Prophylactic antibiotic therapy in chronic obstructive pulmonary disease

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Abstract: Chronic obstructive pulmonary disease (COPD) represents a huge epidemiological burden and is associated with a high incidence of morbidity and mortality. The disease is characterized by chronic inflammation and bacterial colonization. Chronic bacterial colonization leads to chronic inflammation and epithelial damage that in turn may increase bacterial colonization and predispose to acute bacterial infection. Acute exacerbations are a major cause of hospitalization and lead to a deterioration in pulmonary function. Antibiotic treatment of acute bacterial exacerbations is a cornerstone of medical treatment. Conversely, the role of antibiotic prophylaxis in COPD in the stable state is controversial. From a theoretical point of view, antibiotic prophylaxis is intriguing as it could break the vicious circle between chronic bacterial colonization, inflammation and epithelial damage; however, evidence is scarce. This paper reviews the literature and focuses on the most recent data shedding light on this fascinating dilemma.

Keywords: antibiotic prophylaxis, chronic bronchitis, chronic obstructive bronchopulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) represents a huge epidemiological burden affecting 10% of the population over the age of 40 years and is associated with a high incidence of morbidity and mortality [Mannino and Buist, 2007].

COPD is characterized by poorly reversible air flow obstruction and chronic lung inflammation [GOLD, 2008; Hurst and Wedzicha, 2007]. Moreover, bronchial bacterial colonization is frequent in patients with COPD. In almost half of moderate-to-severe COPD patients potentially pathogenic micro-organisms (PPMs) have been demonstrated on bronchoscopy [Weinreich and Korsgaard, 2008; Monsó *et al*. 1999, 1995; Zalacain *et al*. 1999], and colonized patients show both higher inflammation and more frequent and severe exacerbations [Sethi *et al*. 2006; Banerjee *et al*. 2004; Hill *et al*. 2000].

The clinical hallmark of COPD is the recurrence of acute exacerbations, mainly caused by acute infections, which increases local inflammation and leads to pulmonary function deterioration [Wilkinson *et al*. 2003; Patel *et al*. 2002] (Figure 1).

Rationale

COPD is characterized by chronic airways inflammation during the stable phase and acute-on-chronic inflammation in case of exacerbation. Chronic bacterial colonization and acute bacterial infection thus play a major role in initiating and perpetuating such mechanisms.

Chronic bacterial colonization of the damaged respiratory epithelium leads to chronic release of bacterial and host-mediated pro-inflammatory factors that in turn damage the epithelium more, leading to a vicious circle ending in more severe obstruction and increased susceptibility to acute exacerbation.

By reducing bacterial colonization, chronic antibiotic therapy could help in reducing progression of the disease.

Moreover, some antibiotics also have intrinsic anti-inflammatory proprieties, as has already been demonstrated for macrolides in cystic fibrosis and diffuse panbronchiolitis [Shinkai *et al*. 2008; Equi *et al*. 2002; Wolter *et al*. 2002; Kudoh *et al*. 1998].

