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.

Acute bronchitis is a self-limited upper respiratory condition in those without prior pulmonary disease, characterized by cough and lasting about 2 weeks. Sixty-five to eighty percent of patients with acute bronchitis receive antibiotics despite evidence antibiotics are at best marginally effective. 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. 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.

Despite this frequent practice, published reviews do not guide physicians faced with a smoker who has acute bronchitis. 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. 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
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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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,\textsuperscript{18} Williamson,\textsuperscript{20} Hueston,\textsuperscript{21} and Brickfield et al,\textsuperscript{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.\textsuperscript{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 \( P = .05 \)).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{18} Meta-analysis