Moxifloxacin in the management of exacerbations of chronic bronchitis and COPD

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Abstract: Bacteria are isolated in more than 50% of exacerbations of chronic bronchitis (CB) and chronic obstructive pulmonary disease (COPD). The most prevalent respiratory pathogens include Gram-positive (*Streptococcus pneumoniae*) and Gram-negative (*Haemophilus influenzae*, *Moraxella catarrhalis*) microorganims. Moxifloxacin is a fourth-generation fluoroquinolone that has been shown to be effective against respiratory pathogens, including atypicals and those resistant to most common antibiotics. The bioavailability and half-life of moxifloxacin provides potent bactericidal effects at a dose of 400 mg once daily. Among the fluoroquinolones, the ratio of the area under the concentration-time curve (AUC) to minimal inhibitory concentration of moxifloxacin is the highest against *S. pneumoniae*. Moxifloxacin has demonstrated better eradication in exacerbations of CB and COPD compared with standard therapy, in particular, with macrolides. Patients treated with moxifloxacin showed a prolonged time to the next exacerbation and observational studies suggest that moxifloxacin induces a faster release of symptoms of exacerbation. Some guidelines recommend the use of moxifloxacin as first-line therapy in bacterial exacerbations in patients with moderate to severe COPD and in patients with mild COPD with risk factors. The current article reviews the use of moxifloxacin in bacterial exacerbations of CB and COPD.

Keywords: moxifloxacin, antibiotics, exacerbations, chronic bronchitis, COPD

Introduction

After cardiovascular disease, respiratory diseases rank second in terms of mortality, incidence, prevalence, and costs. The European prevalence of chronic obstructive pulmonary disease (COPD) ranges from <2% in France and the UK, to 9% in Spain (Sobradillo et al 2000), and >10% in Germany and Italy (Loddenkemper 2003). Moreover, a European-wide increase in the prevalence and mortality of COPD and other smoking-related diseases, particularly in women, is projected for the coming decades (Peto et al 1992). Chronic bronchitis (CB), a component of COPD, usually associated with frequent exacerbations, is even more prevalent; as an example, 4.1% of the French population aged 25+ years develop this disease (Huchon et al 2002). Nonetheless, the prevalence of CB differs between countries. In a recent study of young European adults, the prevalence of CB in subjects aged 20–44 years ranged from 0.7% in the UK to 9.7% in Spain (De Marco et al 2004), with the prevalence being directly associated with smoking prevalence (Cerveri et al 2001).

Due to the high prevalence and chronic course of these conditions, COPD and CB represent a great burden to society. The mean annual direct medical costs of a COPD patient are an estimated €1800, with 42% of the costs being due to hospitalisations, most because of exacerbations (Miravitlles et al 2003a). Each exacerbation treated in the community has a mean cost of €175, but costs are higher for complicated exacerbations requiring hospital admission (Miravitlles et al 2002).

In addition, COPD and CB are debilitating conditions affecting fundamental aspects of everyday life including normal physical exertion, work, and social and family

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activities (Murray and Lopez 1997). Chronic lung disease thus has substantial effects on health-related quality of life (HRQoL), with increasing CB severity and factors such as frequency and nature of exacerbations being associated with increasing symptoms and deteriorating HRQoL (Seemungal et al 1998; Miravitlles et al 2004a). HRQoL has been found to be significantly adversely affected during exacerbations with increased anxiety about breathlessness and the coughing up of phlegm in public (Nicolson and Anderson 2000).

Bacterial are isolated in 50%–75% of exacerbations (Miravitlles 2002a; Papi et al 2006). Because of the difficulties in establishing a bacteriological diagnosis of respiratory tract infections (RTIs) in ambulatory clinical practice, it is common practice to commence antibiotic treatment empirically. In an analysis of initial antibiotic treatment in Europe for all infections, including RTIs, 85% of these therapies were started empirically (Halls 1993). In view of the limits of the spectrum of activity of some antibiotics, as well as the increasing prevalence of bacterial resistance to older generation agents, multiple antibiotics are administered in some cases of RTIs or when resistant or polymicrobial infection is suspected (Smith et al 1999). There is a continued need to find antibiotics that can be used in empiric treatment regimens so that the patient responds rapidly and the risk of development of resistance is limited.

Moxifloxacin hydrochloride (Avelox®, Bayer AG) is a fluoroquinolone that has been shown to be effective against *Moraxella catarrhalis*, *Haemophilus influenza*, and multi-drug resistant pneumococcal strains (Blondeau 1999; Saravolatz et al 2001; Miravitlles 2005). Moxifloxacin is strongly targeted to alveolar tissue (Soman 1999 et al; Miravitlles 2000), and has shown rapid initial killing and eradication rates for pneumococcal bacteria (Lister and Sanders 2001).

This paper will focus on recent advances in the study of antimicrobial treatment of exacerbations of CB and COPD with moxifloxacin. In this respect, new trials have documented improved outcomes related to time to resolution of symptoms and extended time to the next exacerbation. These new outcomes derive from the better understanding of the natural history of CB and COPD and their exacerbations.

Pharmacology
Mechanism of action

Moxifloxacin is a forth generation fluoroquinolone with bactericidal activity as a result of its interference with topoisomerase II (DNA gyrase) and IV (Scheld 2003).

Topoisomerases are essential enzymes which play a crucial part in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is also known to influence bacterial chromosome division. Kinetic investigations have demonstrated that moxifloxacin exhibits a concentration-dependent killing rate; minimum bactericidal concentrations (MBC) were found to be within the range of the minimum inhibitory concentrations (MIC) (Stass 1999; Krasemann et al 2001).

Antimicrobial activity

Moxifloxacin demonstrates excellent in vitro activity (as assessed by MIC_{90} concentrations of 0.06 to 0.25 mg/L) against all the predominant respiratory pathogens including Gram-positive (*Streptococcus pneumoniae*), Gram-negative (*H. influenzae*, *M. catarrhalis*), anaerobic (peptostreptococci or *Prevotella* spp.), and atypical strains (*C. pneumoniae*, *M. pneumoniae*). Against both beta-lactamase positive and negative *M. catarrhalis* and *H. influenzae*, MIC_{90} values to moxifloxacin were ≤ 0.06 μg/mL. Similarly, moxifloxacin MIC_{90} values ranged from 0.06 to 0.25 μg/mL against clinical isolates of *S. pneumoniae* regardless of penicillin susceptibility (Woodcock 1997; Blondeau 1999) (Table 1).

Pharmacokinetics

Following oral administration moxifloxacin is rapidly and almost completely absorbed, with an absolute bioavailability of approximately 91% (Stass et al 2001). Its penetration into pulmonary tissues is excellent and concentrates in alveolar macrophages (Table 2). Following a 400 mg oral dose, peak concentrations of 3.1 mg/L are reached within 0.5–4 hours post administration. Peak and trough plasma concentrations at steady-state (400 mg once daily) are 3.2 and 0.6 mg/L, respectively. Moxifloxacin is rapidly distributed to extravascular spaces; and an area under the concentration-time curve (AUC) of 35 mg·h L^{-1} is observed after a dose of 400 mg. Moxifloxacin is mainly bound to serum albumin. In vitro and ex vivo experiments have shown a protein binding of approximately 40%–42%, independently of the concentration of the drug (Soman et al 1999; Sullivan et al 1999).

