

# Antibiotics in Chronic Obstructive Pulmonary Disease Exacerbations

## A Meta-analysis

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**Objective.**—A meta-analysis of randomized trials was performed to estimate the effectiveness of antibiotics in treating exacerbations of chronic obstructive pulmonary disease (COPD).

**Data Sources.**—English-language studies published from 1955 through 1994 were retrieved using MEDLINE, *Index Medicus*, bibliographies, and consultation with experts. MEDLINE search terms included “COPD,” “chronic bronchitis,” and “antibiotic(s).”

**Study Selection.**—Only randomized trials that enrolled patients having an exacerbation of COPD, used an antibiotic in the treatment group and placebo in the control group, and provided sufficient data to calculate an effect size were included in the meta-analysis.

**Data Extraction.**—Descriptive and outcome data from each study were independently abstracted by two authors.

**Data Synthesis.**—Overall summary effect size of the nine trials satisfying all inclusion criteria was 0.22 (95% confidence interval [CI], 0.10 to 0.34), indicating a small benefit in the antibiotic-treated group. Similar analysis of the six studies that provided data on peak expiratory flow rate changes revealed a summary effect size of 0.19 (95% CI, 0.03 to 0.35) and a summary change in peak expiratory flow rate of 10.75 L/min (95% CI, 4.96 to 16.54 L/min) in favor of the antibiotic-treated group. Sensitivity analyses did not significantly affect these results.

**Conclusions.**—These analyses suggest a small but statistically significant improvement due to antibiotic therapy in patients with exacerbations of COPD. This antibiotic-associated improvement may be clinically significant, especially in patients with low baseline flow rates.

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CHRONIC obstructive pulmonary disease (COPD) is a clinical syndrome that affects millions of Americans each year. Subdivided into chronic bronchitis and emphysema, COPD is the fourth leading cause of death<sup>1</sup> and affects approximately 20% of adults in the United States.<sup>2</sup> Chronic bronchitis is a clinical diagnosis, defined by the daily production of sputum for at least 3 consecutive months in 2 consecutive years.<sup>3</sup> Exacerbations usually are manifested as an

increase in cough, a change in the color or quantity of sputum, or worsening dyspnea. Although a great number of insults may lead to exacerbations of COPD, the most common identifiable cause is upper respiratory tract infection.<sup>4,5</sup>

Antibiotics have been used for many decades to treat patients with exacerbations of chronic bronchitis, but the efficacy of this therapy is unclear.<sup>6,7</sup> Clinical trials examining this issue have produced mixed results, making it difficult to draw conclusions regarding benefit. Reviews<sup>8-12</sup> and editorials<sup>13-16</sup> have attempted to provide guidance, but qualitative summaries may lack objectivity and do not provide quantitative estimates.

We performed a meta-analysis of the published randomized trials to answer the question, “Are antibiotics beneficial in patients with COPD exacerbations?” Using explicit inclusion criteria and ac-

cepted quantitative methods, a meta-analysis<sup>17-19</sup> provides summary estimates of effectiveness that may clarify the disparate results of previous trials<sup>20</sup> and reduce the bias inherent to qualitative reviews.

## METHODS

### Literature Review

The literature review began with a computerized MEDLINE search using the terms “COPD,” “chronic bronchitis,” “exacerbation,” and “antibiotic(s).” The search included English-language articles published between January 1, 1955, and May 1, 1994. *Index Medicus* was hand searched to locate relevant articles published before 1966. The reference lists of all retrieved articles were scanned, and experts were contacted to identify potential eligible reports not identified in the MEDLINE search.

Inclusion criteria for the meta-analysis consisted of the following: randomized trials using an antibiotic in the treatment group and placebo in the control group; subjects with a presumed diagnosis of COPD (chronic bronchitis or emphysema) and thought to be having an exacerbation; follow-up for at least 5 days; and sufficient data presented to calculate an effect size (ES) of a continuous outcome variable comparing treatment with placebo.

