Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)

Ram FSF, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2009, Issue 1

http://www.thecochranelibrary.com
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>3</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>METHODS</td>
<td>3</td>
</tr>
<tr>
<td>RESULTS</td>
<td>6</td>
</tr>
<tr>
<td>Figure 1.</td>
<td>9</td>
</tr>
<tr>
<td>Figure 2.</td>
<td>10</td>
</tr>
<tr>
<td>Figure 3.</td>
<td>10</td>
</tr>
<tr>
<td>Figure 4.</td>
<td>11</td>
</tr>
<tr>
<td>Figure 5.</td>
<td>11</td>
</tr>
<tr>
<td>Figure 6.</td>
<td>12</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>13</td>
</tr>
<tr>
<td>AUTHORS’ CONCLUSIONS</td>
<td>15</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>15</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>15</td>
</tr>
<tr>
<td>CHARACTERISTICS OF STUDIES</td>
<td>18</td>
</tr>
<tr>
<td>DATA AND ANALYSES</td>
<td>35</td>
</tr>
<tr>
<td>Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Mortality (short-term) during study intervention.</td>
<td>36</td>
</tr>
<tr>
<td>Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration or death).</td>
<td>37</td>
</tr>
<tr>
<td>Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Sputum purulent at end of treatment.</td>
<td>37</td>
</tr>
<tr>
<td>Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 PaCO2 (mmHg).</td>
<td>38</td>
</tr>
<tr>
<td>Analysis 1.5. Comparison 1 Antibiotics versus placebo, Outcome 5 PaO2 (mmHg).</td>
<td>38</td>
</tr>
<tr>
<td>Analysis 1.6. Comparison 1 Antibiotics versus placebo, Outcome 6 PEFR (L/min).</td>
<td>39</td>
</tr>
<tr>
<td>Analysis 1.7. Comparison 1 Antibiotics versus placebo, Outcome 7 Adverse events.</td>
<td>39</td>
</tr>
<tr>
<td>Analysis 1.8. Comparison 1 Antibiotics versus placebo, Outcome 8 Need for additional antibiotics.</td>
<td>44</td>
</tr>
<tr>
<td>Analysis 1.9. Comparison 1 Antibiotics versus placebo, Outcome 9 Respiratory rate (per minute).</td>
<td>44</td>
</tr>
<tr>
<td>Analysis 1.10. Comparison 1 Antibiotics versus placebo, Outcome 10 Heart rate (per minute).</td>
<td>45</td>
</tr>
<tr>
<td>Analysis 1.11. Comparison 1 Antibiotics versus placebo, Outcome 11 FEV1 (L).</td>
<td>45</td>
</tr>
<tr>
<td>Analysis 1.12. Comparison 1 Antibiotics versus placebo, Outcome 12 FVC (L).</td>
<td>46</td>
</tr>
<tr>
<td>Analysis 1.13. Comparison 1 Antibiotics versus placebo, Outcome 13 Duration of hospital stay (days).</td>
<td>46</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>46</td>
</tr>
<tr>
<td>FEEDBACK</td>
<td>48</td>
</tr>
<tr>
<td>HISTORY</td>
<td>49</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>49</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>49</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>49</td>
</tr>
<tr>
<td>INDEX TERMS</td>
<td>50</td>
</tr>
</tbody>
</table>
Antibiotics for exacerbations of chronic obstructive pulmonary disease

Felix SF Ram\textsuperscript{1}, Robert Rodriguez-Roisin\textsuperscript{2}, Alicia Granados-Navarrete\textsuperscript{3}, Judith Garcia-Aymerich\textsuperscript{4}, Neil C Barnes\textsuperscript{5}

\textsuperscript{1}School of Health Sciences, Massey University - Auckland, Auckland, New Zealand. \textsuperscript{2}Servei de Pneumologia, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain. \textsuperscript{3}Respiratory and Environmental Health Research Unit, Institut Municipal d’Investigació Mèdica, University of Barcelona, Barcelona, Spain. \textsuperscript{4}Respiratory and Environmental Health Research Unit, Institut Municipal d’Investigació Médica (IMIM) c/ Doctor Aiguader, 80, Barcelona, Spain. \textsuperscript{5}Department of Respiratory Medicine, London Chest Hospital, London, UK

Contact address: Felix SF Ram, School of Health Sciences, Massey University - Auckland, 24 Portsea Place, Chatswood, North Shore, Auckland, New Zealand. fsfram@yahoo.co.uk. (Editorial group: Cochrane Acute Respiratory Infections Group.)

Cochrane Database of Systematic Reviews, Issue 1, 2009 (Status in this issue: Edited, commented)
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
DOI: 10.1002/14651858.CD004403.pub2
This version first published online: 19 April 2006 in Issue 2, 2006. Re-published online with edits: 21 January 2009 in Issue 1, 2009.
Last assessed as up-to-date: 19 December 2005. (Help document - Dates and Statuses explained)

A B S T R A C T

Background
Most patients with an exacerbation of chronic obstructive pulmonary disease (COPD) are treated with antibiotics. However the value of their use remains uncertain. Some controlled trials of antibiotics have shown benefit (Berry\textsuperscript{1960}; Pines\textsuperscript{1972}) while others have not (Elmes\textsuperscript{1965b}; Nicotra\textsuperscript{1982}).

Objectives
To conduct a systematic review of the literature estimating the value of antibiotics in the management of acute COPD exacerbations.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2005, issue 4) which contains the Acute Respiratory Infections Group's Specialized Register; MEDLINE (1966 to December 2005); EMBASE (1974 to December 2005); Web of Science (December 2005), and other electronically available databases.

Selection criteria
Randomised controlled trials (RCTs) in patients with acute COPD exacerbations comparing antibiotic (for a minimum of five days) and placebo.

Data collection and analysis
Data were analysed using Review Manager software. Continuous data were analysed using weighted mean differences (WMD) and 95% confidence intervals (CI). Relative risks (RR) (and 95% CI) were calculated for all dichotomous data. Where appropriate, number needed to treat to benefit (NNT) and 95% CI were calculated.

Main results
Eleven trials with 917 patients were included. Ten trials used increased cough, sputum volume and purulence diagnostic criteria for COPD exacerbation. Eight-hundred and fifty-seven patients provided data for outcomes including mortality, treatment failure, increased sputum volume, sputum purulence, PaCO$_2$, PaO$_2$, peak flow and adverse events. Antibiotic therapy regardless of antibiotic choice significantly reduced mortality (RR 0.23; 95% CI 0.10 to 0.52 with NNT of 8; 95% CI 6 to 17), treatment failure (RR 0.47; 95% CI 0.36 to 0.62 with NNT of 3; 95% CI 3 to 5) and sputum purulence (RR 0.56; 95% CI 0.41 to 0.77 with NNT of 8; 95% CI 6 to 17). There was a small increase in risk of diarrhoea with antibiotics (RR 2.86; 95% CI 1.06 to 7.76). Antibiotics did not improve arterial blood gases and peak flow.

**Authors’ conclusions**

This review shows that in COPD exacerbations with increased cough and sputum purulence antibiotics, regardless of choice, reduce the risk of short-term mortality by 77%, decrease the risk of treatment failure by 53% and the risk of sputum purulence by 44%; with a small increase in the risk of diarrhoea. These results should be interpreted with caution due to the differences in patient selection, antibiotic choice, small number of included trials and lack of control for interventions that influence outcome, such as use of systemic corticosteroids and ventilatory support. Nevertheless, this review supports antibiotics for patients with COPD exacerbations with increased cough and sputum purulence who are moderately or severely ill.

**PLAIN LANGUAGE SUMMARY**

Despite their widespread use, the value of antibiotics in exacerbations of chronic obstructive pulmonary disease (COPD) remains controversial.

Exacerbations of COPD are often bacterial in origin and antibiotic therapy seems appropriate for suspected bacterial exacerbations. It is increasingly recognised that exacerbations are also caused by viral infections of the upper respiratory tract, or even by no infection, when antibiotic treatment does not seem warranted. In addition, there is a growing incidence of resistance to common antibiotics. Therefore, limiting unnecessary use of antibiotics in exacerbations of COPD is important to help control the incidence of antibiotic resistance. Eleven trials with 917 patients with moderate to severe COPD were included in this review. Use of antibiotics (regardless of the type) reduced the risk of patient deaths by 77% and the risk of the patient not responding to medical intervention by 53%. In addition, the chances of sputum remaining coloured (green-yellow) were reduced by 44%. As expected with antibiotic use there was an increased risk of diarrhoea. This review supports using antibiotics (regardless of the type) for patients with COPD exacerbations who are moderately or severely ill with increased cough and coloured sputum.
BACKGROUND

Description of the condition

The value of antibiotics in exacerbations of chronic obstructive pulmonary disease (COPD) remains controversial despite their widespread use. This controversy is largely based upon data suggesting that at least one third of exacerbations are non-infectious in origin (Celli 2004; GOLD 2005; NICE 2004). In addition, clinical trials of antibiotics in exacerbations have often yielded conflicting data, with several large studies failing to demonstrate a difference between antibiotics and placebo. COPD exacerbations have a serious impact on patients in terms of disease progression, morbidity and mortality, and poor quality of life (Gunen 2005). COPD involves enormous economic costs and, above all, is complex to manage. Exacerbations of COPD are usually assumed to be due to bacterial infection since they may be associated with increased sputum volume and purulence. Unfortunately the selection of antibiotic therapy for exacerbations of COPD is becoming an increasingly daunting task. Few conditions produce such a broad range of outcomes, require such customised approaches, or present with so many options for treatment.

Description of the intervention

As exacerbations of COPD are often bacterial in origin, antibiotic therapy is appropriate for suspected bacterial exacerbations (Soler 1998). Previous trials in patients with COPD have indicated that if there is (1) increased dyspnoea, (2) increased sputum production, or (3) increased purulence of sputum present, then the exacerbation is probably bacterial and is more likely to have a favourable outcome if antibiotics are administered (Anthonisen 1987; Ries 1996). International guidelines (BTS 1997; Celli 2004; GOLD 2005; NICE 2004) recommend antibiotic therapy if two of the three clinical criteria mentioned above are present. The production of purulent sputum, which may or may not be indicative of a bacterial exacerbation, is not necessary for initiation of antibiotic therapy.

How the intervention might work

It is known that the pathogens most often responsible for causing exacerbations of COPD include Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. influenzae), Pseudomonas aeruginosa (P. aeruginosa) and Moraxella catarrhalis (M. catarrhalis). Atypical pathogens are not usually a problem although evidence is emerging that Chlamydia pneumoniae (C. pneumoniae) may occasionally be found (NICE 2004). It is currently nearly impossible to identify the specific pathogen at initial patient assessment, therefore, it is usually necessary to treat the patient with a broad spectrum antibiotic in order to minimise treatment failures due to bacteriological causes. In any case, although sputum culture may be expected to clarify the role of antibiotics the results can be confusing since even in the stable clinical state some patients may be colonised and have a sputum culture that is positive for bacteria (Monso 1995; Riise 1994).

However, it is increasingly recognised that exacerbations may also be due to viral infections of the upper respiratory tract, or may be non-infective, so antibiotic treatment is not always warranted. Most patients are usually treated with a broad-spectrum antibiotic during an exacerbation, and several controlled trials have shown their beneficial effects (Berry 1960; Pines 1972). On the other hand, trials have also shown a lack of efficacy with antibiotic therapy for exacerbations of COPD (Elmes 1965a; Nicotra 1982). In addition, there is a growing incidence of in-vitro resistance among common bacterial agents, such as S. pneumoniae that cause community-acquired pneumonia (Paganin 2004). Therefore, appropriate use of antibiotics in exacerbations of COPD is imperative to help control the emergence of multi-drug resistant organisms.

Why it is important to do this review

Despite the many guidelines on the management of exacerbations of COPD this remains an extremely challenging and controversial area. We therefore decided to conduct a systematic review of the literature in order to help resolve the issues surrounding the value of antibiotic therapy for exacerbations of COPD.

OBJECTIVES

To estimate the value of antibiotic therapy in patients treated for exacerbations of COPD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) using an antibiotic in the treatment group and placebo in the control group. Non-randomised or quasi-RCTs were excluded. Studies were also excluded if they were non-experimental in design or compared one antibiotic with another without a placebo arm. All studies using antibiotics for the prevention of exacerbations were also excluded as a recently completed Cochrane review has addressed this question (Staykova 2003).

Types of participants

Patients with exacerbations of COPD (defined as a worsening of the previously stable situation with one or more of the following symptoms: increased sputum purulence, increased sputum volume, increased dyspnoea, increased wheeze, chest tightness or fluid
The diagnosis of COPD required one or both of the following definitions: (a) a history of chronic progressive symptoms (cough and/or wheeze and/or breathlessness) or (b) objective evidence of airflow obstruction, ideally by spirometric testing, that does not return to normal with treatment (BTS 1997; Celli 2004; GOLD 2005; NICE 2004). Studies that did not use the above criteria but made a clear clinical diagnosis of COPD or chronic bronchitis exacerbation, for example using the Medical Research Council 1965 criteria (MRC 1965), were also considered for inclusion.

Studies of patients with bronchiectasis, asthma, acute bronchitis without underlying COPD or other unrelated co-morbid conditions were excluded.

**Types of interventions**

Oral or intravenous antibiotics administered daily for a minimum period of at least five days.

**Types of outcome measures**

**Primary outcomes**

- Duration of hospital admission (for inpatients) and number of hospital re-admissions (for outpatients).
- Admission to an intensive care unit (ICU) (requiring mechanical support).
- Lung function measured at the end of the study period (for example forced expiratory volume in one second \(FEV_1\), vital capacity (VC), and peak expiratory flow rate (PEFR)).

**Secondary outcomes**

- Mortality during study intervention period.
- Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration, or death).
- Reduction in sputum volume and purulence measured at the end of the study period.
- Arterial blood gases.
- Adverse events measured at the end of the study period.
- Additional course of antibiotics (other than the antibiotics given as study medicine).
- Improvement in dyspnoea measured at the end of the study period.
- Recurrence (time to next exacerbation) or hospital readmission rates, or both.
- Health related quality of life or functional status measures.
- Time off work.