Moxifloxacin is eliminated from plasma with a mean terminal half-life of approximately 12 hours (Stass 1999). After a 400 mg dose, recovery of parent compound and metabolites of moxifloxacin from urine and feces totals approximately 96% (Table 3).

Table I Minimum inhibitory concentrations (MIC) of moxifloxacin and other quinolones against common respiratory pathogens

Bacterium	MIC_{90} (mg/L)			
	Moxifloxacin	Ciprofloxacin	Levofloxacin	Trovafloxacin
S. pneumoniae				
penicillin-sensitive[a]	0.06–0.25	1–2	1–2	0.12–0.25
penicillin-resistant[b]	0.12–0.25	1–2	1–2	0.12–0.25
S. aureus				
methicillin-sensitive	0.12	0.5–1	0.25	0.06
methicillin-resistant	2	32–128	16	2
M. catarrhalis				
beta-lactamase positive	0.012–0.06	0.015–0.06	0.06–0.094	0.03
beta lactamase negative	0.012–0.06	0.015–0.06	0.06	0.03
H. influenzae				
beta-lactamase positive	0.03–0.06	0.015–0.03	0.03–0.47	0.015
beta lactamase negative	0.03–0.06	0.015–0.03	0.03–0.32	0.015

Adapted from Blondeau (1999).
[a]penicillin sensitive indicates a penicillin MIC of $\leq$0.06 µg/mL.
[b]penicillin resistant or non-susceptible indicates an MIC $\geq$0.1 µg/mL.

The pharmacokinetic and pharmacodynamic parameters for antibacterial agents can be integrated into the ratio of the AUC to MIC_{90}, or area under the inhibition curve (AUIC), ie, the AUC/MIC normalized for 24 hours (Schentag et al 1996).

Agents with a low C_{max}, short $t_{1/2}$ and low in vitro activity against a specific pathogen (viz: higher MIC_{90} values) have a lower AUIC than those with high C_{max}, prolonged $t_{1/2}$ and high in vitro activity. Quinolones with AUIC values above 85–125 and C_{max} to MIC ratios of 8–10 have been associated with better clinical and bacteriological cure rates compared with agents with lower AUIC values (Forrest et al 1993). High AUIC values indicate rapid eradication of pathogens and a reduced likelihood of resistance development, as pathogens are killed before they have time to mutate (Schentag et al 1996).

Compared with other fluoroquinolones, moxifloxacin has the highest AUIC ratio against *S. pneumoniae*

Table 2 Tissue concentrations by site 10 hours after oral administration of 400 mg of moxifloxacin

Site	Tissue concentration	Plasma ratio
Plasma	3.1 mg/L	n/a
Saliva	3.6 mg/L	0.75–1.3
Blister fluid	1.61 mg/L	1.71
Bronchial mucosa	5.4 mg/kg	1.7–2.1
Alveolar Macrophages	56.7 mg/kg	18.6–70.0
Epithelial lining fluid	20.7 mg/L	5–7
Interstitial fluid	1.0[a] mg/L	0.8–1.4[a,b]

Data from Stass (1999); Stass et al (2001); Sullivan et al (1999).
[a]unbound concentration.
[b]from 3 hours up to 36 hours post dose.
n/a, not applicable.

(192–400 35 mg·h L^{-1}) (Wise 1999) (Table 3). Despite achieving good tissue penetration, levofloxacin is only moderately active against *S. pneumoniae*, whereas gatifloxacin is more bactericidal but only achieves modest tissue levels. Levofloxacin does not have the chemical structure of moxifloxacin to fight resistance, eg, a methoxy moiety at position C-8 – a substitution that has been shown to select for mutants much less frequently than a hydrogen moiety (Wise 1999). In addition, moxifloxacin has a 7-azabicyclo side chain that makes it more difficult to efflux the antibiotic out of the bacterial cell (Wise 1999).

The approved dose and regimen of oral moxifloxacin for the indication of exacerbations of CB is: 400 mg orally once daily for 5–7 days.

Efficacy of moxifloxacin in exacerbations of chronic bronchitis and COPD
Registration clinical trials

The clinical program for moxifloxacin included four studies comparing the efficacy and safety of moxifloxacin (400 mg once daily, 5 days) with either clarithromycin (500 mg twice daily, 7–10 days) or cefuroxime-axetil (500 mg twice daily, 10 days) in 2381 patients with exacerbations of CB (Miravitlles 2005).

The clinical and bacteriological success rates 7–14 days post-treatment were comparable between the three treatment groups. However, there was a trend towards improved bacteriological success after 5 days of moxifloxacin therapy

Table 3 Main pharmacokinetic/pharmacodynamic parameters of moxifloxacin after an oral dose of 400 mg

Bioavailability	90%
C_{max}	3–4 mg/L
T_{max}	1–2 h
Mean half-life	13 h
Binding to plasma proteins	<40%
Steady state volume of distribution	2–3 L/kg
Renal clearance	24–53 mL/min
Total body clearance	179–246 mL/min
AUC	35–45 mg.h L^{-1}
C_{max}/MIC_{90} (pneumococcus)	25–35
AUC_{24h}/MIC_{90} or AUIC (pneumococcus)	192–400 mg.h L^{-1}

Data from Stass (1999); Stass et al (2001).
Abbreviations: C_{max}, maximal or peak plasma concentration; T_{max}, time to C_{max}; AUC, area under the curve; AUIC, area under the inhibition curve; MIC, minimum inhibitory concentration.

compared with 7–10 days of clarithromycin treatment. The three treatment regimens were also similar with respect to eradication of *S. pneumoniae* and *M. catarrhalis*. In contrast, moxifloxacin showed improved eradication rates against *H. influenzae* (129/132, 97%) as compared with clarithromycin (62/86, 72%) (Niederman et al 2006). Taken together, the studies of the clinical program demonstrated that treatment with moxifloxacin 400 mg once daily for 5 days achieves a clinical response rate of 89% and a bacteriological response rate of 87% (Miravitlles 2005).

Clinical studies of antimicrobials in exacerbations of CB such as those performed in the original clinical program have been limited by factors such as inadequate information on patient condition prior to the exacerbation and lack of long-term follow-up, as well as a lack of prospective control for steroid use, which can positively affect the outcome of the episode (Miravitlles and Torres 2004a), and for prognostic factors that can have a negative impact (Dewan et al 2000; Miravitlles 2001a) (Table 4). After the registration trials, new studies have been designed to evaluate the clinical efficacy of moxifloxacin in different patient populations with exacerbations of chronic bronchial disease. In parallel, new outcomes have been analyzed in this new generation of clinical trials.