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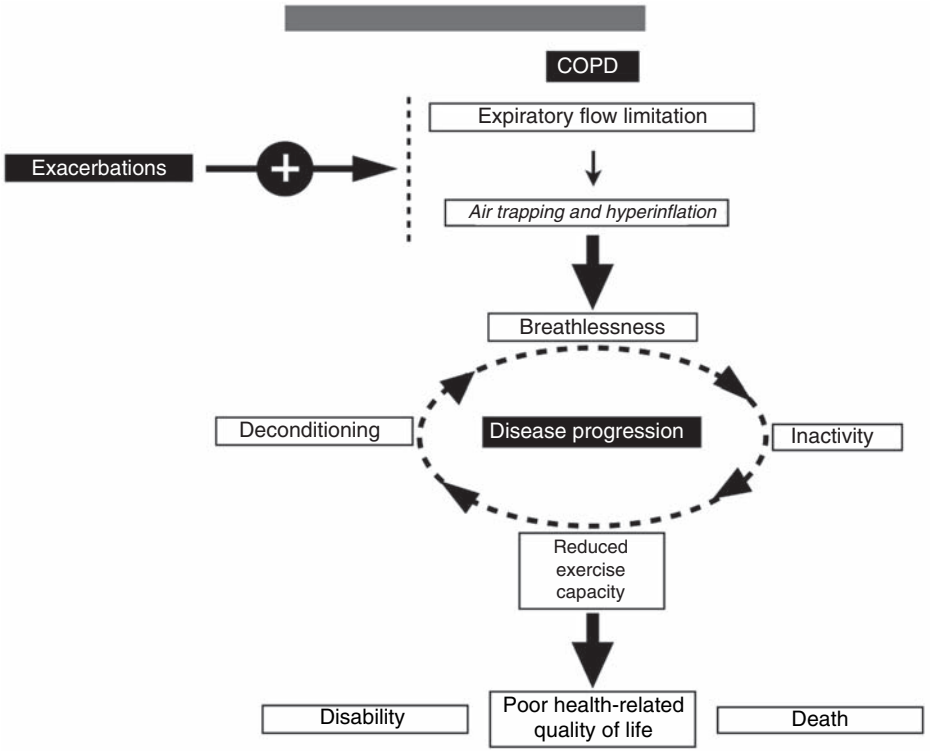

Figure 1. Natural history and disease progression of COPD.

When a new pathogen enters the damaged airway of a COPD patient, it triggers an acute-on-chronic surge of inflammatory mediators that contribute to further damaging the mucosal cells. This impairs host defences and promotes coinfection or infection by colonizing agents. Therefore, prophylactic antibiotic therapy in COPD could eradicate colonizing bacteria and curb the acute inflammatory response; this in turn could prevent acute exacerbations and improve the natural history of the disease (Figure 2).

Current evidence

Randomized controlled trials have been conducted on this topic, and nine of these were deemed acceptable for entering in a Cochrane review, dating back to 2001 [Black *et al*. 2003] (Table 1). In this systematic review, the authors concluded that prophylactic antibiotic therapy has 'a small but significant effect in reducing the days of illness due to acute exacerbation of COPD' but no significant advantage in terms of absolute acute exacerbation number reduction. However, these studies were all published before the 1970s. Meanwhile, new drugs have been engineered, new patterns of antibiotic sensitivity have emerged and understanding of the disease has evolved. Moreover, data showed a small increase in adverse events with antibiotic treatment.

To assess the efficacy of antibiotic prophylaxis in preventing common cold and consequently COPD acute exacerbation, Suzuki *et al*. [2001] performed a randomized controlled unblinded trial comparing long-term erythromycin administration versus placebo. In the trial 109 patients were randomly assigned to receive either erythromycin (200–400 mg/day, 55 patients) or no active treatment (riboflavin 10 mg/day, 54 patients) for 12 months. The relative risk (RR) of developing two or more common colds in the control group compared with that in the erythromycin group was 9.26 (95% confidence interval [CI] 3.92–31.74; $p = 0.0001$). Thirty patients (56%) in the control group and six patients (11%) in the erythromycin group had one or more exacerbations. The RR of experiencing an exacerbation in the control group compared with that in the erythromycin group was 4.71 (95% CI 1.53–14.5; $p = 0.007$). Significantly more patients were hospitalized due to exacerbations in the control group than in the erythromycin

