Should patients with acute exacerbation of chronic bronchitis be treated with antibiotics? Advantages of the use of fluoroquinolones

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ABSTRACT

The pathological changes in chronic bronchitis (CB) produce airflow obstruction, reduce the effectiveness of the mucocilliary drainage system and lead to bacterial colonisation of bronchial secretion. The presence of bacteria induces an inflammatory response mediated by leukocytes. There is a direct relationship between the degree of impairment of the mucocilliary drainage system, the density of bacteria in mucus and the number of leukocytes in the sputum. Purulent sputum is a good marker of a high bacterial load. Eventually, if the number of leukocytes is high, their normal activity could decrease the effectiveness of the drainage system, increase the bronchial obstruction and probably damage the lung parenchyma.Whenever the density of bacteria in the bronchial lumen is $\geq 10^6$ CFU/mL, there is a high probability that the degree of inflammatory response will lead to a vicious cycle which in turn tends to sustain the process. This situation can arise during the clinical course of any acute exacerbation of CB, independently of its aetiology, provided the episode is sufficiently severe and/or prolonged. Fluoroquinolones of the third and fourth generation are bactericidal against most microorganisms usually related to acute exacerbations of CB. Their diffusion to bronchial mucus is adequate. When used in short (5-day) treatment they reduce the bacterial load in a higher proportion than is achieved by β-lactam or macrolide antibiotics given orally. Although the clinical cure rate is similar to that obtained with other antibiotics, the time between exacerbations could be increased.

Keywords Acute exacerbations of chronic bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, fluoroquinolones, respiratory tract infections, review

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INTRODUCTION

Chronic bronchitis (CB) is clinically defined as the presence of productive cough lasting more than three consecutive months over two consecutive years [1]. Patients with a clinical diagnosis of CB suffer from several changes in the respiratory tract. The airway changes, mostly located in bronchioles, include different degrees of: chronic inflammatory infiltration of the mucosa, mainly due to macrophages and T lymphocytes (CD8); reduction of the number of ciliated cells, as well as of the ciliary length; an hypertrophy of bronchial submucosa glands, as well as of caliciform cells, which in turn leads to an excess of mucus production; and progressive fibrosis of the airway wall, including loss of the elastic fibres that keep bronchioles open [2–5].

The above changes are due to the primary and secondary immunological response to the long-term inhalation of smoke, harmful gases or biological dust [6]. In developed countries, tobacco smoke is responsible for more than 90% of cases of CB. However, only 15% of heavy smokers will develop a CB. In nearly 20% of them, the disease will not progress. This fact suggests that a particular baseline genetic individual susceptibility is necessary, as shown by the presence of several polymorphisms in genes that codify for inflammatory mediators, proteases or antiproteases [7,8], by the development of an autoimmune response [9] or perhaps by the presence of chronic viral infection [10–12] or an infection due to *Chlamydophila pneumoniae* [13]. The structural and functional changes that develop in patients with CB will lead to nonreversible and slowly progressive obstruction of the bronchial lumen, as well as

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to a reduction of the effectiveness of the mucociliary drainage system[14].

Microorganisms that eventually enter respiratory airways, via inhaled air or following microaspiration of the pharyngeal contents, impact with the mucus of the airways, and then are trapped by mucin macromolecules. Next, the mucociliary drainage system carries these microorganisms up to the oropharynx. The process of bacterial clearance from the peripheral airways can last up to 6 h [15]. Over this period, the presence of lactoferrin, lysozyme and secretory leukoproteinase inhibitor, among other antimicrobial compounds from bronchial secretion, hampers the growth of microorganisms [16]. The respiratory airways will be kept sterile whenever two factors, i.e., speed of drainage and bacterial growth inhibitory capacity, are greater than the total amount of microorganisms entering the respiratory tract, taking into account their rate of reproduction. Only those microorganisms (*Mycoplasma pneumoniae*, *C. pneumoniae* and *Bordetella pertussis*) that have specific mechanisms which allow them to stick to the bronchial mucosa epithelial layer, and therefore to avoid being moved up to the oropharynx, will eventually produce an infectious tracheobronchitis in healthy people.

