REVIEW

Antibiotic Treatment of Acute Bronchitis in Smokers

A Systematic Review

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OBJECTIVE: **Community physicians in the United States prescribe antibiotics to 80% to 90% of smokers with acute bronchitis. We performed a systematic review of the literature to determine the efficacy of antibiotics for smokers with acute bronchitis.**

DESIGN: **A MEDLINE search was done using the keywords bronchitis, cough, and antibiotics to identify English language articles published from January 1966 to September 2001. Randomized, placebo-controlled trials of antibiotics in previously healthy smokers and nonsmokers with acute bronchitis were included.**

MEASUREMENTS AND MAIN RESULTS: **For each study, we abstracted information on design, size, inclusion criteria, patient characteristics, and outcomes. Of 2,029 articles in the original search, 109 relevant articles were retrieved and reviewed. There have been no studies specifically addressing antibiotic use in smokers with acute bronchitis. Nine randomized, placebo-controlled trials of antibiotics have included 774 patients and over 276 smokers. Lack of subgroup reporting for smokers precluded meta-analysis. In 7 trials, smoking status did not predict or alter patients' response to antibiotics. In one trial, trimethoprim/sulfamethoxazole resulted in less-frequent cough overall, but not among smokers. In another trial, erythromycin reduced symptom scores only among nonsmokers while antibiotic-treated smokers had a trend toward higher symptom scores.**

CONCLUSION: **Although no trials have specifically addressed antibiotic use in smokers with acute bronchitis, existing data suggest that any benefit of antibiotics is the same or less for smokers than for nonsmokers.**

KEY WORDS: **bronchitis, antibiotics; smoking; systematic review.**

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Acute bronchitis is a self-limited upper respiratory condition in those without prior pulmonary disease, characterized by cough and lasting about 2 weeks.[1] Sixty-five to eighty percent of patients with acute bronchitis receive antibiotics[2–5] despite evidence antibiotics are at best marginally effective.[1,6,7] This high rate of antibiotic use is increased even further by certain patient factors, such as smoking.

Oeffinger et al. found that physicians report using antibiotics for 75% of nonsmoking patients with acute bronchitis but for 90% of smokers with acute bronchitis.[8] Dosh et al. found that primary care practitioners, when treating patients with upper respiratory infections, sinusitis, and acute bronchitis, prescribed antibiotics to 64% of nonsmokers and to 81% of smokers.[9]

Despite this frequent practice, published reviews do not guide physicians faced with a smoker who has acute bronchitis.[10–14] A recent joint position paper on antibiotic treatment of acute bronchitis by the Centers for Disease Control and Prevention and the American College of Physicians–American Society of Internal Medicine makes no mention of smoking status affecting the decision to prescribe antibiotics.[15,16] We performed a systematic review of the literature to determine if antibiotics are effective in smokers with acute bronchitis.

METHODS

Inclusion Criteria

Studies were included if they were placebo-controlled, randomized trials of antibiotics in adult patients with acute bronchitis. We defined acute bronchitis as a productive cough of less than a month's duration in a patient without history of cardiac or pulmonary disease and no clinical signs of pneumonia. Patients could have rhonchi or wheezes on auscultation. Chest radiographs to rule out pneumonia were not required. Trials including patients with acute exacerbation of chronic bronchitis were excluded.

Search Strategy

A MEDLINE and pre-MEDLINE search was done using the keywords bronchitis or cough and antibiotics to identify trials, reviews, letters, and editorials published in English between January 1966 and September 2001. Titles and abstracts were screened for suitability, and those deemed appropriate were retrieved and reviewed. References of

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retrieved articles were examined to identify additional studies.

Data Abstraction and Analysis

We abstracted information on study design, patient characteristics, enrollment criteria, main results, and results in smokers. We evaluated strength of study design and follow-up using the method of Jadad et al.[17]

For continuous outcomes, when available, we calculated point estimates and 95% confidence intervals using the 2-sample *t* test. To compare adverse effects of antibiotics with placebo we used Fisher's exact test.

RESULTS

Search Results

The search yielded 2,029 articles. On the basis of title and abstract, 1,920 articles did not meet inclusion criteria We obtained the remaining 109 articles focusing on acute bronchitis. Among these, there were 9 randomized, placebo-controlled studies of antibiotics in smokers and nonsmokers. No studies specifically addressed antibiotic use in smokers.

Because the data on smoking were not reported uniformly or in sufficient detail, we were not able to perform a quantitative meta-analysis. Instead, we present a qualitative review of the 9 placebo-controlled trials of antibiotic use for acute bronchitis, focusing on the results in smokers where available.