**Search methods for identification of studies**

**Electronic searches**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2005, issue 2) which contains the Acute Respiratory Infections Group’s Specialized Register; MEDLINE (1966 to December 2005); EMBASE (1974 to December 2005); the Web of Science, and on-line medical web sites including journal websites (December 2005). See Appendix 1 for the MEDLINE search terms. These search terms were adapted for the other electronic databases.

The review authors then edited the terms in December 2005 and searched for trials in CENTRAL (The Cochrane Library 2005, issue 4), MEDLINE (1966 to December 2005), EMBASE (1974 to December 2005), Web of Science (December 2005) and key respiratory online journal websites and conference proceedings (see below for list) using the following terms.

**MEDLINE**

1 COPD
2 emphysema
3 chronic bronchitis
4 chronic obstructive bronchitis
5 chronic airflow limitation
6 chronic airflow obstruction
7 chronic airways obstruction
8 non-reversible obstructive airways disease
9 chronic obstructive airways disease
10 chronic obstructive lung disease
11 or/1-11
12 antibiotic* penicillin*
13 penicillin G
14 penicillin V
15 amoxicillin
16 ampicillin
17 amoxicillin/clavulanic acid
18 cefalosporin*
19 cefaclor
20 cefalexine
21 cephalotin
22 cefazolin
23 cefixime
24 cefotaxime
25 cefpodoxime
26 cephradine
27 ceftriaxone
28 cefuroxime
29 cefuroxime axetil
30 cefuroxime axetil
31 tetracyclin*
32 demeclocycline
33 doxycycline
34 minocycline
35 oxytetracycline
36 *cycline
37 macrolides
Searching other resources

Bibliographies of each selected RCT were searched for additional papers that may have contained further RCTs. Authors of identified RCTs and pharmaceutical companies producing antibiotics were contacted for other published, unpublished or ongoing studies. Web-based clinical trial registers were also searched for ongoing studies (for example: www.trialscentral.org; www.biomedcentral.com; www.clinicaltrials.gov; www.doh.gov.uk; www.controlled-trials.com).

The following websites were searched: Chest, European Respiratory Journal, Respiratory Medicine, British Medical Journal, American Journal of Respiratory and Critical Care Medicine, American Journal of Respiratory Medicine, Bandolier Pulmonary Medicine, American Journal of Medicine, Respiratory Care Online, Thorax, Journal of the American Medical Association, Canadian Medical Association Journal, Annals of Internal Medicine Home, American Association for Respiratory Care, American Thoracic Society, British Thoracic Society, American College of Chest Physicians, British Lung Foundation, Australian and New Zealand Society of Respiratory Science, GOLD, General Practice Airways Group.

Data collection and analysis

Abbreviations used in the text are defined in Table 1.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Arterial partial pressure of oxygen</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>Arterial partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume</td>
</tr>
<tr>
<td>bpm</td>
<td>Breaths (or beats) per minute</td>
</tr>
</tbody>
</table>

Table 1. Abbreviations used in text
Selection of studies
Two review authors independently selected trials for inclusion and assessed all trials that appeared potentially relevant. Agreement between review authors for inclusion of studies was recorded.

Data extraction and management
All trials were entered and graded using the following Cochrane principles regarding allocation concealment: Grade A - adequate, Grade B - unclear, Grade C - inadequate and Grade D - allocation concealment not used. We discussed methodological study issues such as dropout rates, blinding of outcome assessment, use of intention-to-treat analysis, contamination, and co-interventions on a per study basis. Any disagreements between review authors were resolved by discussion.

All included study authors were contacted in order to obtain further information about their trials. Two review authors independently abstracted data which were double checked before entering into Review Manager (RevMan) 4.2 software.

Measures of treatment effect
We used a fixed-effect model (or random-effects model if statistical heterogeneity was observed) for continuous data. We analysed the data using weighted mean differences (WMD) and 95% confidence intervals (95% CI) for outcomes measured on the same scale. We calculated relative risks (RR) for all dichotomous data and expressed the overall results with 95% CI. Where appropriate, number needed to treat to benefit (NNT) and 95% CI were calculated for good outcomes and number needed to treat to harm (NNH) calculated for 'bad outcomes'. NNT was calculated using the following formula: NNT = 1/ [CER * (1 - RR)] (where CER = control event rate and RR = relative risk).

Subgroup analysis and investigation of heterogeneity
If there was evidence of heterogeneity that was not explained by study quality we intended to conduct the following sub-group and sensitivity analyses.

- Oral versus intravenous antibiotics.
- Outpatients versus hospitalised patients.
- Type and duration of antibiotic intervention.
- Disease severity.
- Location of trial (primary or secondary care).

As meta-analysis of a single trial is nonsensical and not interpretable, we only discussed in detail outcomes that contained more than one trial.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search
Of the 11 included studies, two were conducted in the community (Anthonisen 1987; Jørgensen 1992), eight in hospital inpatient medical wards and one (Nouira 2001) in a medical intensive care unit (ICU). As the aim of this review was to determine the value of antibiotics in exacerbations of COPD all included trials compared an antibiotic with placebo. Identifying which antibiotic or antibiotic class should be used when antibiotic therapy is deemed necessary for an exacerbation would require a separate review and is beyond the scope of this review. One trial was translated from Spanish (Alonso 1992), one was reported as a conference proceeding (Hansen 1990), Manresa 1987 was reported as a clinical letter to a journal, Pines 1968 was a pilot study and reported in summary format only but published with a larger study as one manuscript (the large trial was not included in the review as it did not have a placebo group). The remaining seven studies (Anthonisen 1987; Elmes 1965a; Jørgensen 1992; Nicora 1982; Nouira 2001; Petersen 1967; Pines 1972) were reported as full-text journal articles. All included studies (except Hansen 1990) had inclusion criteria of increased cough and sputum purulence. Further details on included studies are shown in the table 'Characteristics of included studies'.

Alonso 1992 Patients were eligible if they had a clinical diagnosis of COPD at the time of a hospital admission. Patients were excluded if they had received antibiotic treatment during the last two weeks or had another disease such as left ventricular failure, stroke, pneumonia, pneumothorax, non-cutaneous cancer, coma or a temperature greater than 38°C. Ninety patients with a mean age of 68 years (76 male, 14 female) were included in the trial. At hospital admission the following means were recorded: FEV1 30%, FVC 52%, PEF 21%, PaO2 54 mmHg and respiratory rate 27. Sixty-four percent of patients were ex-smokers and 36% were current smokers. All patients were treated with theophylline, inhaled bronchodilators and FiO2 24%.

Anthonisen 1987 Patients in the community were eligible for the trial if they were at least 35 years old and had a clinical diagnosis of COPD. They were also required to have FEV1 more than 70% predicted and TLC greater than 80%. Patients were excluded if responses to bronchodilator increased to greater than 80% of predicted FEV1. Also excluded were those with other diseases serious enough to influence their quality of life or clinical course (for example cancer, stroke) or diseases likely to require antibiotics (for example recurrent sinusitis or urinary tract infection). Following baseline, demographics means were recorded for all patients: FEV1 34%, FVC 60%, FRC 165%, TLC 129%, RV 205%, bronchodilator response to FEV1 112%, PEFR 227 L/min, PaO2 68 mmHg, PaCO2 36 mmHg and pH 7.42.

Elmes 1965a Patients were eligible for the trial if they had a clinical diagnosis of exacerbation of chronic bronchitis at the time of admission to hospital; in addition, if they had at least a three-year
history of productive cough for more than three months in the year, and a history of at least two illnesses with increased sputum during that time. Patients were excluded if they had another disease such as left ventricular failure, lung abscess, carcinoma of the lung, long-standing bronchiectasis, active tuberculosis, evidence of disseminated infection or sepsicaemia, allergy to penicillin or were on adrenal corticoid treatment. Fifty-six patients (20 male, 36 female) were included in the trial, with mean age 63 years. The two study groups were not different at baseline regarding sputum appearance, sputum volume (antibiotic group 43 ml; placebo group 59 ml) or PEFR (antibiotic group 69 L/min; placebo group 89 L/min).

Hansen 1990 This study was published as a conference abstract, therefore, devoid of details. However, all patients were reported to have had a hospital admission due to their COPD exacerbation. Exclusion criteria and baseline demographics were not reported. Jørgensen 1992 Patients with exacerbation of chronic bronchitis (defined as continuous cough and expectoration present for at least three months of the year, in more than two consecutive years) were included. Patients with pneumonia (on auscultation or x-ray), temperature greater than 38.5°C, heart rate greater than 100 bpm, antibiotics within the previous seven days, pregnancy, allergy to penicillin, uncompensated heart failure, treatment with oral steroids or immunosuppressants were excluded. Demographics were as follows, antibiotic group (n = 133): 77 females, 56 males, mean age 59 years and 76% of included patients were smokers; placebo group (n = 137): 78 females, 59 males, mean age 60 years and 72% were smokers.

Manresa 1987 Patients with chronic bronchitis exacerbations were considered for inclusion in the trial if at the time of a hospital admission there was an increase in symptoms (cough, dyspnoea, volume and purulence of sputum). They were excluded if there was evidence of parenchymal consolidation on chest x-ray or of another pulmonary or cardiac disease. Baseline demographics were as follows, antibiotic group: age 66 years, respiratory rate 32 per minute, heart rate 105 bpm, PEFR 169 L/min, PaO$_2$ 40 mmHg, PCO$_2$ 59 mmHg; placebo group: age 67 years, respiratory rate 27 per minute, heart rate 94 bpm, PEFR 177 L/min, PO$_2$ 38 mmHg, PCO$_2$ 66 mmHg.

Nicotra 1982 Patients admitted to hospital with a diagnosis of chronic bronchitis (defined by the presence of significant sputum production for at least three months of the preceding two years) who also had an exacerbation (defined as an increase in dyspnoea, cough, and sputum production) were recruited. Patients were excluded if they had a new or changed parenchymal lung infiltrate, temperature greater than 38.5°C, blood leukocyte count greater than 12000/mm$^3$ (unless with an increase in corticosteroids dosage in previous three days), antibiotic use during previous seven days, or need for mechanical assisted ventilation. Baseline demographics for the antibiotic group was: age 57.0 years, male/female 10/10, sputum volume 60 ml per 24 hours, PaCO$_2$ 45 mmHg, pH 7.39, FVC 1.84 L, FEV$_1$ 0.88 L, PEFR 160 L/min, FEV$_1$/FVC 47%; placebo group: age 55 years, male/female 10/10, PaCO$_2$ 42 mmHg, pH 7.43, FVC 1.67 L, FEV$_1$ 0.92 L, PEFR 159 L/min, FEV$_1$/FVC 53%. Both study groups had 75% current smokers. Nouira 2001 Patients aged 40 years or older who were admitted to the medical ICU for exacerbation of COPD were included in the study. Patients were eligible if they were admitted to the ICU with exacerbation of COPD and required mechanical ventilation within the first 24 hours of admission. Since requirement for mechanical ventilation was a study entry criterion (unlike other included studies) we decided to conduct a sensitivity analysis with and without the inclusion of this trial for all outcomes that this trial contributed data. Patients were excluded if they had received antimicrobial treatment in the previous 10 days, if alveolar infiltrates were present on chest radiographs on admission, and if they had previously enrolled in the study. The absence of radiological signs of pneumonia was confirmed in all patients by consensus of senior physicians; a second chest radiograph was done when needed. Patients with a known history of asthma or bronchiectasis were excluded. Patients were also excluded if they were allergic to quinolone derivatives, were pregnant or breast feeding, were terminally ill or immunocompromised, had hepatic disease or severe renal impairment, or had gastrointestinal disease that could affect drug absorption. Patients with concomitant infection requiring systemic antibacterial therapy were also excluded. Baseline demographics in the antibiotic group were as follows (figures represent means): age 66 years, male/female 42/5, FEV$_1$ 0.79 L, PaCO$_2$ 74 mmHg, pH 7.22, initial non-invasive ventilatory support in 32 (or 68%), conventional ventilatory support initially in 17 (or 36%), smoking history of 55 pack-years (that is a 20 pack of cigarettes smoked daily for 55 years). Placebo group baseline demographics were: age 66 years, male/female 42/4, FEV$_1$ 0.74 L, PaCO$_2$ 79 mmHg, pH 7.21, initial non-invasive ventilatory support in 32 (or 69%), conventional ventilatory support initially in 14 (or 31%), smoking history of 54 pack-years (that is to say, a 20 pack of cigarettes smoked daily for 54 years).

Petersen 1967 Patients were included if they had a diagnosis of chronic bronchitis with cough and expectoration on most days during at least three consecutive months in each of two or more successive years. Most of the patients were classified as having chronic mucopurulent obstructive bronchitis. Only patients aged 45 to 75 years old were selected for inclusion in the trial. Patients were excluded if they had severe deformities of the spine or chest, localised or generalised specific lung disease, or with signs of cardiac insufficiency. Baseline demographics were presented for all patients: mean PEFR (L/min) of 480 (men) and 350 (women); PaCO$_2$ 46 mmHg; RV/TLC 39% (men), 43% (women).

Pines 1968 We could only use data from the pilot study in this trial as the main study did not have a placebo group. Patients were eligible for the trial if they were aged greater than 50 years, had a history of chronic bronchitis for longer than five years and a definite history during the past six weeks of exacerbation of symp-
Patients were eligible for the trial if they were greater than 60 years old and had a history of chronic bronchitis for longer than five years with a definite history during the past six weeks of an exacerbation of symptoms. They were also required to be male, moderately-to-severely ill on admission (as judged by the medical team), have persistent purulent sputum and a PEFR less than 200 L/min. Patients were excluded if they had allergy to penicillin, asthma, bronchiectasis, lung cancer, sputum eosinophilia or blood urea. The trial had 30 participants (15 in each study group). The two groups were comparable with antibiotic and placebo groups, respectively: mean age 66 and 68 years; 8 and 7 were severely ill; mean initial temperature 37°C in both groups; mean white blood cell count 12,100 and 12,000 per mm³; mean sedimentation rate 47 and 52 mm in the first hour; mean PEFR 90 and 85 L/min; mean capillary PCO₂ 68 and 71 mmHg; and all patients had persistently purulent sputum.

