Effectiveness and safety of medicines used in COPD patients
Wang, Yuanyuan

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Effects of Prophylactic Antibiotics on Patients with Stable COPD: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

ABSTRACT

Background
As bacterial infections provoke exacerbations, COPD patients may benefit from prophylactic antibiotics. However, evidence regarding their overall benefit-risk is conflicting.

Objectives
To update previous evidence and systematically evaluate the beneficial and side effects of prophylactic antibiotics on stable COPD patients.

Methods
Several databases were searched up to April 26, 2017 for randomized controlled trials (RCTs) on prophylactic antibiotics in stable COPD patients. The Primary outcomes were exacerbations and quality of life. Duration and schedule of antibiotics were considered in sub-group analyses.

Results
Twelve RCTs involving 3,683 patients were included. Prophylactic antibiotics significantly reduced the frequency of exacerbations (risk ratio [RR] 0.74, 95% CI 0.60-0.92) and the number of patients with one or more exacerbations (RR 0.82, 95% CI 0.74-0.90). Erythromycin and azithromycin appeared the most effective with the number needed to treat ranging from four to seven. Quality of life was also significantly improved by prophylactic antibiotics (mean difference -1.55, 95% CI -2.59 to -0.51). Time to first exacerbation was prolonged in six studies with one conflicting result. Neither the rate of hospitalization nor the rate of adverse events was significantly changed. Furthermore, no significant changes were observed in lung function, bacterial load and airway inflammation. However, antibiotic resistant isolates were significantly increased (OR 4.49, 95% CI 2.48-8.12).

Conclusions
Prophylactic antibiotics were effective in preventing COPD exacerbations and improving quality of life among stable patients with moderate to severe COPD. The choice of prophylactic antibiotics should be analysed and considered case by case, especially for long and continuous use.
INTRODUCTION

COPD is an inflammatory disease that is characterized by persistent respiratory symptoms and airflow limitation. At present, COPD is one of the leading causes of chronic morbidity and mortality worldwide, its burden is predicted to increase in the coming decades due to continuous exposure to risk factors and aging of population globally. In the course of COPD, exacerbation as an acute worsening of respiratory symptoms has a profound negative impact on health outcomes. A vicious circle of infection and inflammation is thought as a key to trigger exacerbations of COPD, about 40-50% of exacerbations are caused by bacteria.

The use of prophylactic antibiotic has been suggested to prevent exacerbations in COPD patients for a long time. However, a Cochrane review in 2003 concluded that antibiotics only contribute to a small 9% reduction of exacerbations and should not be part of routine treatment considering the risk of antibiotic resistance and adverse effects. Ten years later in 2013, the review by Herath et al. concluded a clinically significant benefit in reducing COPD exacerbations from continuous use of prophylactic antibiotics, but not from intermittent way due to only one randomized controlled trial (RCT) included in this subgroup. Influence of different duration of antibiotic intervention were not explored in this study. The most recent review by Ni et al. in 2015 focused on macrolides only and did not evaluate meaningful outcomes including the time to first exacerbation, change of lung function, bacterial load and airway inflammation. The latter outcome is important to support the hypothetical mechanism behind the reduction of exacerbations by antibiotics.

Current recommendation from guidelines about prophylactic antibiotic use in the management of COPD exacerbations is conditional and unspecific. At present, the optimal regimen of prophylactic antibiotics for exacerbations has not been well established, and there are no advices for an appropriate schedule and duration of specific antibiotic intervention. To further enhance information on the public health benefit-risk associated with this intervention, we here aimed to provide a comprehensive overview of the positive and negative effects of prophylactic antibiotics on COPD patients.

METHODS

Search strategy

We performed an update of the previous review by Herath et al. in 2013 according to the PRISMA guidelines. Cochrane Central Register of Controlled Trials (CENTRAL), Medline, EMBASE, Web of Science, CINAHL, AMED and PsycINFO databases were systematically searched for relevant RCTs published from 29 August 2013 (when the review by Herath et al. ended) until 26 April 2017 using key elements of “COPD”,
“RCT” and “antibiotics” (details are presented in Table S1). References from identified studies and relevant review articles were also checked manually. No language restrictions were applied. For the final analysis, we included both the new studies from this searching strategy and previous studies from the review by Herath et al.