Studies were excluded if they were nonexperimental in design, compared one antibiotic with another without a placebo arm, or if antibiotics were given for prevention of exacerbations.

For each study, two authors independently abstracted the author, journal, title, year of publication, sample size, average age of subjects, hospitalized or outpatient status of subjects, antibiotic regimen used, major outcome measure(s) for each study, peak expiratory flow rate (PEFR), and incidence of reported side effects. Discussion and consensus were used to resolve discrepancies in the abstracted data.

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## Analysis

No common outcome measure was available from all nine studies. When multiple outcome measures were available from one study, we chose the outcome that was specifically identified in the study's stated objectives and was measured as a continuous variable (eg, mean number of days ill, severity score by examining physician, PEFr, and symptom score reported by patient). We transformed each outcome into units of SDs, giving a comparable ES for each study. The study-specific ES was the difference in mean outcome for the antibiotic and placebo groups, divided by the pooled SD of the outcome measure. The summary ES across studies was calculated as the weighted average of the study-specific ESs, with weights equal to the inverse of the estimated variance of each. The significance of the summary ES, 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 ESs to an appropriate  $\chi^2$  distribution, with the same weights being used. These calculations were carried out according to standard formulas<sup>21</sup> and are based on

assumptions that the outcomes are normally distributed and the sample sizes are approximately equal in the antibiotic and placebo groups. The first assumption is conservative in its effect, since the variance of each study-specific ES under the implied *t* distribution is larger than the asymptotic variance, which might otherwise be used.<sup>22</sup> Alternative calculations not dependent on the second assumption gave essentially identical results.

We also calculated a summary measure using the six studies providing a common outcome measure, difference between the antibiotic and placebo groups in mean change in PEFr. In this case, the summary measure was the weighted average of the difference between the antibiotic and placebo groups in mean change in PEFr for each study. Weights were given by the inverse of the variance of each mean difference, estimated using the pooled SD for each study. Tests of the significance of the observed summary difference in PEFr and of heterogeneity were also performed.<sup>21</sup>

We carried out two sensitivity analyses. In two studies,<sup>23,24</sup> outcome measures were reported that yielded smaller study-specific ESs than the outcome measures that we chose to use in the main meta-analysis. To determine the impact on the overall summary estimate, we calculated summary effects using these alternative outcome measures. Furthermore, three studies<sup>25-27</sup> gave results based on number of exacerbations rather than number of individual subjects, preventing us from accounting for within-subject correlation and potentially underestimating the variance of the effect measures. Thus, we also calculated a summary effect measure excluding these three studies.

In addition, we summarized data separately for outpatients<sup>25-29</sup> and hospitalized patients.<sup>23,24,30,31</sup>

## RESULTS

The computerized search of MEDLINE retrieved 214 reports. Search of *Index Medicus* revealed 25 additional articles. Nine reports<sup>23-31</sup> satisfied all inclusion criteria and were included in the meta-analysis. One study<sup>32</sup> was excluded because the outcome (proportion of each group that showed improvement) could not be expressed as a continuous variable. Another provided data only in a letter to the editor<sup>33</sup> and therefore was excluded. Reasons for exclusion are delineated in Table 1. Details of the eligible articles appear in Table 2.

The ES for each study and the summary ES are shown in Figure 1. The overall summary ES was 0.22 (95% CI, 0.10 to 0.34), indicating a small benefit (about 0.25 SD) in the antibiotic-treated group. When data from the six studies that provided information on changes in PEFr were summarized using standardized ESs, the summary ES was 0.19 (95% CI, 0.03 to 0.35), as shown in Figure 2. To quantitate the benefit in the antibiotic-treated groups in terms of PEFr, we summarized the actual difference between antibiotic and placebo groups in mean change in PEFr in the same six studies (Figure 3). The summary difference in PEFr was 10.75 L/min (95% CI, 4.96 to 16.54 L/min) in favor of the antibiotic-treated group.

