of



# Antibiotic treatment in exacerbations of chronic obstructive pulmonary disease: recent trial results

Exacerbations are the most frequent cause of hospitalization and death in patients with chronic obstructive pulmonary disease (COPD). In this review, the results of recent trials that have assessed the effect of antibiotics in COPD are discussed, including studies that have evaluated antibiotic therapy for exacerbations and those that have studied the role of long-term antibiotics in exacerbation prophylaxis. Antibiotic therapy may lead to a number of beneficial short- and long-term effects in COPD, but may also cause adverse side effects and promote the development of resistant pathogens. The precise disease phenotypes that should be treated with antibiotics are not well characterized, although biomarkers such as procalcitonin offer a promising approach to guide the judicious use of antibiotic therapy.

#### Keywords: chronic obstructive pulmonary disease • exacerbations • prophylaxis

Worldwide, chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. Exacerbations are the most frequent cause of hospitalization and death among patients with COPD [1-5]. Exacerbations are episodes of symptomatic deterioration that are associated with increased airway inflammation and physiological changes. Exacerbations are triggered by viruses and bacteria in approximately 50-60% of cases [6,7] with around 10% believed to be due to environmental pollutants and 30% with no known cause [7]. Dual virus and bacterial infection has been reported in up to 25% of naturally occurring COPD exacerbations [8,9]. Recent data from a human model of experimental rhinovirus (RV) infection showed that 60% of patients with COPD developed a subsequent bacterial infection following RV challenge, thereby suggesting that primary virus infection may directly precipitate secondary bacterial infection [10].

Since bacteria are believed to be important precipitants of exacerbations, either as primary triggers or following virus infection, there has been much interest in the use of short course antibiotic prescriptions as therapeutic agents for these events. Additionally, some studies have evaluated whether long-term prescription of prophylactic antibiotics may be beneficial in preventing future exacerbations. The aim of this review is to discuss the results of recent clinical trials that have assessed antibiotic therapy in COPD.

### Antibiotic therapy for acute exacerbations of COPD

Given that bacteria are important aetiological triggers for exacerbations, antibiotics are commonly used to treat these events in clinical practice. However, in the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, the evidence for antibiotic use in COPD exacerbations is classed as category B, which is defined as "few randomized trials exist, they are small in size, they are undertaken in a population that differs from the target population of the recommendation or the results are somewhat inconsistent" [11]. Therefore, the role of antibiotics for treatment of exacerbations is unclear and whether specific subgroups of patients with COPD derive more benefit is also unknown.

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In this section, we aim to review recent clinical trials that have evaluated the efficacy of antibiotic therapy in exacerbations of COPD.

### Methods for determining need for antibiotics during acute exacerbations

The clinician's initial decision to initiate antibiotic therapy, at the onset of an exacerbation, may be influenced by a number of factors. These include the patient's symptoms, prior sputum microbiology and systemic markers of infection, such as an elevated C-reactive protein. Current guidelines suggest treatment should be for 5–7 days, although there is no recognized consensus on duration of therapy [12,13]. However, relapse and re-exacerbation are recognized occurrences [14]. Treatment failure may be related to inadequate antibiotic efficacy due to incomplete resolution of the initial infection or re-infection with another bacterial strain.

The GOLD strategy define an exacerbation of COPD as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal dayto-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD" [11]. Anthonisen et al. proposed specific symptomatic features to define a bacterial exacerbation including increased sputum volume, increased sputum purulence and increased dyspnoea [15]. Current guidelines recommend antibiotic therapy in patients with Anthonisen type 1 (worsening dyspnoea with increased sputum volume and purulence) or type 2 (presence of any of these two symptoms, particularly if one is increased sputum purulence) exacerbations. Sputum purulence has previously been shown to correlate with the presence of bacteria [16].

#### Impact of antibiotics on short-term outcomes Placebo-controlled trials

There are a number of studies that have assessed the effect of antibiotics in COPD exacerbations but the majority of these are head-to-head comparisons of different antibiotic agents and there have been very few placebo-controlled trials to date.

### Effect of antibiotics on mortality following acute exacerbation of COPD

A few recent placebo-controlled studies have evaluated the effect of antibiotic therapy on mortality following COPD exacerbation. Daniels *et al.* [17] conducted a randomized controlled trial evaluating the efficacy of doxycycline in exacerbations. The addition of seven days of doxycycline to prednisolone did not lead to a significant improvement in the primary endpoint of 30 day clinical response, but the authors reported a 5.4% mortality rate, at day 10, in the group receiving antibiotics versus a 2.2% (p = 0.05) mortality rate in the placebo group. However, numbers in this study were small and thus firm conclusions are difficult to make.

The use of antibiotics in severe exacerbations was explored by Nouira *et al.* [18]. They carried out a prospective, randomized, double-blind, placebo-controlled trial in 93 patients hospitalized with COPD exacerbation that required mechanical ventilation. In this study, patients were randomized to receive the fluoroquinolone ofloxacin or placebo. This study reported a fivefold reduction in in-hospital mortality in the ofloxacin treated group compared with the placebo group (22 vs 4%; p = 0.01). The need for additional antibiotic therapy was also reduced in the ofloxacin group (35 vs 6% p = 0.0006).

Other studies have conducted head-to-head comparisons between different agents [19,20], but this study design is less informative than placebo-controlled trials for assessing the potential beneficial effects of antibiotics on mortality following COPD exacerbation. Vollenweider *et al.* reported a pooled analysis of all trials evaluating antibiotic use and mortality following an exacerbation and showed no significant effect associated with treatment in non-intensive care unit (ICU) admitted patients [21].