Reductions in the effectiveness of mucociliary drainage system, related to CB pulmonary pathological changes, allow the bacterial colonisation of bronchial lumen. Bacterial population density is directly related to the degree of impairment of the bronchial drainage system, which in turn correlates well with the severity of airway obstruction. In the initial stages of CB, among those patients with FEV_1 values > 60% of those predicted the culture of bronchial secretions can be 'apparently' sterile (bacterial viable counts below 10^3 CFU/mL). When the drainage system and/or the obstruction worsens, the probability of being colonised increases [17] and the bacterial density also increases [18–20]. Any decline in the effectiveness of the drainage system, if lasting long enough, will lead over the following days to a new balance in which bronchial mucus tends to harbour a greater degree of bacterial load. Microorganisms can be kept under very low, even undetectable, numbers in bronchial mucus of patients with stable CB, as confirmed by the fact that, after the sputum culture becomes negative following appropriate antibiotic treatment, the same bacterial phenotype will reappear when clinical relapses of the disease develop [21,22].

The presence of bacteria on the surface of the otherwise normally sterile mucosa triggers the activity of leukocytes, the second defensive mechanism of innate immunity. Toll-like receptors expressed in the epithelium of bronchial mucosa, as well as in macrophages, will recognise specific bacterial components [23]. The activation of nuclear kB factor will start the production of cytokines (interleukins, chemokynes) [24–26] growth factors [27,28], intercellular adherence molecules (selectines, ICAM) [29,30] and arachidonic acid metabolites (B4 leukotriene) [31,32]. Direct consequences include the development of an inflammatory response, with polymorphonuclear leukocytes (PMN) adhering to pulmonary blood vessel endothelium, and migrating into bronchial lumen. The degree of inflammation, as well as the number of PMN cells in the sputum of a CB patient, is directly related to the bacterial density in the bronchial secretion. It has also been noted that a good relationship exists between the gross appearance of the sputum (the greenish color of purulent sputum is due to the presence of leukocyte myeloperoxidase) and the PMN count [33]. A grossly purulent sputum is likely to harbour a high bacterial load in 90% of cases [34].

Antibacterial mechanisms of the neutrophils include, among others, production of reactive oxygen species (ROS), e.g., superoxide anion hydroxyl radicals as well as hydrogen peroxide [35,36], several serine proteases (elastase, proteinase 3, cathepsin G), matrix metalloproteinases and cystein proteinases (cathepsines K, L and S). The protease activity is rapidly neutralised by specific inhibitors, e.g., alpha-1-antitrypsine, alpha-1-macroglobulin, elfin, secretory leukoprotease inhibitor, for tissue inhibitors of matrix metalloproteinases (TIMPs) proteinases and cistatines. ROS can inactivate antiproteases. Free proteases and ROS effects include the enhancement of the inflammatory response, mucus production [37–39] and the likelihood of lung damage [40,41] with the ensuing worsening of the airway obstruction (FEV_1 reduction) [42–45], finally leading to emphysema in animal models [46,47] and very probably also in humans [48].

If the bacterial density is low, leukocyte counts will also be low (giving a mucoid appearance to the sputum), and several antiproteases can easily neutralise the total amount of proteases produced

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by leukocytes. On the other hand, when the bacterial counts are high, the purulent appearance of the sputum is related to the higher concentration of proteases, which can then make ineffective the antiprotease neutralising activity. The final result is likely to be worsening of the respiratory tract obstruction, together with an impairment of the mucocilliary drainage system, which in turn maintains (or even increases) the growth of bacteria. In summary, from a given threshold of bacterial load in the bronchial secretion, the degree of inflammatory response may enter a vicious cycle (VC) which can sustain the process [49]. Fig. 1 summarises these events.

Some data from patients with CB indicate that the severity of the inflammatory response may change as a function of the particular bacteria that prevail in the bronchial mucus. *Pseudomonas aeruginosa* produces a higher degree of inflammation than that produced by *Haemophilus influenzae*, which in turn is higher than that due to *Moraxella catarrhalis* or *Haemophilus parainfluenzae* [50,51]. Overall, the critical density of bacteria in bronchial mucus that leads to the VC lies around $\geq 10^6$ CFU/mL. Chronic production of purulent sputum has been linked with an impairment of FEV_1 [52], as well as with a higher risk of severe chronic obstructive pulmonary disease (COPD) exacerbations requiring hospitalisation [53,54]. Acute exacerbations of CB are associated with the presence of higher bacterial loads in the bronchial mucus [19].