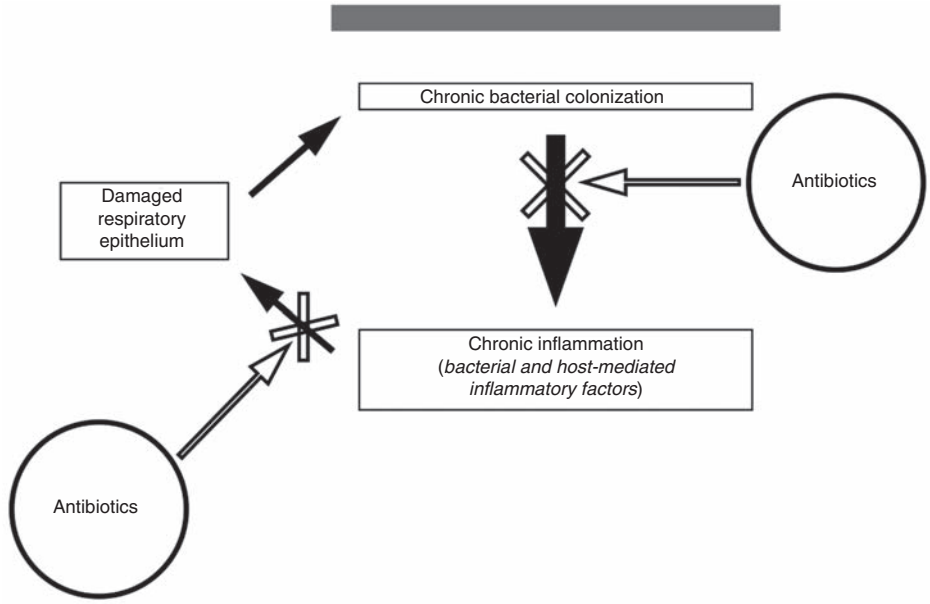

Figure 2. Rationale of antibiotic prophylaxis in COPD.

Table 1. Randomized controlled trials on antibiotic prophylaxys in COPD.

First author	Year of publication	Patients number (in full analysis)	Drug and dose in study (all trials with placebo arm)	Duration of treatment
Goslings	1957	63	Sulphaphenazole 500 mg twice a day or Tetracycline 500 mg twice a day	5 months
Moyes	1957	86	Tetracycline 500 mg three times a day 7 days, then 250 mg three times a day	4 months
Murdoch	1959	23	Sigmamycin 1 caps four times a day or Oxytetracycline 250 mg four times a day	3 months
Francis	1960	185	Tetracycline 250 mg twice a day or Phenoxymethylpenicillin 312 mg twice a day	4 months
Pridie	1960	139	Oxytetracycline 0.5 g once a day or Phenoxymethylpenicillin 500 mg + sulphadiamidine 2 g	6 months
Johnston	1961	40	Phenethicillin 250 mg twice a day	6 months
Fletcher	1966	373	Oxytetracycline 0.5 g in years 1–3, 0.5 g twice a day in year 4, 1 g twice a day in year 5	7 months per year for 5 years
Johnston	1969	79	Tetracycline 500 mg twice a day	6 months per year for 5 years
Liippo	1987	19	Trimethoprim 300 mg once a day	6 months
Banerjee	2005	76	Clarithromycin extended release 500 mg once a day	3 months
Seemungal	2008	109	Erythromycin 250 mg twice a day	1 year
Miravitlles	2009	40	Moxifloxacin 400 mg once a day	5 days
Sethi	2010	1149	Moxifloxacin 400 mg once a day	5 days every 8 weeks for six courses

group ($p = 0.0007$). The authors concluded that erythromycin therapy has beneficial effects on the prevention and severity of exacerbations in COPD patients.

Four years later, a study on 3-month clarithromycin treatment in stable COPD was published [Banerjee *et al.* 2005]. The authors enrolled 76 patients with moderate-to-severe COPD who were randomized to clarithromycin extended release (XL) 500 mg once daily or placebo for 3 months. At the end of the study no difference was detected on health status measured by St George respiratory and short form-36 questionnaires, sputum bacterial numbers or exacerbation rate. The authors concluded that the efficacy of the drug on exacerbation rates could be evaluated only in a long-term study.

This weak evidence is the reason why current Global Initiative for Chronic Obstructive Lung Disease guidelines [GOLD, 2008] discourage prophylactic antibiotic therapy in COPD stating, with level of evidence A, that 'prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in COPD' and that 'there is no current evidence that the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is helpful'.

Similarly, the 2005 European Respiratory Society guidelines for the management of lower respiratory tract infection [Woodhead *et al.* 2005] state, with evidence level A, that 'the prophylactic use of antibiotics in patients with chronic bronchitis or COPD as a matter of prevention is not recommended'. They, however, consider as 'opinion of experts', with evidence level C, the possibility of using long-term antibiotic therapy in those bronchiectasis patients suffering from frequent bacterial exacerbation.

