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Prulifloxacin in the treatment of acute exacerbations of COPD in cigarette smokers

Franco Pasqua, Gianluca Biscione, Girolmina Crigna and Mario Cazzola

***Abstract*:** Smoking is associated with an increased risk of respiratory tract infection in adults likely because components in the smoke might alter properties of the epithelial cell surface. In studies with smokers suffering from acute exacerbations of COPD (AECOPD), the most common bacterial pathogens found were mainly *Haemophilus influenzae*, but also *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*. Therefore, antibiotics should be effective against such possible pathogens. Prulifloxacin has demonstrated *in vitro* activity against all these pathogens. We designed the present study to evaluate the efficacy of prulifloxacin in the treatment of AECOPD in cigarette smokers. We enrolled 61 consecutive smokers hospitalized or out-patients of either sex with symptoms and signs compatible with the usual diagnosis criteria for AECOPD. *Haemophilus influenzae* was the most common bacterial species isolated in the sputum (in 42.6% of the total sample), followed by *S. pneumoniae* (16.5%), *S. aureus* (14.7%), *M. catarrhalis* (11.5%), and others (14.7%). Prulifloxacin 600 mg was given orally once daily for 10 days. Clinical success was observed in 91.8% of patients (67.2% cured and 24.6% improved). Bacteriological eradication rate of *H. influenzae* was 100%. Persistent pathogens were *S. pneumoniae* (2 out of 10), *S. aureus* (1 out of 8), *M. catarrhalis* (1 out of 7), and *P. aeruginosa* (1 out of 3). This study seems to indicate that prulifloxacin is of particular value in the treatment of AECOPD in cigarette smokers.

***Keywords*:** acute exacerbation of COPD, smokers, Haemophilus influenzae, prulifloxacin

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Introduction

The healthy human airway is sterile, with several innate immune mechanisms acting in coordination to maintain this sterility. Smoking appears to disrupt these innate immune mechanisms, and as a consequence, microbial pathogens are able to persist in the lower airway in COPD [Sethi *et al*. 2006]. It has been reported that smoking is a risk factor in patients with chronic obstructive pulmonary disease (COPD) for colonization with *Pseudomonas aeruginosa* [El Ahmer *et al*. 1999], *Haemophilus influenzae* [Miravitlles *et al*. 1999; Zalacain *et al*. 1999], but also *Streptococcus pneumoniae*, *Moraxella catarrhalis* [Zalacain *et al*. 1999] and adenovirus, *Chlamydia pneumoniae*, and *Pneumocystis jiroveci* [Sethi *et al*. 2006]. Although lower airway bacterial colonization has been found both in asymptomatic smokers and in patients with chronic bronchitis, colonization with potential respiratory pathogens is uncommon in patients with chronic bronchitis and recurrent exacerbations without severe airflow obstruction [Qvarfordt *et al*. 2000]. On the contrary, there is evidence that bacterial 'colonization' of the lower airways in stable COPD is not innocuous [Sethi *et al*. 2006]. In fact, bacterial colonization has been associated with greater levels of airway inflammation measured in sputum, increased frequency of exacerbations, and an accelerated decline in lung function [Patel *et al*. 2002; Bresser *et al*. 2000;]. Moreover, lower airway bacterial colonization in the stable state modulates the character and frequency of acute exacerbations of COPD (AECOPD) [Patel *et al*. 2002].

Of the bacterial pathogens that 'colonize' the lower airways in COPD, nontypeable *H. influenzae* is the most frequently isolated [Murphy *et al*. 2004]. It is not a surprise, therefore, that several researchers [Miravitlles *et al*. 1999; Monsó *et al*. 1999;

Cazzola *et al*. 1990] have reported that active smoking is associated independently and very significantly with the isolation of *H. influenzae* in the sputum of exacerbated COPD patients.

Considering that the available data about antibiotic therapy for exacerbations of COPD support a role for their use, probably because bacteria are often responsible for exacerbations [Murphy *et al*. 2000], and given the primary role of *H. influenzae* as a causal pathogen in AECOPD in smokers [Miravitlles *et al*. 1999; Monsó *et al*. 1999; Cazzola *et al*. 1990], it is appropriate to prescribe an empirical antibiotic treatment for these patients choosing an antibiotic that is active against *H. influenzae* and also against other frequent pathogens, such as *S. pneumoniae*, *Staphylococcus aureus*, and *M. catarrhalis* [Wilson, 2005].