The clinical evolution of patients with CB is characterised by the regular appearance of worsening episodes of bronchial inflammation, due to bacterial or viral infection in more than 60% of cases [55,56]. The remaining episodes are due to environmental factors (air pollution, dust, temperature), lack of compliance with baseline treatment or development of cardiac disrythmias, among other infrequently encountered causes. Viral infection is mainly due to rhinovirus [11,12 57] followed by coronavirus, respiratory syncitial virus (RSV), influenza and parainfluenza virus and adenovirus [58]. Recently, it has been demonstrated that human metapneumovirus can play a role in acute exacerbations of CB in up to a 4% of cases [59]. Bacterial infection can be due to the acquisition of a new *H. influenzae* strain [60–63] or, less frequently, of a *M. catarrhalis* [64] strain, very probably showing higher virulence when compared with those strains that have been present before in bronchial mucus [65]. Surface antigenic protein genes of *H. influenzae* can mutate, allowing the microorganisms to escape from immune response [66,67], a property that perhaps could explain some of the exacerbations. Several studies [68–70] demonstrate serological evidence for acute *C. pneumoniae* infection in up to a 5% of CB exacerbations, an observation that was not confirmed by other authors [71].

Independently of the underlying cause, all acute exacerbations of CB carry a risk of further impairment of the mucocilliary drainage system and of an increase in bacterial population density, which in turn can trigger a greater inflammatory response. Even when the initial trigger of the acute exacerbation episode is not a bacterial infection, there is an enhanced risk that, over the next few days, bacteria will participate actively in the process and determine its final evolution when the density threshold level for generating the VC is reached. The likelihood of this series of events depends on two main factors: the severity and duration of the triggering cause and the baseline situation of the CB patient. The greater the bacterial charge at the baseline, the greater the risk that any given phenomenon, independently of its aetiology, will contribute to the bronchial inflammation and lead to exacerbation due to an even higher bacterial load (Fig. 2). Higher bacterial loads under stable clinical conditions are often seen among CB patients with a history of repeated acute exacerbations [72] and/or moderate to severe degrees of bronchial obstruction. The rate of acute exacerbation is higher in patients at more advanced stages of CB as measured by the degree

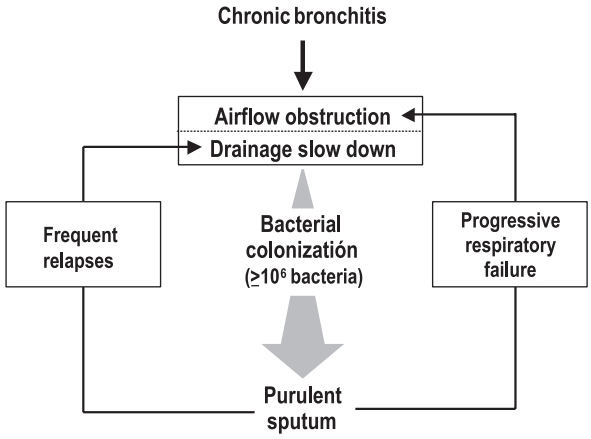

Fig. 1. Development of the 'Vicious Cycle'.