New data

Interesting data have been recently published on the effect of prolonged antibiotic use in moderate-to-severe COPD patients, using two different approaches. One is the immunomodulation effect by long-term, low-dose macrolide administration (as performed by Suzuki *et al.* [2001] in common cold prevention); the second is microbial suppression by the burst antibiotic administration of fluoroquinolones.

Immunomdulation

Two years ago, an English group published a study on long-term administration of erythromycin in COPD [Seemungal *et al.* 2008]. The rationale of this study was the anti-inflammatory and immunomodulating properties of macrolides [Crosbie and Woodhead, 2009; Verleden *et al.* 2006; Tsai *et al.* 2004]. Several studies have shown the antibacterial and anti-inflammatory effects of macrolides on chronic respiratory diseases, as in bronchial asthma [Johnston *et al.* 2006], COPD [Suzuki *et al.* 2001], bronchiectasis [Tsang *et al.* 1999], cystic fibrosis [Equi *et al.* 2002; Wolter *et al.* 2002] and bronchiolitis obliterans syndrome [Verleden *et al.* 2006]. In their single-centre, randomized placebo-controlled trial [Seemungal *et al.* 2008], the authors studied the effects of daily administration of erythromycin in moderate-to-severe COPD patients over a 1-year period in terms of time to first exacerbation. The rationale for the use of a macrolide in the study was for their double antimicrobial and an anti-inflammatory activity, as previously reported. They administered erythromycin (250 mg, twice daily) or placebo for 1 year to 109 patients with moderate to severe COPD (mean age 67.2 years, mean forced expiratory volume in 1 s (FEV_1) 50% ± 18 of predicted). The primary outcomes were the frequency of moderate or severe exacerbations, defined as those requiring antibiotics, oral corticosteroids or hospitalization, and airway inflammation (measured as sputum levels of interleukin (IL)-6, IL-8, myeloperoxidase and serum C-reactive protein or IL-6). Secondary outcome measures were adverse events and FEV_1 decline over time. On multivariate analysis, erythromycin was found effective in reducing exacerbation risk (RR 0.648, CI 95% 0.489–0.859), and delaying the first exacerbation to 271 days median versus 89 days in the placebo group. Moreover treated patients had a median exacerbation length of 9 (6–14) days versus 13 (6–24) in the placebo group ($p = 0.036$). Sputum bacteriology did not change significantly in patients treated with erythromycin. This is not surprising, since the study drug was used mainly for its anti-inflammatory activity, i.e. in a much lower dosage than the therapeutic regimen (approximately one fourth), and *Haemophilus influenzae* strains, the most frequent pathogens found both at enrolment (20% of cases) and at exacerbations (40%), were all constitutionally resistant to erythromycin. Curiously, no detectable effect on airway inflammation or FEV_1 decline

was observed. The lack of detection of any anti-inflammatory effect is explained by the authors with the statistical power of the study, whose primary outcome was the reduction of exacerbation rate. Alternatively, it may depend on the inflammatory markers investigated, since neither neutrophil recruitment nor adhesion molecules were evaluated in the study. There were no differences in adverse events between the two groups. The authors concluded that long-term erythromycin treatment effectively reduces acute exacerbations and, therefore, macrolides have a role in COPD and may be used to augment therapy in patients with moderate to severe COPD.