Pines 1972 Patients were eligible for the trial if they were greater than 60 years old and had a history of chronic bronchitis for longer than five years with a definite history during the past six weeks of an exacerbation of symptoms. They were also required to be male, have a failure of at least one previous treatment with antibiotics, be moderately to severely ill on admission (as judged by the medical team), have persistent purulent sputum and a PEFR less than 200 L/min. Patients were excluded if they had asthma, bronchiectasis or other pulmonary disease, or sputum eosinophilia. At the start of the trial all patients had a mean PEFR ranging from 142 to 149 L/min.

Risk of bias in included studies

All included studies were RCTs and all except one trial (Hansen 1990) stated clearly the allocation of patients to treatment in a random or blinded manner. The Hansen 1990 trial was reported as an abstract only and was, therefore, devoid of details. Using the Cochrane grading system, 10 studies were graded as ’A’ (Alonso 1992; Anthonisen 1987; Elmes 1965a; Jørgensen 1992; Manresa 1987; Nicotra 1982; Nouira 2001; Petersen 1967; Pines 1968; Pines 1972) and one as ’B’ (Hansen 1990). There was total agreement between the two review authors on the Cochrane study quality grading for the 11 included studies. Most of the studies adequately reported withdrawals and dropouts. Authors of all included studies were contacted for additional information or verification of study quality and to obtain further data. To date only two authors (Alonso 1992; Jørgensen 1992) have responded with more data and information. This is not surprising as the majority of the included studies are ’old’, with the earliest included trial published in 1965.

Effects of interventions

Search for studies

The electronic search yielded 409 citations: 296 references were found in EMBASE, MEDLINE and online respiratory journal databases; and 103 citations were obtained from CENTRAL. An additional 10 references were obtained from bibliographic searching of relevant articles. Of a total of 409 abstracts, 31 studies were identified independently as potentially suitable. Two authors independently scanned the full text of 31 studies and excluded 18 studies as not relevant to the review intervention. Reasons for exclusion were provided in the table ’Characteristics of excluded studies’. Two studies are ongoing trials (Fartoukh 2004; NCT00170222). Eleven studies were included (Alonso 1992; Anthonisen 1987; Elmes 1965a; Hansen 1990; Jørgensen 1992; Manresa 1987; Nouira 2001; Nicotra 1982; Petersen 1967; Pines 1968; Pines 1972). There was 100% agreement between the two authors on exclusion and inclusion of studies.

Comparisons and outcomes

Mortality (short-term) during study intervention (Analysis 1.1)

See Analysis 1.1

Four trials with 356 patients reported significantly lower mortality with antibiotic use (Elmes 1965a; Pines 1968; Pines 1972; Nouira 2001). A 77% reduction in RR of mortality was observed with antibiotic use (RR 0.23; 95% CI 0.10 to 0.52), giving an NNT of 8 (95% CI 6 to 17), with the control even rate (CER) being 27/176. When the analysis was conducted without the Nouira 2001 trial, as it was conducted in ICU, the RR reduction was similar, 74% (RR 0.26; 95% CI 0.07 to 1.01; P value 0.05). This implied that the inclusion of the Nouira 2001 trial for this outcome had little impact on the overall estimate (except that the 95% CI for both the RR and NNT became narrower), providing additional support for the robustness of the effect-size estimate for mortality. We re-analysed the outcome with only studies that used an objective definition of COPD (Nouira 2001; Pines 1968; Pines 1972). The results remained significantly in favour of antibiotic therapy and were very similar to that obtained when all studies were included with a RR reduction of 76% (RR 0.24; 95% CI 0.10 to 0.57). Refer to Figure 1 for re-analysed data.
**Figure 1. Mortality: for studies that used an objective definition of COPD.**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>RR (fixed)</th>
<th>95% CI</th>
<th>Weight %</th>
<th>RR (fixed)</th>
<th>95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rume 2001</td>
<td>6/47</td>
<td>3/46</td>
<td>1.22</td>
<td>0.69-2.14</td>
<td>28</td>
<td>0.22</td>
<td>0.69-2.14</td>
<td>A</td>
</tr>
<tr>
<td>Pinna 1990</td>
<td>3/16</td>
<td>3/16</td>
<td>1.00</td>
<td>0.45-2.24</td>
<td>39</td>
<td>0.33</td>
<td>0.45-2.24</td>
<td>A</td>
</tr>
<tr>
<td>Pins 1992</td>
<td>5/86</td>
<td>5/86</td>
<td>1.00</td>
<td>0.45-2.24</td>
<td>39</td>
<td>0.33</td>
<td>0.45-2.24</td>
<td>A</td>
</tr>
<tr>
<td>Total (41% CI)</td>
<td>11/147</td>
<td></td>
<td>1.00</td>
<td>0.24-1.81</td>
<td>39</td>
<td>0.24</td>
<td>0.10-0.83</td>
<td>A</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 0.15, df = 2 (P = 0.92), I² = 0%  
Test for overall effect: Z = 3.24 (P = 0.001)
Treatment failure (Analysis 1.2)

See Analysis 1.2

Six trials with 705 patients reported this outcome (Alonso 1992; Anthonisen 1987; Elmes 1965a; Jørgensen 1992; Pines 1968; Pines 1972) which showed significant RR reduction of 25% in the antibiotic treated group compared to placebo (RR 0.67; 95% CI 0.56 to 0.80). Unfortunately, this overall result included significant heterogeneity (Chi$^2$ 15.46, P value 0.009 and I$^2$ 45.7%). Using a random-effects model or sensitivity analysis with trial quality failed to explain the heterogeneity. Further exploration of trial characteristics revealed that two trials were conducted in the community (Anthonisen 1987; Jørgensen 1992), as opposed to the four trials conducted using hospital in-patients; and were contributing to the heterogeneity. Re-analysis of the data including only the four hospital-based trials (with 321 patients) continued to favour treatment with antibiotics over placebo with a RR reduction of 53% (RR 0.47; 95% CI 0.36 to 0.62) and an NNT of 3 (95% CI 3 to 5) with a CER of 93/159. Heterogeneity test results were not significant (Chi$^2$ 2.69, P value 0.44 and I$^2$ 0%). Figure 2 shows the re-analysed data without the Anthonisen 1987 and Jørgensen 1992 studies. When the two community-based studies (Anthonisen 1987; Jørgensen 1992) were combined the overall result did not show differences between treatment with antibiotic and placebo (RR 0.91; 95% CI 0.70 to 1.18, see Figure 3).

Figure 2. Treatment failure: re-analysed including only four hospital-based trials.

Figure 3. Treatment failure: re-analysis of data using only studies conducted in the community.
Not all included studies used spirometric or objective definitions for COPD diagnosis. Therefore, we re-calculated the outcome with only studies that used an objective definition of COPD (Alonso 1992; Pines 1968; Pines 1972). The results were significantly in favour of antibiotic therapy and very similar to that obtained when all studies were included, with a RR reduction of 49% (RR 0.51; 95% CI 0.38 to 0.69). Refer to Figure 4 for re-calculated results with these three studies.

Figure 4. Treatment failure: for studies that used an objective definition of COPD.

Sputum purulence at end of treatment (Analysis 1.3)

See Analysis 1.3

Three trials with 465 patients reported sputum purulence at the end of the trial (Jørgensen 1992; Pines 1968; Pines 1972). Antibiotic use successfully resolved sputum purulence (RR 0.56; 95% CI 0.41 to 0.77) giving an NNT of 8 (95% CI 6 to 17) with CER of 70/234.

We re-calculated the outcome with only studies that used an objective definition of COPD (Pines 1968; Pines 1972). The results were significantly in favour of antibiotic therapy and very similar to that obtained when all studies were included, with a RR reduction of 48% (RR 0.52; 95% CI 0.37 to 0.72, see Figure 5). Re-analysis including only hospital-based studies (Pines 1968; Pines 1972) continued to favour antibiotic treatment (RR 0.52; 95% CI 0.37 to 0.72, see Figure 6).

Figure 5. Sputum purulence at end of treatment: for studies that used an objective definition of COPD.
Figure 6. Sputum purulent at end of treatment: re-analysed including only two hospital based trials.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>PEI (fixed) 95% CI</th>
<th>RR (fixed) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVS 1972</td>
<td>5/15</td>
<td>10/15</td>
<td>3.74 (0.64, 23.9)</td>
<td>3.00 (0.81, 0.81)</td>
<td>A.</td>
</tr>
<tr>
<td>HIVS 1980</td>
<td>27/92</td>
<td>47/86</td>
<td>3.66 (0.91, 7.66)</td>
<td>3.56 (0.88, 1.41)</td>
<td>A.</td>
</tr>
<tr>
<td>Total</td>
<td>302 (Antibiotic Group)</td>
<td>100 (Placebo Group)</td>
<td>3.62 (0.37, 4.72)</td>
<td>3.56 (0.88, 1.41)</td>
<td></td>
</tr>
</tbody>
</table>

Test for homogeneity: CH² = 11.20, df = 1 (P = 0.0003), P < 0.01.
Test for overall effect: Z = 2.29 (P = 0.0216)
PaCO₂ (Analysis 1.4)
Three trials with 117 patients (Alonso 1992; Manresa 1987; Nicotra 1982) provided data for this outcome which showed that there were no differences between the antibiotic and placebo groups (WMD 0.99 mmHg; 95% CI -3.01 to 4.99).

PaO₂ (Analysis 1.5)
Three trials with 117 patients (Alonso 1992; Manresa 1987; Nicotra 1982) provided data towards this outcome which showed that there were no differences between the antibiotic and placebo groups (WMD -0.27 mmHg; 95% CI -4.83 to 4.28).

PEFR (Analysis 1.6)
Three trials with 285 patients (Jørgensen 1992; Manresa 1987; Nicotra 1982) provided data on PEFR which did not show any difference between the antibiotic and placebo groups (WMD 0.54 L/min; 95% CI -22.57 to 23.64).

Adverse events (Analysis 1.7)

Diarrhoea (Analysis 1.7.1)
Two studies with 363 patients (Jørgensen 1992; Nouira 2001) provided data on the number of patients experiencing diarrhoea with increased RR in patients on antibiotics (RR 2.86; 95% CI 1.06 to 7.76) a number needed to treat to harm (NNH) of 20 (95% CI 10 to 100) with a CER of 5/183.

Overall adverse events (Analysis 1.7.6)
Two studies with 268 patients (Nouira 2001; Pines 1972) provided data on the overall incidence of adverse events in the study groups. There were significantly fewer adverse events with placebo (RR 2.91; 95% CI 1.48 to 5.72) with a NNH of 7 (95% CI 4 to 7).

Outcomes with only one included trial

The following outcomes were not discussed in detail as they only contained data from one included trial (meta-analysis of single trials are not interpretable): need for additional antibiotics, respiratory rate, heart rate, FEV1 and FVC. Two studies measured duration of hospital stay (Manresa 1987; Nouira 2001). However, there was significant heterogeneity in the overall estimate and any sensitivity analysis would leave one study in this outcome. Therefore, this outcome was also not discussed in detail. These outcomes are included in the review for completeness and as Cochrane reviews are regularly updated these outcomes may in future contain more trials.

DISCUSSION

Summary of main results
Eleven placebo-controlled RCTs with 917 patients met our inclusion criteria for this review. The results showed decreases in mortality, treatment failure and sputum purulence with antibiotic therapy (compared to placebo) in the management of patients with exacerbations of COPD. However, there was an increased risk of diarrhoea with antibiotic use.

Our systematic review is in agreement with a previously published meta-analysis (Saint 1995). However, the Saint 1995 meta-analysis provided an overall summary effect of all included studies and included trials that did not meet our inclusion criteria (Berry 1960a, not an RCT; Elmes 1957, prophylactic use of antibiotics; and Fear 1962, patients were in stable disease and not having an exacerbation). Furthermore, we included five additional trials (Alonso 1992; Hansen 1990; Manresa 1987; Nouira 2001; Pines 1968). Like our review the Saint 1995 review considered all antibiotic agents together in the analysis. However, they did not plan a priori subgroup analyses but did perform several post hoc analyses based on level of care (in-patient or out-patient) and on a selection of particular outcome measures from individual reports. Unlike our review the authors of the Saint 1995 review combined results from included studies as effect sizes (or standardised mean differences), which is a dimensionless unit measure of efficacy. Nevertheless, the authors concluded an overall combined standardised mean effect size estimate of 0.22 (95% CI 0.1 to 0.34) indicating a small but statistically significant effect favouring antibiotics over placebo. Because standardised mean effect sizes are difficult to interpret clinically, Saint 1995 also analysed a subset of trials that reported PEFR to show that the overall standardised effect size (of 0.22) was in agreement with outcomes with clinically meaningful units, such as an increase in PEFR of 10.75 L/min (95% CI 4.96 to 16.54). Although this may be true for PEFR it may not be true for other outcomes in the meta-analysis and the authors of the Saint 1995 meta-analysis did not provide results for other outcome measures. To avoid difficulty in interpreting and understanding standardised effect sizes we used outcome data that were clinically measurable and understandable.

Due to the limited number of included studies and incomplete data reporting in published studies, it was not possible to investi-
gate a relationship between antibiotic efficacy and severity of illness or on bacterial cultures. An analysis was stratified by location of care (community or in-patients). Two of the included trials did analyse the efficacy of antibiotics according to subgroups that were defined either by evidence of bacterial infection or severity of illness (Anthonisen 1987; Elmes 1965). One trial found that a priori criteria that were purported to select patients with signs of infection (using the Winnipeg criteria, Anthonisen 1987) showed better outcomes with antibiotic versus placebo treatment (Anthonisen 1987). Patients with type-1 exacerbations (who met all the following three criteria: increases in amount of sputum, purulence of sputum, and dyspnoea) benefited the most, with resolution of symptoms in 63% of the antibiotic-treated exacerbations and 43% of the placebo-treated exacerbations. Those with type-2 exacerbations (who met two of the above three criteria) showed an intermediate (not statistically significant) benefit, with 70% resolving on antibiotics and 60% resolving on placebo. Patients with type-3 exacerbations (who met one of the above three criteria) did not show any benefit, with 74% of exacerbations resolving on antibiotics and 70% resolving on placebo.

