Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

Samantha C Herath¹, Phillippa Poole²

¹Woolcock Institute of Medical Research, 431 Glebe Point Road, Sydney, Australia. ²Department of Medicine, University of Auckland, Auckland, New Zealand

Contact address: Samantha C Herath, Woolcock Institute of Medical Research, 431 Glebe Point Road, Sydney, New South Wales, 2037, Australia. scherath@yahoo.com.

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ABSTRACT

Background
There has been renewal of interest in the use of prophylactic antibiotics to reduce the frequency of exacerbations and improve quality of life in chronic obstructive pulmonary disease (COPD).

Objectives
To determine whether or not regular treatment of COPD patients with prophylactic antibiotics reduces exacerbations or affects quality of life.

Search methods
We searched the Cochrane Airways Group Trials Register and bibliographies of relevant studies. The latest literature search was August 2013.

Selection criteria
Randomised controlled trials (RCTs) that compared prophylactic antibiotics with placebo in patients with COPD.

Data collection and analysis
We used the standard methods of The Cochrane Collaboration. Data were extracted and analysed by two independent review authors.

Main results
Seven RCTs involving 3170 patients were included in this systematic review. All studies were published between 2001 and 2011. Five studies were of continuous antibiotics and two studies were of intermittent antibiotic prophylaxis (termed 'pulsed' for this review). The antibiotics investigated were azithromycin, erythromycin, clarithromycin and moxifloxacin. Azithromycin, erythromycin and clarithromycin are macrolides while moxifloxacin is a fourth-generation synthetic fluoroquinolone antibacterial agent. The study duration varied from three months to 36 months and all used intention-to-treat analysis. Most of the results were of moderate quality. The risk of bias of the included studies was generally low, and we did not downgrade the quality of evidence for risk of bias.
The trials recruited participants with a mean age of 66 years and with at least a moderate severity of COPD. Three trials included participants with frequent exacerbations and two trials recruited participants requiring systemic steroids or antibiotics, or both, or who were at the end stage of their disease and required oxygen.

The primary outcomes for this review were the number of exacerbations and quality of life.

With use of continuous prophylactic antibiotics the number of patients experiencing an exacerbation was reduced (odds ratio (OR) 0.55; 95% confidence interval (CI) 0.39 to 0.77, 3 studies, 1262 participants, high quality). This represented a reduction from 69% of participants in the control group compared to 54% in the treatment group (95% CI 46% to 63%) and the number needed to treat to prevent one exacerbation (NNTb) was therefore 8 (95% CI 5 to 18). The frequency of exacerbations was also reduced with continuous prophylactic antibiotic treatment (rate ratio 0.73; 95% CI 0.58 to 0.91).

Use of pulsed antibiotic treatment showed a non-significant reduction in the number of people with exacerbations (OR 0.87; 95% CI 0.69 to 1.09, 1 study, 1149 participants, moderate quality) and the test for interaction showed that this result was significantly different from the effect on exacerbations with continuous antibiotics.

There was a statistically significant improvement in quality of life with both continuous and pulsed antibiotic treatment but this was smaller than the four unit improvement that is regarded as being clinically significant (MD -1.78; 95% CI -2.95 to -0.61, 2 studies, 1962 participants, moderate quality).

Neither pulsed nor continuous antibiotics showed a significant effect on the secondary outcomes of frequency of hospital admissions, change in lung function, serious adverse events or all-cause mortality (moderate quality evidence).

The adverse events that were recorded varied among the trials depending on the different antibiotics used. Azithromycin was associated with a significant hearing loss in the treatment group. The moxifloxacin pulsed study reported a significantly higher number of adverse events in the treatment arm due to the marked increase in gastrointestinal adverse events (P < 0.001). Some adverse events that led to drug discontinuation, such as development of long QTc or tinnitus, were not significantly more frequent in the treatment group than the placebo group but pose important considerations in clinical practice.

The development of antibiotic resistance in the community is of major concern. One study found newly colonised patients to have higher rates of antibiotic resistance. Patients colonised with moxifloxacin-sensitive pseudomonas at initiation of therapy rapidly became resistant with the quinolone treatment.

Authors’ conclusions

Use of continuous prophylactic antibiotics results in a clinically significant benefit in reducing exacerbations in COPD patients. All trials of continuous antibiotics used macrolides hence the noted benefit applies only to the use of continuous macrolide antibiotics. The impact of pulsed antibiotics remains uncertain and requires further research.

The trials in this review included patients who were frequent exacerbators and needed treatment with antibiotics or systemic steroids, or who were on supplemental oxygen. There were also older individuals with a mean age of 66 years. The results of these trials apply only to the group of patients who were studied in these trials and may not be generalisable to other groups.

Because of concerns about antibiotic resistance and specific adverse effects, consideration of prophylactic antibiotic use should be mindful of the balance between benefits to individual patients and the potential harms to society created by antibiotic overuse.

**PLAIN LANGUAGE SUMMARY**

Preventative antibiotic therapy for people with COPD

**What is COPD?**

COPD is a common chronic respiratory disease mainly affecting people who smoke now or have done so previously. It could become the third leading cause of death worldwide by 2030. People with COPD experience gradually worsening shortness of breath and cough with sputum because of permanent damage to their airways and lungs. Those with COPD may have flare-ups (or exacerbations) that usually occur after respiratory infections. Exacerbations may lead to further irreversible loss of lung function with days off work, hospital admission, reduction in quality of life and they may even cause death.

**Why did we do this review?**
We wanted to find out if giving antibiotics to prevent a flare-up, ‘prophylactic’ antibiotics, would reduce the frequency of infections and improve quality of life. Studies that were taken into consideration used either continuous prophylactic antibiotics on a daily basis or prophylactic antibiotics that were used intermittently.

**What evidence did we find?**

We found seven randomised controlled trials (RCTs) involving 3170 patients. All studies were published between 2001 and 2011. Five studies were of continuous antibiotics and two studies were of intermittent antibiotic prophylaxis. The antibiotics investigated were azithromycin, erythromycin, clarithromycin and moxifloxacin. On average, the people involved in the trials were 66 years old and had either moderate or severe COPD. Three trials included participants with frequent exacerbations and two of the trials recruited participants requiring systemic steroids or antibiotics, or both, or who were at the end stage of their disease and required oxygen.

**Results and conclusions**

We found that with the use of continuous daily antibiotics the number of patients who developed an exacerbation reduced markedly. For every eight patients treated, one person would be prevented from suffering an exacerbation. There may have been a benefit on patient-reported quality of life with the antibiotics. On the other hand, use of antibiotics did not significantly affect the number of deaths due to any cause, the frequency of hospitalisation, or the loss of lung function during the study period.

Even though there may be fewer exacerbations with continuous antibiotics there are considerable drawbacks. First, there were specific adverse events associated with the antibiotics, which differed according to the antibiotic used; second, patients have to take antibiotics regularly for years or months; finally, the resulting increase in antibiotic resistance will have implications for both individual patients and the wider community through reducing the effectiveness of currently available antibiotics.

Because of concerns about antibiotic resistance and specific adverse effects, consideration of prophylactic antibiotic use should be mindful of the balance between benefits to individual patients and the potential harms to society created by antibiotic overuse.