Clinical efficacy of moxifloxacin: short-term outcomes

The MOSAIC study (Wilson et al 2004, 2006) was a multicenter, multinational, randomized study of two parallel treatment arms including outpatients aged >45 years with stable CB, history of smoking of ≥20 packs/year, ≥2 documented exacerbations in the previous year,

and FEV_1<85% of predicted value. Patients with a severe exacerbation of CB within 12 months of enrolment were randomized to receive either oral moxifloxacin 400 mg once daily for 5 days or one of the comparators: amoxicillin 500 mg tid for 7 days, clarithromycin 500 mg bid for 7 days or cefuroxime-axetil 250 mg bid for 7 days. Patients were assessed at screening, end of treatment and 7–10 days after treatment, and were contacted by phone monthly until a new exacerbation occurred or up to a maximum of 9 months. Clinical cure was defined as a return to pre-exacerbation status, and clinical success as cure and improvement combined, overall and by strata of steroid use and prognostic factors. Other efficacy measures were needed for further antimicrobials, time to next exacerbation, and bacteriological treatment success. Of 1935 enrolled patients, 733 (37.9%) had severe (Anthonisen type I) exacerbation within 12 months of screening and were randomized; 730 receiving either moxifloxacin (n = 354) or comparator (n = 376). Clinical success was seen in 83.0%–87.6% of patients across treatment arms and populations, with statistical equivalence in all populations except a significant difference in favor of moxifloxacin patients not receiving steroids. However,

Table 4 Risk factors for relapse after ambulatory treatment of exacerbations of chronic bronchitis and COPD

1. Risk factors for frequent exacerbations (more than two per year)

    Increasing age
    Severity of FEV_1 impairment
    Chronic bronchial mucus hypersecretion
    Frequent past exacerbations
    Daily cough and wheeze
    Bronchitic symptoms

2. Risk factors for relapse

    Coexisting cardiopulmonary disease
    Increasing number of previous visits to the GP for respiratory problems
    Increasing number of previous exacerbations
    Increasing baseline dyspnoea
    Severity of FEV_1 impairment
    Use of home oxygen

3. Risk factors for hospital admission

    Significant comorbidities
    Severity of FEV_1 impairment
    High admission rates for previous exacerbations
    Three or more admissions previous year
    Underprescription of LTOT
    Lack or reduction in physical activity

From Adams et al (2000); Dewan et al (2000); Miravitlles (2000b); Miravitlles et al (2001a, b); Prescott et al (1995); Seemungal et al (1998).
Abbreviations: LTOT, long-term oxygen therapy.

clinical cure rates were significantly higher with moxifloxacin (70.9%) compared with the comparators (62.8%) (95% confidence interval (CI) of the difference = 0.3%–15.6%); the clinical cure rate was also significantly greater in the moxifloxacin arm when analyzed by prognostic factors of age, airway obstruction, number of exacerbations of CB in the previous year, duration of CB and cardiopulmonary comorbidity (Wilson et al 2004).

Bacterial eradication with moxifloxacin in bacteriologically evaluable patients was significantly higher with moxifloxacin compared with the control antibiotics (91.5% vs 81%; 95% CI = 0.4%–22%) (Wilson et al 2004). Bacterial eradication with moxifloxacin has been demonstrated to be superior compared with macrolides. In a pooled analysis of moxifloxacin phase III trials compared with macrolide agents in eradication of *H. influenzae*, the results showed superiority of moxifloxacin against both azithromycin and clarithromycin. Eradication of *H. influenzae* with moxifloxacin was 93% (133/143) compared with 73.2% (109/149) with macrolides, p = 0.001. Considering both macrolides separately, eradication rates were 96.8% with moxifloxacin vs 84.6%

with azithromycin (p = 0.019) and 90.1% with moxifloxacin vs 64.3% with clarithromycin (p = 0.001) (Niederman et al 2006) (Figure 1).

The results of the MOSAIC trial also showed that up to 14.8% of patients treated with a comparator antibiotic required a second prescription of antibiotics to control symptoms of exacerbation, compared with only 8.8% of patients randomized to receive moxifloxacin (p = 0.03) (Wilson et al 2004).

Although initially designed to demonstrate non-inferiority of moxifloxacin over standard therapy, the MOSAIC study was the first clinical trial to demonstrate the superiority of an antibitic, moxifloxacin, over the comparators in clinical cure and bacteriological eradication rates.

A recent publication has provided a systematic analysis and meta-analysis of published clinical trials with moxifloxacin in the treatment of exacerbations of CB up to June 2005 (Miravitlles et al 2007a) with the objective to determine the superiority of moxifloxacin over standard therapy in this indication. A total of 45 studies were identified, but only 9 fulfilled the inclusion criteria in the meta-analysis. Of them, 5 were randomized and double-blind and 4 were randomized and open labeled.
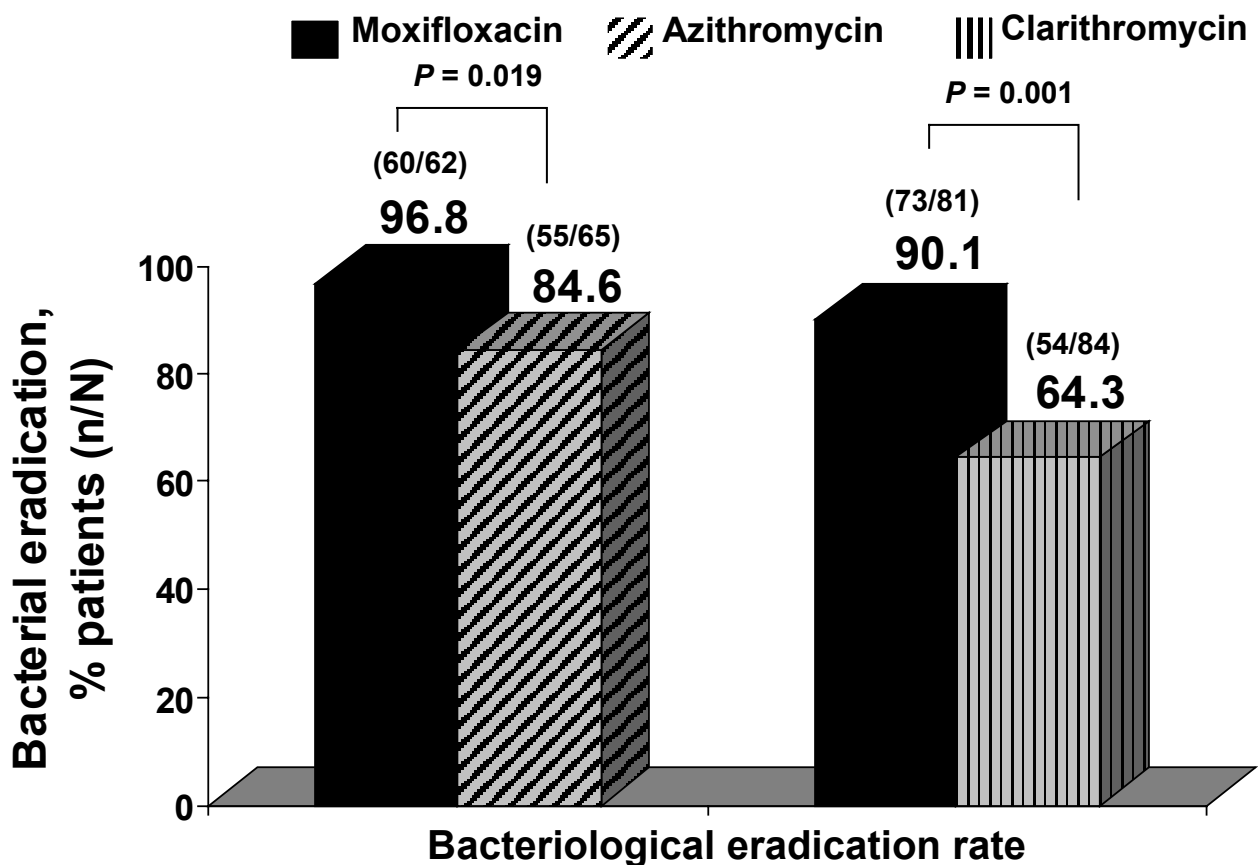

Figure 1 Eradication rates for *H. influenzae* in exacerbations of CB treated with moxifloxacin or macrolides. Derived from Niederman et al (2006).