**Selection criteria**

Studies included in this review met the following criteria: (1) focus on the effects of prophylactic antibiotics in COPD patients; (2) study designs must be RCTs with placebo group; (3) COPD patients should be aged over 18 years and with a well-defined diagnosis of COPD and confirmed evidence of persistent airflow limitation (the presence of a post-bronchodilator FEV₁/FVC < 0.7); (4) prophylactic antibiotics must be given for a minimum period of 12 weeks; (5) patients must be clinically stable without exacerbation for at least three weeks before enrolment. Studies that focused on combined antibiotics (≥ 2) and studies of patients with other respiratory disease (e.g. bronchiectasis, asthma) or related genetic diseases such as cystic fibrosis and primary ciliary dyskinesia were excluded.

**Outcomes and data analysis**

The Primary outcomes were: number of patients with exacerbations; frequency of exacerbation; health-related quality of life assessed by the St Georges Respiratory Questionnaire (SGRQ). The Secondary outcomes were: the median time to first exacerbation; frequency of hospitalization; all-cause mortality; adverse events; antibiotic resistance; change in lung functions, bacteria load and airway inflammation. The influence of different schedules and durations of prophylactic antibiotic use on exacerbations and quality of life in COPD patients were explored. For the missing of standard deviation of SGRQ score change in two studies, we calculated it according to Cochrane guideline (see Supplement data). All analyses were done in accordance with the intention-to-treat principle using Review Manager Version 5.3. Risk ratio (RR) or OR was calculated for binary outcomes, while mean difference (MD) was for continuous outcomes. Generic inverse variance (GIV) methods were used for non-standard types of both dichotomous and continuous data. Summary measures were pooled using random-effects models. If data could not be combined, we performed a descriptive analysis. Statistical heterogeneity among studies was assessed using conventional chi-squared ($X^2$, or Chi²) test and $I^2$ statistic of inconsistency. Sensitivity analysis was performed by removing studies with a high risk for bias or deviation. A funnel plot was used to assess publication bias.
Figure 1. Flow diagram of literature search and study selection.

RESULTS

Search results

From the 667 records generated by new search strategy, five new RCT studies were eligible and included (Figure 1). Together with the previous seven studies from the review by Herath et al., a total of twelve RCTs were included for this systematic review. However, of all twelve studies, one was a conference abstract, one was not blinded, one did not report effect measures. In total, nine studies were qualified for the meta-analysis.
Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Studies (1st author, year)</th>
<th>Study design</th>
<th>Country</th>
<th>Patients (T/P)</th>
<th>Age (year) (T/P)</th>
<th>FEV1/FVC ratio (%) (T/P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous included studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>He, 2010</td>
<td>RCT</td>
<td>UK</td>
<td>18:18</td>
<td>68.8:69.3</td>
<td>46.9:48.6</td>
</tr>
<tr>
<td>Mygind, 2010</td>
<td>RCT</td>
<td>Denmark</td>
<td>287:288</td>
<td>71 (Median)</td>
<td>NA</td>
</tr>
<tr>
<td>Sethi, 2010</td>
<td>RCT</td>
<td>US</td>
<td>569:580</td>
<td>66.1:66.6</td>
<td>45.0:46.3</td>
</tr>
<tr>
<td>Seemungal, 2008</td>
<td>RCT</td>
<td>UK</td>
<td>53:56</td>
<td>66.6:67.8</td>
<td>48.9:50.9</td>
</tr>
<tr>
<td>Banerjee, 2005</td>
<td>RCT</td>
<td>UK</td>
<td>31:36</td>
<td>65.1:68.1</td>
<td>43.8:45.5</td>
</tr>
<tr>
<td>Suzuki, 2001</td>
<td>RCT</td>
<td>Japan</td>
<td>55:54</td>
<td>69.1:71.7</td>
<td>NA</td>
</tr>
<tr>
<td>New included studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shafuddin, 2015</td>
<td>RCT</td>
<td>New Zealand</td>
<td>97:94</td>
<td>67.6:66.7</td>
<td>41.5:43.7</td>
</tr>
<tr>
<td>Simpson, 2014</td>
<td>RCT</td>
<td>Australia</td>
<td>15:15</td>
<td>71.7:69.9</td>
<td>52.3:51.3</td>
</tr>
<tr>
<td>Uzun, 2014</td>
<td>RCT</td>
<td>Netherlands</td>
<td>47:45</td>
<td>64.7:64.9</td>
<td>38.0:40.3</td>
</tr>
<tr>
<td>Berkhof, 2013</td>
<td>RCT</td>
<td>Netherlands</td>
<td>42:42</td>
<td>67:68</td>
<td>42.2:43.2</td>
</tr>
</tbody>
</table>