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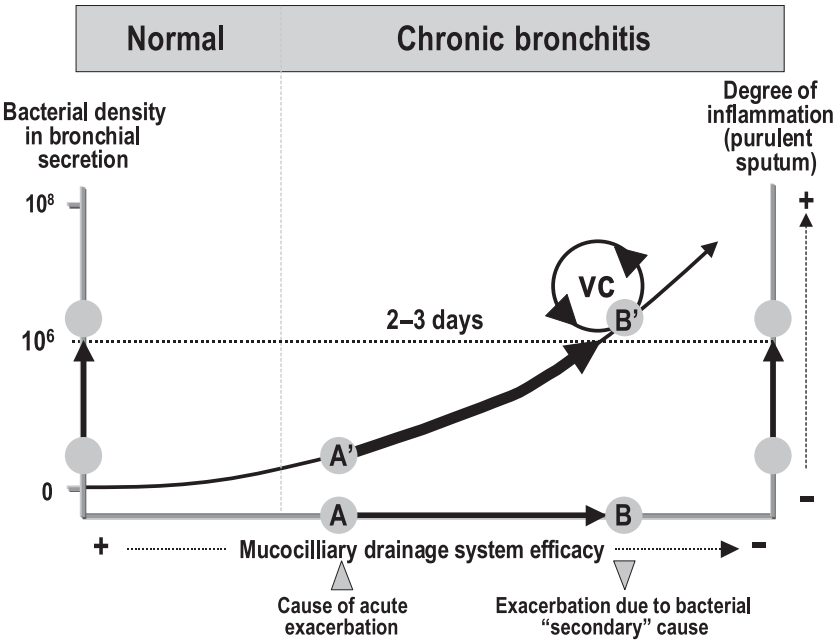

Fig. 2. Sequence of events leading to the start of the VC in patients with CB: A patient with CB start from point A, where the bacterial load (left axis), and therefore the degree of purulent sputum (right axis) is low, as represented by the A′ point, due to a mild impairment of the mucocilliary drainage system. Once a cause for the acute exacerbation is present, the drainage system is hampered, and patient's status can move to B point, which corresponds to a B′ level of bacterial load and purulent sputum. If the B′ point is close to or above the threshold level (> 10^6 cfu/ml bacterial density), the Vicious Cycle can start (see text). Adequate antibiotic treatment can reduce the degree of bacterial load, moving the patient down to point A′.

of bronchial obstruction [73–75]. In a significant proportion of patients with acute exacerbation of CB, the recovery is incomplete [76].

Bacterial species often found in the cultures of bronchial secretion from CB patients, if sputum samples are taken either during clinically stable phases or during acute exacerbations, are (in decreasing order), non-typable *H. influenzae*, *Streptococcus pneumoniae* and *M. catarrhalis* [77].

In those patients with severe airflow impairment ($FEV_1 < 40\%$), enteric Gram-negative bacilli (enteric GNB) (*Escherichia coli*, *Klebsiella*, *Enterobacter*) [78,79], as well as nonfermentative GNB, mostly *P. aeruginosa* [80,81], can also be isolated from bronchial secretions. Other bacteria found less frequently include *Staphylococcus aureus* and *H. parainfluenzae*. The presence of GNB is due, to a great extent, to the higher rate of antibiotic usage as treatment for acute exacerbations among patients with moderate or severe CB. Risk factors for pharyngeal colonisation by GNB, e.g., advanced age and severe underlying conditions (diabetes mellitus, chronic renal failure, cirrhosis of the liver, cancer or any other chronic debilitating disease) are also risk factors for pharyngeal colonisation among patients with CB.

Up to 20% of bronchial secretion samples from CB patients will give a growth of polymicrobial flora. Often different *H. influenzae* strains coexist in the same patient, even with differences in their antibiotic susceptibility [82]. The presence of pneumococci reduces the likelihood of colonisation or infection by *H. influenzae* [83]. The association of *H. influenzae* with pneumococci is found less frequently than expected, taking into account the high frequency of their independent isolation as a single pathogen.

DIRECTIONS FOR ANTIBIOTIC USE IN ACUTE EXACERBATIONS OF CB

Following the evidence presented, the clinical decision for or against using antibiotic treatment in patients with acute exacerbation of CB must not rely on finding a bacterial infection as the primary cause of the exacerbation, a situation that in turn is often difficult to identify [84], but rather on the acknowledgment of those situations in which bacterial presence is a likely factor contributing

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to the exacerbation, irrespectively of the initial cause triggering the current episode.

The benefits of an antibiotic treatment for acute exacerbations of CB are a matter of debate. Well known, published studies, where antibiotic was compared to placebo, did not show statistically significant differences [85–88]. Reasons that could explain these results include a low number of patients in the studies, lack of stratification of patients according to severity scores of the acute exacerbation, as well as the selection of antibiotics or the antibiotic dosage, that may not be deemed optimal, according to current knowledge of pharmacodynamics.