Prulifloxacin, the lipophilic prodrug of ulifloxacin, is an oral fluoroquinolone antibacterial agent with a broad-spectrum *in vitro* activity against Gram-negative and -positive bacteria, and a long elimination half-life, which allows the once-daily administration [Cazzola *et al*. 2006]. In addition, it penetrates extensively into lung tissues [Matera, 2006]. Its MIC_{90} against *Haemophilus* spp. is $\leq$0.015 md/dl, which is better than that of levofloxacin 0.03 mg/dl [Matera, 2006].

These features suggest that plurifloxacin should be considered an appropriate antibiotic for the treatment of AECOPD in smokers. In order to confirm this hypothesis, we treated a consecutive group of smokers that came to our observation because of an AECOPD with this fluoroquinolone.

Patients and methods

Sixty-one consecutive eligible adult smokers suffering from COPD, hospitalized or outpatients, of both sexes, with symptoms and signs compatible with the usual diagnosis criteria for acute exacerbation (e.g., increased cough, dyspnoea, increased sputum volume, and increased sputum purulence) and a positive culture of a pre-therapy sputum specimen with a respiratory pathogen, were enrolled in the study. The patients also had to be appropriate candidates for oral therapy. Written informed consent was obtained before patient enrolment.

Patients were excluded if they were pregnant or if they had pneumonia or bronchopneumonia (shown by acute infiltrations on admission chest X-ray), cystic fibrosis, active tuberculosis, lung cancer/metastases; unstable COPD, severe bronchiectasis, severe malabsorption syndrome, neutropenia, AIDS, progressively fatal disease, renal impairment, severe hepatic disease, a lowered seizure threshold, a history of epilepsy or hypersensitivity to fluoroquinolones. Patients were also excluded if they required a systemic antibiotic for another infection or if they had received antibiotic treatment in the 30 days before study entry.

All participants underwent clinical evaluation and bacteriological examination of sputum before therapy and at 3–5 (post therapy) and 10–14 (late post therapy) days after the completion of treatment.

Patients received oral prulifloxacin 600 mg once daily for 10 days and a short course of oral prednisolone 25 mg/die.

Clinical (symptomatic) response was assessed by the investigators as follows: *cure*: an elimination of signs and symptoms and no recurrence at the follow-up visits; *improvement*: a significant, but incomplete, resolution of signs or symptoms; *relapse*: worsening of signs and symptoms following an initial improvement; *failure*: no improvement. Patients were designated as *unappreciable* if they could not be assigned to a category and were disqualified for efficacy analysis.

At post therapy, bacteriological response was based on microbiological culture data as follows: *eradication*: pathogen eliminated; *persistence*: culture positive for original pathogen; *colonization*: culture positive for a new pathogen without the signs of infection; *superinfection*: culture positive for a new pathogen during therapy (required symptomatic response). At late post therapy visit, it was based as follows: *eradication*: pathogen eliminated; *relapse*: recurrence of the same pathogen with or without the development of resistance (required a positive follow-up culture preceded by at least one negative culture); *colonization*: culture positive for a new pathogen without the signs of infection; *eradication with reinfection*: culture positive for a new pathogen after treatment (required symptomatic response of failure or relapse). If no follow-up sputum specimen was produced for culture, the following

definitions were assigned: *presumed microbiological persistence*: no follow-up culture obtained with a symptomatic response of relapse or failure; *presumptive eradication*: implied absence of appropriate material for culture, or culture not clinically indicated (required symptomatic response of cure or improvement); *indeterminate*: could not be evaluated (bacteriological response could not be defined or categorized), or new antibiotic started for a condition other than the study indication before appropriate material for culture was obtained, or no pathogen isolated from the pre-therapy culture.

Patients were examined also for evidence of adverse drug reactions.

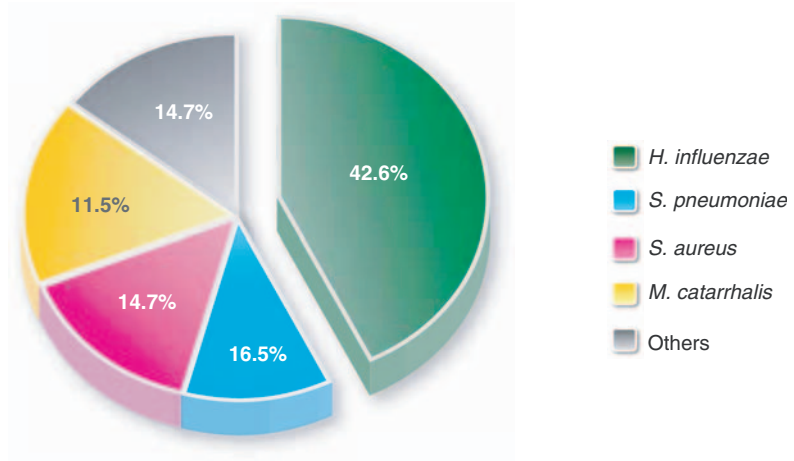


Figure 1. Most common bacterial species isolated in sputum of 61 smokers suffering from AECOPD.