T/P: Treatment group versus Placebo group; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonists; LAMA: long-acting muscarinic antagonist; SABA: short-acting beta-2 agonists; SAMA: short-acting muscarinic antagonist; NA: data were not available; *This study designed different treatment arms with one common placebo arm; †The study included 2 treatment arms, according to preset criteria, we only include the arm about single antibiotic use, the other arm in this study about combined antibiotic treatment is excluded.

Characteristics of included studies

The characteristics of twelve included studies are shown in Table 1, other specific baseline characteristics about COPD severity and exacerbation history were summarized in Table S2. All these studies were conducted over the last seventeen years involving 3,683 stable COPD patients, with 2932 patients involved in the meta-analysis. All included studies focused on one antibiotic arm with one placebo arm except the study by Brill et al.,16 which compared three antibiotics with one common placebo and we treated this study as three independent RCTs (Trial 1-3: T1, T2, T3). In all, six antibiotics were investigated in this review: azithromycin,11,13,16-19 erythromycin,12,14,20 moxifloxacin,16,21 clarithromycin,15 roxithromycin22 and doxycycline.16 The duration of treatment ranged from 3 to 36 months with study size ranging from 30 to 1,149 patients.
Effects of prophylactic antibiotics on COPD

<table>
<thead>
<tr>
<th>Prophylactic Antibiotics (dose)</th>
<th>Duration of treatment &amp; follow up (months)</th>
<th>Maintenance medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin, 250 mg daily</td>
<td>12 / 12</td>
<td>ICS, LABA, LAMA</td>
</tr>
<tr>
<td>Erythromycin, 125 mg, 3 times a day; Azithromycin, 500 mg daily, 3 days a month</td>
<td>6 / 6</td>
<td>ICS, Theophylline, inhaled anticholinergic, inhaled β-adrenergic</td>
</tr>
<tr>
<td>Moxifloxacin, 400 mg daily, 5 days every 8 weeks</td>
<td>12 / 18</td>
<td>LABA, LAMA, SABA, SAMA, ICS, theophylline;</td>
</tr>
<tr>
<td>Erythromycin, 250 mg twice daily</td>
<td>12 / 12</td>
<td>LABA, LAMA, theophylline</td>
</tr>
<tr>
<td>Clarithromycin, 500 mg once daily</td>
<td>3 / 3</td>
<td>ICS</td>
</tr>
<tr>
<td>Erythromycin, 200-400 mg daily</td>
<td>12 / 12</td>
<td>Inhaled anticholinergic, theophylline</td>
</tr>
</tbody>
</table>

T₁: Moxifloxacin, 400 mg, 5 times every 4 weeks; T₂: Doxycycline, 100 mg daily; T₃: Azithromycin, 250 mg, 3 times a week; Roxithromycin, 300 mg daily | 3.25 / 3.25 | ICS |
| Azithromycin, 250 mg daily | 3 / 6 | Not available |
| Azithromycin, 500 mg, 3 times a week | 12 / 12 | LABA, LAMA, SABA, SAMA, ICS, Prednisolone |
| Azithromycin, 250 mg, 3 times a week | 3 / 4.5 | LABA, LAMA, ICS |

