COPD Evidence Tables

The evidence tables are presented in section order.

The methodological quality of each paper was rated using the Scottish Intercollegiate Guidelines Network (SIGN) system (Scottish Intercollegiate Guidelines Network. SIGN 50 Guideline Developers Handbook, 2001; ID 19457):

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>++</td>
<td>All or most of the SIGN methodology checklist criteria were fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought very unlikely to alter.</td>
</tr>
<tr>
<td>+</td>
<td>Some of the criteria were fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.</td>
</tr>
<tr>
<td>-</td>
<td>Few or no criteria were fulfilled. The conclusions of the study are thought likely or very likely to alter.</td>
</tr>
</tbody>
</table>
### Managing Stable COPD
#### Prophylactic antibiotic therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Design</th>
<th>Inclusion / exclusion criteria</th>
<th>Lung Function</th>
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</tr>
</thead>
</table>
| Pridie, R. 1960, "A trial of continuous winter chemotherapy in chronic bronchitis". *Lancet*. Ref ID: 1376 | N=151 | Random sampling not random allocation, double blind, placebo controlled | Inclusion:  
- Adults with chronic bronchitis with some exertional dyspnoea  
- At least one disabling resp’ illness with 2/12 cough and sputum over the previous three winters.  
- Age range not clear, possibly 20-70+ yrs, N=5 pts in the  
- 20-29yr-age bracket.  
- No operational | Average FEV1 (L) <1 =91 pts 1-1.99 =170pts ≥ 2 =31pts | ✔ | • 24 weeks duration  
• Oxytetracycline 0.5g daily  
• Potassium phenoxyphthyl-penicillin 500mg with sulphadimidine 2g in combined tablets daily.  
• Placebo | Sputum  
No significant difference in purulence between the 3 groups at any stage of the trial.  
**Ventilatory Function**  
No significant difference between the groups  
**Subjective assessment**  
No significant difference between the 3 groups of reduction in dyspnoea or change exercise levels | - | GPs were asked to discontinue the trial tablets during an exacerbation and to give customary treatment for acute bronchitis. All other usual supportive measure, such as bronchodilators were continued as necessary throughout the trial. No further di... |
| Definition of classification of chronic bronchitis. Exclusion:  
| Active TB  
| Bronchiectasis  
| Ca bronchus  
| Other chest disease (not specified by author). | Exacerbations and time off work  
No significant differences between the groups. | Details given of concomitant medication. |
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</table>
- Males aged 40-59 years  
- History of recurrent infection but with mild disability  
- Productive cough (grade 2, MRC 1960)  
- At least two chest illnesses with increased phlegm  
- Absence from work >3wks during the previous three yrs.  
- No operational definition of classification of chronic bronchitis.  
Exclusion:  
- Any other disabling condition. | FEV1 >1.4 L | X                           | Sputum culture.  
A specimen of sputum was assessed for purulence and volume at baseline and during the trial for the effect of chemotherapy.  
Sputum was graded as mucoid, mucopurulent or mucoid or purulent. | Duration mid Sept to April each year  
- Oxytetracycline 0.5g once daily alone and with chloramphenicol or sulfonamide.  
- Placebo  
- During the 4th yr the dose was increased to 0.5 g bd and in the 5th yr 1 g bd. | Number of illnesses  
Significant heterogeneity between clinics p<0.001 hence treat with caution as factors other than treatment could be associated with greater variation in the number of illnesses  
Duration of illness  
Not significant  
Lung function  
No differences between groups found.  
Sputum  
No significant differences found | - | Report of the first 5 years. Concomitant medication not documented. |
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</table>
| Pines, A. 1967, "Controlled trials of a sulphonamide given weekly to prevent exacerbations of chronic bronchitis.", *BMJ*. Ref ID: 1377 | N=60 | Randomised double blind placebo controlled trial | Inclusion:  
- Long hospital stay.  
- History of at least one acute exacerbation during the previous yr, treatment by antibiotics of confinement to bed at home.  
- Purulent sputum @ admission.  
- Males  
- Aged 40-70yrs  
- No operational definition of classification of chronic bronchitis. | Initial maximal PFR  
- <100 l/min=5pts  
- 100-200 l/min=21pts  
- >200 l/min=4pts | ✓ | Follow up for 4 to 8 months.  
- Four tablets of placebo or of sulphormethoxine (2g) were given weekly for a period of 10 wks whether relapse occurred or not. | Trial I: Difference in % exacerbations between sulphormethoxine and controls is 40% (95% CI 14-68%).  
Trial II: Difference in % exacerbations between sulphormethoxine and controls is 30% (95% CI 3-51%). | - | Concomitant medication not documented. |
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</table>
- Males / 38-60 yrs  
- Attending chest clinic  
- History of productive cough 3yrs  
- >2 resp illnesses causing absence from work  
- No operational definition of classification of chronic bronchitis. | Total initial FEV1 1.66 L | ✓ | - Five yr study  
- Four treatment groups:  
  - P=Placebo  
  - T=Tetracycline 500mg bd  
  - TP=Tetracycline for 2 winters then placebo for three.  
  - PT=Placebo for two winters and then Tetracycline for three. | A significant reduction found in number of exacerbations in those who suffered more than one exacerbation each winter. Average decline in FEV1 over the 5-year period was not significant. No significant difference between the groups in lung volume, diffusing capacity, blood gases. | - | All groups received a 5-day course of tetracycline for any acute exacerbation. In addition, anti-influenza vaccine was given to all in the 2nd and 4th yrs. Concomitant medication not documented. |
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- Males aged 41-80yrs  
- Chronic bronchitis defined by ATS  
Exclusion:  
- Malignancy  
- Cardiac, renal, or hepatic failure.  
- Alcohol or drug abuse  
- Corticosteroid or immunosuppressive therapy  
- Asthma  
- Collagen vascular disorders  
- Diabetes mellitus | Mean value of FEV1 35% | ✓ | Individual treatment periods ranged from 12 to 36 months (average 26)  
- Phenoxy methyl penicillin 250mg  
- Placebo | N=9 pre-treatment had positive cultures (of these 6/9 received intervention and 3/9 received placebo). Proportion of carriers between two groups not statistically significant.  
During follow-up 7/5 in control group had positive cultures (equating to 10/65 cultures) whereas 0/74 cultures obtained from patients treated with penicillin grew s.pneumoniae (p=0.0015). | - | All pts were immunised with influenza vaccine  
No pt had received pneumococcal vaccine prior to completion of the study. Concomitant medication not documented. |
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- N=29 had chronic bronchitis associated with extensive bilateral bronchiectasis, advanced emphysema or recurrent and severe bronchial asthma.  
- N=1 chronic otitis media and acute purulent meningitis | LF not documented | ✗ sputum culture |  
- Duration of study ranged from 2 wks to 20 months  
- Chlortetracycline 250 mg bd  
- Placebo |
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  - Male outpatients  
  - Persistent productive cough.  
  - Undue effort dyspnoea  
  - History of previous acute infective exacerbations  
  - No operational definition of classification of chronic bronchitis.  