Microbial suppression

Other trials have been performed recently on moxifloxacin. Miravitlles *et al.* [2009] investigated the efficacy of a 5-day course of 400 mg moxifloxacin for the eradication of bacterial airways colonization in COPD patients. They enrolled 40 COPD patients (mean age 69 years, mean FEV_1% 53 ± 16 of predicted in the intervention group and 47 ± 15 in the control group) with evidence of bacterial colonization by PPMs in a randomized placebo-controlled trial of a 5-day course of oral moxifloxacin (400 mg daily). The primary outcome was the eradication of PPMs at 2 weeks after randomization. Secondary outcome measures were eradication of PPMs at 8 weeks, acquisition of new strains of PPMs at 8 weeks, and exacerbation frequency at 5 months after randomization. At 2 weeks, the colonization rate by PPMs was 25% (5 out of 20 patients) versus 70% (14 out of 20 patients) in the moxifloxacin and placebo groups, respectively ($p = 0.01$). However, at 8 weeks 70% of treated patients had acquired a new strain of PPM versus 60% of the placebo group ($p > 0.25$), while persistence of the baseline colonizing PPM at 8 weeks was detected in 5% of the moxifloxacin arm versus 25% of the placebo arm ($p = 0.18$), resulting in an overall colonization rate at 8 weeks of 75% versus 80% in the treatment and control groups, respectively. No difference in acute exacerbation rate or time to the first exacerbation was detected between the two groups of patients. The authors found the acquisition of a new colonizing strain of PPM to be significantly associated with the appearance of a new exacerbation (odds ratio [OR]: 9.63, CI 95%, 1.01–91.64).

The findings of this study provided the background rationale for a multicentre placebo-controlled study of intermittent moxifloxacin therapy for the prevention of acute exacerbations of chronic bronchitis (AECB), the PULSE study (Pulsed Moxifloxacin Usage and its Long-term Impact on the Reduction of Subsequent Exacerbations, www.ClinicalTrials.gov [NCT00473460]) [Sethi *et al.* 2010]. The rationale of the trial of chronic intermittent pulsed suppressive antibiotic therapy is summarized by the following expected results: (a) reduction of pulmonary damage resulting from the chronic interplay between bacterial colonization and host inflammatory response; (b) fewer and less severe exacerbations of COPD; (c) decrease of deterioration of pulmonary function over time; (d) improved quality of life for COPD subjects. The study enrolled 1157 patients with moderate-to-severe COPD (at least 50% of patients with FEV_1 <50% predicted) who were randomized in a double-blind, placebo-controlled trial to receive moxifloxacin 400 mg orally once daily (573 patients) or placebo once a day for 5 days (584 patients). Treatment was repeated every 8 weeks for a total of six courses. Patients were repeatedly assessed clinically and microbiologically during the 48-week treatment period, and for a further 24-week follow up. At 48 weeks, suppressive antibiotic therapy with moxifloxacin was effective mainly in the subgroup of patients with purulent/mucopurulent sputum production at baseline ($n = 323$); the *post-hoc* analysis of per-protocol (PP) patients showed an OR 0.55 (95% CI 0.36–0.84, $p = 0.006$). Conversely, in the whole population, the drug effect was less remarkable; the OR for suffering an exacerbation with moxifloxacin versus placebo in the PP population ($n = 738$) was 0.75 (95% CI 0.565–0.994, $p = 0.046$), and in the intent-to-treat (ITT) population ($n = 1149$) the OR was 0.81 (95% CI 0.645–1.008, $p = 0.059$).

Microbiological data from the PULSE study were presented last year by Sethi and Alder [2009] in the form of a poster at the European Congress of Clinical Microbiology and Infectious Diseases 2009. Sputum samples were collected from all 1149 patients in the ITT population at all clinic visits. Moxifloxacin susceptibility testing was performed for *Haemophilus* spp., *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* from both treatment arms. At randomization, the most frequent

isolates were *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae*, *S. aureus* and *P. aeruginosa*. Eradication in the moxifloxacin group was observed in the majority of the patients colonized by *H. influenzae*, *H. parainfluenzae*, and *S. pneumoniae*, but not in those colonized by *S. aureus* or *P. aeruginosa*. Spontaneous eradication was seen at a significantly lower frequency in the placebo group. Minimum inhibitory concentration (MIC) values remained stable for most sputum bacterial species isolated during the study. However, transient increases in MIC for *S. aureus* and *P. aeruginosa* in some isolates were observed during the study, but these appeared to be independent of treatment arm or timing. In conclusion, these data show that treatment with moxifloxacin induces a higher eradication of primary pathogens compared with placebo treatment with inconsistent moxifloxacin-related increase in MIC during the 48-week PULSE study or the 24-week follow-up period.