Another trial matched patients based on severity of illness, which was defined by two or more of the following: fever higher than 37.5°C, pulmonary consolidation, or purulent sputum (Elmes 1965). The trial was terminated prematurely for reasons unrelated to its results and before a significant effect of antibiotic treatment was found. However, this analysis was based on an assessment that was not blinded to bacteriologic results and, thus, may have been biased. A later independent, blinded assessment failed to find a significant difference between antibiotic and placebo-treated patients. Patients in the placebo group with greater severity of illness had more relapses in hospital than did less severely ill patients; however, this relationship was not found in the antibiotic group. It should be noted that the criteria for ‘severely ill’ (met by 19 of the 74 patients in the trial) would have resulted in exclusion from other included studies of exacerbation of COPD, because of either fever or pulmonary consolidation.

Studies varied with regard to whether corticosteroid treatment was permitted (see ‘Characteristics of included studies’ table). Only one study provided any information on the association of corticosteroid treatment with antibiotic efficacy (Anthonisen 1987). In this study corticosteroid therapy was permitted but was not prescribed or assigned in any way by the study protocol. Corticosteroids were used in approximately 42% of the 362 exacerbations. The success rate was reported to be better for antibiotic than placebo-treated patients both in patients who were on corticosteroids and those who were not.

The different study populations appear to have clinically important differences in severity of illness. The ‘Characteristics of included studies’ table describes the study populations in terms of source of patients, lung function, sputum purulence and level of care. When outcome data were re-analysed with or without the two studies conducted in the community (Anthonisen 1987; Jorgensen 1992) the results did not differ. In addition, outcomes did not differ when results were re-analysed with or without the one trial conducted in an ICU (Nouira 2001).

One trial (Pines 1968) described a pilot trial comparing penicillin and streptomycin with placebo in 30 patients hospitalised with exacerbation of chronic bronchitis. All patients had purulent sputum and half were described as severely ill. The study population had a mean age of 67.5 years, a mean PaCO₂ of 70 mmHg, a mean PEFR of 88 L/min, a mean leukocyte count of 12 x 10⁹/L, and a fever of 37.3°C. Patients were examined daily by a clinical assessor who was blinded to treatment assignment and their clinical status was graded based on ‘obvious changes in their degree of well-being, colour and dyspnoea’ but not on the state of the sputum; the results were not stratified according to severity of illness. In the antibiotic treated group, ten patients improved, three remained in an unchanged condition, two deteriorated and one died. In the placebo group, three patients improved, three remained unchanged, nine deteriorated and three died. As the difference in deterioration was statistically significant the trial was halted early. The investigators concluded that it was unethical to include a placebo group in the subsequent larger trial.

**Limitations of the review**

Since the definition of COPD has changed over the years, our approach was to accept the inclusion of patients with a spirometric definition of COPD, COPD-like symptoms, or both. The small number of studies limited stratified analysis according to COPD definition. However, a re-analysis of the outcomes with only inclusion of studies that used an objective criteria for COPD diagnosis (for outcomes of mortality, treatment failure and sputum purulence) did not alter the overall effect size or the significance of these outcome results. This provides support that even though these older studies did not use an objective definition for the diagnosis of COPD (as per recent COPD guidelines) they did in fact recruit patients with COPD. Nevertheless, differences in disease definition may bias our results and this cannot be avoided as it reflects the history of research in COPD.

The different study populations appear to have clinically important differences in severity of illness. The ‘Characteristics of included studies’ table describes the study populations in terms of lung function, sputum purulence and level of care. Again, the small number of included studies did not allow for stratified analysis according to severity of COPD. Nevertheless, the results from this review are applicable to patients with moderate to severe COPD. Another limitation of the present systematic review is publication bias, which is a potential threat to any systematic review. Studies demonstrating a positive effect for antibiotic use are more likely to be published than negative studies. In order to minimise missing studies we used extensive trial search criteria with no language restrictions and made every effort to detect any unpublished or ongoing studies.

Of the 11 included studies, four (Anthonisen 1987; Nouira 2001;...
Pines 1968; Pines 1972) concluded that the use of antibiotics with usual medical care was beneficial. When the results from included studies were combined using meta-analytical techniques we showed that antibiotics were clinically superior to placebo in the management of exacerbations of COPD. Since the earlier included trials were conducted before the emergence of multi-drug-resistant organisms (in particular to ß-lactams and macrolides) and new antibiotics, they showed only minimal benefit with antibiotic treatment in the more severe exacerbations. Therefore, it is likely that the newer antibiotic therapies available now may lead to improved outcomes in patients with exacerbations.

AUTHORS’ CONCLUSIONS

Implications for practice

This review has clearly shown that in exacerbations of COPD associated with increased cough and sputum purulence, antibiotic therapy, regardless of choice, significantly decreases short-term mortality, treatment failure and sputum purulence. As might be expected, this effect is greatest in the severe group of patients who are admitted to hospital. Analysis restricted to community-based studies did not find differences between antibiotic and placebo. These results should be interpreted with caution as the included trials had important differences in selection of patients, choice of antibiotic and only a small number of trials were included in the review. Nevertheless, this review supports the use of antibiotics for most patients with increased cough and sputum purulence with exacerbations of COPD who are moderately or severely ill.

Implications for research

Good quality RCTs of antibiotic treatment for exacerbations with COPD have shown evidence of clinical benefit. This is most evident in those patients admitted to hospital but is also applicable to those patients with increased cough, sputum purulence and dyspnoea who are treated as out-patients. We do not believe that it would be appropriate or ethical to conduct further studies using placebo in patients admitted to hospital. However, further research is needed on those patients with non-purulent exacerbations (with explicit definitions of COPD, COPD exacerbation and outcome measures) looking at the effect of severity of disease on treatment; what effect concomitant treatment may have, particularly corticosteroids; which is the best antibiotic for treating exacerbations of COPD; and what is the ideal duration of treatment. The priority for research should be to look at patients with definite COPD who do not fulfil the three criteria set by Anthonisen for an exacerbation; and longitudinal studies looking at exacerbation in participants for whom all three Anthonisen criteria are fulfilled. Furthermore, an exact definition of what disease the individuals have should be a priority for any research. Given the differences between hospital and community-based studies, and the lack of studies in the community, some research should be devoted to this large subset of people with exacerbations.

ACKNOWLEDGEMENTS

We are grateful for support from staff of the Cochrane Acute Respiratory Infections Group, namely Elizabeth Dooley (Review Group Co-ordinator) and Ruth Foxlee (Trials Search Co-ordinator). We would also like to thank JL Alonso Martinez and AF Jørgensen for responding to our requests for further information about their studies. The authors also wish to thank the following referees for commenting on the draft review: Janet Wale, Lorne Becker, An de Sutter, Robert Ware and Bruce Arroll.

REFERENCES

References to studies included in this review

Alonso 1992 (published and unpublished data)

Anthonisen 1987 (published data only)

Elmes 1965a (published data only)

Hansen 1990 (published data only)

Jørgensen 1992 (published and unpublished data)

Manresa 1987 [published data only]

Nicotra 1982 [published data only]

Nouira 2001 [published data only]

Petersen 1967 [published data only]

Pines 1968 [published data only]

Pines 1972 [published data only]

References to studies excluded from this review

Allegre 1996 [published data only]

Berry 1960a [published data only]

Elmes 1957 [published data only]

Fear 1962 [published data only]

Goddard 2003 [published data only]

Gomez 2000 [published data only]

Hauke 2002 [published data only]

Jacobsen 2002 [published data only]

Kauf 1967 [published data only]

King 1996 [published data only]

Leophonte 1998 [published data only]

Lirasc 2000 [published data only]

Peng 2003 [published data only]

Sachs 1995 [published data only]

Sohy 2002 [published data only]

Soler 2003 [published data only]

**Suzuki 2001** (published data only)

**Wilson 2004** (published data only)

### References to ongoing studies

**Fartoukh 2004** (published data only)

**NCT00170222** (published data only)

### Additional references

**Anonymous 1987**

**Anthonisen 1987**

**Bach 2001**

**Bent 1999**

**Berry 1960**

**BTS 1997**

**Burrows 1969**
**Characteristics of included studies**  
*ordered by study ID*

### Alonso 1992

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised double-blinded placebo controlled trial</th>
</tr>
</thead>
</table>
| **Participants** | SOURCE OF PARTICIPANTS: patients admitted to hospital with exacerbation of COPD  
INCLUSION CRITERIA: patients were eligible for the trial if they had a clinical diagnosis of COPD at the time of a hospital admission  
EXCLUSION CRITERIA: if they did receive antibiotic treatment during the last two weeks. Other disease such as LVF, stroke, pneumonia, pneumothorax, non cutaneous cancer, coma, T > 38 C  
BASELINE DEMOGRAPHICS: 90 patients included; mean age 68 years. 76 male, 14 female. Data presented for all patients in both study groups at hospital admission : Mean (SD); FEV1 29.98% (11.07); FVC 52.37% (16.02); PEFR 20.94 (10.66); PO2 mmHg 54.14 (12.59); respiratory rate 27.4 (4.81); numerical score 5.17 (1.88)  
Data presented for all patients in both study groups at hospital discharge: Mean (SD); FEV1 39.51% (16.80); FVC 66.73% (17.86); PEFR 31.01(16.30); PaO2 mmHg 62.42 (11.39); respiratory rate 22.3 (4.90); numerical score 2.84(1.83). All patients were treated with theophylline, inhaled bronchodilators and FiO2 24%. If the numerical score was high they received, 6-methylprednisolone 0.75 mg/Kg/d |

---

**C H A R A C T E R I S T I C S O F S T U D I E S**

**Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)**

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Alonso 1992

**DEFINITION OF EXACERBATION:** defined in terms of increased dyspnea, sputum production and sputum purulence

**INITIATION & FOLLOW UP:** once the patients were admitted to hospital for exacerbation, they received in a double-blinded manner, a 7, 2+/ - 1 days, either placebo or antibiotic according to a prearranged random schedule

Follow up regime, not explicitly described

**TREATMENT GROUP:** trimethoprim-sulfamethoxazole (160 mg/800 mg)/12 h, 29 patients. amoxicillin/clavulanic acid 500/125 mg /8 h, 32 patients

**CONTROL GROUP:** 29 patients. Neither the patient nor the medical staff knew which medication was active (“unidosis system” provided by the Hospital Pharmacy Service”)

### Outcomes

**USED IN REVIEW:**
- PaCO2
- PaO2

**NOT USED IN REVIEW DUE TO INCOMPLETE DATA:**
- side effects
- length of stay
- use of additional antibiotics
- spirometry

### Notes

**JUSTIFICATION FOR ALLOCATION CONCEALMENT:** Allocation of patients to study group was pre-determined using a random schedule

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

### Anthonisnen 1987

**Methods**
Randomised double-blinded placebo controlled trial

**Participants**

SOURCE OF PARTICIPANTS: patients were recruited from the community with stable COPD and followed. When an exacerbation developed they were given randomised to with antibiotic or placebo for 10 days

INCLUSION CRITERIA: patients were eligible for the trial if they were at least 35 yrs old and had a clinical diagnosis of COPD, not asthma. They were also required to have a FEV1 and FVC < 70% predicted. TLC > 80%

EXCLUSION CRITERIA: if FEV1 increased to 80% of predicted post bronchodilator use. Other disease serious enough to influence their quality of life or clinical course (e.g. cancer, LVF, stroke) or other disease likely to require antibiotic (e.g. recurrent sinusitis or UTI)

BASELINE DEMOGRAPHICS: data presented for all patients in both study groups: Mean (SD): FEV1 33.9% (13.7), FVC 59.5% (16.8), FRC 164.6% (34.4), TLC 128.9% (19.7), RV 205.3% (51.5), bron-
Cheidilator response for FEV1 111.8% (17.6), PEFR 227.5 L/min (96.1), PaO2 68.3 mmHg (9.9), PaCO2 36.6 mmHg (6.1), pH 7.42 (0.03)

**Interventions**

**DEFINITION OF EXACERBATION:** defined in terms of increased dyspnea, sputum production and sputum purulence

**INITIATION & FOLLOW UP:** when an exacerbation developed the patient was given in a double-blinded manner, a 10-day course of either placebo or antibiotic according to a pre-arranged random schedule. Exacerbations were followed at 3-day intervals by home visits for 21 days

**TREATMENT GROUP:** 57 in group; trimethoprim/sulfamethoxazole (160 mg/800 mg bid), amoxicillin (0.25g qid) or doxycycline (200 mg initially followed by 0.1 g daily). The choice of antibiotic was made by the patient’s physician since these agents were known not to differ in effectiveness in exacerbations of COPD

**CONTROL GROUP:** 59 in group. Appropriate placebo for each drug was supplied to the investigators so neither the patient nor the medical staff knew which medication was active

**Outcomes**

**USED IN REVIEW:**
treatment failure

**NOT USED IN REVIEW DUE TO INCOMPLETE DATA:**
PEFR, side effects

**Notes**

**JUSTIFICATION FOR ALLOCATION CONCEALMENT:** allocation of patients to study group was pre-determined using a random schedule

---

**Elmes 1965a**

**Methods**

Randomised double-blinded placebo controlled trial

**Participants**

**SOURCE OF PARTICIPANTS:** patients admitted to hospital with exacerbation of COPD

**INCLUSION CRITERIA:** patients were eligible for the trial if they had a clinical diagnosis of acute exacerbation of chronic bronchitis at the time admission in a non teaching hospital

**EXCLUSION CRITERIA:** if they had disease such as LVF, Lung abscess, carcinoma of the lung, long-standing bronchiectasis, active tuberculosis, evidence of disseminated infection or septicaemia, allergy to penicillin and patients with adrenal corticoid treatment