All studies concluded that the efficacy of treatment with moxifloxacin was at least as good as treatment with the comparator. One of the studies concluded that eradication and cure rates were superior with moxifloxacin versus comparators, as highlighted above (Wilson et al 2004).

The global analysis included 3905 randomized patients and showed an aggregated superior clinical success rate of moxifloxacin of 1.5% (95% CI = –0.4%–3.4%) which did not reach statistical significance, but showed a trend towards a better clinical outcome with moxifloxacin (Figure 2). It is of note that these results were obtained from a combined analysis of studies individually designed to show equivalence between both treatment arms and without enough statistical power to demonstrate superiority.

Long-term outcomes: prevention of exacerbations with moxifloxacin

The most important unmet need in the treatment of exacerbations of COPD is the prevention of recurrence (Miravitlles et al 2007b). One of the characteristics of the MOSAIC trial was the follow-up period of up to 9 months after recovery from the exacerbation. The hypothesis was that a better eradication rate with moxifloxacin would translate into a prolonged time to the next exacerbation. In 405 patients with new exacerbations during the follow-up period, the mean time to event was 10 days longer with moxifloxacin treatment (127.6 ± 68.1 days) than comparators (116.7 ± 68.8), with more patients receiving the comparator having new exacerbations within 60 days of treatment (51/208, 24.5%) than moxifloxacin (31/197, 15.7%). The log rank test showed a significant difference in favor of moxifloxacin for up to 5 months of follow-up (p = 0.03) (Wilson et al 2004).

In a secondary analysis, the authors attempted to identify the variables independently and significantly associated with a prolonged time to the next exacerbation. Treatment with moxifloxacin was associated with a prolonged time to recurrence (hazard ratio for recurrence with moxifloxacin versus comparators 0.82; 95% CI = 0.68–0.98) (Wilson et al 2006).

This effect of moxifloxacin on time to relapse has not been observed with other fluoroquinolones. In a recent study, levofloxacin was compared with clarithromycin in a group of 434 patients with exacerbations of CB. After a 1-year follow-up, no differences in time free from exacerbation were observed between patients treated with levofloxacin (mean of 100.5 days) or clarithromycin (95 days), p = 0.32 (Lode et al 2004). These results may be the consequence of a lower antibacterial activity of levofloxacin compared to moxifloxacin or more likely to the inclusion of a milder patient population in the latter study, making clinical differences against macrolides less likely (Miravitlles and Torres 2004b).

The rationale for the prevention of exacerbations with moxifloxacin derives from a combination of at least three different factors: a) an immunomodulatory effect of the drug (Dalhoff and Shalit 2003); b) the rapid and more complete eradication prevents epithelial damage and restores the local defence mechanisms of the bronchial mucosa (De Benedetto and Sevieri 2006); c) as a consequence of the better eradication, fewer viable pathogens remain in the bronchial tissue after antimicrobial treatment, requiring longer for the bacterial population to increase sufficiently to induce a new exacerbation (Chodosh 2005). This last hypothesis is also known as the "fall and rise" hypothesis of bacterial exacerbation of CB (Miravitlles 2002b). In clinical trials with

Author	Effect	Min	Max.	Cases	p
Chodosh 2000	-0,016	-0,070	0,037	272	0,553
Hautamaki 2001	-0,011	-0,056	0,034	461	0,643
Starakis 2004	-0,006	-0,105	0,094	153	0,909
De Abate 2000	-0,003	-0,062	0,057	464	0,926
Wilson 1999	0,008	-0,041	0,056	649	0,762
Grassi 2002	0,016	-0,042	0,073	423	0,595
Kreis 2000	0,043	-0,031	0,116	399	0,257
Schaberg 2001	0,045	0,004	0,087	512	0,031
Wilson 2004	0,076	-0,001	0,154	572	0,055
Combined (Fixed effects)	0,015	-0,004	0,033	3905	0,120
Combined (random effects)	0,015	-0,004	0,034	3905	0,125

Heterogeneity: X2= 8.65 GL=8 p=0.37
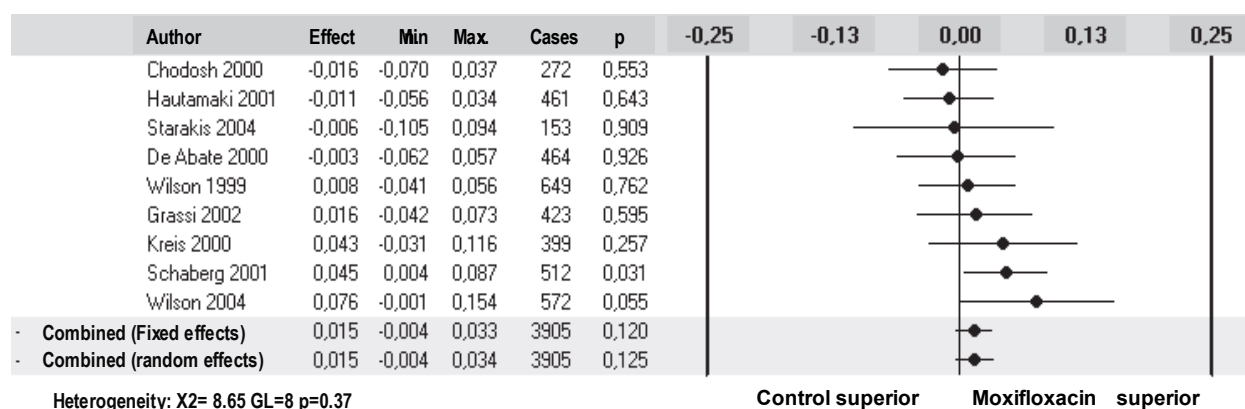
Control superior   Moxifloxacin superior

Figure 2 Results of the meta-analysis of clinical trials with moxifloxacin in exacerbations of CB and COPD. Data obtained from 9 studies including 3,905 patients. Reproduced with permission from Miravitlles M, Molina J, Brosa M. 2007a. Clinical efficacy of moxifloxacin in the treatment of exacerbations of chronic bronchitis: a systematic review and meta-analysis. *Arch Bronconeumol*, 43:22–28. Copyright © 2007 Elsevier.

antibiotics, a prolonged time to the next exacerbation has been observed in patients who eradicate the bronchial pathogen after an exacerbation compared with those who cured the exacerbation but without effective eradication (Chodosh et al 1998). According to the "fall and rise" hypothesis, patients who effectively eradicate bacteria would need a longer time to achieve the threshold of bacterial counts compared with patients who cured the exacerbation but in whom bacteria still persisted after antibiotic treatment (Miravitlles 2002b). This hypothesis would also explain why patients with acute exacerbations may be clinically cured even without eradication of the bacterial pathogen (Wilson et al 1999). This is not proof that this particular bacterium is not the cause of the exacerbation, but does demonstrate that the antibiotic only needs to reduce bacterial counts to below the threshold to eliminate symptoms. Nevertheless, if eradication also occurs, the time for a number of bacteria above the threshold to be reached will be longer (Figure 3).