Sensitivity analyses using different outcomes and excluding the three studies that based outcomes on the number of exacerbations rather than the number of subjects did not significantly affect the results. Subanalysis including only data on outpatients<sup>25-29</sup> revealed a summary ES of 0.17 (95% CI, 0.03 to 0.30), and an analysis including only data from hospitalized patients<sup>23,24,30,31</sup> showed a summary ES of 0.38 (95% CI, 0.13 to 0.62).

A test of heterogeneity failed to reach statistical significance in any analysis,

Table 1.—Reasons for Exclusion of Reports From Literature Search

Primary Reason for Exclusion	No. of Reports
Not original data	76
No control group	61
Main intervention was not antibiotic therapy	48
Included non-COPD* patients	22
Letters to the editor	10
Failure to randomize	6
Antibiotics used for prophylaxis of exacerbations	6
Unable to express outcome as a continuous variable	1
<b>Total</b>	<b>230</b>

\*COPD indicates chronic obstructive pulmonary disease.

Table 2.—Randomized Trials of Antibiotics in Chronic Obstructive Pulmonary Disease Exacerbations

Source, y	Setting	No. of Subjects	Antibiotic Regimen	Main Outcome Measure(s)†	Effect Size‡
Elmes et al, 1957 <sup>25</sup>	Outpatient	113*	Oxytetracycline	Days of illness	0.30
Berry et al, 1960 <sup>28</sup>	Outpatient	33	Oxytetracycline	Overall symptom score	0.71
Fear and Edwards, 1962 <sup>26</sup>	Outpatient	119*	Oxytetracycline	Overall score by physician	0.31
Elmes et al, 1965 <sup>23</sup>	Inpatient	56	Ampicillin	Change in PEFr	0.49
Petersen et al, 1967 <sup>30</sup>	Inpatient	19	Chloramphenicol	Change in PEFr	-0.04
Pines et al, 1972 <sup>31</sup>	Inpatient	149	Tetracycline	Overall score by physician/change in PEFr	0.39
Nicotra et al, 1982 <sup>24</sup>	Inpatient	40	Tetracycline	Final PaO <sub>2</sub> /change in PEFr	0.38
Anthonisen et al, 1987 <sup>27</sup>	Outpatient	310*	Combination of sulfamethoxazole and trimethoprim, amoxicillin, or doxycycline	Days of illness/change in PEFr	0.23
Jorgensen et al, 1992 <sup>29</sup>	Outpatient	262	Amoxicillin	Overall score by physician/change in PEFr	-0.09

\*Studies in which the unit of analysis is number of exacerbations; in the other studies, the unit of analysis is the number of patients.

†PEFr indicates peak expiratory flow rate.

‡Effect size is the difference between the mean outcome in the antibiotic and placebo groups divided by the pooled SD.

suggesting that the results of the studies were homogeneous in all analyses and could be combined.

## COMMENT

Exacerbation of COPD is a common medical problem that is likely to become more frequent as the US population ages.<sup>1,34</sup> Exacerbation in patients with COPD is often treated with a course of oral antibiotics,<sup>35-38</sup> although the efficacy of this therapy has not been conclusively established by a large randomized trial.

Our meta-analyses show a small but statistically significant improvement due to antibiotic therapy in patients with COPD exacerbations. Because of the diversity of the outcome measures, a summary estimate of the effect of antibiotics was based on units of SD.<sup>19,39,40</sup> This method is useful for deciding whether antibiotics are beneficial but does not quantitate the benefit.

Analysis of the difference between antibiotic and placebo groups in mean change in PEFr from the six studies that provided such data showed a summary improvement of 10.75 L/min favoring the antibiotic group. This antibiotic-associated improvement is small but could be clinically significant, especially in COPD patients with low baseline PEFr.