Results

Haemophilus influenzae was the most common bacterial species isolated in the sputum (in 42.6% of the total sample), followed by *S. pneumoniae* (16.5%), *S. aureus* (14.7%), *M. catarrhalis* (11.5%), and others (14.7%) (Figure 1).

Clinical success was observed in 91.8% of patients (67.2% cured and 24.6% improved) (Figure 2).

Bacteriological eradication rate of *H. influenzae* was 100%. Persistent pathogens were *S. pneumoniae* (2 out of 10), *S. aureus* (1 out of 8), *M. catarrhalis* (1 out of 7), and *P. aeruginosa* (1 out of 3) (Figure 3). We did not find any relapse or reinfection when the causal pathogen was effectively or presumptively eradicated.

There were no drug-related side effects.

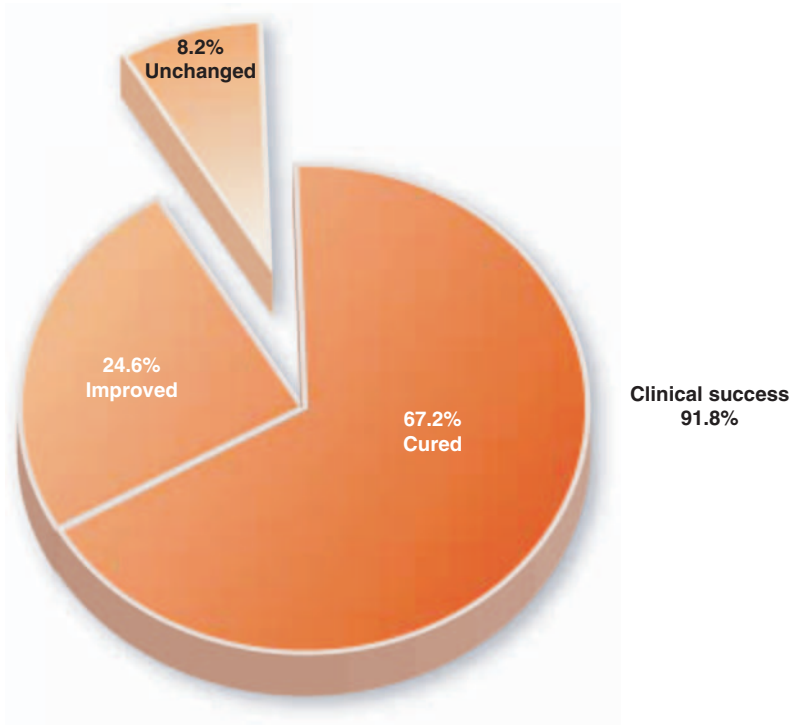


Figure 2. Clinical success rates.

Discussion

Our study confirms that smokers are particularly susceptible to infection by *H. influenzae*. Some findings may explain this result. Roberts and Cole [1979] observed that a regular supplement of nicotine in the bronchial secretions of a heavy smoker may be sufficient to encourage an excessive multiplication of *H. influenzae*. It has also been shown that alveolar lining material from healthy subjects can support the growth of *H. influenzae* without addition of hemin or nicotinamide-adenine dinucleotide, which are essential nutrients for this bacterium [Bell *et al.* 1981]. Moreover, it has been documented that cigarette smoke exposure attenuates alveolar macrophages responses after innate stimulation, including pathways typically associated with bacterial and viral infections [Gaschler *et al.* 2008] and that there is an impaired alveolar macrophage response to *Haemophilus* antigens in COPD [Berenson *et al.* 2006].