The quantitative or "fall and rise" hypothesis may explain the basic mechanism of bacterial exacerbations in patients with chronic bronchial colonisation and frequent exacerbations. In this group of patients, the change in the serotype of the colonising bacteria may act as a trigger that initiates profiliation of microorganisms in some cases. The "fall and rise" can also explain relapses when bacteria have not been eradicated after antibiotic treatment of the exacerbation. In contrast, the change of serotype of infective bacteria may be crucial in patients who do not suffer frequent exacerbations, ie, less than two in a year. It is difficult to explain the appearance of an exacerbation more than four months after a preceding episode based only on bacterial growth in the airways without any precipitating factor, such as change in serotype (Sethi et al 2002). New evidence is required on the complex relationship between microorganisms and the host, particularly considering that important therapeutic implications may be derived from these findings. In fact, if the new exacerbation is caused by the regrowth of the same bacteria that remained unkilled, the logical approach to treatment would be to use a different antibiotic and rotation of antibiotics should be recommended
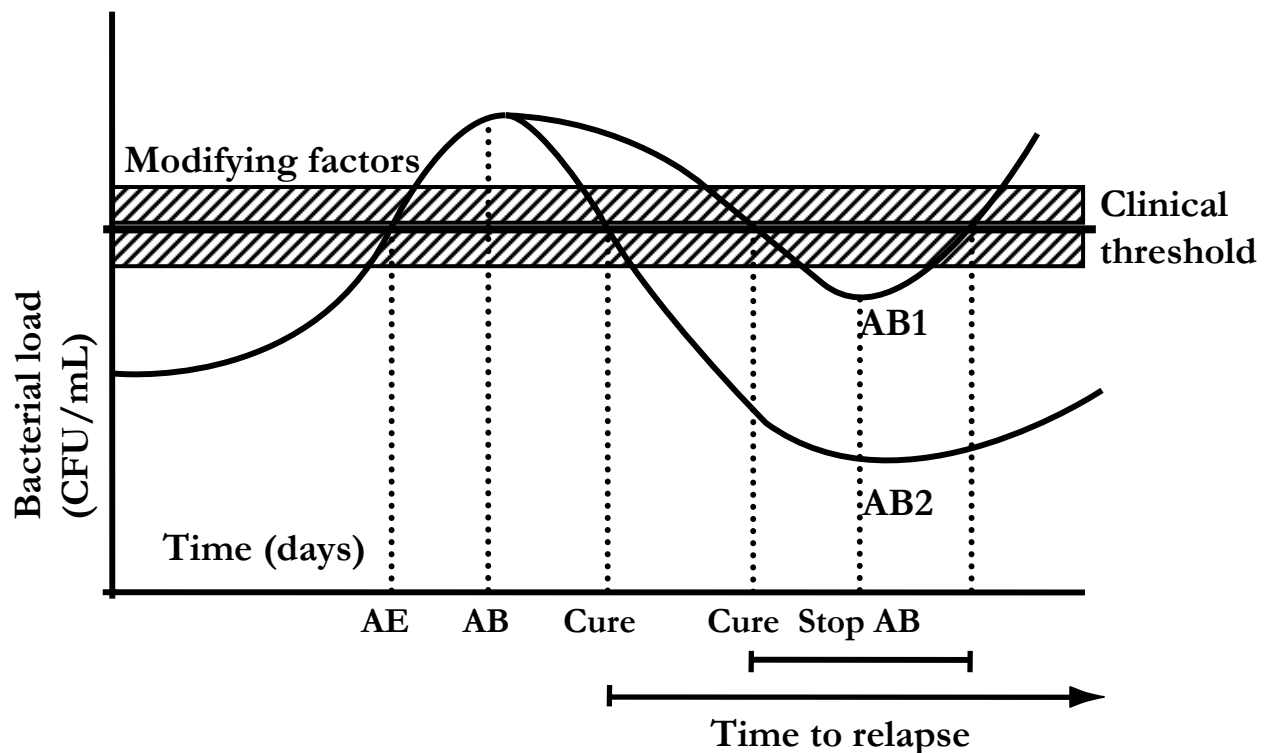

Figure 3 The "fall and rise" hypothesis of bacterial exacerbations of COPD.
Note: Some patients with COPD have bacterial colonization of the lower airways. This colonisation is usually due to potentially pathogenic microorganisms (PPMs) in low concentrations (low colony forming units [CFU]/mL). Under special circumstances, these PPMs may proliferate and produce increasing inflammatory reaction in the host. When this proliferation exceeds a threshold, symptoms of acute exacerbation may appear. Under antimicrobial therapy, CFU/mL decrease, and when the threshold is crossed, clinical symptoms will disappear. When the intensity and speed of bactericidal activity of the antimicrobial increases (AB2), recovery will be more rapid and time to the next exacerbation will be prolonged. Antimicrobial activity will produce a "fall" in bacterial concentrations, which if not completely eradicated after the pressure of antimicrobial disappears, will "rise" again. Some modifying factors (risk factors, see Table 4) may change the threshold of clinical symptoms.
Modified from Miravitlles (2002b).

to prevent bacteriological failure and the development of resistance. In contrast, if new exacerbations are caused by the acquisition of new strains, the same antibiotic can be used in repeated exacerbations without concern about increased exposure to the same antibiotic.

Speed of recovery after antibiotic treatment of an exacerbation

Fast recovery of the symptoms of an exacerbation is highly demanded by patients (Miravitlles et al 2007b). Antibiotics that exhibit faster bacterial killing in vitro should provide faster relief of symptoms in patients with exacerbations of CB and COPD.

Observational studies and cross-sectional analyses in patients with CB and COPD have suggested that patients recover from symptoms of exacerbations more rapidly with moxifloxacin than with other commonly used treatments (Kreis et al 2000; Miravitlles et al 2003b, 2004b).

One large, multicenter comparative study using a 2-year protocol (IMPAC study) showed a significant reduction in the time to recovery from exacerbations of moderate to severe COPD (Miravitlles et al 2003b). In 441 patients with COPD, all with a FEV_1 <50% predicted (mean FEV_1 = 36% predicted), the investigators treated 614 exacerbations with moxifloxacin (exacerbations = 111) and 503 with either amoxicillin/clavulanate, cefuroxime, or clarithromycin. Moxifloxacin was available in the second study year only. In year 2, exacerbations treated with moxifloxacin resulted in complete recovery from symptoms in a mean of 4.6 days, compared with 5.8 days for the other treatments administered (p = 0.02). In the longitudinal analysis of 27 patients treated with moxifloxacin who had received other treatments in year 1, the mean time to recovery from exacerbations was significantly reduced from a mean of 6.8–3.7 days (p = 0.02). These results were confirmed in another study, the EFEMAP study (Estudio FarmacoEconómico de Moxifloxacino en las Agudizaciones de la EPOC), with mild to moderate COPD patients in primary care centers (Miravitlles et al 2004b). A total of 1456 patients with COPD (mean FEV_1 = 52% predicted) received either moxifloxacin (n = 575), amoxicillin/ clavulate (n = 460), or clarithromycin (n = 421). Clinical success was observed in 97.2%, 93.1%, and 94.4% of the cases, respectively, without significant differences among the groups. However, symptoms of purulence and the volume of expectoration resolved a mean of one day earlier with moxifloxacin compared with the other groups (Miravitlles et al 2004b). In a secondary analysis of the EFEMAP study, the factors associated significantly and independently with a slow recovery (more than 5 days) were the use of long-term oxygen therapy (odds ratio (OR) = 1.97; 95% CI = 1.35–2.85); the increased use of rescue medication with short-acting beta-2 agonists (OR = 1.51; 95% CI = 1.17–1.92); and the use of amoxicillin/clavulanate or clarithromycin compared with moxifloxacin (OR = 2.94; 95% CI = 2.22–3.84 and OR = 2.43; 95% CI = 1.17–3.22, respectively) (Miravitlles et al 2005). Although all studies consistently indicate a faster resolution of symptoms of exacerbations with moxifloxacin compared to other frequently used antibiotics, these results must be interpreted with caution because they derive from observational studies and, as such, are subjected to possible sources of biases.