Are there any other possible advantages of antibiotic administration?

In the past 2 years interesting data have been published from a large retrospective cohort of Dutch patients, focusing on antibiotic treatment of AECB [Roede *et al*. 2008]. In their work, they analysed 18,928 patients and found antibiotic treatment (added to standard medical treatment) to be protective from subsequent exacerbations and even death at 2 years. More interestingly, patients who were prescribed an antibiotic for any cause but AECB had a lower risk of acute exacerbation (RR 0.82, CI 99% 0.78–0.87). Another retrospective study from the same group [Roede *et al*. 2009] confirmed the protective role of antibiotic treatment outside AECBs (RR of subsequent AECB 0.56, CI 95% 0.48–0.71). These results were derived from a very large cohort of patients and sound promising. However, these studies are retrospective, and the diagnosis of AECB was presumptive, based on the prescription of oral corticosteroids. Therefore, these observations should be confirmed in large prospective studies and weighted against the drawbacks of antibiotic treatment, particularly the risk of increasing rates of resistance among respiratory pathogens. Taken together, all these recent data suggest a possible role of antibiotic prophylaxis in the management of COPD, particularly in patients with moderate-to-severe disease with frequent exacerbations. However, the evidence is not as robust as it is for the population with cystic fibrosis [Southern *et al*. 2004; Equi *et al*. 2002; Wolter *et al*. 2002], or in patients with bronchiectasis, where a recent Cochrane review observed overall only a small benefit on volume and purulence but no significant effect on the natural history of the disease [Evans *et al*. 2007]. The presence of bronchiectasis was not addressed in the studies on erythromycin and moxifloxacin; as both studies enrolled the more severe COPD patients, it cannot be ruled out that the efficacy of antibiotic therapy may have been due mainly to the subgroup of subjects with unknown bronchiectasis and/or colonized with multiresistant organisms.

Warnings

The interest in antibiotic prophylaxis in COPD refers not only to the data on efficacy, but also to the findings on safety, in terms of side effects and antibiotic resistance. The topic of safety, and particularly the possible risk of increasing bacterial resistance, is crucial. Around 10% of the general population is affected by COPD and the disease is deemed to increase in the next years. This means that, should antibiotic prophylaxis be recommended worldwide, around 30 million American and 50 million European COPD patients would be treated with long-term antibiotics. These huge figures require the special attention of a safety drug profile and the possible adverse effects on the epidemiology of bacterial resistance in the community. In two recent trials on long-term antibiotic treatment in COPD, no significant adverse events were observed in the antibiotic group compared with the placebo group. However, macrolides have significant effects on cardiac conduction [McComb *et al*. 1984] and may be important promoters of antimicrobial resistance [Malhotra-Kumar *et al*. 2007].

In the PULSE study, the data on microbiology showed a transient increase of moxifloxacin MIC. However, quinolones may induce *Clostridium difficile* diarrhoea [Pépin *et al*. 2005], and moxifloxacin may have a negative influence on local antibiotic sensitivities amongst Gram-negative organisms [Ryan *et al*. 2008].

Conclusion

Considering all the new data provided on erythromycin and from the PULSE study on moxifloxacin as a prolonged antibiotic treatment in steady state COPD, we concluded that findings on anti-inflammatory and/or antibacterial effect may have some beneficial effects in reducing acute exacerbations.

However, considering the huge population possibly involved in such prolonged treatments and the risk of adverse events in terms of side effects and/or incidence of resistance, it will be safer to wait for further data before antibiotic prophylaxis can be considered in COPD as an evidence-based recommendation. Nevertheless, the possible benefit in a particular subgroup of patients, such as those who are more functionally compromised, have purulent sputum or suffer from frequent exacerbations is intriguing and requires further evaluation with a focus not only on clinical efficacy but also on safety.

Conflicts of interest statement

The authors declare no conflicts of interest.

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