3 different treatment arms with one common placebo arm; †The study included 2 treatment arms, according to preset criteria, we only include the arm about single antibiotic use, the other arm in this study about combined antibiotic treatment is excluded;

Quality assessment
The review authors’ judgment about each risk of bias item in each study can be seen in Figure S1.1. The risk of bias items presented as percentage across all included studies were presented in Figure S1.2. There was no reporting bias in all included studies; only 2 studies have potential high risk in the blinding process. For the remaining of bias items, only a small proportion of unclear bias exists. Overall, low risk of bias dominates in all domains of bias.

Primary outcomes
Seven studies involving 2,642 participants reported the number of patients with exacerbations (Figure 2), which was significantly reduced (RR 0.82, 95% CI 0.74-0.90) by prophylactic antibiotics and there was no difference between continuous
and intermittent subgroups. However, the difference between other subgroups with a distinct trend toward significance (p = 0.07) suggested that using antibiotics ≤ 6 months may achieve better treatment effects (RR 0.59, 95% CI 0.40-0.86) than longer time (RR 0.84, 95% CI 0.77-0.93), which requires further confirmation. The risk difference (RD) between antibiotic and placebo groups is presented in Figure 3, for erythromycin, the RD is substantial (RD -0.24, 95% CI -0.39 to -0.08), the corresponding number needed to treat (NNT) was 4; for azithromycin, the RD was moderate (RD -0.14, 95% CI -0.20 to -0.08), the NNT was 7; no statistically significant effect for moxifloxacin intervention.

Figure 2. Forest plot of risk ratio (antibiotics versus placebo) for total number of patients with one or more exacerbations stratified by (a) schedule of prophylactic antibiotics and (b) duration of prophylactic antibiotics. M-H: Mantel-Haenszel; *Studies reviewed by Herath et al. in 2013.
Use of prophylactic antibiotic was also associated with a significant reduction in the frequency of exacerbations (RR 0.74, 95% CI 0.60-0.92, Figure 4). As the study by Brill et al.\textsuperscript{16} has a potential risk of bias in the blinding process, a sensitivity analysis was done with the other 6 studies, which resulted in a 31% RR reduction of exacerbations among patients taking prophylactic antibiotics (RR 0.69, 95% CI 0.58-0.82). In subgroup analysis showed in Figure 4, macrolides (azithromycin, erythromycin and roxithromycin) showed beneficial effects on frequency reduction of exacerbations, the benefits from both azithromycin and erythromycin were of clinical significance. However, this beneficial effect was not seen in the use of moxifloxacin and doxycycline. These subgroup differences for frequency of exacerbations were of statistical significance (p = 0.02).

Health-related quality of life using SGRQ was measured in seven studies.\textsuperscript{11,12,16-19,21} When we performed a sensitivity analysis by removing the study by Berkhof et al.,\textsuperscript{18} which was very different from the other data, the heterogeneity reduced sharply ($I^2$ changed from 92% to 0%). Hence, only the remaining 6 studies were included for the final meta-analysis. The pooled result indicated that prophylactic antibiotics led to a significant improvement in the total SGRQ score (MD -1.55, 95% CI -2.59 to -0.51, Figure 5). In subgroup analysis, the improvement of SGRQ score was not seen in both continuous and intermittent antibiotics. However, another subgroup result indicated that the total