Previous studies have highlighted the possibility of dealing with AECOPD in smokers by using those

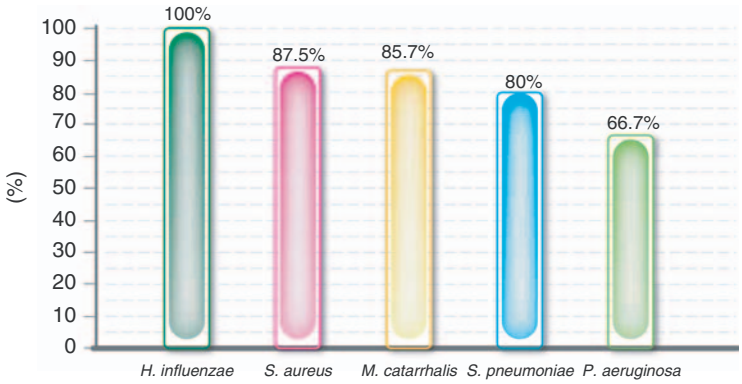


Figure 3. Bacteriological responses by organism.

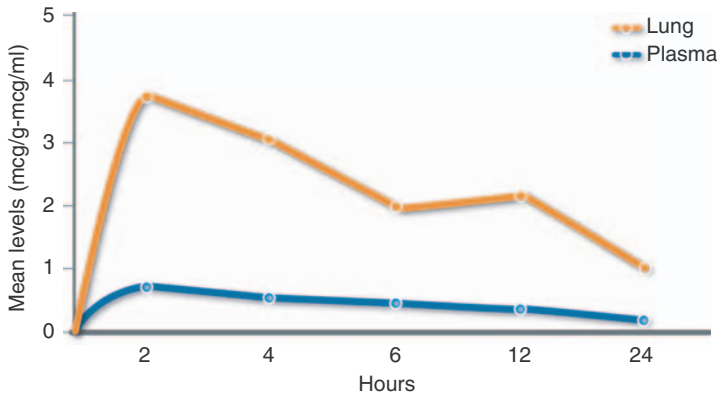
cephalosporins that are particularly active on *H. influenzae* [Cazzola *et al.* 1991; Brown, 1987]. However, emergence of antimicrobial resistance over the past two decades in common community-acquired respiratory tract pathogens [principally penicillin- and/or erythromycin-resistant *S. pneumoniae* (also multidrug-resistant strains) and β-lactamase-producing *H. influenzae* and *M. catarrhalis*] has complicated empiric therapy approaches, requiring reliance on advanced-generation oral agents including macrolides, cephalosporins, β-lactam/β-lactamase inhibitor combinations, and respiratory fluoroquinolones [Anzueto *et al.* 2007; Mandell *et al.* 2003]. In particular, the fluoroquinolone class of antimicrobial agents is being increasingly used empirically as resistance has developed to the more traditional antimicrobial agents [Patel and Wilson, 2006; Blasi *et al.* 2003].

Indeed, due to their potency, their broad spectra of antimicrobial activity, favorable pharmacokinetics, and safety profile, newer fluoroquinolones have been recommended as first-line therapy for patients with AECOPD who are at higher risk of failure with standard therapies [Grossman, 2000; Sethi, 1999]. The excellent distribution of fluoroquinolones in the respiratory tissue may contribute to explain the high-efficacy rates observed in patients with respiratory infections. The emergence of fluoroquinolone resistance among respiratory pathogens has been uncommon, although sporadic examples of resistance developing in patients with COPD or bronchiectasis have been observed [Chen *et al.* 1999].

Prulifloxacin is a new therapeutic prospect in the antimicrobial therapy of AECOPD [Blasi *et al.* 2007; Cazzola and Donner, 2006]. Although a careful evaluation of the activity of prulifloxacin against *S. pneumoniae* needs to be made before it can be considered suitable for the empirical therapy of acute exacerbation of chronic bronchitis [Cazzola and Donner, 2006], the antimicrobial spectrum and the results of clinical trials indicate the possible role of this fluoroquinolone in the treatment of exacerbations of outpatients with moderate to severe COPD, which are generally caused by Gram-negative bacteria (mainly *H. influenzae*), *Enterobacteriaceae*, and *Pseudomonas* spp. [Blasi *et al.* 2007]. Prulifloxacin's pharmacokinetic/pharmacodynamic behavior [Cazzola *et al.* 2006] and the possibility of using this agent on a once-daily basis, favoring patient compliance with therapy – a key factor in the successful treatment of any infection – accounts for considering prulifloxacin an interesting antibacterial option for the treatment of AECOPD in smokers, also considering that smokers tend to be less compliant to medication [McNagny *et al.* 1997; Shea *et al.* 1992].