The penetration of β-lactam antibiotics into the bronchial secretion is due to a passive diffusion of their free fraction (unbound to proteins). In the best-case scenario, β-lactam antibiotic levels in bronchial secretion will be *c*. 20% of their maximum plasma peak level. Antibiotics such as cephaclor, cefuroxime or erythromycin, when administered orally at the usually recommended doses, will not last long enough in bronchial mucus at levels above the MIC_{90} for *H. influenzae* to develop their optimal antibacterial efficacy.

A meta-analysis including nine randomised, placebo-controlled, clinical trials, conducted between 1957 and 1992, showed a slight benefit favouring antibiotic against placebo when clinical efficacy and peak-flow improvement were considered as end-points [89]. The study conducted by Anthonisen *et al.* [90], in which patients were stratified according to the severity of the acute exacerbation, showed that benefits of antibiotic treatment (measured by the clinical improvement as well as by the FEV_1 values speed of improvement) were particularly significant when the acute exacerbation episode was characterised by the presence of dyspnoea, increased volume of sputum and purulent appearance of the sputum. Benefit was lower, albeit still significant, when only two of these three criteria were met. Similar results were obtained in another study where patients were also classified into three groups according to the severity of their bronchial obstruction, measured by the FEV_1 values. Although antibiotic treatment efficacy was better than placebo in all groups, benefits were higher in the group of patients with a higher degree of functional impairment [91].

Very important and valuable data regarding antibiotic treatment of patients with acute exacerbations of CB were provided by a double blind, randomised clinical trial, in which ofloxacin was compared with placebo [92]. The study included patients with a severe acute exacerbations of CB, requiring mechanical ventilation. Patients in the ofloxacin group less often needed other antibiotic treatment. The total duration of mechanical ventilation, length of hospital stay, as well as mortality rate were significantly lower in the ofloxacin than in the placebo group.

The use of antibiotics in patients with acute exacerbations of CB can be decided following an assessment of the clinical presentation of the acute episode and of the baseline status of the patient. This procedure allows the identification of two main groups of CB patients likely to benefit from antibiotic treatment: (1) patients with severe acute exacerbations, who require hospital admission, or patients with purulent sputum production (a very good marker of the presence of high bacterial counts); and (2) patients with any degree of severity of the acute exacerbation, but with advanced-stage CB, as determined by severe airflow obstruction ($FEV_1 < 40\%$), a prior history of three or more acute exacerbations during the last year, or a prior episode of severe acute exacerbation that had required hospital admission.

The study conducted by Anthonisen *et al.* [90] suggests that episodes of acute exacerbation of CB in which at least two out of the following three criteria were present (the so called Type II exacerbations), will benefit from antibiotic treatment. The criteria include increase in shortness of breath, increase in sputum volume and production of purulent sputum. The relative weight of the presence of purulent sputum is likely to be higher than the presence of the other two criteria, and probably justifies, in itself, the use of antibiotics. Patients with acute exacerbations clinically characterised only by increased dyspnoea or increased volume of sputum production have not been analysed independently. Nevertheless, a recent study showed that patients with acute exacerbations of CB who started the antibiotic treatment earlier had a significantly faster recovery rate, and also that those patients who commonly do not consult a primary physician when an acute exacerbation appears had a higher likelihood of being admitted to the hospital because of a more severe episode [93].

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ADVANTAGES OF FLUOROQUINOLONE USE AS ANTIBIOTIC TREATMENT IN PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS: CLINICAL EXPERIENCE

The fluoroquinolone (FQ) class of antibiotics offers several advantages of special interest for clinicians when used as empirical treatment for respiratory tract infections. Their bactericidal effect is rapid and dependent on the concentration achieved at the primary site of infection. Both properties give a basis for the use of short-term (5 days) treatment in patients with acute exacerbations of CB. The extended half-lives of most FQ allow their use in a single daily dose.