**BASELINE DEMOGRAPHICS:** 74 patients initially included, only 56 randomised

Mean age 63 years. 20 male, 36 female

The two groups were comparable (stated by authors) for age, sex and sputum appearance, but neither for ventilatory capacity on admission (mean peak flow Ampicillin group 69.2; mean peak flow control group 89.2), nor for sputum volume (ampicillin group 43.8 ml and control group 59.8 ml)
### Elmes 1965a (Continued)

| Interventions | DEFINITION OF EXACERBATION: defined in terms of, sputum production and sputum purulence  
INITIATION & FOLLOW UP: once the patients were admitted in the trial, they received, in a double 
blinded manner, a 7 days, either placebo or antibiotic according to a prearranged random schedule  
Follow up at day 7, at the end of hospital discharge (mean 18 days) and at 6 and 18 months after discharge  
TREATMENT GROUP: 29 patients  
Ampicillin capsules 1 g/6 h, three days and 0.5 g/6 h, four days  
CONTROL GROUP: 29 patients. Neither the patient nor the medical staff knew which medication was 
active (treatment was provided by the Hospital Pharmacist and the system arranged by the statistician) |
| Outcomes | USED IN REVIEW:  
treatment failure  
mortality  
NOT USED IN REVIEW DUE TO INCOMPLETE DATA:  
length of hospital stay  
increase in peak flow  
sputum volume, appearance and bacterial culture  
secondary bacterial invasion.  
relapses in hospital and after discharge  
side effects |
| Notes | JUSTIFICATION FOR ALLOCATION CONCEALMENT: allocation of patients to study group was 
pre-determined using a random schedule |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

### Hansen 1990

| Methods | Randomised double-blind placebo controlled trial |
| Participants | SOURCE OF PARTICIPANTS: patients admitted to hospital with exacerbation of COPD  
INCLUSION CRITERIA: hospital admission for COPD  
EXCLUSION CRITERIA: not available  
BASELINE DEMOGRAPHICS: not available |
| Interventions | DEFINITION OF EXACERBATION: hospital admission for COPD  
INITIATION & FOLLOW UP: during hospitalisation (period not specified) patients were randomised to one week of treatment (antibiotic or placebo)  
Daily assessment first week; and then at two weeks, and 1 and 3 months  
TREATMENT GROUP: amoxacillin 750 mg twice daily; 7 days; n = 19  
CONTROL GROUP: placebo; 7 days; n = 21 |
Hansen 1990  

Outcomes  
USED IN REVIEW: Nil  
NOT USED IN REVIEW DUE TO INCOMPLETE DATA:  
spirometry  
bacteria in sputum  
leukocyte count

Notes  
JUSTIFICATION FOR ALLOCATION CONCEALMENT:  
since it is an abstract, information is very limited

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Jørgensen 1992

Methods  
Randomised double-blind placebo controlled trial

Participants  
SOURCE OF PARTICIPANTS: patients were sourced from general practice community in Denmark  
INCLUSION CRITERIA:  
subjects above 18 years of age with acute exacerbation of chronic bronchitis (defined as continuous cough and expectoration, present for at least 3 months of the year, in more than 2 consecutive years)  
EXCLUSION CRITERIA: patients with pneumonia (on auscultation or X-ray), temperature > 38.5 °C, heart rate > 100 bpm, antibiotics within the previous 7 days, pregnancy, allergy to penicillin, uncompensated heart disease, treatment with oral steroids or immunosuppressants  
BASELINE DEMOGRAPHICS:  
antibiotic group (n = 133)  
77 females/56 males  
age (mean) 59.7  
smokers 76%  
Placebo group (n = 137)  
78 females/59 males  
age (mean) 60.4  
smokers 72%

Interventions  
DEFINITION OF EXACERBATION: subjective worsening due to change in sputum (increased volume, change of viscosity or colour) possibly accompanied by cough or dyspnea, lasting for more than 3 days  
INITIATION & FOLLOW UP: patients were identified in primary care and, after informed verbally and in writing, they gave informed consent and were randomised to treatment or placebo (visit 1). Peak-flow was measured twice daily by patients. On day 8, patients were revisited by doctors (visit 2)  
TREATMENT GROUP:  
1 tablet 750 mg amoxicillin (Imacilin), 7 days; n = 133  
CONTROL GROUP:  
placebo twice daily, 7 days; n = 137
Outcomes

**USED IN REVIEW:**
treatment failure
sputum purulence
adverse events

**NOT USED IN REVIEW DUE TO INCOMPLETE DATA:**
PEFR
clinical symptoms

Notes

**JUSTIFICATION FOR ALLOCATION CONCEALMENT:**
"patients were randomised to treatment or placebo", with no more details

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

**Manresa 1987**

Methods

Randomised double-blind placebo controlled trial

Participants

**SOURCE OF PARTICIPANTS:** patients admitted to hospital with exacerbation of COPD

**INCLUSION CRITERIA:** at the time of a hospital admission: increase in symptoms (cough, dyspnea, and volume and purulence of sputum)

**EXCLUSION CRITERIA:** evidence of parenchymal consolidation on chest x-ray or of other pulmonary or cardiac disease

**BASELINE DEMOGRAPHICS:**
- **antibiotic group:**
  - age (yr) 66 (7)
  - days in hospital 12.8 (4),
  - respiratory rate 32 (7) per min, heart rate 105 (20) bpm, PEFR 169 (45) L/min, PO2 40 (6) mmHg, PCO2 59 (15) mmHg
- **Placebo group:**
  - age (yr) 67 (6)
  - days in hospital 12.3 (4),
  - respiratory rate 27 (9) per min, heart rate 94 (8) bpm, PEFR 177 (55) L/min, PO2 38 (8) mmHg, PCO2 66 (8) mmHg

Interventions

**DEFINITION OF EXACERBATIOn:** increase in symptoms (cough, dyspnea, and volume and purulence of sputum) with no evidence of parenchymal consolidation on chest X-ray or of other pulmonary or cardiac disease

**INITIATION & FOLLOW UP:** during the admission (time not specified), subjects were allocated at random to antibiotic or placebo

Assessments on days 0, 4 and 8.

**TREATMENT GROUP:** ceflcor 500 mg, 3 times a day; 8 days; n = 11
CONTROL GROUP: placebo; 8 days; n = 8

Outcomes

USED IN REVIEW:
duration of hospital stay respiratory rate
heart rate
peak flow
PaO2
PaCO2

NOT USED IN REVIEW DUE TO INCOMPLETE DATA:
bacteria in sputum culture
sputum volume
sputum purulence
neutrophilia in bronchial secretions

Notes

JUSTIFICATION FOR ALLOCATION CONCEALMENT: "subjects were allocated at random", with no more details

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Nicotra 1982

Methods

Randomised double-blind placebo controlled trial

Participants

SOURCE OF PARTICIPANTS: patients admitted to hospital with exacerbation of COPD
INCLUSION CRITERIA: patients admitted to hospital with a diagnosis of chronic bronchitis (defined by the presence of significant sputum production for at least 3 months of the preceding 2 years), who also has an exacerbation (defined as the increase in dyspnea, cough, and sputum production)
EXCLUSION CRITERIA: new or changed parenchymal lung infiltrate, temperature greater than 38.5 °C, blood leukocyte count > 12000/mm3 (unless an increase in corticosteroids dosage in previous 3 days), antibiotic use during previous 7 days, or need for mechanical assisted ventilation
BASELINE DEMOGRAPHICS:
antibiotic group:
age (yr) 57.0 (8.6)
male/female 10/10
physical findings (physician questionnaire) 5.42 (2.17)
symptom score (patient questionnaire) 7.65 (4.15)
sputum 60.3 (47.2) ml per 24 hours, Sputum pathogens Streptococcus pneumoniae, Hemophilus influenzae, Other pathogens.
blood leukocyte count (*103/ml) 8.70 (2.60)
hemoglobin 14.6 (1.50) g/dl,
PO2 58.3 (13.6) mmHg, (A-a) DO2 (mmHg) 35.7 (12.9)
Nicotra 1982  (Continued)

<table>
<thead>
<tr>
<th>PCO2 (mmHg) 45.4 (9.4)</th>
<th>Placebo group:</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.39 (0.05)</td>
<td>age (yr) 55.0 (10.0)</td>
</tr>
<tr>
<td>HCO3 26.4 (5.00)</td>
<td>male/female 10/10</td>
</tr>
<tr>
<td>FVC (L) 1.84 (0.66)</td>
<td>physical findings (physician questionnaire) 6.65 (1.22)</td>
</tr>
<tr>
<td>FEV1 (l) 0.88 (0.33)</td>
<td>symptom score (patient questionnaire) 8.45 (3.28)</td>
</tr>
<tr>
<td>PEFR (l/min) 160 (72)</td>
<td>sputum volume/24 h (ml) 48.5 (38.6)</td>
</tr>
<tr>
<td>FEV1/FVC (%) 47.6 (11.1)</td>
<td>sputum pathogens Streptococcus pneumoniae, Hemophilus influenzae, Other pathogens</td>
</tr>
<tr>
<td>Placebo group:</td>
<td>blood leukocyte count (*103/ml) 9.80 (3.90)</td>
</tr>
<tr>
<td></td>
<td>hemoglobin (g/dl) 15.5 (1.60)</td>
</tr>
<tr>
<td></td>
<td>PO2 (mmHg) 60.3 (17.5)</td>
</tr>
<tr>
<td></td>
<td>(A-a)DO2 36.2 (12.7) mmHg,</td>
</tr>
<tr>
<td></td>
<td>PCO2 42.6 (12.6) mmHg, pH 7.43 (0.06)</td>
</tr>
<tr>
<td></td>
<td>HCO3 27.8 (6.60) (meq/dl),</td>
</tr>
<tr>
<td></td>
<td>FVC 1.67 (0.70) L, FEV1 0.92 (0.54) L, PEFR 159 (105) L/min, FEV1/FVC 53.3 (13.0)%</td>
</tr>
<tr>
<td>Both groups: 75% current smokers</td>
<td></td>
</tr>
</tbody>
</table>

**Interventions**

**DEFINITION OF EXACERBATION:** increase in dyspnea, cough, and sputum production

**INITIATION & FOLLOW UP:** within 12 hours of admission, patients were identified, given informed consent, and randomly assigned to treatment or placebo

**Outcomes**

**TREATMENT GROUP:** tetracycline 500 mg, four times daily, 7 days; n = 20

**CONTROL GROUP:** placebo identical in appearance to treatment, four times daily, 7 days; n = 20

**Notes**

**OUTCOMES USED IN REVIEW:**

- PaO2
- PaCO2
- PEFR
- FVC
- FEV1

**NOT USED IN REVIEW DUE TO INCOMPLETE DATA:**

- sputum volume
- sputum purulence
- pathogens in sputum

**JUSTIFICATION FOR ALLOCATION CONCEALMENT:** patients were randomly assigned to treatment or placebo. Neither patients nor physicians were aware of what treatment had been assigned.
**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

**Nouira 2001**

**Methods**
Randomised double-blind placebo controlled trial

**Participants**

SOURCE OF PARTICIPANTS: consecutive patients admitted to medical ICU (Tunisia) with exacerbation of COPD

**INCLUSION CRITERIA:**
from January, 1996, to December, 1999, consecutive patients aged 40 years or older, who were admitted to the medical ICUs of Fattouma Bourguiba Hospital (Monastir, Tunisia) and Farhat Hached Hospital (Souss, Tunisia) for acute exacerbation of COPD, were included in the study. Patients were eligible if they were admitted to the ICU with acute exacerbation of COPD - diagnosed on the basis of clinical history, physical examination, and chest radiograph-and had an acute respiratory failure requiring mechanical ventilation within the first 24 h of admission. Acute respiratory failure was defined as association of exacerbation of dyspnoea with at least two of the following: respiratory rate greater than 30 breaths per min; arterial partial pressure of carbon dioxide greater than 6 kPa; and arterial pH below 730 after the patient had been breathing spontaneously for at least 10 min

**EXCLUSION CRITERIA:**
patients were excluded from the study if they had received antimicrobial treatment in the previous 10 days, if alveolar infiltrates were present on chest radiographs on admission, and if they had previously enrolled in the study. The absence of radiological signs of pneumonia was confirmed in all patients by consensus of senior physicians; a second chest radiograph was done when needed. Patients with a known history of asthma or bronchiectasis were excluded. Patients were also excluded if they were allergic to quinolone derivatives, were pregnant or breast feeding, were terminally ill or immunocompromised, had hepatic disease or severe renal impairment, or had gastrointestinal disease that could affect drug absorption. Patients with concomitant infection requiring systemic antibacterial therapy were also excluded

**BASELINE DEMOGRAPHICS:**

<table>
<thead>
<tr>
<th>Antibiotic group</th>
<th>Age (yr)</th>
<th>Duration of chronic bronchitis</th>
<th>FEV1 (L/s)</th>
<th>Exacerbations in past year</th>
<th>Temp</th>
<th>Blood leucocytes/uL</th>
<th>PaCO2 (mmHg)</th>
<th>pH</th>
<th>Initial ventilatory support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>66.2</td>
<td>11 (7)</td>
<td>0.79</td>
<td>1.7 (1.6)</td>
<td>37.5</td>
<td>10970</td>
<td>74 (22)</td>
<td>7.22</td>
<td>32 (or 68%)</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>66.5</td>
<td>11 (5)</td>
<td>0.74</td>
<td>1.6 (1.2)</td>
<td>37.7</td>
<td>11560</td>
<td>79 (21)</td>
<td>7.21</td>
<td>32 (or 69%)</td>
</tr>
</tbody>
</table>
**Interventions**

**DEFINITION OF EXACERBATION:** diagnosed on the basis of clinical history, physical examination, and chest radiograph.

**INITIATION & FOLLOW UP:**
within 24 hours of admission patients required mechanical ventilation. Acute respiratory failure was defined as association of exacerbation of dyspnoea with at least two of the following: respiratory rate greater than 30 breaths per min; arterial partial pressure of carbon dioxide greater than 45 mmHg; and arterial pH below 7.30 after the patient had been breathing spontaneously for at least 10 min.

All patients were monitored until their discharge from hospital.

**TREATMENT GROUP:**
once daily dose of ofloxacin 400 mg (Hoechst Marion Roussel). All treatments were given orally as two tablets of 200 mg every day for 10 consecutive days in the morning. Intubated patients were given the same regimen via a nasogastric or orogastric tube. Patients transferred from the ICU to another ward during this 10-day period were asked to complete the study treatment with the agreement of their physician.