### Effect of antibiotics on treatment failure following acute exacerbation of COPD

Studies have also assessed the role of antibiotics in reducing the endpoint of treatment failure. Treatment failure is interpreted individually in each trial but is typically based on a clinical assessment of the patient's symptoms made by the study investigators during follow-up assessment. Features associated with new infection or persistent signs or symptoms are classified as treatment failure.

Llor et al. explored the use of antibiotics in the outpatient setting in patients with mild-to-moderate COPD [22]. This study was a multicenter, doubleblind, placebo-controlled trial. Three hundred and ten patients received either amoxicillin/clavulanate or placebo for 8 days. A greater proportion of patients in the antibiotic group compared with the placebo group achieved clinical cure at the end of therapy visit (74.1 vs 59.9%; p = 0.016). The relative risk of treatment failure was 1.12 (95% CI: 1.02-1.22) in the placebo group compared with the treatment arm. Clinical cure at day 20 was significantly greater in the antibiotic group (81.6 vs 67.8%; p = 0.006). However, it should be noted that corticosteroid use was not regulated in this study and may have had a confounding effect. Additionally, the investigators defined an exacerbation as at least one Anthonisen criteria being fulfilled but current

guidelines suggest that antibiotic therapy should only be used when at least two criteria are fulfilled [15].

The additive effect of antibiotic therapy, in combination with corticosteroid therapy during acute exacerbations of COPD, was investigated by Daniels et al. [17]. 223 hospitalized patients, with stage 1-4 COPD, were randomized either to receive placebo or doxycycline in addition to systemic corticosteroids. In total, 265 patients with class 1 or 2 Anthonisen exacerbations were included. Doxycycline showed superiority to placebo in terms of clinical success at day 10 (80 vs 69%; p = 0.03) and symptomatic improvement analyzed using visual analog scales (mean difference of -2.3; p = 0.03). Doxycycline therapy also improved microbiological response (defined as confirmed or clinically defined eradication of pathogen from sputum) leading to 67% bacteriological success versus 34% in the placebo group (p < 0.001). By day 30 there was no significant difference in clinical success between the antibiotic and placebo groups. It may be possible that the effect of antibiotics is more minimal when administered in combination with corticosteroids and this may explain differences between this and other studies in which corticosteroids are not administered, or applied to only a minority of patients. Other endpoints including recovery of lung function and resolution of systemic inflammation were not significantly affected by antibiotic therapy in this study.

Puhan *et al.* [23] conducted a systematic review of all existing randomized placebo-controlled trials that have assessed the effects of antibiotics in patients with COPD. 13 trials (1557 patients) were included and it was concluded that antibiotics did not reduce treatment failures in patients with mild-to-moderate exacerbations but had beneficial effects in hospitalized patients with severe exacerbations.

### Effect of antibiotics on length of hospital stay following exacerbation of COPD

Very few studies to date have assessed the effect of antibiotic therapy on length of hospital stay, which may be considered to be a less objective parameter than other endpoints due to the influence of social factors unrelated to disease. In the study described previously by Nouira *et al.* [18] length of hospital stay was evaluated in ventilated patients treated with ofloxacin versus placebo. They reported a reduced mean length of hospital stay associated with ofloxacin therapy (14.9 vs 24.5%; p = 0.01).

# Effect of antibiotics on symptoms & health-related quality of life

Only a few studies have assessed the effect of antibiotic therapy on patient-related outcomes. Daniels *et al.* [17] used visual analog scales to score symptoms of dys-

pnoea, cough, fatigue and sputum purulence. This study showed a significant improvement in the symptom scores associated with antibiotic therapy versus placebo at day 30.

The St George's respiratory questionnaire (SGRQ) is a standardized tool used to measure health-related quality of life. Sethi *et al.* [24] used this tool to assess the response to antibiotic therapy in a double-blind placebo-controlled trial evaluating moxifloxacin therapy. Total SGRQ scores improved from baseline following both moxifloxacin and placebo treatment. At week 48 the mean change from baseline of the SGRQ score was -4.8 for patients receiving moxifloxacin and -3.5 for those receiving placebo (p = 0.33).

### Adverse events associated with antibiotic therapy in exacerbations

Antibiotics are well recognized to have the potential to cause side effects. The most commonly observed side effects are gastrointestinal including diarrhea, nausea and vomiting [25]. The risk of Clostridium difficile associated diarrhea may also be increased by antibiotic use [26]. In the previously described study by Llor et al. [22], 14.5% of patients in the antibiotic group reported adverse events compared with 7.9% in the placebo group (p = 0.048). Of the 35 adverse events reported 32 of these were gastrointestinal side-effects, two were allergic reactions and one was an unclassified reaction. In contrast, Daniels et al. [17] demonstrated no difference in mild gastrointestinal side-effects between antibiotic and placebo groups (3 vs 4%; p-value not given). Adverse reactions in both groups included heartburn, diarrhea, nausea but all reactions were mild and selflimiting. However, with regards to serious adverse events (including pneumonia, urinary tract infection and myocardial infarction), these occurred more frequently in the antibiotic group (9 vs 5%; p value not given). However, whether these adverse events were causally related to antibiotic therapy is unclear. In the study by Nouira et al. [18], no significant difference in adverse events was reported between the antibiotic and placebo group (11 vs 9%; p = 0.75). Vollenweider et al. performed a pooled analysis of 16 antibiotic trials and reported an increased risk of diarrhea associated with antibiotic use (OR 2.62; 95% CI: 1.11-6.17) [21].