The antimicrobial spectrum of activity of the so-called third generation FQ (levofloxacin, gatifloxacin and gemifloxacin) or the fourth generation FQ (moxifloxacin, garenoxacin) include the most important microorganisms involved in acute exacerbations of CB, e.g., *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, together with other microorganisms also identified occasionally, e.g., *C. pneumoniae* and *M. pneumoniae*. In addition, FQ are active against a high percentage of Enterobacteriaceae, and ciprofloxacin as well as levofloxacin is active against a high number of *P. aeruginosa* strains. Although the activity of levofloxacin against *P. aeruginosa* is lower than that of ciprofloxacin, the in-vivo efficacy of both quinolones is similar, because the pharmacokinetic properties of levofloxacin are more favourable and allow this antibiotic to achieve an area under the concentration-time curve over 24 h in steady state divided by the MIC (AUC/MIC) ratio equivalent to that of ciprofloxacin [94]. The antibacterial spectrum of activity of FQ acquires paramount importance whenever there is a high antibiotic resistance rate, as recorded in several areas of the world, where *H. influenzae* and notably *M. catarrhalis* strains are β-lactamase producers in 30% and 90% of cases, respectively, and also where *S. pneumoniae* strains show macrolide and penicillin-resistance in nearly 30% of cases [95,96].

The diffusion of FQ antibiotics to lung tissue is sufficient. Levels achieved are higher than plasma levels both in alveolar fluid and inside alveolar macrophages and, to a lesser extent, in bronchial mucosa [97–100]. Second-generation FQ levels in bronchial secretion reach values of 80– 200% of plasma levels [101,102]. There are no data available for third and fourth generation FQ. The pharmacodynamic parameter that best predicts the clinical efficacy of a FQ is the AUC/MIC. The complete elimination of *S. pneumoniae* is achieved with AUC/MIC values above 30 [103,104]. When the infection is due to *P. aeruginosa* or enteric GNB, AUC/MIC values above 125 are needed [105], which in turn requires the use of ciprofloxacin at doses of 750 mg every 12 h or levofloxacin at doses of 500 mg every 12 h. The optimal AUC/MIC values for *H. influenzae* and *M. catarrhalis* are unknown, but are probably very close to the values registered for pneumococci.

The potential existence of high bacterial loads in acute exacerbations of CB is an important risk factor for selection of resistant mutants. Mutations occur spontaneously at the region that genetically determines quinolone resistance (QRDR) of parC and/or gyrA. A single mutation usually produces a slight increase of the MIC and, depending on the intrinsic FQ activity, the antibiotic could still be effective. However, if a second mutation appears, this will certainly lead to bacterial cross-resistance against all FQ [106].

When an antibiotic susceptibility test is performed, minor changes in resistance level must be identified because they might point to the existence of a first step mutation. Then, the use of FQ should be avoided in order to prevent the selection of strains that developed a second step mutation, which implies cross-resistance. For the same reason, it is prudent to avoid long duration FQ treatments in patients with CB, as well as to avoid the use of FQ in patients with CB who have been treated recently with FQ. The *H. influenzae* and *S. pneumoniae* bacterial populations present in bronchial secretions of a CB patient are often heterogeneous. Clones with different antibiotic susceptibility can easily coexist [82]. The FQ resistant clone, perhaps arising from a prior FQ treatment, could remain hidden by the vast sensitive population, but it can be rapidly selected and will prevail after a few days when a new FQ antibiotic treatment course has started.

Since the beginning of the widespread use of FQ antibiotics as treatment for respiratory tract infection, several isolated cases [107,108], together with small outbreaks [109], of FQ-resistant *S. pneumoniae* respiratory tract infections have been reported, notably in CB patients previously

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treated with FQ [110]. Most of the resistant isolates had no relationship and clone dissemination is sparse to date [106].

Epidemiological studies conducted recently in the United States [111–113], Canada [114] and several European Union countries [115–117], showed that the resistance rate of pneumococci to FQ is still below the 1% level. Rare cases of FQ-resistant *H. influenzae* [118] have been reported, but both *H. influenzae* and *M. catarrhalis* remain uniformly sensitive to FQ [119].