A economic analysis derived from the results of the EFEMAP study has shown that exacerbations treated with moxifloxacin generated a direct medical cost similar to those treated with amoxicillin/clavulanate (€111.46; 95% CI = €73.4–149.5 compared with €109.45; 95% CI = €68.2–150.7, respectively); and lower, although not significantly, than those treated with clarithromycin (€138.95; 95% CI = €89.4–188.5). These differences were mainly due to the higher costs associated with relapse in the group treated with clarithromycin (Llor et al 2004) (Figure 4).

Clinical efficacy of moxifloxacin in patients belonging to risk groups

Failure rates after ambulatory treatment derive from clinical trials on antibiotics in CB and range from 7% to 12%. Nevertheless, these results cannot be extrapolated to everyday practice, since patients included in clinical trials consist of CB patients and include subjects with ages ranging from 18 to 90 years, a significant proportion of never smokers, and individuals without ventilatory impairment (not COPD) (Miravitlles and Torres 2004b). However, more recently, some studies have addressed treatment failure in observational "real-life" studies and showed a failure rate ranging from 12% to 26% (Dewan et al 2000; Adams et al 2000; Miravitlles 2000b; Miravitlles et al 2001a; Macfarlane et al 2001). Identification of risk factors for failure may permit the implementation of more aggressive broad spectrum treatment and closer follow-up. In a further step, risk factors associated with relapse should be incorporated into management guidelines to aid in identifying at-risk patients. Among the risk factors, severity of the underlying pulmonary disease is probably the most important. A summary of the main risk factors for relapse is presented in Table 4.
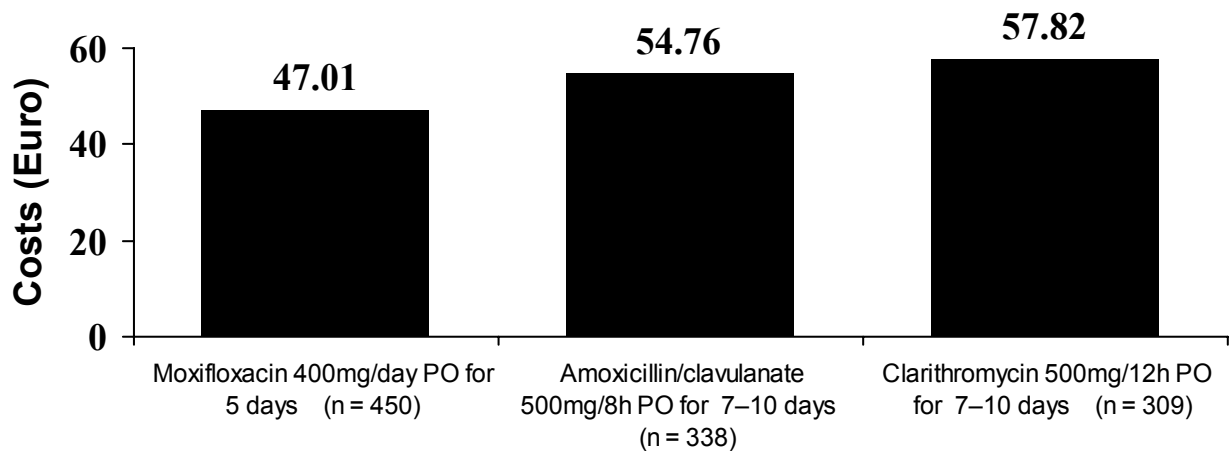
Figure 4 Mean cost per patient incurred by treatment failures of exacerbations of CB and COPD in each group. Derived from Llor et al (2004).

Some of the studies included in the meta-analysis of clinical trials evaluated the efficacy of moxifloxacin in patients belonging to different risk groups. In a study comparing moxifloxacin and amoxicillin-clavulanate (Schaberg et al 2001), individuals older than 60 years showed a significantly better success rate with moxifloxacin ($p = 0.048$) and a tendency towards a better outcome with moxifloxacin in patients with cardiopulmonary comorbidity ($p = 0.054$). The MOSAIC study has also demonstrated the superiority of moxifloxacin over the comparators in elderly patients and those with a higher number of previous exacerbations (Wilson 2006). Table 5 presents the results of moxifloxacin and comparators in patients belonging to different risk groups.

The main studies of moxifloxacin for the treatment of exacerbations of CB and COPD are summarized in Table 6.

Safety
Adverse events
Moxifloxacin has shown a highly favorable safety and tolerability profile in clinical trials as well as in the clinical setting. In a meta-analysis of data from clinical trials and post-marketing surveillance comprising over 25 million patient treatments, the most frequent adverse events reported in clinical trials were nausea (7.1%), diarrhea (5.2%), and dizziness (2.6%) following the administration of a dosage of 400 mg, once daily (Ball et al 2004). In all cases the frequency of side-effects was not statistically different to that of the comparators. There was no evidence that moxifloxacin caused disturbances in glucose metabolism in patients with or without diabetes

mellitus, and there was no evidence of an increased risk of adverse cardiovascular events (Ball 2004).

Conclusions
The prevalence of chronic bronchial diseases caused by tobacco smoking, namely CB and COPD is great in developed and developing countries. Exacerbations constitute the mean cause for medical consultation of patients with these diseases and bacterial infection is involved in more than half of the cases. Most of the microorganisms involved in pathogenesis of exacerbations of CB and COPD have developed diverse degrees of resistance to the traditional antibiotics used as first-line treatment. Development of resistance is caused by the increased volume of prescription, the inadequate indication of the antibiotic and/or inadequate administration or treatment compliance by the patient. Patients with acute (viral) bronchitis and those with exacerbations without changes in the volume or characteristics of sputum should not be treated with antibiotics. When bacterial infection is suspected, there is a growing tendency to treat exacerbations more aggressively with shorter courses of antimicrobials to help reduce antibiotic resistance (Perez-Gorricho and Ripoll 2003). This is possible with the new generation fluoroquinolones such as moxifloxacin. Moxifloxacin is a fourth generation fluoroquinolone that has an excellent in vitro activity against the most common respiratory pathogens and its rapid bactericidal action allows short-course 5-day therapy for exacerbations of CB and COPD. In addition, its long half-life allows administration in single daily doses. The once-daily, short-course administration guarantees better patient compliance and makes the development of resistance less likely.

