who test positive for *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* (39), although there is no evidence from randomized trials to support this practice. In a randomized trial using erythromycin to treat acute bronchitis, King et al (37) found no difference in outcomes between patients who tested positive and those who tested negative for *Mycoplasma pneumoniae*. More research is needed to determine if there are subgroups of patients who are likely to have a substantial benefit from treatment with antibiotics.

The studies included in this meta-analysis examined the effect of one of three different antibiotics (erythromycin, doxycycline, trimethoprim/sulfamethoxazole). None of the studies used one of the newer macrolide or floroquinolone antibiotics. We are not aware of any randomized, placebo-controlled trials of these agents in adults with acute bronchitis. Future studies should determine the risks and benefits associated with use of these newer antibiotics.

In summary, we found a statistically significant benefit from the use of antibiotics in acute bronchitis. Treatment reduced the duration of cough and sputum production by approximately one half day. The decision to use antibiotics for the treatment of adults with acute bronchitis must be weighed against the costs associated with widespread use of these agents. In healthy patients with acute bronchitis who have no evidence of chronic pulmonary disease, we believe that the small benefit associated with antibiotic treatment does not outweigh the risk of side effects and the increase in antibiotic resistance.

Note Added in Proof: After this paper was submitted, a meta-analysis on a similar topic was published: Smucny JJ, Becker LA, Glazier RH, McIsaac W. Are antibiotics effective treatment for acute bronchitis? A meta-analysis. *J Fam Pract*. 1998;47:453–460.

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