# Head-to-head trials of antibiotics for COPD exacerbation

A number of studies have compared different antibiotics for the treatment of COPD exacerbations and evaluated a range of endpoints. These studies are less informative than placebo-controlled trials in determining the overall value of antibiotic therapy for treatment of exacerbation but offer some useful information to clinicians about which specific antibiotic to choose. Some of the existing head-to-head antibiotic trials for COPD exacerbations are summarized in Table 1.

### Long-term outcome of antibiotics in acute exacerbations

Some placebo-controlled and head-to-head trials have also evaluated whether short course antibiotic prescriptions, in the context of exacerbation, can affect longterm re-exacerbation rates. Llor et al. [22] assessed the number of days until the next exacerbation following antibiotic therapy. There was a significant increase in the time to the next exacerbation associated with antibiotic therapy (233 days for amoxicillin/clavulanate vs 160 days for placebo; p = 0.015). Wilson *et al.* [29] also evaluated the long-term effects of antibiotic therapy on a composite endpoint defined as the time to treatment failure and/or occurrence of a new exacerbation and/or any antibiotic use for a further acute exacerbation during the 9-month follow-up period. Clinical failure was shown to be significantly longer in moxifloxacin compared with comparator drugs on Kaplan meier analysis (p = 0.015) and failure rates were similar at the end of therapy 8.3 versus 9.9% (p value not given) with increasing divergence at 4 and 8 week post therapy.

Not all studies have demonstrated this beneficial effect of short antibiotic courses on long-term outcomes. Ruiz-Gonzalez *et al.* [20] demonstrated no significant difference in infection-free interval following acute exacerbation of COPD between patients treated with levofloxacin versus standard therapy (median 112 vs 101 days; p = 0.72). Lode *et al.* [27] also demonstrated no difference in the exacerbation-free interval following antibiotic therapy with levofloxacin and clarithromycin with a total of 43.6% of patients in the antibiotic group compared with 47.9% in the placebo group (p = 0.967) exhibiting no relapse during at 12 months post-therapy.

# Biomarkers to guide antibiotic therapy for acute exacerbations of COPD

As described previously, antibiotic therapy is associated with increased incidence of complications such as *Clostridium difficile* associated diarrhea. Antibiotic over-use can also lead to the development of antibiotic resistant bacterial strains and may be associated with

pulmonary disea	se exacerbation.			live
Author and year	Study details	Treatment	Outcome	Ref.
Ruiz-Gonzales <i>et al.</i> (2004)	Randomized open label (n = 116)	Levofloxacin vs standard therapy (clarithromycin or cefuroxime or amoxicillin/clavulanate)	Trend toward reduced exacerbation rate in levofloxacin group. 66 versus 79% in standard therapy group exacerbations (p = 0.40)	[20]
Lode <i>et al.</i> (2007)	Randomized, double-blinded multicenter	Levofloxacin vs clarithromycin	Prolonged exacerbation free interval at 1 year with levofloxacin compared with placebo. 300 days vs 350 days (p = 0.594)	[27]
	(n = 511)		Increased bacterial eradication with levofloxacin	
Petitpretz e <i>t al.</i> (2007)	Randomized, open label, multicenter (n = 585)	Levofloxacin vs cefuroxime	Trend toward increased clinical success at the end of treatment with levofloxacin compared with cefuroxime 82.8 vs 79.8% (p = 0.428)	[28]
Nouira e <i>t al.</i> (2010)	Randomized, double-blind, multicenter	Trimethoprim-sulfamethoxazole vs ciprofloxacin	Combined in-hospital death and additional antibiotic prescriptions were similar for both groups	[19]
	(n = 170)		Mean exacerbation free interval was similar	
Wilson <i>et al.</i> (2012)	Randomized, double-blind, multicenter (n = 1492)	Moxifloxacin vs amoxicillin/ clavulanic acid	Reduced clinical failure with moxifloxacin therapy (19% in moxifloxacin group vs 25.4% in amoxicillin/clavulanic acid group; p = 0.016)	[29]
			Trend toward higher bacterial eradication rate with moxifloxicin therapy in patients with confirmed pathogens (70.4 vs 64.4%; p = 0.078)	

inappropriate healthcare costs. Therefore, there has been considerable interest in the potential use of biomarkers to guide and potentially reduce antibiotic therapy for COPD exacerbations. Procalcitonin is a biomarker that is specifically elevated in response to bacterial infection. Bacterial infection induces a ubiquitous increase in *CALC-1* gene expression and release of procalcitonin from all tissues and cell types, which is thought to be secondary to bacterial endotoxins and exotoxins [30]. The rise in procalcitonin is blocked by cytokines released in viral infections and therefore this biomarker has been proposed as a potential distinguishing biomarker for bacterial exacerbations of COPD. Importantly, corticosteroids do not attenuate the production of procalcitonin [31].

Four randomized trials have shown that use of procalcitonin to guide antibiotic therapy for COPD exacerbation is associated with a reduction in antibiotic use without a corresponding increase in the rates of adverse outcomes including death, admission to the intensive care unit, re-exacerbation and readmission to hospital [32-35]. One trial [32] limited their study to COPD exacerbations alone with all others studies evaluating a range of lower respiratory tract infections [32,34,35]. The studies by Stolz et al. [32], Christ-Crain et al. [33] and Schuetz et al. [35] used a similar algorithm in which antibiotics were only prescribed if procalcitonin levels were >0.25 ng/ml. If antibiotics were prescribed, procalcitonin levels were rechecked and stopped once levels reached <0.25 ng/ml. Table 2 summarizes the existing trials that have evaluated procalcitonin as a biomarker for antibiotic therapy.