Study Characteristics

The 9 placebo-controlled trials involved a total of 774 patients and over 276 smokers (Table 1).[18–26] The proportion of smokers in these trials ranged from 32% to 75%, averaging 49% overall. The mean age of patients in these trials ranged from 30 to 43 years old. One trial did not report the percentage of smoking patients or age distributions.[18] The mean quality score by the method of Jadad and colleagues was 3.9 (range 3 to 5) out of a maximum of 5, indicating some deficiencies in blinding, randomization, or follow-up.

The trials evaluated 3 different antibiotics: doxycycline, trimethoprim/sulfamethoxazole (TMP/SMX), and erythromycin. Six trials assessed some combination of 3 main continuous outcomes: duration of cough, duration of yellow sputum, and time off work. The remaining 3 trials assessed other outcomes: activity level, symptom scores, physician assessment, and duration of fever.

Efficacy of Antibiotics

In 5 of the 9 studies, antibiotics showed no overall benefit. In the trials by Stott and West,[18] Williamson,[20] Hueston,[24] and Brickfield et al.[21] smoking status did not alter the lack of response to antibiotics. The trial by Brickfield et al. demonstrated a trend toward decreased symptom scores only among nonsmokers receiving erythromycin. Among smokers, those receiving erythromycin had significantly worse scores for headache on day 1 and chest congestion on days 1, 2, and 3 compared to smokers receiving placebo. Smokers receiving erythromycin did not have significantly better scores than smokers receiving placebo for any outcome, including mean number of days to symptom improvement or physician assessment. The study by Scherl et al. did not stratify by smoking status.[23]

One of the 9 trials, by Franks and Gleiner, which evaluated TMP/SMX, showed a reduction in the presence of cough over 7 days in all patients treated (93% in the TMP/SMX group versus 99% in the placebo group; 1-tailed $P = .05$).[19] Most other outcomes, including cough frequency, cough amount, and activity level, trended toward benefit among all patients taking TMP/SMX. Among smokers, the authors found no statistical benefit of TMP/SMX for any outcome.

Three of the 9 randomized, placebo-controlled trials report decreased duration of daytime cough, days off work, and sputum production score for antibiotic-treated patients.[22,25,26] These benefits represented less than 1 day of coughing, less than 1 day off work, and a decrease in sputum production scores of unclear clinical significance. For all 3 trials, smoking status neither enhanced nor diminished patients' response to antibiotics.

Adverse effects averaged 11% (range among trials 0% to 37%) in the placebo-treated patients and 16% (range among trials 6% to 36%) in the antibiotic-treated patients in 7 trials ($P = .08$). The most frequent adverse effects were gastrointestinal upset, nausea, and vomiting. Two trials did not report adverse effects.[23,24] No trial stratified adverse effects by smoking status.

DISCUSSION

Antibiotic prescription for smokers with acute bronchitis is common, but our review of 9 placebo-controlled trials suggests—contrary to conventional wisdom—that smokers derive no greater benefit from antibiotics than do nonsmokers. The results of 2 trials suggested that smokers may benefit less from antibiotics than do nonsmokers.

Brickfield and colleagues demonstrated consistent trends toward decreased symptom scores among only nonsmokers receiving erythromycin.[21] They also found increasing symptom scores for smokers receiving erythromycin compared to smokers receiving placebo. Because all differences occurred on or before day 3, baseline differences between groups may explain this finding. Franks and Gleiner[19] found a decreased proportion of patients with cough among those taking TMP/SMX, but there was no benefit when patients were stratified by smoking status.

These results are limited by the small sample sizes of the trials reviewed. Individually, these trials may have lacked statistical power to detect differences between subgroups. The largest of the trials included only 212 patients with an unknown number of smokers.[18] Meta-analysis

Table 1. Randomized Placebo-controlled Trials of Antibiotics in Smokers with Acute Bronchitis