Moxifloxacin is 4- to 10-fold more active than levofloxacin against *S. pneumoniae*. A greater intrinsic activity is linked

Table 5 Clinical success rates with moxifloxacin and comparators in patients belonging to risk groups in clinical trials of exacerbations of chronic bronchitis and COPD

Risk factor	Moxifloxacin	Comparator/s	p value
Age >60 years	46/51 (90.1%)	47/52 (90.4%)	1.00[a]
	167/184 (90.8%)	161/181 (89.0%)	0.081[b]
	145/152 (95.4%)	122/137 (89.1%)	0.048[c]
More than 3 exacerbations previous year	36/42 (85.7%)	30/35 (85.7%)	1.00[a]
	138/160 (86.3%)	136/160 (85.0%)	0.043[b]
	111/118 (84.1%)	103/110 (83.6%)	NS[c]
Cardiopulmonary comorbidity	22/26 (84.6%)	15/19 (78.9%)	0.74[a]
	21/25 (84.0%)	19/28 (67.9%)	0.010[b]
	192/202 (95.0%)	166/185 (89.7%)	0.054[c]
Concomitant use of oral corticosteroids	33/38 (86.8%)	28/32 (87.5%)	1.00[a]
	140/160 (87.5%)	105/128 (82%)	0.027[b]
	48/50 (96%)	37/44 (84.1%)	NS[c]
FEV_1 (%) < 50%	70/119 (58.0%)	69/130 (53.1%)	0.36[d]
	66/69 (95.6%)	67/69 (97.1%)	NS[c]

Adapted from Miravitlles et al 2007a.
[a]Starakis et al (2004); [b]Wilson et al (1999); [c]Schaberg et al (2001); [d]Wilson et al (2004).
NS = nonsignificant differences; p value not reported in the original publication.

with faster eradication and reduced susceptibility of the development of resistance. In fact, some reports have described the development of resistance of *S. pneumoniae* during treatment with levofloxacin (Davidson et al 2002), but no reports have shown the same phenomenon in patients treated with more active fluoroquinolones such as moxifloxacin or gatifloxacin. Therefore, these findings support the concept of "use the best first". The most potent agent of the class should be used as first line therapy to avoid the development of resistance to the entire class of antimicrobials, particularly in moderate to severe cases or those with risk factors for relapse or poor compliance.

Moxifloxacin has demonstrated better eradication in exacerbations of CB and COPD compared to standard therapy, in particular compared to macrolides. The complete eradication of bacteria present in the airways is important for the prevention of resistance development (Stratton 2003) and for clinical outcome. The persistence of bacteria after antibiotic treatment of an exacerbation has been associated with increased inflammation, poorer evolution of the baseline disease and early recurrence of exacerbation. Fast and complete eradication of bacteria may induce a "virtuous circle" preserving and/or restoring the integrity of the bronchial mucosa and making it more resistant to further bacterial colonization and the development of exacerbations. In addition, the reduction in the frequency of exacerbations will contribute to preserve pulmonary function and health status (De Benedetto and Sevieri 2006) (Figure 5). In the

MOSAIC trial, patients treated with moxifloxacin showed a significantly better eradication, together with an extended time to the next exacerbation compared with the standard treatments.

The results obtained in registration trials of patients with exacerbations of CB and COPD, together with the new trials performed after launching moxifloxacin have had an impact on the development of guidelines of antibacterial treatment of exacerbations. The Canadian guidelines indicate fluoroquinolones as the first-line treatment for patients with exacerbated CB with risk factors (FEV_1 <50% predicted, more than 4 exacerbations/year, cardiac disease, use of home oxygen, chronic steroid use or antibiotic use in the past 3 months) and second-line therapy in uncomplicated CB (Balter et al 2003). The Latin American guidelines recommend moxifloxacin as first-line therapy in exacerbated COPD patients with FEV_1 between 35% to 50%, those with an FEV_1 <35% without risk factors for *Pseudomonas* infection and those with FEV_1 >50% with risk factors (ALAT Work Group 2004). Recent guidelines published in Spain by the Spanish Society of Pneumologists and Thoracic Surgeons and the Spanish Society of Geriatrics recommend moxifloxacin as first-line therapy in patients with suspected bacterial exacerbation of COPD with an FEV_1 <50% predicted and without risk factors for *Pseudomonas* infection and in patients with FEV_1 >50% with risk factors (Miravitlles and Martín Graczyk 2006) (Figure 6).

The appropriate use of moxifloxacin in patients with exacerbated chronic bronchial disease and clear criteria of

Table 6 A summary of clinical trials with moxifloxacin (400 mg once daily) in E-CB and E-COPD

Study	Design	Patients	Test of cure	Outcomes by treatment group		
				Treatment group	Clinical response rate	Bacteriological response rate
Chodosh et al 2000	Randomized, double-blind	E-CB, N = 926	0–6 days post-treatment	5-day MOX (n = 312) 10-day MOX (n = 302) 10-day CLR (n = 312)	89% 91% 91%	94% 95% 91%
Wilson 1999	Randomized, double-blind	E-CB Type I/II, N = 649	7 days post-treatment	5-day MOX (n = 322) 7-day CLR (n = 327)	89% 88%	77% 62%
DeAbate et al 2000	Randomized, double-blind	E-CB, N = 567	14–21 days post-treatment	5-day MOX (n = 283) 5-day AZM (n = 284)	88% 88%	95% 94%
Wilson et al 2004	Randomized, double-blind	E-CB Type I, N = 730	7–10 days post-treatment	5-day MOX (n = 354) 7-day comparator (n = 376) (AMX, CLR or CFU)	87% 84%	91% 81%
Kreis et al 2000	Randomized, open-label	E-CB, N = 124	14–21 days post-treatment	5-day MOX (n = 62) 5-day AZM (n = 62)	85% 88%	n/a n/a
Miravitlles et al 2003	Observational, open-label	E-COPD; FEV$_1$ <50% N = 441	30 days post-treatment; relapse-free period	5-day MOX (111 AEs) 7-day comparator (503 AEs) (AMX, CLR or CFU)	66% 65%	n/a
Grassi et al 2002	Randomized, open-label	E-CB, Types I and II; N = 423	10 days post-treatment	5-day MOX 7-day CRO	91% 89%	92% 91%
Schaberg et al 2001	Randomized, open-label	E-CB, N = 512	14 days post-treatment	5-day MOX 7-day AMX-CLA	96% 92%	88% 90%
Landen et al 2001	Observational, open-label	CA-RTIs E-CB; N = 7944	3–10 days post-treatment	5- to 10-day MOX	97%	n/a
Lorenz et al 2001	Open-label	E-CB Type I, N = 328	12 days from treatment onset	5-day MOX	91%	n/a
Hautamaki et al 2001	Randomized, double-blind	E-CB, N = 461	7–21 days post-treatment	5-day MOX 7-day LEV	93% 94%	96% 96%
Miravitlles et al 2004b	Observational, open-label	E-CB types I and II N = 1456	10 days from treatment onset	5-day MOX 7-day CLR 7-day AMX-CLA	97% 94% 93%	n/a
Starakis et al 2004	Randomized, open-label	E-CB types I and II N = 153	14 days from treatment onset	5-day MOX 7-day AMX-CLA	88% 89%	91% 70%
Urueta-Robledo et al 2006	Randomized, double-blind	E-CB; N = 437	7–14 days post-treatment	5-day MOX 7-day LEV	91% 94%	93% 94%
Miravitlles et al 2001b	Observational, open-label	E-CB, N = 5737	7 days post-treatment	5- to 10-day MOX	93%	n/a

Updated from Miravitlles (2005).