A limitation of procalcitonin use is that serial testing can be inconvenient for the patient and many laboratories may not have access to procalcitonin testing, which also limits its usage in clinical settings. However, the availability of emerging technologies for rapid point-of-care measurement of procalcitonin and other biomarkers is likely to improve this limitation, as such approaches become more widely adopted [36]. More studies are needed to explore the role of procalcitonin in the outpatient setting, although it remains a promising approach to allow targeted antibiotic use in COPD exacerbations.

#### **Long-term prophylactic antibiotics for COPD** Rationale for prophylactic antibiotic use in patients with COPD

Patients with COPD are frequently colonized with bacterial pathogens which may be cultured during periods of clinical stability [37]. Colonization may occur with potentially pathogenic microorganisms (PPM) such as *S. pneumoniae*, *M. catarrhalis* and *Haemophilus* species and non-PPMs including gastrointestinal and oropharyngeal flora such as Corynebacterium and Neisseria species [38]. In certain circumstances such as the chronic mucus hypersecretion associated with COPD, these PPMs may proliferate and induce a more robust inflammatory response in the host [39]. It is hypothesized that symptoms appear when this inflammatory response exceeds a threshold to induce new symptoms and that when antibiotics are introduced, the bacterial load decreases [40]. If the organism is not completely eradicated, the bacterial load may increase again leading to the potential for another exacerbation. This is known as the 'fall and rise hypothesis' of COPD exacerbation pathogenesis [41]. Some studies have suggested that exacerbations may be triggered by an increase in the concentrations of existing PPM [42,43], but others have shown no difference or reduced concentrations of PPM between exacerbation and stable states [44]. Other studies, which have employed molecular typing, have suggested that acquisition of new bacterial strains or antigenic change in existing strains may be the more important mechanism for triggering acute exacerbations [45,46]. This has led to development of an alternative hypothesis based on the acquisition of new bacterial strains or antigenic changes in pre-existing strains as drivers of exacerbations in COPD [47].

Multiple factors are believed to contribute to the impairment of antibacterial host defense in COPD patients. Cigarette smoking damages the ciliary bronchial epithelium which leads to impaired mucociliary clearance and impaired tracheobronchial clearance [48]. This impairment in the clearance of mucus and secretions may lead to pathogen retention and lower airways colonization. There is evidence that bacterial phagocytic function of neutrophils and macrophage function is impaired in COPD [49-51]. Cigarette smoke causes upregulation of pro-inflammatory mediators via the activation of alveolar macrophages and epithelial cells [52]. Pattern recognition receptors (PRRs) such as Toll-like receptor (TLR) 2 and TLR-4 play a key role in facilitating the interaction between pathogenassociated molecular patterns (PAMPS) and the host. PRR-PAMP interactions trigger signaling cascades leading to induction of antibacterial responses [53]. Droemann et al. reported that alveolar macrophages from patients with COPD had reduced expression of TLR-2 and TLR-4 in comparison to healthy nonsmokers [52]. Similarly MacRedmond et al. showed that the expression of TLR-4 was downregulated on nasal epithelium of smokers compared with nonsmoking control subjects [52,54]. All these factors may contribute toward impaired antibacterial host defenses in COPD.

Currently available therapies to reduce exacerbations in COPD include inhaled corticosteroids, long-acting β-agonists and pneumococcal and influenza vaccina-

Table 2. Existing t	rials that have assessed proc	alcitonin guided antibiotic us	e.	
Author and year	Study design	Primary endpoint	Main finding	Ref.
Schuetz <i>et al.</i> (2009) ProHOSP	n = 1359 (n = 228 with COPD) Multicenter, non- inferiority, randomized controlled trial	Overall adverse outcome within 30 days of presenting to ED, procalcitonin vs control group	Overall antibiotic usage was reduced in procalcitonin group 75.4 vs 87.7% in control. Rate difference -12.2 (95% Cl: 16.3–8.1)	[35]
			Reduced adverse event rate in procalcitonin group 19.8 vs 28.8%. Rate difference -8.2 (95% Cl: -12.7 to -3.7)	
			Shorter mean length of hospital stay in control group. 9.2 days vs 9.4 (95% Cl -6.9 to 11)	
Stolz <i>et al.</i> (2007) ProCOLD	n = 208 all with COPD exacerbation randomized controlled trial	Procalcitonin guided therapy vs standard therapy: atibiotic use at index	40% antibiotic use in procalcitonin guided therapy group vs 72% in standard therapy group; p = <0.0001	[32]
		exacerbation (in Emergency department) and total antibiotic exposure in 6-month period	No difference in the mean time to next exacerbation. 76.7 days in procalcitonin group vs 76.1 days ( $p = 0.819$ )	
Christ-Crain et al. (2004) ProRESP	n = 243 (n = 60 with COPD) Cluster randomized, controlled, single-blinded trial	Primary end point was antibiotic exposure in procalcitonin guided therapy group vs standard	Antibiotics were prescribed in 44% in procalcitonin group compared with 83% in standard therapy group; p < 0.0001	[33]
		therapy	Procalcitonin guided therapy had a reduced length of hospital stay. 10.7 days vs 11.2; p = 0.89	
			Mortality was equal of 3% in both groups; p = 0.95	
Kristofferson et al. (2009) 1-PCT	n = 210 randomized, controlled trial	Length of hospital stay (days) and duration of antibiotic treatment), single PCT guided treatment vs	Shorter duration of antibiotics: 5.1 days in procalcitonin vs 6.8 days in standard treatment group ( $p = 0.007$ )	[34]
		standard treatment	Trend toward reduced length of stay in procalcitonin group 5.9 days vs 6.7 days in control group ( $p = 0.22$ )	
CI: Confidence interval; E	D: Emergency department; PCT: Procald	citonin.		

tions [55]. Despite optimal therapy, a large proportion of patients with COPD continue to suffer frequent exacerbations [56]. Given the relatively few established treatment options for prevention of exacerbations in COPD, there has been much interest in the use of long-term antibiotics as prophylactic agents in COPD.