		Subjects		Results		
Study, Year	Antibiotic	Total, *n*	Smokers, *n*	Main Outcomes	All Patients, Mean Difference*	Smokers†
Stott and West, 1976[18]	Doxycycline	212	NA	Days of cough Days of yellow sputum	−0.1 (−0.9 to 07) 0.6 (−0.2 to1.4)	"smoking habits did not affect the duration of purulent sputum"
Franks and Gleiner, 1984[19]	Trimethoprim/ sulfamethoxazole	67	35	Cough frequency score Cough amount score Activity level score	0.3 (−0.3 to 0.8) 0.2 (−0.3 to 0.7) 0.2 (−0.6 to 1.0)	"analysis of variance did not show any benefit for subgroups stratified by smoking status"
Williamson, 1984[20]	Doxycycline	74	24	Days of cough Days of purulent sputum Days off work	−1.9 −0.2 (−1.3 to 0.9) −0.9 (−1.9 to 0.1)	"the doxycycline (smokers) fared no better than the control (smokers) on any of the outcome parameters"
Brickfield et al., 1986[21]	Erythromycin	50	23	Cough score Sputum production score Work disablity score	NA§ NA§ NA§	"all of the differences favoring erythromycin occurred in the nonsmoker group, and all of the differences favoring placebo occurred in the smoker group"
Dunlay et al., 1987[22]	Erythromycin	63	24	Sputum production score Symptom mean score	0.5 (0.0 to 1.0) 0.6 (−0.1 to 1.1)	"smoker and nonsmoker symptom severity scores were not statistically different on any day"
Scherl et al., 1987[23]	Doxycycline	31	11	Days of cough Days of sputum production Days of fever Days off work	1.4 (−0.5 to 3.3) 1.9 (−0.1 to 3.9) 0.5 (−0.9 to 1.9) 0.5 (−0.9 to 1.9)	NA
Hueston, 1994[24]	Erythromycin	46	23	Days of productive cough	−0.4 (−2.4 to 1.6)‖	"no difference in response rates was seen in smokers as compared with nonsmokers"
Verheij et al., 1994[25]	Doxycycline	140	105	Days with frequent cough Days of productive cough Days of feeling ill Days of impaired activities	1.5 (0.4 to 2.6) 0.5 (−0.4 to 1.4) 0.8 (−0.3 to 1.9) 0.9 (−0.1 to 1.9)	"smoking habits. . .did not show a significant increase in R^2 values in stepwise multiple regression"
King et al., 1996[26]	Erythromycin	91	31	Days off work Coughing frequency	1.4 (0.4 to 2.3) NA/NS	"using logistic regression analysis, responses to erythromycin and placebo treatment did not differ based on. . . smoking status"

* *Mean difference is mean duration or score in the placebo group minus mean duration or score in the antibiotic group. Positive numbers indicate benefit of antibiotic. 95% confidence intervals are in parentheses.*

† *No study provided sufficient data to calculate point estimates and confidence intervals for outcomes of smoking patients.*

‡ *Confidence interval from negative infinity to positive infinity, P = .5.*

§ *Point estimates and confidence intervals not available. Trend toward benefit of antibiotic among only nonsmokers reported in text of original article.*

‖ *From Bent et al., reference 6.*

NA, not available; NS, not significant according to original article text.

of the 276 smokers included in the other trials was not possible due to insufficient reporting stratified by smoking status.

Another limitation of this study is that these results apply only to relatively healthy patients. Patients who participated in these trials were fairly young and had no comorbid cardiac or pulmonary disease. In contrast, antibiotics have been shown to be beneficial for patients with acute exacerbations of chronic bronchitis, regardless of smoking status.[27]

Controversy over antibiotics has overshadowed other interventions with potential benefits for patients with acute bronchitis, such as β-agonists. At 1 week, 41% of patients randomized to oral albuterol and 82% of patients randomized to erythromycin were still coughing (P = .004).[28] Of 17 smokers in this trial, 45% given albuterol and 100% given erythromycin were still coughing at 1 week (P = .03). In a randomized, placebo-controlled trial, 78% of patients receiving inhaled albuterol returned to work at day 4, compared to 52% in the placebo group (P = .05).[24] At 1 week, 61% of patients given inhaled albuterol were still coughing, compared to 91% of patients in the placebo group (P = .02). In another study, inhaled fenoterol reduced symptoms for patients with wheezing on auscultation, bronchial hyper-responsiveness, or evidence of airflow obstruction.[29] Of 36 smokers in this trial, 72% in the fenoterol group and 48% in the placebo group had a reduction in total symptoms on day 7 (P = .19). Although β-agonists are generally well-tolerated, patients should be warned of common adverse effects, such as tremulousness, nervousness, or palpitations.[30]

Physicians should use an episode of acute bronchitis to counsel patients to stop smoking. Smokers should be told they are at risk for a prolonged course of illness[31] and of the risk of progression to chronic bronchitis if they continue smoking.[32] Physicians should offer a referral for counseling and offer nicotine replacement if patients are serious about quitting.

Given the current evidence, it is unlikely that antibiotics are more useful in smokers with acute bronchitis than nonsmokers. To definitively determine this, further trials are warranted in smokers with acute bronchitis. These trials should have well-defined inclusion criteria, have sufficient power to detect meaningful clinical differences between groups, and use validated outcome measures. In the meantime, smokers and nonsmokers alike should use symptomatic treatment, including inhaled β-agonists, cough suppressants, analgesics, and antipyretics,[15,16] and should avoid the use of antibiotics for acute bronchitis.

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