Table 1 includes the results of double blind, randomised studies in which ciprofloxacin [120–122], grepafloxacin [123], levofloxacin [124,125], gemifloxacin [126,127], gatifloxacin [128,129] and moxifloxacin [130–133] are compared with different macrolide antibiotics (azythromycin, clarithromycin) or β-lactam antibiotics (amoxyclin-clavulanate, cefuroxime axetil) as treatment for acute exacerbations of CB. All FQ except ciprofloxacin have been used in 5-day treatment courses against 7–10 day treatment courses for the comparator antibiotics. Most studies include CB patients with type I or type II acute exacerbations, as determined by Anthonisen's study criteria [90]. The clinical response, assessed at days 7–21 after treatment was deemed to be favourable in 80–90% of cases. None of the studies showed statistically significant differences between treatment arms. Bacterial elimination rates ranged from 60 to 98%. In four of the 14 studies, the sputum culture become negative in a significantly higher percentage of patients treated with a FQ when compared with any other antibiotic used [120,121,130,133]. Several studies conducted by Chodosh [120] and Wilson [127], where the time interval from the end of antibiotic treatment to the next acute exacerbation episode was analysed, demonstrate that the interval free of disease was significantly longer in the group of patients treated with FQ. Besides the advantages evident from these results, which include a better quality

Table 1. Double blind, randomized clinical trials, where FQ are compared against other antibiotics for the treatment of patients with acute exacerbations of chronic bronchitis

Author/year	Antibiotics	Dose (mg/h)	Days	total number of patients assessed	mean age (years)	type of exacerbation[§]	% with favorable evolution (at 7–21 days)	bacteriologic eradication cases/total (%)
Chodosh[121] 1998	Ciprofloxacin	500/12	14	99	61	I-II-III	90	86/95 (91) **
	Clarithromycin	500/12	14	91	62		82	67/87 (77)
Chodosh[122] 1998	Ciprofloxacin	500/12	14	103	57	nd	93	89/93 (96) **
	Cefuroxime	500/12	14	105	58		90	80/97 (82)
Grassi[123] 2002	Ciprofloxacin	500/12	10	110	65	II	85[#]	46/50 (92)
	Pruliflofloxacin	600/12	10	112	67		85	47/53 (89)
Langan[124] 1999	Grepafloxacin	400/24	5	156	57	II	72	58/89 (65)
	Grepafloxacin	400/24	10	157	56		81	58/86 (67)
	Clarithromycin	250/12	10	160	57		73	62/104 (60)
Masterton[125] 2001	Levofloxacin	500/24	5	238	61	II	83	92/112 (82))
	Levofloxacin	500/24	7	244	59		85	84/101 (83
Amsden[126] 2003	Azythromycin	500-250/24	5	108	58	I-II	82	22/23 (96)
	Levofloxacin	500/24	7	104	59	I-II	86	17/20 (85)
Wilson[127] 2002	Gemifloxacin	320/24	5	351	59	I	85	39/45 (87)
	Clarithromycin	500/12	7	358	58		85	38/52 (73)
Sethi[128] 2004	Gemifloxacin	320/24	5	170	62	I-II	88	(78)
	Levofloxacin	500/24	7	164	63		85	(86)
Gotfried[129] 2001	Gatifloxacin	400/24	5	174	48	I-II	89	85/87 (98)
	Gatifloxacin	400/24	7	175	49		88	75/80 (94)
	Clarithromycin	500/12	10	178	48		89	87/89 (98)
Soler[130] 2003	Gatifloxacin	200/24	5	138	62	II	82	55/65 (86)
	Gatifloxacin	400/24	5	136	60		81	47/61 (77)
	Amoxy-Clav.	500/8	10	126	62		82	51/67 (76)
Wilson[131] 1999	Moxifloxacin	400/12	5	322	60	I-II	89	89/115 (77) **
	Clarithromycin	500/12	7	327	60		88	71/114 (62)
Chodosh[132]2000	Moxifloxacin	400/24	5	143	57	I-II	89	127/143 (89)
	Moxifloxacin	400/24	10	148	55		91	135/148 (91)
	Clarithromycin	500/12	10	129	54		91	110/129 (85)
DeAbate[133] 2000	Moxifloxacin	400/24	5	221	54	I-II	88	105/119 (88)
	Azythromycin	500-250	5	243	54		88	102/118 (86)
Wilson[134] 2004	Moxifloxacin	400/24	5	274	64	I	70	62/71 (91) **
	Other Atb: Amoxycillin	500/8						
	Clarithromycin	500/12	7	298	63		62	66/79 (81)
	Cefuroxime	250/12						

[*] assessment performed at days 2-7 after treatment
[†] assessment performed at day 2 after treatment
[§] Type of exacerbation following Anthonisen's classification[91]
[**] $p < 0.05$

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of life for patients and lower cost of illness, a reduction in the number of acute exacerbation episodes implies a better preservation of antibiotic susceptibility due to its lesser usage, but also a slowing in the rate of damage to the patient's respiratory function, which several other studies linked to the annual number of acute exacerbations [43].