### Clinical trials evaluating the use of prophylactic antibiotics

Over the last decade, several trials have been undertaken to assess the effect of long-term prophylactic antibiotics on the reduction of exacerbations in patients with COPD. The potential beneficial implications may include a reduction in the length and severity of in-patient hospital stays, reduction in the financial burden on the healthcare system, improved health-related quality of life and potentially an attenuation of lung function decline through reduction of the pro-inflammatory processes of exacerbations.

Existing trials have assessed the use of continuous antibiotic therapy [57-63] or intermittent pulsed therapy [64,65] and have investigated a range of endpoints including exacerbation frequency, inflammatory markers in sputum and health-related quality of life. Macrolides are the most commonly evaluated antibiotic agent with all except one of the existing studies evaluating this specific antibiotic class. The rationale for the use of macrolide antibiotics relates to their combined antibacterial and immunomodulatory/anti-inflammatory properties [66]. In addition to direct antibacterial effects, macrolides also have anti-inflammatory properties, This has been demonstrated in several respiratory conditions including asthma, cystic fibrosis and COPD. This effect may be of particular interest in the use of prophylactic antibiotics in COPD as it adds a potential extra beneficial property that could theoretically reduce disease progression.

A number of specific airway anti-inflammatory effects of macrolides have been demonstrated including attenuation of neutrophil chemokines such as IL8 and proline-glycine-proline (PGP), [67-69] lymphocyte chemokine CCL5/regulated upon activation, normal T cells expressed and secreted (RANTES) [70] and, proinflammatory cytokine TNF- $\alpha$  [71]. The suppression of IL-8 has been specifically shown to occur independently of antibacterial properties [69].

### Effect of antibiotic prophylaxis on exacerbation frequency

In one of the largest trials to date, Albert et al. randomized patients into a group receiving azithromycin 250 mg once daily or placebo for a period of 12 months. The study reported that in the azithromycin group, the time to first exacerbation was longer than in the placebo group (266 days vs 174 days, respectively; p < 0.001). The overall rate of exacerbations in the treatment group was reduced compared with placebo (OR 1.48 vs 1.83; p = 0.01) [58]. Seemungal et al. [57] studied exacerbation frequency over a 12 month period following the use of erythromycin 250 mg twice daily compared with standard therapy in patients with COPD, and defined exacerbations as being moderate or severe if they required antibiotics, corticosteroids or hospital admission. The rate ratio for exacerbations in the treatment arm compared with placebo arm was 0.65 (95% CI: 0.49-0.86; p = 0.003). It was concluded that macrolide therapy significantly reduced the frequency and severity of exacerbations. A similar study conducted by Suzuki et al. [63] showed that the use of macrolides reduced the incidence of the common cold over a 1-year period. The relative risk of exacerbation in the control group compared with the treatment group was 4.71 (95% CI: 1.53-14.5; p = 0.007). He *et al.* demonstrated that the time to first exacerbation was longer in patients treated with longterm erythromycin therapy compared with placebo using Kaplan-Meier analysis (p = 0.032) [61].

Banerjee *et al.* investigated the use of oral, continuous clarithromycin in patients with COPD-compared placebo. Primary endpoints included rate of exacerbations, sputum bacterial numbers and health-related quality of life. In contrast to the studies described above, this study demonstrated no significant change in the rate of exacerbations in patients receiving clarithromycin compared with placebo [59].

The effect of pulsed antibiotics on exacerbation frequency has also been evaluated in a study by Sethi *et al.* 5-day courses of moxifloxacin therapy every 8 weeks was associated with a reduction in exacerbations in the intention-to-treat group (20%), the per-protocol group (25%) and the per-protocol group with purulent/mucopurulent sputum at baseline (45%). Of note, no resistance patterns developed and no unexpected side effects were encountered [64].

Table 3 summarizes the existing trials that have assessed long-term antibiotic therapy in COPD. The majority of existing trials show that long-term antibiotic therapy can reduce exacerbation frequency in COPD. However, whether specific COPD phenotypes may derive differential benefit from long-term antibiotic therapy remains unclear.

### Effect of antibiotic prophylaxis on respiratory symptoms & health-related quality of life

The study by Albert *et al.* [58] (previously described) also evaluated health-related quality of life outcomes following continuous use of azithromycin in COPD over a 1 year period. SGRQ scores were evaluated and improved significantly in the azithromycin group compared with placebo (a mean [ $\pm$  SD] decrease of 2.8  $\pm$  12.1 vs 0.6  $\pm$ 11.4, p = 0.006) [58]. Although there was a significant difference between the antibiotic and placebo groups, the effect failed to reach the threshold of a change greater than 4 points, which is widely recognized to be the minimum clinically relevant change. Banerjee *et al.* also assessed health-related quality of life in patients treated with clarithromycin or placebo for 3 months. In contrast to the study by Albert *et al.*, they found no significant improvement in quality of life using SGRQ [59].