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotics Events Total</th>
<th>Placebo Events Total</th>
<th>Risk Difference M-H, Random, 95% CI</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albert 2011*</td>
<td>317</td>
<td>570</td>
<td>360</td>
<td>572</td>
</tr>
<tr>
<td>Berkhof 2013</td>
<td>10</td>
<td>42</td>
<td>17</td>
<td>42</td>
</tr>
<tr>
<td>Simpson 2014</td>
<td>4</td>
<td>15</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Uzun 2014</td>
<td>34</td>
<td>47</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>674</td>
<td>674</td>
<td>55.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>365</td>
<td>446</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau^2 = 0.00, Ch^2 = 3.31, df = 3 (P = 0.35); I^2 = 9%</td>
<td></td>
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<tr>
<td></td>
<td>Test for overall effect: Z = 4.30 (P &lt; 0.0001)</td>
<td></td>
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<tr>
<td>Erythromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>He 2010*</td>
<td>9</td>
<td>18</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Sismondi 2008*</td>
<td>28</td>
<td>53</td>
<td>42</td>
<td>56</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>71</td>
<td>74</td>
<td>15.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>57</td>
<td>56</td>
<td></td>
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<tr>
<td></td>
<td>Heterogeneity: Tau^2 = 0.00, Ch^2 = 0.10, df = 1 (P = 0.75); I^2 = 0%</td>
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<td></td>
<td>Test for overall effect: Z = 3.05 (P = 0.002)</td>
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<tr>
<td>Moxifloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sehit 2010*</td>
<td>269</td>
<td>569</td>
<td>295</td>
<td>580</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>569</td>
<td>580</td>
<td>28.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>269</td>
<td>295</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 1.22 (P = 0.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total (95% CI)</td>
<td>1514</td>
<td>1528</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>671</td>
<td>759</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau^2 = 0.00, Ch^2 = 12.54, df = 5 (P = 0.03); I^2 = 62%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 3.82 (P = 0.0001)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Test for subgroup differences: Ch^2 = 9.16, df = 2 (P = 0.01), I^2 = 76.2%</td>
<td></td>
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</tr>
</tbody>
</table>

Figure 3. Forest plot of risk difference (antibiotics versus placebo) for total number of patients with one or more exacerbations stratified by types of antibiotics. M-H: Mantel-Haenszel test; *Studies reviewed by Herath et al. in 2013.
Chapter 2

Section 2.1.1

30

moxifloxacin and doxycycline. These subgroup differences for frequency of exacerbations were of statistical significance \( (p = 0.02) \).

Health-related quality of life using SGRQ was measured in seven studies. When we performed a sensitivity analysis by removing the study by Berkhof et al., \( \text{18} \) which was very different from the other data, the heterogeneity reduced sharply \( (I^2 \text{ changed from 92\% to 0\%}) \). Hence, only the remaining 6 studies were included for the final meta-analysis.

The pooled result indicated that prophylactic antibiotics led to a significant improvement in the total SGRQ score \( (\text{MD} = -1.55, 95\% \text{ CI} = -2.59 \text{ to } -0.51, \text{Figure 5}) \).

In subgroup analysis, the improvement of SGRQ score was not seen in both continuous and intermittent antibiotics. However, another study reported the component scores of SGRQ (Figure S2). Both the symptom \( (\text{MD} = -3.89, 95\% \text{ CI} = -5.48 \text{ to } -2.31) \) and impact \( (\text{MD} = -1.32, 95\% \text{ CI} = -2.61 \text{ to } -0.03) \) scores were improved with prophylactic antibiotics. However, the activity score did not show any significant improvement. Of note, none of these improvements mentioned above in SGRQ score reached the hypothesized clinically beneficial level \( (> 4\text{-unit reduction}) \).\(^{10}\)

Figure 4. Forest plot of risk ratio (antibiotics versus placebo) for frequency of exacerbations stratified by types of antibiotics. SE: standard error; IV: inverse variance; *Studies reviewed by Herath et al. in 2013; \( T_{1-3} \): three independent RCTs in study by Brill et al.

SGRQ score significantly changed by long-term intervention \( (\text{MD} = -1.70, 95\% \text{ CI} = -2.81 \text{ to } -0.60) \), although it was not changed by short-term \( (\leq 6) \) intervention \( (\text{MD} = -0.34, 95\% \text{ CI} = -3.43 \text{ to } 2.75) \).