Abbreviations: AMX, amoxicillin; AMX-CLA, amoxicillin-clavulanate; AZM, azithromycin; CA-RTIs, community-acquired respiratory tract infections; CFU, cefuroxime-axetil; E, exacerbation; CLR, clarithromycin; CRO, ceftriaxone; E-CB, exacerbation of chronic bronchitis; E-COPD, exacerbation of chronic obstructive pulmonary disease; LEV, levofloxacin; MOX, moxifloxacin; n/a, not assessed.
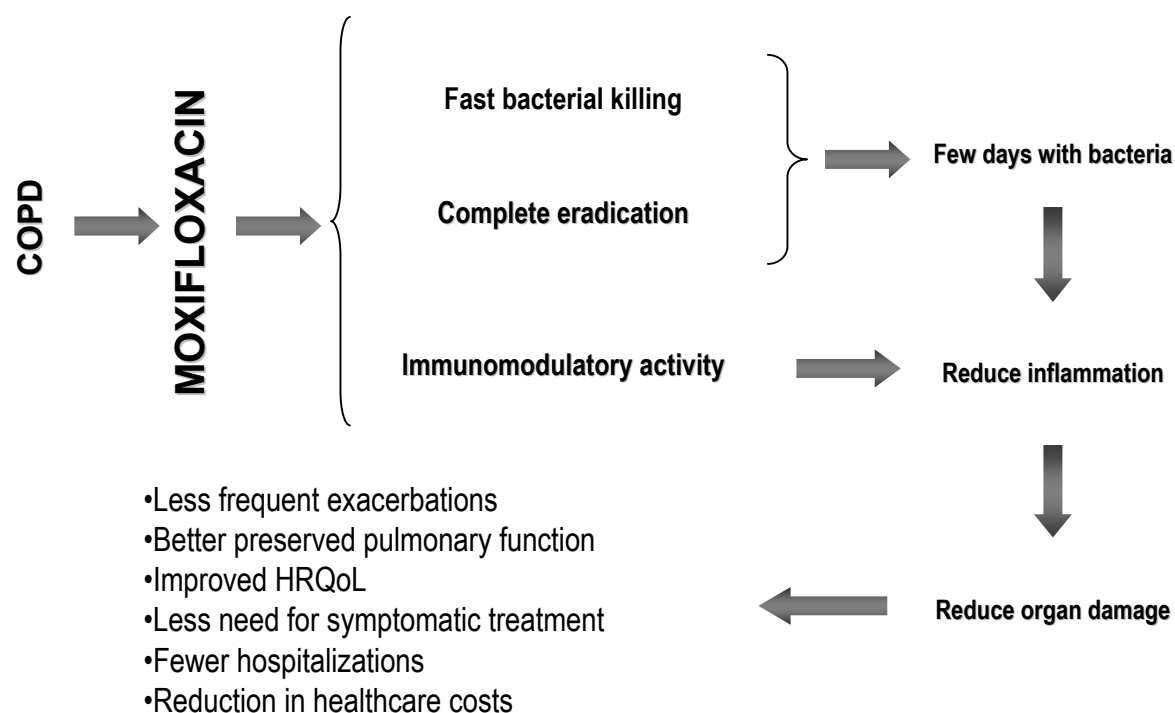
Figure 5 The "virtuous circle" of antibiotic treatment of exacerbations of CB and COPD. Derived from De Benedetto and Sevieri (2006).
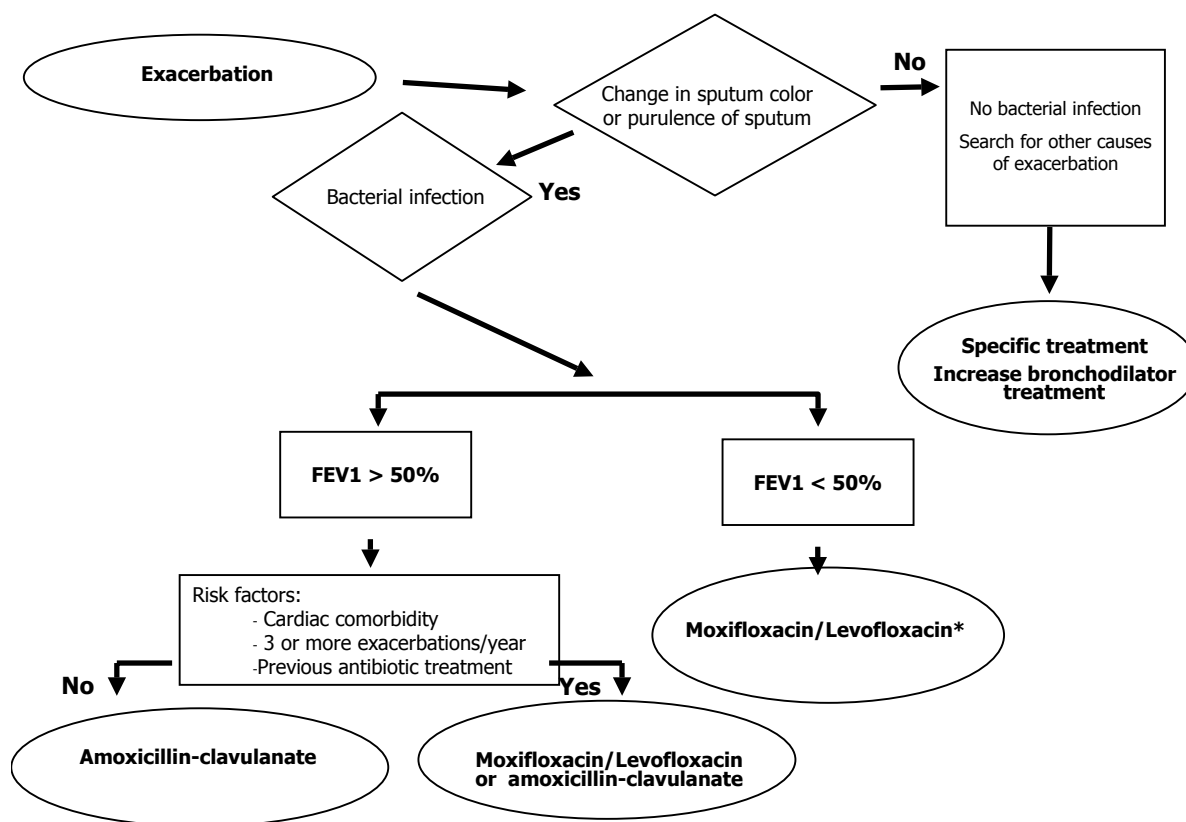

Figure 6 Algorithm of antibiotic treatment of ambulatory patients with exacerbations of COPD from the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Spanish Society of Geriatry and Gerontology (SEEG). Derived from Miravitlles and Martín Graczyk (2006).
Note: *Except in patients with risk factors for infection with *P. aeruginosa*, such as impaired lung function, bronchiectasis, and prior use of antibiotics (Eller et al 1998; Miravitlles et al 1999; Monsó et al 2003).

bacterial infection may improve the short- and long-term clinical outcome. Restriction of the use of fluoroquinolones, such as moxifloxacin, in patients with acute bronchitis, suspected viral infections or benign infections that can be successfully treated with older antibiotics will help to preserve the antibacterial activity of the class. The use of the most active fluoroquinolone first ("use the best first") may also contribute to preserve the antibacterial activity of all quinolones and allow its use in patients who really benefit from the better outcome obtained with moxifloxacin. Physicians need to be familiar with criteria for suspecting bacterial infection in exacerbated patients and identify risk factors for relapse in order to indicate the use of moxifloxacin according to local and international guidelines.

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