Berkoff *et al.* evaluated cough specific health status as a primary outcome in a small randomized controlled trial evaluating the use of azithromycin 250 mg three-times per week for 3 months. Using the Leicester cough questionnaire, they found a clinically significant improvement in total scores in the azithromycin group when compared with placebo (difference  $1.3 \pm 0.5$ , 95% CI: 0.3-2.3, p = 0.01) [60].

## Effect of antibiotic prophylaxis on markers of airway inflammation

The study by He *et al.* described previously also evaluated the effect of long-term antibiotic therapy on markers of airway inflammation in COPD patients. Neutrophil numbers in sputum were found to be significantly lower in patients on erythromycin compared with the control group (2.75 ( $10^6/ml$ ) vs 2.25 ( $10^6/ml$ ); p = 0.005) [61]. Whether such effects would have a

Table 3. Sumr	mary of trials Investigating prophylactic a	ntibiotics in chr	onic obstru	ctive pul	monary disease.		
Author and year	Study design	Continuous F	ulsed Neb	ulized	Findings	Adverse effects in treatment groups	Ref.
Albert R <i>et al.</i> (2011)	Randomized, double-blind controlled trial with 1142 patients. Azithromycin group – n = 266, placebo group – n = 174	×			Median time to first exacerbation longer in Azithromycin group vs placebo	Hearing reduction	[58]
				•,	Frequency in exacerbations higher in placebo group SGRQ scores improved significantly in Azithromycin group		
Berkhoff F et al. (2013)	Randomized controlled trial of 84 patients treated with Azithromycin 250mg 3 times a week (n = 42) vs placebo (n = 42). Primary outcome was cough- specific health status at 12 weeks	×			significant improvement in cough specific health status using the Leicester Cough Questionnaire in patients treated with azithromycin	Diarrhea and taste disturbance	[60]
Seemungal T et al. (2008)	Randomized, double-blind placebo- controlled trial of 109 patients. Erythromycin 250 mg BD for 12 months (n = 53) vs Placebo (n = 56) Primary outcome was number of moderate-to- severe exacerbations	×			Macrolide therapy significantly reduced the rate and severity of exacerbations Length of exacerbation was shorter in the erythromycin treatment group	Z	[57]
Suzuki T <i>et al.</i> (2001)	Prospective, randomized, controlled, unblinded trial. 109 patients randomized into erythromycin treatment 200 or 400 mg/day (n = 55) or placebo (n = 54) over 12 months. Risk and frequency of catching the common cold and COPD exacerbations were investigated	×			The mean number of common colds was significantly lower in the treatment group ( $1.24 \pm 0.07 \text{ vs} 4.54 \pm 0.02$ , respectively, per person; p = 0.0002) More patients were hospitalized for exacerbations in the control group (p = 0.0007) The total number of exacerbations was significantly lower in the treatment group vs placebo (p < 0.0001)	One patient – diarrhea and anorexia	[63]

Table 3. Sumn	nary of trials Investigating prophylactic a	ntibiotics in ch	ironic obs	structive pu	Imonary disease (cont.).		
Author and year	Study design	Continuous	Pulsed	Nebulized	Findings	Adverse effects in treatment groups	Ref.
Pomares X <i>et al.</i> (2011)	Retrospective study. 20 patients were treated with azithromycin 500 mg three- times a week over 12 months. Analysis focused on number of exacerbations, number of admissions, length of hospital stay and bacterial infection during treatment	×			Reduction in number of exacerbations in azithromycin group vs placebo Reduction in number of hospital admissions Reduction in length of hospital stay	Dyspepsia	[62]
He Z et al. (2010)	Randomized, double-blind, placebo- controlled trial of Erythromycin (n = 18) 125mg TDS vs placebo (n = 18) over 6 months. Primary outcomes were neutrophil number in sputum and number of exacerbations	×			Neutrophil count was significantly decreased in the erythromcyin group vs placebo (p = 0.005) Mean exacerbation rate was lower in the treatment group vs placebo (relative risk = 0.0554, p = 0.042) Time to first exacerbation was delayed in the erythromycin group vs placebo using Kaplan-Maier survival analysis (p = 0.032)	Abdominal pain	[61]
Banerjee <i>et al.</i> (2005)	Prospective, randomized, double-blind, controlled trial of treatment with oral Clarithromycin (n = 31) vs placebo (n = 36). Health status, sputum bacterial numbers and rate of exacerbations were investigated	×			No significant difference in health status, exacerbations rates or sputum bacterial numbers in clarithromycin group vs placebo		[59]
Sethi S <i>et al.</i> (2010)	Randomized, double-blind, placebo- controlled trial of Moxifloxacin 400 mg OD for 5 days (n = 573) vs placebo (n = 584). 5 day treatment repeated every 8 weeks for a total of 6 courses. The study looked at frequency of exacerbations, number of hospital admissions for exacerbations and changes in health-related quality of life		×		There was a reduction in the odds ratio of the moxifloxacin group: ITT population (by 20%) PP population (by 25%) PP population with purulent/ mucupurulent sputum at baseline (BY 48%)	Nausea, vomiting, diarrhea, hypersensitivity, urticaria, dyspnoea	[64]