Four studies\(^{12,17,19,21}\) also reported the component scores of SGRQ (Figure S2). Both the symptom \( (\text{MD} = -3.89, 95\% \text{ CI} = -5.48 \text{ to } -2.31) \) and impact \( (\text{MD} = -1.32, 95\% \text{ CI} = -2.61 \text{ to } -0.03) \) scores were improved with prophylactic antibiotics. However, the activity score did not show any significant improvement. Of note, none of these improvements mentioned above in SGRQ score reached the hypothesized clinically beneficial level \( (> 4\text{-unit reduction}) \).\(^{10}\)
Secondary outcomes

Seven studies involving 2,803 patients reported the median time to first exacerbation (Table S3). Four studies indicated that using prophylactic antibiotics lengthened the median time to first exacerbation significantly.\textsuperscript{12,17,19,20} Two other studies found a similar trend, but without statistical significance.\textsuperscript{18,21} Only one study showed the opposite result in antibiotic and placebo arms.\textsuperscript{22}
The frequency of hospitalization related to COPD was pooled from five studies with 2,576 participants, no significant difference was observed between antibiotic and placebo groups (RR 0.94, 95% CI 0.83-1.06, Figure 6). Also, no difference in the rate of all-cause mortality were found between the two arms (Figure S3).

Eight studies involving 2,833 participants reported adverse events related to antibiotic use. Overall, there was no significant difference between two comparison arms in the rate of adverse events (RR 1.09, 95% CI 0.84-1.42, Figure 7). As there was a lack of uniform definition about adverse events, the heterogeneity was substantial ($I^2 = 73\%$). Considering that the result by Shafuddin et al. was deviant from the other seven studies, a sensitivity analysis was, therefore, performed after removal of this study. The homogeneous result also did not show significant difference between two arms (RR 0.93, 95% CI 0.83-1.05, $I^2 = 2\%$). In subgroups, gastrointestinal disorders were more frequent in the intervention group than control group (RR 1.87, 95 CI 0.98-3.59,
**Effects of prophylactic antibiotics on COPD**

Three studies reported the change of bacterial load. 

Although both Brill et al. and Simpson et al. have found the more reduction of bacterial load by prophylactic antibiotic compared with placebo, the results did not reach the level of statistical significance, even both quantitative culture and 16S qPCR methods were used by Brill et al. Benerjee et al. also did not find a significant difference between pre- and post-sputum cfu numbers/bacterial (PPM) isolates in two arms.

**Figure 8.** Forest plot of odds ratio (antibiotics versus placebo) for antibiotic resistance stratified by (a) schedule of prophylactic antibiotics and (b) duration of prophylactic antibiotics. IV: inverse variance; *Studies reviewed by Herath et al. in 2013; T1-3: three independent RCTs in study by Brill et al.*

Eight studies had the bacteriological assessments (see Table S4), however, only three studies with five RCTs reported the quantitative results for antibiotic resistance. Due to the different definition about bacterial resistant outcome in study by Uzun et al., only the other homogeneous studies involving four RCTs were included for pooled results (OR 4.49, 95% CI 2.48-8.12, Figure 8), long-term (versus short-term) and continuous (versus intermittent) antibiotic intervention seems to cause more antibiotic resistance, although these subgroup difference did not reach statistical significant level. Antibiotic resistance appeared in all types of antibiotics involved (Figure 9), although the result
from moxifloxacin did not reach statistical significance. No subgroup differences about this outcome were seen among azithromycin, moxifloxacin and doxycycline (p = 0.63).

Eight studies\textsuperscript{11,13,16-18,20-22} provided the data on changes of lung function (Table S5). However, no study found significant increase by antibiotic intervention compared with placebo. Mygind \textit{et al.} did not compare the lung function change directly, but measured and compared the lung function in both groups at enrolment and endpoint separately, they also did not find any significant difference.\textsuperscript{13}

Three studies reported the change of bacterial load.\textsuperscript{11,15,16} Although both Brill \textit{et al.} and Simpson \textit{et al.} have found the more reduction of bacterial load by prophylactic antibiotic compared with placebo, the results did not reach the level of statistical significance, even both quantitative culture and 16S qPCR methods were used by Brill \textit{et al.} Benerjee \textit{et al.} also did not find a significant difference between pre- and post-sputum cfu numbers/bacterial (PPM) isolates in two arms.