In this study, prulifloxacin has not only proved to be very effective, as expected, against gram-negative bacteria, especially against *H. influenzae*, but it was also able to successfully control AECOPD caused by *S. pneumoniae* and *S. aureus*. The *in vitro* activity of ulifloxacin against strains of methicillin-susceptible *S. aureus* is fairly good with a reported MIC_{90} value of <0.5 µg/ml [Prats *et al.* 2002; Montanari *et al.* 2001]. On the contrary, the *in vitro* data are not homogeneous in defining the activity of prulifloxacin against *S. pneumoniae* [Prats *et al.* 2002; Montanari *et al.* 2001]. It is likely, however, that the high and long-lasting penetration of prulifloxacin into the pulmonary tissues (Figure 4) determines the relationship between its tissue pharmacokinetics and pharmacodynamics that is quite different from that in blood [Cazzola *et al.* 2006; Matera, 2006]. This essential difference could explain the high rate of *in vivo* efficacy showed by prulifloxacin against the majority of *S. pneumoniae* strains found in the sputum of patients with AECOPD.

In conclusion, the results of our study show that 600 mg prulifloxacin od was effective and well tolerated in the treatment of AECOPD in adult smokers. Prulifloxacin was extremely active against the main pathogen of clinical relevance in smokers, *H. influenzae*, and it was also active against *S. pneumoniae*, *S. aureus*, and *M. catarrhalis*. Thus, prulifloxacin 600 mg od can be



Mod. from E. Concia et al.(2005) Clin. Pharmacokinet;44(12)

Figure 4. Ulifloxacin lung and plasma levels (prulifloxacin 600 mg oral single dose). Lung levels have been corrected for blood contamination. Adapted from Concia *et al.* (2005) *Clin Pharmacokinet*; 44: 1287–1294.

considered a first choice treatment for AECOPD in smokers.

Conflict of interest statement

None declared.

References

Anzueto, A., Bishai, W.R. and Pottumarthy, S. (2007) Role of oral extended-spectrum cephems in the treatment of acute exacerbation of chronic bronchitis. *Diagn Microbiol Infect Dis* 57(Suppl.): 31S–38S.

Bell, D.Y., Haseman, J.A., Spock, A., McLennan, G. and Hook, G.E. (1981) Plasma proteins of the bronchoalveolar surface of the lungs of smokers and nonsmokers. *Am Rev Respir Dis* 124: 72–79.

Berenson, C.S., Wrona, C.T., Grove, L.J., Maloney, J., Garlipp, M.A., Wallace, P.K. *et al.* (2006) Impaired alveolar macrophage response to *Haemophilus* antigens in chronic obstructive lung disease. *Am J Respir Crit Care Med* 174: 31–40.

Blasi, F., Tarsia, P., Cosentini, R., Cazzola, M. and Allegra, L. (2003) Therapeutic potential of the new quinolones in the treatment of lower respiratory tract infections. *Expert Opin Investig Drugs* 12: 1165–1177.

Blasi, F., Aliberti, S., Tarsia, P., Santus, P., Centanni, S. and Allegra, L. (2007) Prulifloxacin: a brief review of its potential in the treatment of acute exacerbation of chronic bronchitis. *Int J Chron Obstruct Pulmon Dis* 2: 27–31.

Bresser, P., Out, T.A., van Alphen, L., Jansen, H.M. and Lutter, R. (2000) Airway inflammation in nonobstructive and obstructive chronic bronchitis with chronic *Haemophilus influenzae* airway infection: comparison with noninfected patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 162: 947–952.

Brown, R.B. (1987) Rauchen und Infektion der tiefen Atemwege. *Infection* 15(Suppl. 3): S123–S128.

Cazzola, M., Ariano, R., Gioia, V., Mancini, V., Rimordi, R., Scala, G. *et al.* (1990) Bacterial isolates and cigarette smoking in patients with chronic bronchitis: results from an Italian multicenter survey. *Clin Ther* 12: 105–117.

Cazzola, M., Franco, C., Gioia, V., Legnani, D., Mancini, V., Polverino, M. *et al.* (1991) Cefaclor in the treatment of infective exacerbations of chronic bronchitis in cigarette smokers. *J Chemother* 3: 245–249.

Cazzola, M. and Donner, C.F. (2006) The need for a new fluoroquinolone. *Pulm Pharmacol Ther* 19(Suppl. 1): 1–3.

Cazzola, M., Salvatori, E., Dionisio, P. and Allegra, L. (2006) Prulifloxacin: a new fluoroquinolone for the treatment of acute exacerbation of chronic bronchitis. *Pulm Pharmacol Ther* 19(Suppl. 1): 30–37.