*Exclusion:*  
  - TB  
  - Antibiotic therapy | LF not documented | ✓ |  
  - 1 yr duration  
  - Tetracycline 250mg bd  
  - Placebo | While the trial was in progress additional treatment considered necessary apart from antibiotics was allowed. This included a variety of the following: sedatives, expectorant cough mixtures, anti spasmodics, digitalis and mersalyl.  

All pts given 1g of yeast daily.
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| Cherniack N et al, 1959, Long-term treatment of bronchiectasis and chronic bronchitis. A.M.A. Archives of Internal Medicine ID 1379 | N=67 | Quasi randomised, double blind placebo controlled    | Inclusion:  
  - Broncho-graphy revealed one or more areas of bronchiectasis.  
  - Bronchitis  
  - Where broncho-graphy could not be performed, the diagnosis of the respiratory illness was listed as undetermined (hence N=8 pts in the undetermined group).  
  - History of chronic productive cough >1yr  
  - Repeated lower respiratory tract infections without another reason for the cough | Vital Capacity % before treatment range of mean results for 4 groups 56 to 71.  
  1 sec vital capacity % before treatment range of mean results for 4 groups 55 to 63.  
  Max Breathing Capacity % mean of results 42 to 62 | ✓              | - 3 to 22 months duration  
 - Tetracycline  
 - Oleandomycin-penicillin  
 - Penicillin  
 - Placebo | Pts were considered to have a respiratory tract illness pyrexia 100 F, symptoms involving the respiratory tract in which there was either an acute exacerbation of previous symptoms or the appearance of new symptoms, acute appearance of dyspnoea Con-comitant medication not documented. |
and sputum.