The results of our meta-analysis should be interpreted with caution. The trials reviewed used diverse subject selection criteria, measured various outcomes, and used several different antibiotic regimens. Despite use of disparate subject selection criteria, tests of heterogeneity did not suggest that the patient populations were significantly different. Pooling of disparate outcomes provides a good estimate of the overall direction of benefit but does not allow direct assignment of the likely clinical benefit. However, because two thirds of the studies measured PEFr, we were able to calculate a clinically meaningful summary estimate. It is reassuring that the overall standardized ES from all nine studies is similar to the same measure calculated from the six studies used to calculate the overall difference in PEFr. Although different antibiotics were used for varying durations, all groups were given treatment for at least 5 days. The spectrum of organisms covered by the various antibiotics used were similar, representing the most common pathogens causing COPD exacerbation. Thus, it is unlikely that the specific regimen used made a significant difference in efficacy.

The outcome that was standardized and used in the overall summary ES was often chosen from among several outcomes. Outcome measures could have

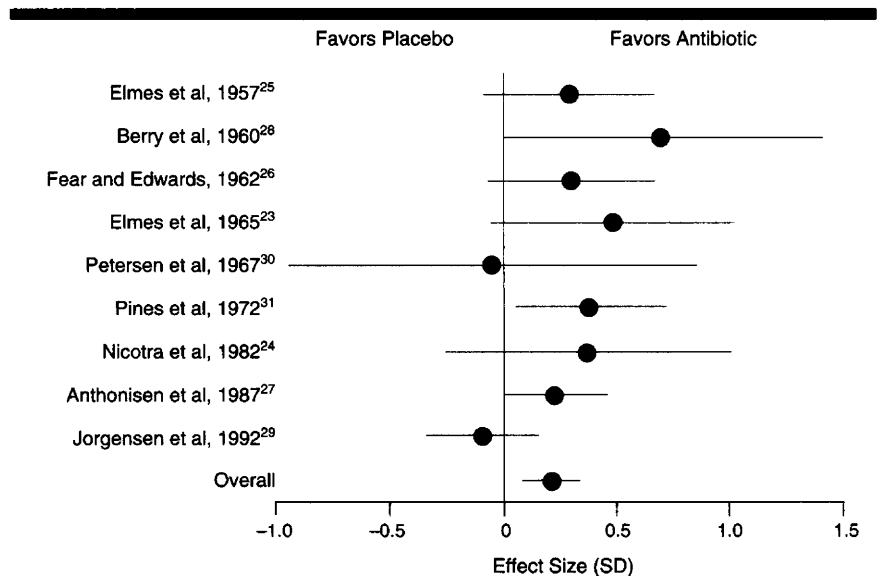


Figure 1.—Effect sizes of randomized trials and summary overall estimate. Effect size is the difference between the mean outcome in the antibiotic and placebo groups divided by the pooled SD. Horizontal lines denote 95% confidence intervals. Dots represent point estimates.