**CONTROL GROUP:**
placebo identical in appearance to treatment, with the same dosing regime.

**Outcomes**

**USED IN REVIEW:**
mortality
need for additional antibiotics
duration of stay
FEV1
FVC
adverse events

**NOT USED IN REVIEW DUE TO INCOMPLETE DATA:**

**Notes**

**JUSTIFICATION FOR ALLOCATION CONCEALMENT:** patients were randomly assigned to treatment or placebo using random numbers. All drugs and placebo packages were prepared and numbered by the hospital pharmacy and were used consecutively. Assignments of patients were placed in closed envelopes with identification numbers that were stored in the ICU. All study investigators and hospital staff were masked to the treatment status until data completion.

**Petersen 1967**

**Methods**
Randomised double-blinded controlled trial

**Participants**

SOURCE OF PARTICIPANTS: patients admitted to hospital with exacerbation of COPD.

INCLUSION CRITERIA: the criterion used for the diagnosis of chronic bronchitis was a story of cough and expectoration on most days during at least three consecutive months in each of two or more successive years. Most of the patients were classified as having chronic mucopurulent obstructive bronchitis. Only patients aged 45 to 75 yrs old were selected for inclusion in the trial.
EXCLUSION CRITERIA: severe deformities of the spine or chest, with localised or generalised specific lung disease, or with signs of cardiac insufficiency were excluded.

BASELINE DEMOGRAPHICS: data presented for all patients in the 3 study groups: Mean PEFR 480 L/min for men and 350 L/min for women, PaCO2 46.1 mmHg (all patients). RV/TLC 39% men and 43% women.

DEFINITION OF EXACERBATION: patients admitted to the hospital ward for acute exacerbations in chronic bronchitis (during Oct 1, 1964 to May 1, 1965).

INITIATION & FOLLOW UP: when an exacerbation developed requiring hospital admission the patient was given in a single-blinded manner, placebo (10 ml 3.3% potassium chloride, tid, and Ca lactate, 0.5 g, qid) (Group A), physiotherapy plus treatment as in the placebo arm (Group B) (both arms for 28 days), expectorant (as in the placebo group) (Group C) or antibiotic (chloramphenicol, 0.5 g, qid, and potassium chloride as in the other groups) (Group D) (the latter 2 arms for 210 days) according to a pre-arranged random schedule. Hospitalisations were followed at Days 0, 3, 6, 10 and 28 days.

GROUP A (placebo): 10. Group B: 10; Group C, 9; Group D, 9.

USED IN REVIEW:

 nil

NOT USED IN REVIEW DUE TO INCOMPLETE DATA:
clinical assessment (changes in the temperature and sputum volume), ESR, and lung function (PEF, VC, RV%, Gas mixing, V/Q), sputum.

JUSTIFICATION FOR ALLOCATION CONCEALMENT: allocation of patients to study group was pre-determined using a table of random numbers, including the value of RV/TLC% above or below 50% with no more details.

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

### Pines 1968

**Methods**
Details of only the pilot study was used for this review as this trial had a placebo arm and the main trial didn't. Randomised double-blinded placebo controlled trial.

**Participants**
SOURCE OF PARTICIPANTS: patients admitted to hospital with exacerbation of COPD.
INCLUSION CRITERIA: patients were eligible for the trial if they were > 50 yrs old and had a history of chronic bronchitis > 5 yrs and a definite history during the past 6 wks of an exacerbation of symptoms. They were also required to be male, moderately-to-severely ill on admission (as judged by the receiving SHO), persistent purulent sputum and have a PEFR < 200 L/min (unless too ill to do so).
EXCLUSION CRITERIA: to have allergy to penicillin, asthma, extensive bronchiectasis, active tbc, lung cancer, sputum eosinophilia (> 10%) or blood urea > 60 mg/100 ml.
### Baseline Demographics

30 patients were recruited 15 in the antibiotic and 15 in the placebo group. The two groups were comparable with the following results: mean age 66.9 & 68.1; 8 & 7 were severely ill; mean initial fever 37.3°C & 37.2°C; mean white count 12,100 & 12,000 /cu.mm; mean sedimentation rate 47 & 52 mm in the first hour; mean PEFR 90 & 85 L/min; mean PCO2 68 & 71 mmHg. All patients had persistently purulent sputum.

### Interventions

**Definition of Exacerbation:** not defined  
**Initiation & Follow Up:** a placebo injection of saline was compared with a combined injection of penicillin three million units and streptomycin 0.5 g, both injections given twice daily for 14 days; the streptomycin was stopped on the seventh day all patients were seen daily and any who deteriorated clinically were at once withdrawn from the trial and promptly treated with high doses of ampicillin, chloramphenicol or cephaloridine.  
**Treatment Group:** 15 in group treated with combined injection of penicillin three million units and streptomycin 0.5 g, both injections given twice daily for 14 days; the streptomycin was stopped on the seventh day.  
**Control Group:** 15 in the placebo group. A placebo injection of saline was given twice daily for 14 days.

### Outcomes

**Used in Review:** treatment failure  
**Mortality**  
**Sputum Colour**  
**Not Used in Review Due to Incomplete-Absent Data:** PCO2, PEFR, Temperature

### Notes

**Justification for Allocation Concealment:** allocation of patients to study group was pre-determined using a random schedule. All patients were seen daily by a "blind" assessor.

### Risk of Bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

#### Pines 1972

**Methods**

Randomised double-blinded controlled trial

**Participants**

SOURCE OF PARTICIPANTS: patients admitted to hospital with exacerbation of COPD.  
**Inclusion Criteria:** patients were eligible for the trial if they were > 60 yrs old and had a history of chronic bronchitis > 5 yrs and a definite history during the past 6 wks of an exacerbation of symptoms. They were also required to be male, to have a failure of at least one previous treatment with antibiotics.
moderately severely ill on admission (as judged by the receiving SHO), persistent purulent sputum and have a PEFR < 200 L/min

EXCLUSION CRITERIA: to have asthma, bronchiectasis or other pulmonary disease, or sputum eosinophilia (> 10%)

BASELINE DEMOGRAPHICS: data presented for all patients in the 3 study groups: Mean PEFR 149.0, 142.0, and 146.0 L/min

| Interventions | DEFINITION OF EXACERBATION: not defined
INITIATION & FOLLOW UP: when an exacerbation developed the patient was given in a double-blinded manner, a 12-day course of either placebo or antibiotic according to a pre-arranged random schedule. Exacerbations were followed at the beginning and end of trial and 1 and 4 wks later
TREATMENT GROUP: 89 in group oral tetracycline hydrochloride (500 mg, qid) or 84 in group oral chloramphenicol (500 mg, qid, to a total of 24 g)
CONTROL GROUP: 86 in group. Appropriate placebo for each drug was supplied to the investigators so neither the patient nor the medical staff knew which medication was active. Yet, patients or staff could identify their treatments by opening the capsule, by crushing it in their mouths or by the after taste. Hence the assessments were made by independent trained observers, who did not know whether the patients were receiving treatment or placebo

| Outcomes | USED IN REVIEW:
treatment failure
mortality
sputum colour

NOT USED IN REVIEW DUE TO INCOMPLETE-ABSENT DATA:
FEV1
PaCO2

| Notes | JUSTIFICATION FOR ALLOCATION CONCEALMENT: allocation of patients to study group was pre-determined using a random schedule

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

T = temperature
h = hourly
wks = weeks
yrs = years
LVF = left ventricular failure
PaCO2 = Carbon dioxide arterial tension
PaO2 = Oxygen arterial tension
FEV1 = forced expiratory volume in one second
FVC = forced vital capacity
TLC = total lung capacity
UTI = Urinary tract infection
RV = residual volume
FRC = functional residual capacity
### Characteristics of excluded studies

[ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegra 1996</td>
<td>Study has no placebo group as sparfloxacin is compared to amoxicillin and clavulanic acid</td>
</tr>
<tr>
<td>Berry 1960a</td>
<td>Patients not randomly allocated to study groups but according to the judgement of the clinician as either antibiotic necessary, antibiotic unnecessary or intermediate need for antibiotic</td>
</tr>
<tr>
<td>Elmes 1957</td>
<td>Prophylactic use of antibiotics</td>
</tr>
<tr>
<td>Fear 1962</td>
<td>Patients in stable state of their disease</td>
</tr>
<tr>
<td>Goddard 2003</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Gomez 2000</td>
<td>Prophylactic antibiotic use. Patients treated with azithromycin (500 mg/day) for three days every 21 days during the winter months, and a control group without treatment</td>
</tr>
<tr>
<td>Hauke 2002</td>
<td>No placebo arm in study</td>
</tr>
<tr>
<td>Jacobsen 2002</td>
<td>Not an RCT but a retrospective chart review</td>
</tr>
<tr>
<td>Kaul 1967</td>
<td>No placebo arm in study</td>
</tr>
<tr>
<td>King 1996</td>
<td>Study not in patients with COPD but in patients with acute bronchitis who are otherwise healthy adults</td>
</tr>
<tr>
<td>Leophonte 1998</td>
<td>Study not in patients with COPD but in patients with acute bronchitis who are otherwise healthy adults</td>
</tr>
<tr>
<td>Lirsac 2000</td>
<td>There were no placebo antibiotic control group as both study groups received antibiotic therapy from day 1 (amoxycillin 500 mg plus clavulanic acid 125, 3 tablets/day). In addition the treatment group also received fenspiride (3 x 80 mg/d from day 0 to day 30) and the control group received a placebo</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
</tr>
<tr>
<td>Peng 2003</td>
<td>Not an RCT but a retrospective cohort study</td>
</tr>
<tr>
<td>Sachs 1995</td>
<td>Trial included a mixture of both COPD and asthmatic patients with the data not presented separately</td>
</tr>
<tr>
<td>Sohy 2002</td>
<td>Not an RCT but a narrative review</td>
</tr>
<tr>
<td>Soler 2003</td>
<td>No placebo arm in study</td>
</tr>
<tr>
<td>Suzuki 2001</td>
<td>Prophylactic antibiotic use</td>
</tr>
<tr>
<td>Wilson 2004</td>
<td>No placebo arm in trial. Moxifloxacin was compared to standard antibiotic therapy</td>
</tr>
</tbody>
</table>

**Characteristics of ongoing studies**  
*ordered by study ID*

**Fartoukh 2004**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>ANTEAB: a study of early antibiotic therapy in intensive care management of acute exacerbations of chronic obstructive lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Patients included are those with documented or suspected COLD, exclusive of other bronchial or lung disease, and admitted for acute exacerbation, in the absence of overt sepsis or broncho-pneumonia, and having no other organ failure. Patients recently hospitalised, having received antibiotics for &gt; 24 h, or on long-term steroids will not be included. Co-interventions (bronchodilators, steroids) are controlled for.</td>
</tr>
<tr>
<td>Participants</td>
<td>This is a multicentre, randomised, double-blind controlled trial, comparing amoxicillin-clavulanic acid administered for 7 days to a placebo. Patients will be administered the antibiotic or placebo within 24 hours of admission.</td>
</tr>
<tr>
<td>Interventions</td>
<td>EXPECTED RESULTS: a 20% reduction of the duration of clinical symptoms of exacerbation is expected. To this end, 520 patients are planned to be included in 15 centres in a 2-year period. Secondary end-points are the incidence of documented infection (lower respiratory tract or other sites), antibiotic use, the proportion of patients having infection with resistant bacteria, the incidence of endotracheal intubation, the duration of stay and mortality in the ICU and the hospital.</td>
</tr>
<tr>
<td>Starting date</td>
<td>Started in 2004, 2 year study to be completed in 2006</td>
</tr>
</tbody>
</table>
| Contact information | Fartoukh M, Similowski T, Brun-Buisson C.  
Service de Pneumologie et Reanimation Respiratoire, Hôpital Tenon, Paris, France |
INTRODUCTION: Intensive Care Unit (ICU) admission for acute exacerbation of chronic obstructive lung disease (COLD) is a major cause of morbidity and mortality in such patients. Although bacterial and/or viral infections are considered as the major precipitating factor, the antibiotic strategy in this setting is unclear. The potential benefit of routine antibiotic therapy in the absence of evidence of overt infection remains controversial, and has not been adequately studied in patients admitted to the ICU. To assess the benefit (or lack thereof) of routine early systemic antibiotic therapy in patients with COLD admitted to the ICU.

