Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)

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Background

Chronic obstructive pulmonary disease (COPD) is a lung disease characterised by persistent or chronic airflow limitation. It is typically progressive in nature and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles or gases.[1] Smoking is the main risk factor for COPD, with a small proportion of cases linked to passive smoking and genetic diseases, for example alpha$_1$ antitrypsin deficiency.

The World Health Organisation has predicted that COPD will be the third leading cause of death worldwide by 2030 and the Global Burden of Disease Study estimated that more than 300 million people were affected by COPD in 2013.[2] The prevalence of the disease varies by country, with rates highest in low socioeconomic countries.

The signs and symptoms of COPD include dyspnoea, chronic cough and sputum production. Exacerbations of the disease are acute in onset and involve an increase in one or more symptoms, for example increased level of dyspnoea, worsening of chronic cough or increase in sputum production for a sustained period of time (over 48 hours). The risk of exacerbation increases with the severity of airflow limitation in a patient and is often linked to respiratory infections and exposure to environmental pollution, for example black smoke particulate matter.[3] Exacerbations of COPD can lead to increased morbidity including potential loss of lung function due to inflammation, and resultant deconditioning that can lead to time off work and loss of independence.

There are a range of evidence-based approaches aimed at reducing the risk COPD exacerbations. These include avoidance of cigarette smoke and air pollution, vaccination against influenza and pneumococcal disease and preventive medication

regimes involving inhaled drugs, for example long acting beta agonists and corticosteroids and/or oral medicines such as phosphodiesterase 4 inhibitors. The use of prophylactic antibiotics has also been proposed as a preventative measure, with the aim of reducing the bacterial load and thus limiting progression of the disease. In addition, some antibiotics have anti-inflammatory properties that can also modify disease progression.

Objectives

The primary objective of this review [4] was to determine whether or not regular treatment (continuous, intermittent or pulsed) with prophylactic antibiotics reduces exacerbations or affects quality of life in patients with COPD. This review was an update of one conducted in 2013.[5]

Intervention/Methods

The review included randomised controlled trials (RCTs), including cluster RCTs and crossover trials, that compared use of antibiotics versus a placebo. The studies included adults, over the age of 18 with a definitive diagnosis of COPD. Patients with bronchiectasis, asthma or genetic disease for example cystic fibrosis, were excluded.
The interventions involved the administration of oral antibiotics, including penicillin, quinolones, macrolides and sulphonamides, in applicable daily doses at least three times per month for a period of at least three months.
There were two primary outcomes considered:

1. Number of exacerbations – this included the total number of patients who experienced exacerbations and the frequency of exacerbations in the study period; and,
2. Health-related quality of life.

Secondary outcome measures included:

- Duration and severity of exacerbations;
- Days of disability;
- Frequency and duration of hospital admissions;
- Reduction in lung function from baseline as measured by FEV_1 and FVC;

- Drug resistance as measured by microbial sensitivity;
- Death due to all-cause mortality, including respiratory causes; and,
- Adverse effects.

Results

There were 16 studies included in this review, seven from the original 2013 review [5] and nine new studies. However, two studies were prematurely terminated so the authors reported on the results from only 14 studies, representing a total of 3932 participants. The studies ranged from three to 36 months in duration and the antibiotics investigated included: azithromycin, erythromycin, clarithromycin, doxycycline, roxithromycin and moxifloxacin.

Three studies compared the use of continuous antibiotic therapy to placebo and the results showed that the number of patients experiencing one or more exacerbations was significantly reduced with the use of prophylactic antibiotics. Further analysis showed that pulsed treatment regimens had a smaller treatment effect than continuous and intermittent regimens. The rate of exacerbations per patient per year was also reduced with continuous and intermittent antibiotic prophylaxis, in a finding that was statistically significant. A significant difference was also identified for the median length of time to first exacerbation, which was lengthened in patients who received continuous antibiotic therapy and in one study of intermittent antibiotic therapy compared to placebo.

Health-related quality of life was explored in nine studies, and where an improvement in quality of life was identified, it was associated with continuous and intermittent antibiotic prophylaxis with no clear improvement found with pulsed antibiotic regimes. No significant differences were identified for the secondary outcomes: frequency of hospital admissions; change in lung function; serious adverse events or all-cause mortality, however for both mortality and adverse events, confidence intervals were too wide to rule out an effect.

The specific adverse events reported in some of the studies may have clinical relevance based on their severity, these. The adverse events varied according to the type of antibiotic used, for example azithromycin was associated with a significant hearing loss in the treatment group. The use of moxifloxacin was linked to an increase in gastrointestinal adverse events in a finding that was statistically significant. Some adverse events were not significantly more frequent in the treatment groups, however the seriousness of these, for example development of long QTc or tinnitus, led to discontinuation of the antibiotics concerned. The development of antibiotic resistance was addressed in six studies (n = 2486 participants) with four studies identifying evidence of antibiotic resistance.

Conclusions

This authors concluded that the prophylactic use of macrolide prophylactic antibiotics for a period of up to 12 months in patients diagnosed with COPD is likely to reduce the number of patients with exacerbations, exacerbation frequency, median time to first exacerbation and possible health-related quality of life. These benefits were associated with continuous and intermittent macrolide regimes, with pulsed regimes found to be less effective.

The adverse events associated with these regimens, were found to include serious effects such as hearing loss, and the development of antibiotic resistance. Therefore, the benefits should be balanced against the potential risks before treatment is prescribed and patients routinely monitored for any adverse effects.

Implications for Practice

COPD is a common respiratory disease and one that is expected to increase in prevalence, with the WHO projecting that it will be the third largest cause of death worldwide by 2030. Therefore, it is likely that nurses will encounter patients with COPD in their practice across a range of clinical environments. For this reason, nurses should remain up to date with best practice for prevention of exacerbations in their COPD patients, including the benefits and risks of prophylactic treatment with antibiotics.

References

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