The change of airway inflammation was only reported in two studies.\textsuperscript{11,16} The study by Brill \textit{et al.} showed that no significant changes were seen in cytokines IL-6, IL-8 and IL-1β in any of three antibiotic arms compared with placebo.\textsuperscript{16} Similarly, Simpson \textit{et al.} also did not report a significant reduction in sputum neutrophil proportion level of IL-8 in those who received azithromycin compared to placebo group.\textsuperscript{11}
DISCUSSION

This update of previous systematic reviews demonstrates that prophylactic antibiotic use could significantly lower the risk of exacerbations by 26% and prevent stable COPD patients from getting exacerbations by 18%, which is consistent with the result by Herath et al., but the difference is that our review with more RCTs suggest that intermittent antibiotics may also be effective in preventing exacerbations, although the result is of boundary significance. Moreover, in contrast with the result by Ni et al., we found both short-term (≤ 6 months) and long-term (> 6 months) treatments can prevent patients from exacerbations significantly. A short-term treatment even had better prevention effects than long-term treatment. Considering all included patients are clinically stable without exacerbation before enrolment, the above benefit from short therapy is likely due to the benefits of less resistance and adverse events or shorter follow-up time to detect related exacerbations compared with long therapy.

Besides duration and schedule of antibiotics, the types of antibiotics also have a profound influence on preventing exacerbations of COPD. In our pre-specified subgroup analysis, we did not find significant effect from moxifloxacin and doxycycline intervention on preventing exacerbations, although a previous study showed moxifloxacin is equivalent and bacteriologically superior to other antibiotic regimens routinely used. However, our results confirmed the superiority of macrolides (azithromycin, erythromycin) in preventing exacerbations of COPD. This benefit of macrolides has also been confirmed previously in patients with cystic fibrosis and non-cystic fibrosis bronchiectasis.

Although the optimal treatment using macrolide for preventing exacerbation was already conditional recommended by related guidelines, the mechanisms behind are not totally clear. Many studies have confirmed that macrolides with 14 and 15-membered macrocyclic lactone ring have properties such as anti-inflammatory, antiviral and potential immune-modulation, which were proved to be beneficial for COPD patients. Therefore, some researchers hypothesized that prevention of exacerbation by macrolides may due to its antimicrobial effects or anti-inflammatory effects or both. However, neither of the above mechanisms could be supported by evidence in our review. More studies are needed in future to explore the answers to this question.

Regarding the health-related quality of life, our review showed a significant reduction in the total score of SGRQ with no heterogeneity. This is consistent with the association study by Martin et al. From our study, duration longer than 6 months of antibiotic intervention can significantly improve the total score of SGRQ. As the health-related quality of life is influenced largely by the frequency of exacerbations in COPD patients, it will be an ideal therapy if both the exacerbation and quality of life change towards the same positive direction. Our subgroup analysis in both exacerbation and quality of life showed the positive results in longer duration (above 6 months) of prophylactic
antibiotics. However, as the improvements of total SGRQ score did not reach a clinical significant level, further research were still in need to explore the influence of prophylactic antibiotic use on quality of life in the real world.

The benefits achieved by prophylactic antibiotics always came at the expense of a variety of adverse events according to the earlier reviewers. However, we did not find significant differences in the overall rate of adverse events between antibiotic and placebo arms. It is worth noting that the heterogeneity was substantial due to the variety of definition and measurement methods, thus much consistent definition is needed for future study. Furthermore, much attention should be given to the gastrointestinal disorder by antibiotic use as this disorder was also observed in patients with cystic fibrosis. Although not established as an endpoint in our review, hearing loss caused by azithromycin also should draw much attention.