**NCT00170222**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>The value of antibiotic treatment of exacerbations of hospitalised COPD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Ages eligible for study: 45 years and above, genders eligible for study: both criteria</td>
</tr>
<tr>
<td></td>
<td>Inclusion Criteria:</td>
</tr>
<tr>
<td></td>
<td>l acute exacerbation of COPD type I or II according to GOLD</td>
</tr>
<tr>
<td></td>
<td>l ability to perform lung function tests</td>
</tr>
<tr>
<td></td>
<td>l ability to take oral medication</td>
</tr>
<tr>
<td></td>
<td>Exclusion Criteria:</td>
</tr>
<tr>
<td></td>
<td>l Pregnant or lactating women, or women of childbearing age not using an acceptable method of contraception.</td>
</tr>
<tr>
<td></td>
<td>l Pretreatment (&gt; 24 hours) with an antibiotic for the present exacerbation.</td>
</tr>
<tr>
<td></td>
<td>l Pretreatment with corticosteroids (&gt;30 mg for more than 4 days) for the present exacerbation.</td>
</tr>
<tr>
<td></td>
<td>l Progression or new radiographic abnormalities on the chest x-ray.</td>
</tr>
<tr>
<td></td>
<td>l Severe exacerbation that required mechanical ventilation.</td>
</tr>
<tr>
<td></td>
<td>l History of bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>l Recent or unresolved lung malignancy.</td>
</tr>
<tr>
<td></td>
<td>l Other disease likely to require antibiotic therapy.</td>
</tr>
<tr>
<td></td>
<td>l Significant gastrointestinal or other conditions that may affect study drug absorption.</td>
</tr>
<tr>
<td></td>
<td>l Class III or IV congestive heart failure or stroke.</td>
</tr>
<tr>
<td></td>
<td>l Immunodeficiency disorders such as AIDS, humoral immune defect, ciliary dysfunction etc. and the use of immunosuppressive drugs (&gt; 30 mg prednisolone maintenance dose or equivalent for more than 4 weeks).</td>
</tr>
<tr>
<td></td>
<td>l Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>l Tuberculosis</td>
</tr>
<tr>
<td></td>
<td>l Impaired renal function (creatinine clearance &lt; 20 ml/min).</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Study type: interventional</td>
</tr>
<tr>
<td></td>
<td>study design: treatment, randomized, double-blind, placebo control, parallel assignment, efficacy study</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Further study details:</td>
</tr>
<tr>
<td></td>
<td>primary outcomes: clinical efficacy at the end of treatment.</td>
</tr>
<tr>
<td></td>
<td>Secondary outcomes: treatment failure at follow up; number of exacerbation.</td>
</tr>
<tr>
<td></td>
<td>Expected total enrollment: 258</td>
</tr>
</tbody>
</table>
### Starting date

| **Study start:** July 2002; expected completion: December 2006 |
| **Last follow up:** August 2005; data entry closure: October 2006 |

### Contact information

- Please refer to this study by ClinicalTrials.gov identifier NCT00170222
- Johannes MA Daniels, drs +31725482750 hans.daniels@zonnet.nl
- Dominic Snijders, drs +31725484444 Ext. 5071 d.snijders@mca.nl
- Medisch centrum Alkmaar, Alkmaar, Noord-holland, 1815 JD, Netherlands; Recruiting
- Dominic Snijders, drs, Principal Investigator
- Study chairs or principal investigators
- Johannes MA Daniels, drs, Principal Investigator, Pulmo-science
- Dominic Snijders, drs, Principal Investigator, Pulmo-science

### Notes

- Study ID Numbers: M02-007
- Last Updated: September 14, 2005
- Record first received: September 9, 2005
- ClinicalTrials.gov Identifier: NCT00170222
- Health Authority: Netherlands: Dutch Health Care Inspectorate
- ClinicalTrials.gov processed this record on 2005-10-20
Comparison 1. Antibiotics versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mortality (short-term) during study intervention</td>
<td>4</td>
<td>356</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.23 [0.10, 0.52]</td>
</tr>
<tr>
<td>2 Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration or death)</td>
<td>6</td>
<td>705</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.67 [0.56, 0.81]</td>
</tr>
<tr>
<td>3 Sputum purulent at end of treatment</td>
<td>3</td>
<td>465</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.56 [0.41, 0.77]</td>
</tr>
<tr>
<td>4 PaCO2 (mmHg)</td>
<td>3</td>
<td>117</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.99 [-3.01, 4.99]</td>
</tr>
<tr>
<td>5 PaO2 (mmHg)</td>
<td>3</td>
<td>117</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.27 [-4.83, 4.28]</td>
</tr>
<tr>
<td>6 PEFR (L/min)</td>
<td>3</td>
<td>285</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.54 [-22.57, 23.64]</td>
</tr>
<tr>
<td>7 Adverse events</td>
<td>3</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td></td>
</tr>
<tr>
<td>7.1 Diarrhoea</td>
<td>2</td>
<td>363</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.86 [1.06, 7.76]</td>
</tr>
<tr>
<td>7.2 Dyspepsia</td>
<td>1</td>
<td>270</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.52 [0.13, 2.02]</td>
</tr>
<tr>
<td>7.3 Pain in mouth</td>
<td>1</td>
<td>270</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>7.21 [0.38, 138.24]</td>
</tr>
<tr>
<td>7.4 Exanthema, itching</td>
<td>1</td>
<td>270</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>3.09 [0.33, 29.34]</td>
</tr>
<tr>
<td>7.5 Abnormal serum</td>
<td>1</td>
<td>93</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.65 [0.11, 3.73]</td>
</tr>
<tr>
<td>7.6 Overall (adverse events not separated)</td>
<td>2</td>
<td>268</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.91 [1.48, 5.72]</td>
</tr>
<tr>
<td>8 Need for additional antibiotics</td>
<td>1</td>
<td>93</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.19 [0.08, 0.45]</td>
</tr>
<tr>
<td>9 Respiratory rate (per minute)</td>
<td>1</td>
<td>19</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>1.01 [-3.19, 5.19]</td>
</tr>
<tr>
<td>10 Heart rate (per minute)</td>
<td>1</td>
<td>19</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>11 FEV1 (L)</td>
<td>1</td>
<td>40</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.06 [-0.34, 0.22]</td>
</tr>
<tr>
<td>12 FVC (L)</td>
<td>1</td>
<td>40</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.21 [-0.21, 0.63]</td>
</tr>
<tr>
<td>13 Duration of hospital stay (days)</td>
<td>2</td>
<td>112</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-5.14 [-7.56, -2.71]</td>
</tr>
</tbody>
</table>
**Analysis 1.1. Comparison 1 Antibiotics versus placebo, Outcome 1 Mortality (short-term) during study intervention.**

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 1 Mortality (short-term) during study intervention

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Elmes 1965a</td>
<td>1/29</td>
<td>5/29</td>
<td>18.0 %</td>
<td>0.20 [ 0.02, 1.61 ]</td>
<td></td>
</tr>
<tr>
<td>Nouira 2001</td>
<td>4/47</td>
<td>18/46</td>
<td>65.6 %</td>
<td>0.22 [ 0.08, 0.59 ]</td>
<td></td>
</tr>
<tr>
<td>Pines 1968</td>
<td>1/15</td>
<td>3/15</td>
<td>10.8 %</td>
<td>0.33 [ 0.04, 2.85 ]</td>
<td></td>
</tr>
<tr>
<td>Pines 1972</td>
<td>0/89</td>
<td>1/86</td>
<td>5.5 %</td>
<td>0.32 [ 0.01, 7.80 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>180</strong></td>
<td><strong>176</strong></td>
<td>100.0 %</td>
<td><strong>0.23 [ 0.10, 0.52 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Antibiotic Group), 27 (Placebo Group)

Heterogeneity: $\chi^2 = 0.19$, df = 3 ($P = 0.98$); $I^2 = 0.0$

Test for overall effect: $Z = 3.55$ ($P = 0.00038$)
Analysis 1.2. Comparison 1 Antibiotics versus placebo, Outcome 2 Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration or death).

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 2 Treatment failure (no resolution or deterioration of symptoms after trial medication of any duration or death)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alonso 1992</td>
<td>2/29</td>
<td>6/29</td>
<td>3.5 % 0.33 [0.07, 1.52]</td>
<td>3.5 %</td>
<td>0.33 [0.07, 1.52]</td>
</tr>
<tr>
<td>Anthonisen 1987</td>
<td>19/57</td>
<td>28/59</td>
<td>16.2 % 0.70 [0.45, 1.11]</td>
<td>16.2 %</td>
<td>0.70 [0.45, 1.11]</td>
</tr>
<tr>
<td>Elmes 1965a</td>
<td>6/29</td>
<td>19/29</td>
<td>11.2 % 0.32 [0.15, 0.68]</td>
<td>11.2 %</td>
<td>0.32 [0.15, 0.68]</td>
</tr>
<tr>
<td>Jørgensen 1992</td>
<td>49/132</td>
<td>49/136</td>
<td>28.4 % 1.03 [0.75, 1.41]</td>
<td>28.4 %</td>
<td>1.03 [0.75, 1.41]</td>
</tr>
<tr>
<td>Pines 1968</td>
<td>6/15</td>
<td>15/15</td>
<td>9.1 % 0.42 [0.23, 0.76]</td>
<td>9.1 %</td>
<td>0.42 [0.23, 0.76]</td>
</tr>
<tr>
<td>Pines 1972</td>
<td>31/89</td>
<td>53/86</td>
<td>31.7 % 0.57 [0.41, 0.79]</td>
<td>31.7 %</td>
<td>0.57 [0.41, 0.79]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>351</strong></td>
<td><strong>354</strong></td>
<td><strong>100.0 % 0.67 [0.56, 0.81]</strong></td>
<td><strong>100.0 % 0.67 [0.56, 0.81]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 15.15, df = 5 (P = 0.01); I² = 67%
Test for overall effect: Z = 4.27 (P = 0.000020)

Analysis 1.3. Comparison 1 Antibiotics versus placebo, Outcome 3 Sputum purulent at end of treatment.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 3 Sputum purulent at end of treatment

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jørgensen 1992</td>
<td>8/127</td>
<td>10/133</td>
<td>13.8 % 0.84 [0.34, 2.06]</td>
<td>13.8 %</td>
<td>0.84 [0.34, 2.06]</td>
</tr>
<tr>
<td>Pines 1968</td>
<td>5/15</td>
<td>13/15</td>
<td>18.4 % 0.38 [0.18, 0.81]</td>
<td>18.4 %</td>
<td>0.38 [0.18, 0.81]</td>
</tr>
<tr>
<td>Pines 1972</td>
<td>27/89</td>
<td>47/86</td>
<td>67.7 % 0.56 [0.38, 0.80]</td>
<td>67.7 %</td>
<td>0.56 [0.38, 0.80]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>231</strong></td>
<td><strong>234</strong></td>
<td><strong>100.0 % 0.56 [0.41, 0.77]</strong></td>
<td><strong>100.0 % 0.56 [0.41, 0.77]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.77, df = 2 (P = 0.41); I² = 0.0%
Test for overall effect: Z = 3.61 (P = 0.000031)
Analysis 1.4. Comparison 1 Antibiotics versus placebo, Outcome 4 PaCO2 (mmHg).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Alonso 1992</td>
<td>29</td>
<td>62.76 (11.53)</td>
<td>29</td>
<td>63.86 (13.26)</td>
<td>39.1 %</td>
</tr>
<tr>
<td>Manresa 1987</td>
<td>11</td>
<td>51 (9)</td>
<td>8</td>
<td>46 (8)</td>
<td>27.1 %</td>
</tr>
<tr>
<td>Nicotra 1982</td>
<td>20</td>
<td>41.8 (9.4)</td>
<td>20</td>
<td>41.6 (12.6)</td>
<td>33.7 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>60</strong></td>
<td></td>
<td><strong>57</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 1.51, \text{df} = 2 (P = 0.47); I^2 = 0.0\%

Test for overall effect: \( Z = 0.49 \) (\( P = 0.63 \))

Analysis 1.5. Comparison 1 Antibiotics versus placebo, Outcome 5 PaO2 (mmHg).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Alonso 1992</td>
<td>29</td>
<td>45.2 (9.5)</td>
<td>29</td>
<td>46.6 (13.26)</td>
<td>58.9 %</td>
</tr>
<tr>
<td>Manresa 1987</td>
<td>11</td>
<td>57 (12)</td>
<td>8</td>
<td>61 (11)</td>
<td>19.1 %</td>
</tr>
<tr>
<td>Nicotra 1982</td>
<td>20</td>
<td>74.1 (13.6)</td>
<td>20</td>
<td>68.1 (17.5)</td>
<td>22.0 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>60</strong></td>
<td></td>
<td><strong>57</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 2.23, \text{df} = 2 (P = 0.33); I^2 = 10\%

Test for overall effect: \( Z = 0.12 \) (\( P = 0.91 \))
### Analysis 1.6. Comparison 1 Antibiotics versus placebo, Outcome 6 PEFR (L/min).

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 6 PEFR (L/min)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jrgensen 1992</td>
<td>104 278.17 (108.36)</td>
<td>122 279.06 (106.41)</td>
<td>-0.89 [ -29.00, 27.22 ]</td>
<td>67.5 %</td>
<td>-0.89 [ -29.00, 27.22 ]</td>
</tr>
<tr>
<td>Manresa 1987</td>
<td>11 213 (57)</td>
<td>8 219 (70)</td>
<td>-6.00 [ -65.06, 53.06 ]</td>
<td>15.3 %</td>
<td>-6.00 [ -65.06, 53.06 ]</td>
</tr>
<tr>
<td>Nicotra 1982</td>
<td>20 198 (72)</td>
<td>20 186 (105)</td>
<td>12.00 [ -43.80, 67.80 ]</td>
<td>17.1 %</td>
<td>12.00 [ -43.80, 67.80 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>135</strong></td>
<td><strong>150</strong></td>
<td><strong>0.54 [ -22.57, 23.64 ]</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.54 [ -22.57, 23.64 ]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2 = 0.22$, df = 2 (P = 0.90); I$^2$ = 0.0%

Test for overall effect: Z = 0.05 (P = 0.96)

### Analysis 1.7. Comparison 1 Antibiotics versus placebo, Outcome 7 Adverse events.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 7 Adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Diarrhoea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jrgensen 1992</td>
<td>13/133</td>
<td>4/137</td>
<td>3.35 [ 1.12, 10.01 ]</td>
<td>79.6 %</td>
<td>3.35 [ 1.12, 10.01 ]</td>
</tr>
<tr>
<td>Nouira 2001</td>
<td>1/47</td>
<td>1/46</td>
<td>0.98 [ 0.06, 15.19 ]</td>
<td>20.4 %</td>
<td>0.98 [ 0.06, 15.19 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>180</strong></td>
<td><strong>183</strong></td>
<td><strong>2.86 [ 1.06, 7.76 ]</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.86 [ 1.06, 7.76 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 14 (Antibiotic Group), 5 (Placebo Group)

Heterogeneity: Chi$^2 = 0.67$, df = 1 (P = 0.41); I$^2$ = 0.0%

Test for overall effect: Z = 2.07 (P = 0.039)

| **2 Dyspepsia**   |                  |               |            |        |            |
| Jrgensen 1992     | 3/133 | 6/137 | 0.52 [ 0.13, 2.02 ] | 100.0 % | 0.52 [ 0.13, 2.02 ] |
| **Subtotal (95% CI)** | **133** | **137** | **0.52 [ 0.13, 2.02 ]** | **100.0 %** | **0.52 [ 0.13, 2.02 ]** |

Total events: 3 (Antibiotic Group), 6 (Placebo Group)