- No operational definition of classification of chronic bronchitis.

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| Francis, R. 1960, "Chemotherapy in chronic bronchitis. Influence of daily penicillin and tetracycline on exacerbations and their cost.", *BMJ*. Ref ID: 1380 | N=226 | Randomised, double blind placebo controlled | Inclusion:  
- Males, age range 30-65yrs  
- History of winter cough and sputum for the >3yrs  
- Absent from work at >2 occasions because of bronchitis with purulent sputum  
- No operational definition of classification of chronic bronchitis.  
Exclusion:  
- Wheezing  
- Heart failure  
- If radiographic changes other | LF not documented | × sputum culture  
Nasal swabs taken before and after trial for culture | Duration 4/12 Jan to April.  
Tetracycline 250mg bd  
Penicillin V 312mg bd  
Placebo | Definition of “bronchitic exacerbation” was an increase in cough with the appearance of pus in the sputum or an increase in the amount of pus over the amount usually present”.  
Concomitant medication not documented. |
than those of bronchitis and emphysema were present.

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</table>
| Francis, R. 1961, "Chemotherapy of bronchitis. Influence of penicillin and tetracycline administered daily, or intermittently for exacerbations", BMJ. Ref ID: 1381 | N=519| Cross over, no placebo | Inclusion:  
  • Males, age range 30-65yrs  
  • History of winter cough and sputum for the >3yrs  
  • Absent from work at >2 occasions because of bronchitis with purulent sputum  
  • No operational definition of classification of chronic bronchitis.  
Exclusion:  
  • Wheezing  
  • Heart failure  
  • If radiographic changes other than those of bronchitis and than those of bronchitis and emphysema were present. | LF not documented | ✔  | Antibiotics administered each day throughout the winter. 153 days duration.  
  • Tetracycline  
  • Penicillin V | Definition of “bronchitic exacerbation” was an increase in cough with the appearance of pus in the sputum or an increase in the amount of pus over the amount usually present”. Concomitant medication not documented. |
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</table>
- Average age 61yrs  
- Chronic bronchitis defined according to ATS classification. | Mean FEV1 @ entry 1.33L  
Range 0.5 to 2.9 L. | ✓ |  
- Followed up for 3 to 29 months.  
- Ampicillin and tetracycline in doses of 1g day (1 capsule every 12 hrs for 5 days) compared to placebo  

Pts were instructed to take their drug only if they developed symptoms of a cold. “Either therapy or prophylaxis was prescribed at each clinic visit depending on whether a pt was judged to have an acute exacerbation”. Severity of exacerbation not graded. Concomitant
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</table>
• Simple chronic bronchitis of >2yrs  
• No operational definition of classification of chronic bronchitis.  
Exclusion:  
• Asthma  
• Bronchiectasis  
• (Confirmed by FEV & FVC, results not given). | FEV & FVC undertaken but no values given. | ✓ | • For the first 10 days of each month starting in November and continuing for the 6 winter months.  
• Continued for 1yr in N=32 and 2 yrs in N=22  
• Erythromycin 500mg | Con-comitant medication not documented |
• Indian population  
• No demographics  
• No LF / disease profile |
• No placebo group  
• Outcome measure was the “well-being of the pts at the end of the winter” as quoted in Ruben F (1988). |
Overview used for cross referencing |
Lepper, M. 1964, "Natural history of placebo treated patients with chronic bronchial disease observed for 7 years.", *Antimicrobial Agents & Chemotherapy* pp. 692-698. Ref ID: 1371