Along the use of prophylactic antibiotics, another growing concern regarding the development of antibiotic resistance also appears. In this review, the increased resistant isolates were seen during the intervention of prophylactic antibiotics, which involved macrolides (azithromycin), tetracycline (doxycycline), and quinolones (moxifloxacin). At the same time, as lots of conflicting reports existed with heterogeneous definitions, much related evidence from studies of uniform criteria is needed for further exploration. Before that, clinicians should pay much attention especially to long and continuous use of antibiotics considering potential risk of bacterial resistance for future treatment of infections. Furthermore, although the use of macrolides in preventing exacerbations was considered as a cost-effective strategy, the rather quick bacterial resistance induced by macrolides should not be ignored. Its use should at best be limited to high-risk populations based on consideration of age, exacerbation frequency in previous year, COPD severity and comorbidity conditions. The choice of antibiotics should be based on the community resistant pattern and their benefits and potential risks must be weighted by analysing the specific situation case by case.

Although the obvious benefits of antibiotics in prevention of exacerbations, we did not find any reduction in the rate of hospital admission by antibiotic intervention, which are in contrast with the result by Donath et al. Moreover, as hospitalization for exacerbation is always associated with poor prognosis and increased mortality in COPD patients, there was also no difference in the rate of all-cause mortality between antibiotic and placebo groups. Besides, the lung function was not improved in any of the included studies after the antibiotic intervention. There is still no conclusive clinical trial evidence up to now that any existing medication for COPD could modify the long-term decline in lung function.
Study limitations and future perspectives

There were several limitations in this review. Firstly, there were some notable heterogeneous results between studies. On the one hand, due to limited information available, we could not totally analysis and exclude the influence of potential difference in distribution of baseline characteristics especially like COPD severity, exacerbation history and bacterial colonization on outcomes, although all included patients were relative stable with similar COPD severity (GOLD 2-4). On the other hand, heterogeneity also existed between antibiotic therapies, as regimen, dosages, durations and follow-up time of antibiotic intervention were different. Secondly, the included patients may concomitantly take other therapies such as influenza vaccines, bronchodilators or inhaled corticosteroid, which could also have a potential impact on related outcomes if these factors are not comparable between antibiotic and placebo groups. For example, LABA/LAMA combination as a maintenance therapy of COPD could reduce the rate of exacerbation.\(^{35,36}\) Thirdly, the definitions and measurements of some outcomes were different, like the varying definitions of adverse events and varying methods for identifying antibiotic resistance. Finally, due to limited studies included, we could not evaluate the effects of the different doses of a specific antibiotic on COPD patients.

In the future, more RCTs of high quality are needed to explore a more personalized therapy by studying the optimal dose, duration and schedule of specific antibiotic use, preferably macrolides, with therapeutic drug monitoring on more homogenous COPD patients. Besides, uniform standards for evaluating the effects of antibiotic use should be made. Considering the safety of antibiotics, how to avoid or reduce the side effects such as gastrointestinal events and bacterial resistance during long-term use of antibiotic is still a problem that needs to be tackled.

CONCLUSIONS

This updated systematic review confirms the benefit of prophylactic antibiotics in preventing exacerbations in stable patients with moderate to severe COPD, this benefit existed in all subgroups ignoring the different duration and schedules of antibiotic intervention. The overall quality of life was also significantly increased by prophylactic antibiotics. However, this benefit was only observed in long-term (above 6 months) subgroup of antibiotics. At the same time, considering the possible risk of bacterial resistance, long-term and continuous prophylactic antibiotics are at best limited to high risk of population with severe COPD and history of frequent exacerbations and the choice of antibiotic should be based on local bacterial resistance pattern. Furthermore, much attention should be paid to some adverse effects like gastrointestinal disorders and hearing loss.
SUPPLEMENTARY MATERIALS

Table S1-S5 and Figures S1-S4 are available as Supplementary data at JAC Online (https://doi.org/10.1093/jac/dky326)
REFERENCES