Heterogeneity: not applicable
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>3 Pain in mouth</td>
<td>3/133</td>
<td>0/137</td>
<td>100.0 % 7.21 [ 0.38, 138.24 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>133</strong></td>
<td><strong>137</strong></td>
<td>100.0 % 7.21 [ 0.38, 138.24 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 3 (Antibiotic Group), 0 (Placebo Group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.31 (P = 0.19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Exanthema, itching</td>
<td>3/133</td>
<td>1/137</td>
<td>100.0 % 3.09 [ 0.33, 29.34 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>133</strong></td>
<td><strong>137</strong></td>
<td>100.0 % 3.09 [ 0.33, 29.34 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 3 (Antibiotic Group), 1 (Placebo Group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.98 (P = 0.33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Abnormal serum</td>
<td>2/47</td>
<td>3/46</td>
<td>100.0 % 0.65 [ 0.11, 3.73 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>47</strong></td>
<td><strong>46</strong></td>
<td>100.0 % 0.65 [ 0.11, 3.73 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 2 (Antibiotic Group), 3 (Placebo Group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.48 (P = 0.63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Overall (adverse events not separated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nouira 2001</td>
<td>5/47</td>
<td>4/46</td>
<td>39.8 % 1.22 [ 0.35, 4.27 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>136</strong></td>
<td><strong>132</strong></td>
<td>100.0 % 2.91 [ 1.48, 5.72 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 30 (Antibiotic Group), 10 (Placebo Group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Ch squared = 2.42, df = 1 (P = 0.12); I² =59%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.09 (P = 0.0020)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 0.95 (P = 0.34)
Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 7 Adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio (M-H,Fixed,95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jørgensen 1992</td>
<td>13/133</td>
<td>4/137</td>
<td>3.35 [1.12, 10.01]</td>
<td>79.6 %</td>
</tr>
<tr>
<td>Nouira 2001</td>
<td>1/47</td>
<td>1/46</td>
<td>0.98 [0.06, 15.19]</td>
<td>20.4 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>180</strong></td>
<td><strong>183</strong></td>
<td>2.86 [1.06, 7.76]</td>
<td>100.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Dyspepsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jørgensen 1992</td>
<td>3/133</td>
<td>6/137</td>
<td>0.52 [0.13, 2.02]</td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>133</strong></td>
<td><strong>137</strong></td>
<td>0.52 [0.13, 2.02]</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>
### Antibiotics for Exacerbations of Chronic Obstructive Pulmonary Disease

#### Outcome: 7 Adverse Events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>3 Pain in mouth</td>
<td>3/133</td>
<td>0/137</td>
<td>7.21 [0.38, 138.24]</td>
<td>100.0%</td>
<td>7.21 [0.38, 138.24]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>133</strong></td>
<td><strong>137</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>7.21 [0.38, 138.24]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 3 (Antibiotic Group), 0 (Placebo Group)

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

---

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>4 Exanthema, itching</td>
<td>3/133</td>
<td>1/137</td>
<td>3.09 [0.33, 29.34]</td>
<td>100.0%</td>
<td>3.09 [0.33, 29.34]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>133</strong></td>
<td><strong>137</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>3.09 [0.33, 29.34]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 3 (Antibiotic Group), 1 (Placebo Group)

Heterogeneity: not applicable

Test for overall effect: Z = 0.98 (P = 0.33)
Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 7 Adverse events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
<th>Weight M-H,Fixed</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Abnormal serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nouira 2001</td>
<td>2/47</td>
<td>3/46</td>
<td></td>
<td>100.0 %</td>
<td>0.65 [0.11, 3.73 ]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 47 46 100.0 % 0.65 [0.11, 3.73 ]

Total events: 2 (Antibiotic Group), 3 (Placebo Group)
Heterogeneity: not applicable
Test for overall effect: Z = 0.48 (P = 0.63)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
<th>Weight M-H,Fixed</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Overall (adverse events not separated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nouira 2001</td>
<td>5/47</td>
<td>4/46</td>
<td></td>
<td>39.8 %</td>
<td>1.22 [0.35, 4.27 ]</td>
</tr>
<tr>
<td>Pins 1972</td>
<td>25/89</td>
<td>6/86</td>
<td></td>
<td>60.2 %</td>
<td>4.03 [1.74, 9.33 ]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 136 132 100.0 % 2.91 [1.48, 5.72 ]

Total events: 30 (Antibiotic Group), 10 (Placebo Group)
Heterogeneity: Chi² = 2.42, df = 1 (P = 0.12); I² =59%
Test for overall effect: Z = 3.09 (P = 0.0020)
Analysis 1.8. Comparison 1 Antibiotics versus placebo, Outcome 8 Need for additional antibiotics.

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 8 Need for additional antibiotics

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nouira 2001</td>
<td>5/47</td>
<td>26/46</td>
<td>0.19</td>
<td>100.0%</td>
<td>0.19 [ 0.08, 0.45 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>47</td>
<td>46</td>
<td>100.0%</td>
<td>0.19 [ 0.08, 0.45 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 5 (Antibiotic Group), 26 (Placebo Group)
Heterogeneity: not applicable
Test for overall effect: Z = 3.78 (P = 0.00016)

Analysis 1.9. Comparison 1 Antibiotics versus placebo, Outcome 9 Respiratory rate (per minute).

Review: Antibiotics for exacerbations of chronic obstructive pulmonary disease

Comparison: 1 Antibiotics versus placebo

Outcome: 9 Respiratory rate (per minute)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manresa 1987</td>
<td>11 20 (4)</td>
<td>8 19 (5)</td>
<td>1.00 [ -3.19, 5.19 ]</td>
<td>100.0%</td>
<td>1.00 [-3.19, 5.19 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>11</td>
<td>8</td>
<td>100.0%</td>
<td>1.00 [-3.19, 5.19 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

Antibiotics for exacerbations of chronic obstructive pulmonary disease (Review)
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Analysis 1.10. Comparison 1 Antibiotics versus placebo, Outcome 10 Heart rate (per minute).

**Review:** Antibiotics for exacerbations of chronic obstructive pulmonary disease  
**Comparison:** 1 Antibiotics versus placebo  
**Outcome:** 10 Heart rate (per minute)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group Mean (SD)</th>
<th>Placebo Group Mean (SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manresa 1987</td>
<td>11 85 (15)</td>
<td>8 85 (8)</td>
<td></td>
<td>100.0%</td>
<td>0.0 [-10.45, 10.45 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>11</strong></td>
<td><strong>8</strong></td>
<td></td>
<td>100.0%</td>
<td>0.0 [-10.45, 10.45 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable  
Test for overall effect: Z = 0.0 (P = 1.0)

### Analysis 1.11. Comparison 1 Antibiotics versus placebo, Outcome 11 FEV1 (L).

**Review:** Antibiotics for exacerbations of chronic obstructive pulmonary disease  
**Comparison:** 1 Antibiotics versus placebo  
**Outcome:** 11 FEV1 (L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group Mean (SD)</th>
<th>Placebo Group Mean (SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotra 1982</td>
<td>20 1.02 (0.33)</td>
<td>20 1.08 (0.54)</td>
<td></td>
<td>100.0%</td>
<td>-0.06 [-0.34, 0.22 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20</strong></td>
<td><strong>20</strong></td>
<td></td>
<td>100.0%</td>
<td>-0.06 [-0.34, 0.22 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable  
Test for overall effect: Z = 0.42 (P = 0.67)
### Analysis 1.12. Comparison 1 Antibiotics versus placebo, Outcome 12 FVC (L).

**Review:** Antibiotics for exacerbations of chronic obstructive pulmonary disease

**Comparison:** 1 Antibiotics versus placebo

**Outcome:** 12 FVC (L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotra 1982</td>
<td>20</td>
<td>20</td>
<td>2.16 (0.66)</td>
<td>100.0%</td>
<td>0.21 [-0.21, 0.63]</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 20 20 100.0% 0.21 [-0.21, 0.63]

Heterogeneity: not applicable

Test for overall effect: Z = 0.98 (P = 0.33)

### Analysis 1.13. Comparison 1 Antibiotics versus placebo, Outcome 13 Duration of hospital stay (days).

**Review:** Antibiotics for exacerbations of chronic obstructive pulmonary disease

**Comparison:** 1 Antibiotics versus placebo

**Outcome:** 13 Duration of hospital stay (days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotic Group</th>
<th>Placebo Group</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manresa 1987</td>
<td>11</td>
<td>8</td>
<td>12.8 (4)</td>
<td>44.2%</td>
<td>0.50 [-3.14, 4.14]</td>
</tr>
<tr>
<td>Nouira 2001</td>
<td>47</td>
<td>46</td>
<td>14.9 (7.4)</td>
<td>55.8%</td>
<td>-9.60 [-12.84, -6.36]</td>
</tr>
</tbody>
</table>

**Total (95% CI):** 58 54 100.0% -5.14 [-7.56, -2.71]

Heterogeneity: Chi² = 16.48, df = 1 (P = 0.00005); I² = 94%

Test for overall effect: Z = 4.16 (P = 0.000032)
Appendix 1. MEDLINE search 01/10/04

MEDLINE
1 exp Pulmonary Disease, Chronic Obstructive/
2 COPD
3 exp EMPHYSEMA/
4 emphysema
5 exp Bronchitis, Chronic/
6 chronic bronchitis
7 chronic obstructive bronchitis
8 chronic airflow limitation
9 chronic airflow obstruction
10 chronic airways obstruction
11 obstructive airways disease
12 (chronic obstructive airways disease or COAD)
13 chronic obstructive lung disease
14 or/1-13
15 exp ANTIBIOTICS, LACT AM/ or ANTIBIOTICS/
16 exp Amoxicillin-Potassium Clavulanate Combination/
17 (penicillin$ or penicillin G or penicillin V or amoxycillin or ampicillin or amoxicillin clavulanic acid)
18 exp CEPHALOSPORINS/
19 (cephalospor$ or cefalosporin$ or cefaclor or cefazolin or cefixime or cefotaxime or cepodoxime or cephradine or cefixime or cefuroxime or cefuroxime axetil)
20 exp ANTIBIOTICS, TETRACYCLINE/
21 (tetracyclin$ or demeclocycline or doxycycline or minocycline or oxytetracycline)
22 exp ANTIBIOTICS, MACROLIDE/
23 (macrolid$ or azithromycin or clarithromycin or dirithromycin or erythromycin or roxithromycin or telithromycin or troleandomycin)
24 exp Anti-Infective Agents, Fluoroquinolone/
25 (fluoroquinol$ or ciprofloxacin or gatifloxacin or gemifloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or $floxacin)
26 chloramphenicol.mp. or exp CHLORAMPHENICOL/
27 cotrimoxazole.mp. or Trimethoprim-Sulfamethoxazole Combination/
28 exp CARBAPENEMS/
29 (carbapenem$ or meropenem or imipenem)
30 antibiotic$  
31 or/15-30
32 14 and 31
33 exp Placebos/
34 placebo$  
35 or/33-34
36 RANDOMIZED CONTROLLED TRIAL.pt.  
37 CONTROLLED CLINICAL TRIAL.pt.  
38 RANDOMIZED CONTROLLED TRIALS.sh.  
39 RANDOM ALLOCATION.sh.  
40 DOUBLE BLIND METHOD.sh.  
41 SINGLE-BLIND METHOD.sh.  
42 or/36-41
43 (ANIMAL not HUMAN).sh.  
44 42 not 43  
45 CLINICAL TRIAL.pt.  
46 exp Clinical Trials/
Feedback

Antibiotics for exacerbations of chronic obstructi

Summary
Feedback: While authors concluded that: "... in COPD exacerbations ... antibiotics ... reduce the risk of short-term mortality by 77%, decrease the risk of treatment failure by 53% and the risk of sputum purulence by 44%; with a small increase in the risk of diarrhoea. These results should be interpreted with caution ... Nevertheless, this review supports antibiotics for patients with COPD exacerbations ..."

The plain language statement bring the other message IN BOLD: “Despite their widespread use, the value of antibiotics in exacerbations of chronic obstructive pulmonary disease (COPD) remains controversial”

I believe that this is quite clear misinforormation of consumers.

Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We thank Dr Vasily Vlassov for his interest in our review. Dr Vasily Vlassov may find the introductory sentence contradictory in the plain language summary. This is becasue this opening sentence is part of the thinking of the backgrond to the topic whereas the “added” comment in our results is part of the conclusions that are modulated by the "methodological nature” and the evidence provided from the 11 trials included in the review.

Felix Ram

Contributors

Vasiliy Vlassov

WHAT’S NEW

Last assessed as up-to-date: 19 December 2005.
HISTORY
Review first published: Issue 2, 2006

25 July 2006  Amended  Data entry error for treatment failure outcome corrected for one study. Review conclusions unaffected.
5 June 2006  Feedback has been incorporated  Feedback comment and reply added to review.

CONTRIBUTIONS OF AUTHORS
FSFR conceived the idea for the review and wrote the protocol.
All authors (FSFR, JGA, NCB, AGN, RRR) contributed towards the following: trial selection, data and trial characteristics extraction, trial grading and review writing. FSFR is the guarantor for this review.

DECLARATIONS OF INTEREST
Neil Barnes (NCB) has lectured for and had consultancy arrangements with GlaxoSmithKline and AstraZeneca who both make antibiotics. He has had research funded by GlaxoSmithKline, AstraZeneca and Bayer Pharmaceuticals who all make antibiotics. Roberto Rodriguez-Roisin (RRR) has lectured for Almirall Prodesfarma, AstraZeneca, GlaxoSmithKline and Pfizer and has had consultancy arrangements with Almirall Prodesfarma, Chiesi Wasserman, GlaxoSmithKline, Laboratorios Dr Esteve SA and Pfizer. He has also received research funding from Almirall Prodesfarma, AstraZeneca, GlaxoSmithKline, Laboratorios Dr Esteve SA and Pfizer, who all manufacturer antibiotics. The remaining three authors (FSFR, JGA and AGN) do not have any known conflicts of interest.

SOURCES OF SUPPORT
Internal sources
- No sources of support supplied
External sources

- RRR is supported by Red Respira-ISCIII-RTIC-03/11 and la Generalitat de Catalunya (2001/SGR00386), Spain.
- JGA was supported by Red RESPIRA (RTIC C03/11), Instituto de Salud Carlos III, Spain.
- ANG was partially supported by RCESP (ISCIII, C03/09), Spain.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [* therapeutic use]; Cough [drug therapy]; Pulmonary Disease, Chronic Obstructive [* drug therapy]; Randomized Controlled Trials as Topic; Sputum [secretion]

MeSH check words

Humans