Author and Study year Gomez J <i>et al.</i> Prosp (2000) at the	ע הוומוז ווועכזרואמ הוווא או טאוואומר הר מוו			נו מר נו אר המ	iiioiiai y uisease (contr.).		
Gomez J <i>et al.</i> Prosp (2000) at the	y design	Continuous	Pulsed N	Vebulized	Findings	Adverse effects in treatment groups	Ref.
500 = 54) withc done	pective, randomized trial looking e intermittent use of Azithromycin ng OD for 3 days every 21 days (n compared with a control group our treatment (n = 40). This was : over winter		×		Intermittent azithromycin treatment significantly reduced the number of exacerbations vs control group (187 and 249, respectively) Hospital admissions were also lower in the treatment group vs control group (22 and 45, respectively)	None noted	[65]
Dal Negro 13 pa <i>et al.</i> (2008) cours All pa for m trial 1 inflar	atient trial of 300 mg BD 14 day se of tobramycin nebulized solution. atients were sputum positive nultiresistant <i>P. aeruginosa.</i> The looked at clinical outcome and mmatory markers		×		There was a significant reduction in inflammatory markers IL-B, IL-8, ECP, eosinophil count There was a reduction in exacerbations by 42% <i>P. aeruginos</i> a density fell significantly at 6 months	None noted	[72]
Sethi <i>et al.</i> Rand (2012) contr treat nebu days end p	lomized double-blind, placebo- olled trial. 322 patients either ed with levofloxacin 240 mg BD lized for 5 days, treated every 28 for 9–12 cycles vs placebo. Primary ooint used was exacerbation rates		×		No reduction in exacerbation rate rate ratio 1.09 (90% CI: 0.86– 1.39) No prolongation in time to first exacerbation hazard ratio 1.02 (90% CI: 0.78–1.34)	Yes adverse events: (87.0 vs 92.1% p = not given). Serious events 29.6 vs 33.6% (p = not given)	[73]

positive effect on disease progression remains unclear. The previously described study by Seemungal *et al.* also evaluated sputum and serum inflammatory markers but found no significant difference between the treatment and placebo arms in terms of sputum IL-6, IL-8 and myeloperoxidase or serum IL-6 and C-reactive protein at baseline or over the 12-month study period [57].

#### Nebulized antibiotics in COPD

The use of nebulized antibiotics as prophylactic agents in COPD patients is an emerging area of interest. A number of studies have evaluated the use of nebulized antibiotics in the context of patients with cystic fibrosis (CF) or non-CF bronchiectasis and shown beneficial effects in reducing exacerbations [74–76]. Nebulized antibiotics provide therapy in a localized, targeted response and may thus cause fewer systemic side-effects. Studies have suggested that this localized approach provides better treatment for the reduction and eradication of bacterial pathogens within respiratory secretions [77].

Relatively few studies have evaluated the effect of nebulized antibiotics in patients with COPD. Dal Negro *et al.* recruited 13 patients in a study to assess the effect of a short course of nebulized tobramycin 300 mg BD (2 week course) on inflammatory markers and cell counts of patients with severe COPD known to be colonized with multiresistant *P. aeruginosa*. This study demonstrated a significant reduction in inflammatory markers IL-8, IL- $\beta$ , ECP (eosinophilic cationic protein), and eosinophils in sputum. It also showed a reduction in exacerbation frequency by 42% and a reduction in the bacterial density of *P. aeruginosa* in sputum 6 months after administration [72]. A Phase II trial carried out by Sethi *et al.* examined the effect of pulsed inhaled levofloxacin on 322 COPD patients. The primary endpoints were time to first exacerbation and number of exacerbations. This study showed no effect of nebulized antibiotics on either endpoint but the inhaled formulation was well tolerated by all patients included in the study [73].

## Possible disadvantages of prophylactic antibiotic use

The main concerns for the use of long-term prophylactic antibiotics are the emergence of bacterial resistance and adverse drug-related side effects. Table 3 summarizes the range of adverse drug effects that have been documented in existing studies. The main adverse effects encountered with macrolide use were gastrointestinal symptoms of nausea, taste disturbance, dyspepsia, vomiting and diarrhea. Although generally well tolerated in short courses, long-term use may pose a challenge in terms of patient tolerance and adherence. None of the existing studies documented any electrocardiographical changes or cardiac arrhythmias in patients treated with long-term macrolides. However, emerging data have suggested that macrolides may increase the risk of acute coronary events [58].



Figure 1. The beneficial and detrimental effects of antibiotic use in chronic obstructive pulmonary disease. COPD: Chronic obstructive pulmonary disease.

Although the theoretical risk of antimicrobial resistance is present, there are no significant resistance pat-

tern data documented in any of these studies. Albert *et al.* reported that although patients randomized to

#### **Executive summary**

This review discusses the results of recent clinical trails that have evaluated the use of antibiotic therapy in patients with chronic obstructive pulmonary disease (COPD). Bacteria are thought to be important precipitants of exacerbations. Exacerbations are the most frequent cause of hospitalization and death.

#### Antibiotic therapy for exacerbations of COPD

• There is limited evidence to support the use of antibiotics in exacerbations, as defined by the Global Initiative for Chronic Obstructive Lung Disease strategy.

#### Methods for determining need for antibiotics during acute exacerbations

- Clinicians often initiate antibiotic therapy depending on various factors including: patient's symptoms, systemic markers of infection and positive microbiology.
- Anthonisen criteria uses specific symptomatic features to define an exacerbation. If a patient exhibits features of Anthonisen type 1 or 2 exacerbations, antibiotics are recommended.

#### Impact of antibiotics on short-term outcomes

- Daniels et al. demonstrated no difference in mortality rate at day 10 but did show reduced mortality at day 30 in the antibiotic treated group.
- Reduction in mortality, in mechanically ventilated patients, in antibiotic-treated group.
- Not all studies have demonstrated this reduced mortality.