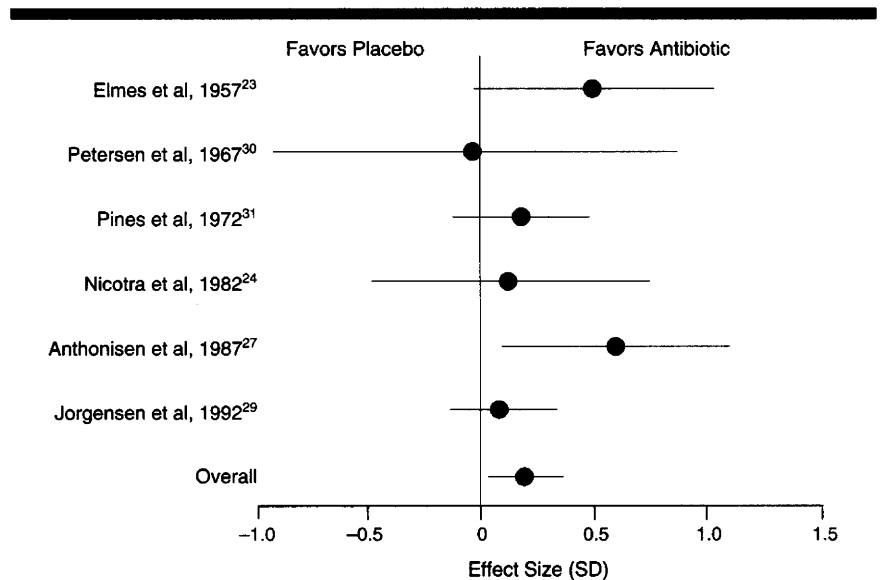


Figure 2.—Effect sizes of difference in peak expiratory flow rate change in the six randomized trials and summary estimate. Effect size is the difference between the mean outcome in the antibiotic and placebo groups divided by the pooled SD. Horizontal lines denote 95% confidence intervals. Dots represent point estimates.

been selected preferentially to show benefit to antibiotic-treated patients. We addressed this possible bias by selecting outcome measures based on each study's stated objectives and by performing sensitivity analyses using other outcomes. In no case did the use of a different outcome measure significantly change the overall summary effect.

Basing outcome measures on the number of exacerbations rather than the number of patients with exacerbations could

bias the results in favor of finding a difference between the antibiotic and placebo group because within-subject correlation between multiple exacerbations may underestimate the actual variability of the ES. However, only three of the summarized studies measured outcomes based on number of exacerbations. In addition, when we doubled the estimated variance, thereby halving the weights of each of the three studies in question, summary effect was not significantly different.

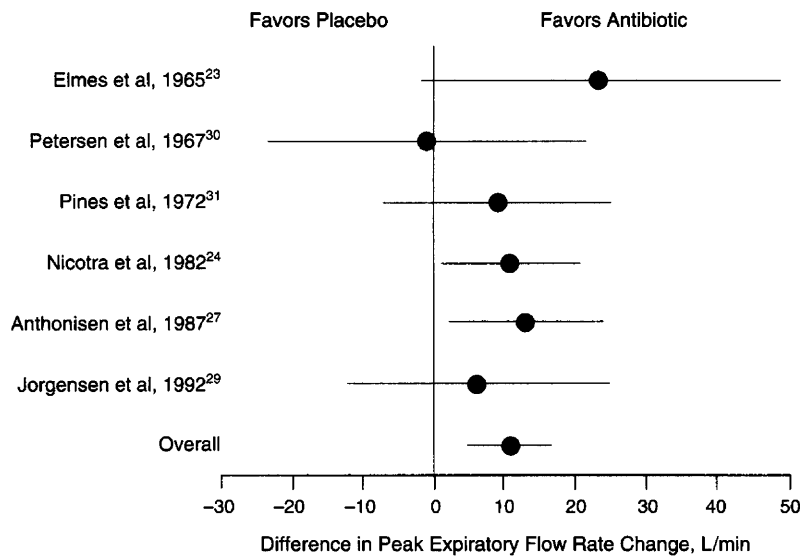


Figure 3.—Difference in peak expiratory flow rate change (liters/minute) in the six randomized trials and summary estimate. Horizontal lines denote 95% confidence intervals. Dots represent point estimates.

Finally, publication bias also must be considered since this meta-analysis included only published trials.<sup>41</sup> Summary

ESs may be inflated due to publication bias if positive studies are more likely to be published than negative studies. How-

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ever, because there is uncertainty regarding the benefit of antibiotics, we believe that studies that show no benefit from antibiotics in COPD exacerbations are as likely to be published as those that show benefit. For example, of the nine original studies that we used for analysis, five did not show a statistically significant benefit in the antibiotic-treated group, yet were published. The study that was not included in the analysis because no continuous outcome was reported<sup>32</sup> found a large benefit to antibiotic use.

In conclusion, the overall summary standardized ES and the summary improvement in PEFr suggest similar benefit from antibiotic therapy in patients with COPD exacerbations. The benefit was relatively small (a 10.75-L/min improvement in PEFr) but may be clinically significant, especially in patients with severe disease. Hospitalized patients appeared to benefit more than outpatients, perhaps because they are sicker at the start of therapy.

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