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<tbody>
<tr>
<td>N=</td>
<td>N=109. Location=Japan. Duration of follow-up=12 months commencing October, 4 wks after commencing erythromycin or riboflavin.</td>
</tr>
<tr>
<td>Research Design</td>
<td>RCT (unblinded)</td>
</tr>
<tr>
<td>Aim</td>
<td>To compare the rate and number of common colds and exacerbations</td>
</tr>
<tr>
<td>Operational Definition</td>
<td>All pts fulfilled ATS criteria for COPD</td>
</tr>
<tr>
<td></td>
<td>A common cold was defined as a total symptom score of &gt;5. Ten symptoms were recorded; sneezing, nasal discharge, nasal congestion, malaise, headache, chills, feverishness, sore throat, hoarseness and cough. Symptoms were rated for severity on a scale from 0 to 3.</td>
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<td></td>
<td>COPD exacerbations were defined as an acute and sustained worsening of COPD symptoms requiring changes to regular treatment including antimicrobial therapy and or short courses of systemic steroids.</td>
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<td></td>
<td>Severity of exacerbation was defined as mild to moderate if pts could be treated without hospitalisation and as severe if hospitalisation was required.</td>
</tr>
<tr>
<td>Population</td>
<td>COPD</td>
</tr>
<tr>
<td>Intervention</td>
<td>N=55 Erythromycin 200 to 400 mg/d for 12 months</td>
</tr>
<tr>
<td>Comparison</td>
<td>N=54 Control riboflavin 10mg/d for 12 months</td>
</tr>
<tr>
<td>Outcome</td>
<td>Common cold rate</td>
</tr>
<tr>
<td></td>
<td>Exacerbation of COPD.</td>
</tr>
<tr>
<td></td>
<td>Death rate</td>
</tr>
<tr>
<td></td>
<td>Adverse events</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Pts with bronchiectasis or diffuse panbronchiolitis were excluded. Concomitant medication included sustained release theophylline and inhaled anticholinergic agents but not corticosteroids.</td>
</tr>
</tbody>
</table>
Average age 71 years  
Gender male / female=91/17  
FEV1 at baseline = control group 1.30 / erythromycin group 1.47 L

**Results**

**Common cold**  
Was significantly lower in the erythromycin group (1.24 +/- 0.07 per person) than in the control group (4.54 +/- 0.02 per person)  
p=0.0002  
76% of the control group compared to 13% of the erythromycin group experienced common colds.  
The relative risk of experiencing a common cold more than once a year in the control group compared with that of the erythromycin group was 9.26 (95% CI 3.92 to 31.74; p=0.0001).

**Exacerbations**  
The total number of exacerbations was significantly lower in the erythromycin group compared to the control group (p<0.0001).  
56% of control group and 11% of erythromycin group patients had at least one exacerbation.  
The relative risk of experiencing one or more exacerbations in the control group compared with that in the erythromycin group was 4.71 (95% CI, 1.53 to 14.5) p=0.007.  
Significantly more severe exacerbations were observed in the control group than in the erythromycin group (p=0.0007).

**Death rate**  
Nil in either group

**Adverse events**  
No serious adverse events

**SIGN Quality Rating**

<table>
<thead>
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</table>
| N=9 studies (N=1555 subjects) N range= N=23 (Murdoch 1959) – N=497 (Fletcher 1966)  
Location=Chest clinics  
**Research Design** Meta-analysis- Randomised placebo controlled trials.  
**Aim** To determine whether treatment with prophylactic antibiotics reduces the frequency of exacerbations and/or days of disability in subjects with chronic bronchitis.  