#### Effect of antibiotics on treatment failure following acute exacerbation of COPD

- There has been conflicting evidence assessing antibiotics in mild/moderate COPD.
- In the outpatient setting, in those with mild/moderate COPD there is a greater relative risk of treatment failure in placebo treatment group. There was also greater clinical cure at day 20.
- Antibiotic therapy and corticosteroid therapy was superior to placebo therapy at day 10 and demonstrated superiority in terms of clinical success however this was not sustained until day 30.
- However, in hospitalized patients, beneficial effects were only seen in those with severe exacerbations.

#### Effects of antibiotics on length of hospital stay following acute exacerbation of COPD

• There is limited information with regards to the effect on length of stay. However, in ventilated patients, antibiotics is associated with a reduced length of stay.

#### Effect of antibiotics on symptoms & health-related quality of life

• Symptomatic improvement with antibiotics has been demonstrated and an improvement in health related quality of life.

#### Adverse events associated with antibiotic therapy in exacerbations

- The most commonly associated side effects are gastrointestinal.
- The risk of Clostridium difficile associated diarrhea may be increased with antibiotic use.
- There is conflicting evidence with regards to the incidence of side effects in the antibiotic and placebo groups.
- Long-term outcome of antibiotics in acute exacerbations

• Some studies have shown an increased time to next exacerbation, in antibiotic group, but this has not been shown consistently.

#### Biomarkers to guide antibiotic therapy for acute exacerbations

 Procalcitonin is specifically elevated in bacterial infections. Four trials have shown that procalcitonin to guide antibiotic therapy for COPD exacerbation is associated with a reduction in antibiotic use without a corresponding increase in adverse outcomes. Long-term prophylactic antibiotics for COPD

### Rationale for prophylactic antibiotic use in patients with COPD

- Patients with COPD are frequently colonized with bacterial pathogens. It has been suggested that exacerbations are triggered by an increase in the concentrations of existing potentially pathogenic microorganisms.
- Multiple factors impair the antibacterial host defense.

#### Clinical trials evaluating the use of prophylactic antibiotics

- Continuous and intermittent pulsed therapy has been investigated.
- Azithromycin has been shown to significantly reduce the frequency and severity of exacerbations. However, these effects are not consistent.

#### Effect of antibiotic prophylaxis on markers of airway inflammation

• Neutrophil numbers are significantly lower in patients treated with erythromycin, but no significant difference in IL-6, IL-8, myeloperoxidase or C-reactive protein.

#### Nebulized antibiotics in COPD

• The use of nebulized antibiotics as prophylaxis is an emerging area of interest. Dal Negro demonstrated a reduction in inflammatory markers a reduction in the bacterial density.

#### Possible disadvantes of prophylactic antibiotic use

• Theoretical risk of antimicrobial resistance but further investigation is warranted.

receive antibiotics were less likely to be colonized by bacterial pathogens, they were more susceptible to be colonized by macrolide-resistant pathogens [58]. However, other large studies have disputed this and further studies are warranted [57,62].

#### **Summary & conclusion**

For severe exacerbations of COPD such as patients requiring ICU admission and mechanical ventilation, antibiotic therapy is clearly indicated and may be associated with improved mortality. However, the role of antibiotic therapy in less severe exacerbations including hospitalized patients not managed on the ICU and outpatients is unclear. There is some evidence that antibiotic therapy during acute exacerbation may reduce treatment failure and also some data suggesting that it may have long-term beneficial effects by reducing the risk of re-exacerbation. However, the specific subgroups of patients presenting with COPD exacerbation that should receive antibiotics is still undefined. Biomarkers such as procalcitionin may provide a means of distinguishing exacerbations triggered by bacteria from other aetiological causes and allow more targeted therapy, but further evaluation of these approaches is required.

Existing evidence suggests that the use of prophylactic antibiotics for stable COPD can reduce the rate of exacerbations, reduce hospital admissions, improve quality of life and may dampen the host inflammatory response with theoretically beneficial effects on disease progression. Current guidance suggests that a subgroup of patients with severe COPD and a history of frequent exacerbations, may derive benefit from the use of prophylactic antibiotic therapy as part of their standard treatment but the precise disease phenotypes that should be treated with this approach are not fully characterized. There is little evidence so far to comment on the advantage of nebulized antibiotics in patients with COPD and preliminary results have been inconclusive. However, the benefits of a localized, targeted treatment with low systemic consequences is promising and further research into these approaches is therefore warranted.

Areas of concern for long-term use of antibiotic therapy include the potential for development of resistant

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pathogens in an already vulnerable group of patients, and the adverse side effects of long-term oral and nebulized antibiotic use. Therefore, large multicenter studies are now needed to further evaluate these approaches and quantify potential adverse effects and also to determine if specific disease phenotypes exist that may derive more benefit from use of long-term antibiotic therapy.

#### **Future perspective**

There remain a considerable number of unanswered questions regarding the effects and role of antibiotics in COPD exacerbations. A major difficulty is the lack of a sensitive biomarker that can accurately distinguish exacerbations triggered by bacterial pathogens from other aetiological causes. Development of more sensitive biomarkers that can be measured in the blood and/or breath will aid in more accurate stratification of patients requiring antibiotics and thus ultimately allow more judicious use of antibiotics.

The emergence of novel culture independent molecular microbiological techniques also has the potential to revolutionise this area and future studies will need to focus on the effects of antibiotics on both the causative pathogen and the resident airway microbiota during exacerbations. Modulation of the microbiota by direct instillation of specific bacteria that have beneficial effects is a theoretical possibility but remains speculative at present.

Finally, the increasing recognition of the influence of virus infection on direct precipitation of secondary bacterial infection also raises the possibility that preventative antiviral therapies may be a realistic alternative to the use of antibiotics to reduce the burden of bacterial infections in COPD (Figure 1).

#### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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