Chen, D.K., McGeer, A., de Azavedo, J.C. and Low, D.E. (1999) Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *N Engl J Med* 341: 233–239.

El Ahmer, O.R., Essery, S.D., Saadi, A.T., Raza, M.W., Ogilvie, M.M., Weir, D.M. *et al.* (1999) The effect of cigarette smoke on adherence of respiratory pathogens to buccal epithelial cells. *FEMS Immunol Med Microbiol* 23: 27–36.

Gaschler, G.J., Zavitz, C.C., Bauer, C.M., Skrtic, M., Lindahl, M., Robbins, C.S. *et al.* (2008) Cigarette smoke exposure attenuates cytokine production by mouse alveolar macrophages. *Am J Respir Cell Mol Biol* 38: 218–226.

Grossman, R.F. (2000) Cost-effective therapy for acute exacerbation of chronic bronchitis. *Semin Respir Infect* 15: 71–81.

Mandell, L.A., Bartlett, J.G., Dowell, S.F., File Jr, T.M., Musher, D.M. and Whitney, C. (2003)

Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 37: 1405–1433.

Matera, M.G. (2006) Pharmacologic characteristics of prulifloxacin. *Pulm Pharmacol Ther* 19(Suppl. 1): 20–29.

McNagny, S.E., Ahluwalia, J.S., Clark, W.S. and Resnicow, K.A. (1997) Cigarette smoking and severe uncontrolled hypertension in inner-city African Americans. *Am J Med* 103: 121–127.

Miravitlles, M., Espinosa, C., Fernandez-Laso, E., Martos, J.A., Maldonado, J.A. and Gallego, M. (1999) Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 116: 40–46.

Monsó, E., Rosell, A., Bonet, G., Manterola, J., Cardona, P.J., Ruiz, J. *et al.* (1999) Risk factors for lower airway bacterial colonization in chronic bronchitis. *Eur Respir J* 13: 338–342.

Montanari, M.P., Mingoia, M. and Varaldo, P.E. (2001) *In vitro* antibacterial activities of AF 3013, the active metabolite of prulifloxacin, against nosocomial and community Italian isolates. *Antimicrob Agents Chemother* 45: 3616–3622.

Murphy, T.F., Sethi, S. and Niederman, M.S. (2000) The role of bacteria in exacerbations of COPD. A constructive view. *Chest* 118: 204–209.

Murphy, T.F., Brauer, A.L., Schiffmacher, A.T. and Sethi, S. (2004) Persistent colonization by *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 170: 266–272.

Patel, I.S., Seemungal, T.A., Wilks, M., Lloyd-Owen, S.J., Donaldson, G.C. and Wedzicha, J.A. (2002) Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax* 57: 759–764.

Patel, A. and Wilson, R. (2006) Newer fluoroquinolones in the treatment of acute exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis* 1: 243–250.

Prats, G., Roig, C., Miro, E., Navarro, F. and Mirelis, B. (2002) *In vitro* activity of the active metabolite of prulifloxacin (AF 3013) compared with six other fluoroquinolones. *Eur J Clin Microbiol Infect Dis* 21: 328–334.

Qvarfordt, I., Riise, G.C., Andersson, B.A. and Larsson, S. (2000) Lower airway bacterial colonization in asymptomatic smokers and smokers with chronic bronchitis and recurrent exacerbations. *Respir Med* 94: 881–887.

Roberts, D. and Cole, P. (1979) Effect of tobacco and nicotine on growth of Haemophilus influenzae in vitro. *J Clin Pathol* 32: 728–731.

Sethi, S. (1999) Infectious exacerbations of chronic bronchitis: diagnosis and management. *J Antimicrob Chemother* 43(Suppl. A): 97–105.

Sethi, S., Maloney, J., Grove, L., Wrona, C. and Berenson, C.S. (2006) Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 173: 991–998.

Shea, S., Misra, D., Ehrlich, M.H., Field, L. and Francis, C.K. (1992) Correlates of nonadherence to hypertension treatment in an inner-city minority population. *Am J Public Health* 82: 1607–1612.

Wilson, R. (2005) . Treatment of COPD exacerbations: antibiotics. *Eur Respir Rev* 14: 32–38.

Zalacain, R., Sobradillo, V., Amilibia, J., Barrón, J., Achótegui, V., Pijoan, J.I. *et al.* (1999) Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 13: 343–348.