<p>| N=1148 |</p>
<table>
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<tr>
<th><strong>Operational Definition</strong></th>
<th>Chronic bronchitis as defined by the criteria of the Medical Research Council.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Adults with chronic bronchitis and/or with chronic obstructive pulmonary disease. Studies of patients with bronchitis and asthma were excluded.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Oral antibiotics including penicillin, amoxycillin, tetracycline, oxytetracycline, erythromycin, and sulphonamides administered daily for a period of at least three months. N not available- only total N provided- see studies included.</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Placebo (except Moyes 1957 who had placebo plus aminophylline 0.1mg tid). N not available- only total N provided- see studies included.</td>
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<tr>
<td><strong>Outcome</strong></td>
<td><strong>Primary outcomes</strong>&lt;br&gt;The number of acute exacerbations defined as an increase in cough and in the volume and/or purulence of sputum. The proportion of patients not having an exacerbation during the course of the study was also assessed;&lt;br&gt;The number of days of disability variously defined as days in bed, days off work or days where the subject was unable to undertake normal activities.&lt;br&gt;<strong>Secondary outcomes</strong>&lt;br&gt;The duration of exacerbations;&lt;br&gt;The number of additional doses of antibiotics required for treatment of the exacerbations;&lt;br&gt;The adverse effects of treatment.</td>
</tr>
<tr>
<td><strong>Characteristics</strong></td>
<td>Information available is limited to sex and % men and these details are not available for all studies.</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><strong>Primary outcomes</strong>&lt;br&gt;The number of acute exacerbations.&lt;br&gt;The likelihood of having an exacerbation at any time during the course of the study was decreased with treatment (RR 0.91, 95% CI 0.84 to 0.99). The exacerbation rate was high in most studies so this translates into an average number needed to treat of 14 (95% CI 128 to 8) to prevent one exacerbation in each study. This figure should be interpreted with caution in view of the variable length of the different studies.&lt;br&gt;The number of days of disability variously defined as days in bed, days off work or days where the subject was unable to undertake normal activities.&lt;br&gt;The reduction in the days of disability is primarily due to the reduction in the number of days of disability for each exacerbation with a weighted mean difference of –2.08 days (95% CI –0.09 to 0.10).&lt;br&gt;<strong>Secondary outcomes</strong>&lt;br&gt;The number of additional doses of antibiotics required for treatment of the exacerbations;&lt;br&gt;Of the 1055 subjects studied, 587 were randomized to an antibiotic. 420 of the 587 subjects receiving an antibiotic were treated with a tetracycline. The reduction in exacerbations with tetracyclines was 0.12 exacerbations per patient per year (95% CI –0.32 to 0.08) and was not statistically significant. Prophylactic antibiotics did reduce the days of disability. With prophylactic antibiotics the SMD was –0.37 (95% CI –0.59 to –0.15). The days of disability can also be expressed as days per participation per month. When the results were expressed this way, the weighted mean difference was 0.95 fewer days of disability per participant per month (95% CI –1.89 to –0.01). This represents a reduction of 22% compared with placebo. The results for treatment with tetracyclines showed a similar reduction in days of...</td>
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disability to treatment with other classes of antibiotics. Fletcher 1966 showed a reduction in the days of disability from 1.14 days per participant per month with placebo treatment to 0.86 days per participant per month with placebo treatment to 0.86 days per participant per month with oxytetracycline prophylaxis. This effect was statistically significant and sensitivity analyses was carried out using imputed standard deviations. This gave a very similar SMD of weighted mean difference of −0.28 (95% CI −0.43 to −0.13) but the WMD fell to 0.33 fewer days of disability per month (95% CI −0.60 to −0.07), as the days of disability in this study were generally lower than other studies. Only one study contributed to the analysis of the effect of prophylactic antibiotics on additional courses of antibiotics but no effect was seen with a mean difference of 0.0 (95% CI −0.09 to 0.10).

**The adverse effects of treatment.**

There was little difference in the frequency of adverse effects between the placebo and antibiotic groups. The weighted mean difference was 0.01 adverse effects per patient per year treated (95% CI 0.00 to 0.02).

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<thead>
<tr>
<th>SIGN Quality Rating</th>
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<tr>
<td>Hierarchy of Evidence Grading</td>
<td>Ia</td>
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<tr>
<td><strong>Studies Included</strong></td>
<td>Fletcher 1966, N=497; Francis 1969, N=252; Goslings 1957, N=69; Johnstone 1961, N=40; Johnstone 1969, N=120; Liippo 1987, N=24; Moyes 1957, N=90; Murdoch 1959, N=23; Pirdie 1960, N=151. The present Cochrane review was found following a re-run literature search- 3 articles included in this study (Fletcher 1966, Johnstone 1969, Pirdie 1960) were already critically reviewed individually prior to this.</td>
</tr>
<tr>
<td><strong>NCC CC ID</strong></td>
<td>19362</td>
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