Overall, data gathered from clinical effectiveness studies using different FQ antibiotics suggest that: (1) with intrinsic differences in activity, different antibacterial spectrums of activity or differences in their ability to penetrate in bronchial mucus can achieve similar clinical cure rates, provided that they were able to reduce bacterial population density below the threshold where the inflammatory response tends to remain for a long period or even worsen; and (2) the antibiotic that achieves a greater reduction in bacterial load after an acute exacerbation is able to defer longer the next exacerbation episode. This could be explained by the fact that not only must the following exacerbation episode start from lower bacterial load counts, but more probably by the improvement of inflammation related to a lower bacterial load, because patients with persistent colonisation show greater degrees of inflammation throughout their periods of clinical stability [134].

Among the possible secondary or untoward effects of FQ use, which can be particularly relevant when they are prescribed for patients with CB are: (1) development of tendon injuries; (2) possible prolonged QT interval; and (3) interactions with other drugs. Nearly 1% of patients under FQ treatment will develop arthralgia and, very infrequently, Achilles' tendon injury, including a risk of tendon rupture. This untoward effect is more likely to develop in patients with chronic renal failure and/or patients treated with steroid drugs [135]. The median duration of FQ treatment before the onset of tendon injury was 8 days [135]. The prolonged QT interval was the main factor for the market withdrawal of sparfloxacin and grepafloxacin. In healthy volunteers, a 1000 mg dose of levofloxacin and a 1500 mg dose of ciprofloxacin induce a 4 ms prolongation of the QT interval. In the same study, a dose of 800 mg of moxifloxacin resulted in a 16 ms QT prolongation [136]. The risk of cardiac dysrhythmias (torsades de pointes) is very low, but could be increased if the patient has hypokaliemia, has a major cardiac disease or is taking several antiarrhythmic drugs (amiodarone, quinidine, procainamide, sotalol), tricyclic antidepressants or other antipsychotic drug treatment, which also lead to QT prolongation. Hypotension has been described with the use of garenoxacin.

Among possible drug–drug interactions, there is a low probability of the development of a nonsoluble compound whenever FQ are administered together with cations (calcium, iron, zinc, aluminum). For this reason, mineral dietary supplements, antacid compounds and sucralfate can significantly reduce FQ absorption if the antibiotic is not taken at least 4 h before or 2 h after. Ciprofloxacin can increase the plasma levels of theophylline because of its inhibition of P-450 cytochrome. The effect of levofloxacin, gatifloxacin and moxifloxacin on theophylline metabolism is minimal. Gatifloxacin can interact with oral hypoglycemic agents, and induce hypoglycemia [137].

Treatment of CB acute exacerbations with FQ antibiotics achieves clinical cure rates at least similar to those of other antibiotic groups (β-lactams, macrolides). FQ have the additional advantage that a single daily oral dose, used over a 5-day treatment course, is usually enough. A greater efficacy of FQ antibiotics in reducing bacterial load, as well as the likely implications of this effect on the duration of the interval free of exacerbations, together with a slowing of the rate of functional impairment, justify the consideration of FQ as the first-choice antibiotic treatment, notably in those patients with moderate to severe CB ($FEV_1 < 60\%$), age above 65 years or comorbid conditions (diabetes, cardiac disease, cirrhosis of the liver, chronic renal failure). In patients with mild CB ($FEV_1 \geq 60\%$), aged below 65 years and without comorbidity, FQ antibiotics are an option for treatment as are amoxycillin-clavulanate or telithromycin (used in those areas with high resistance rates to macrolides among pneumococci). It is prudent to state clearly this difference, in order to avoid a widespread use of FQ for all CB acute exacerbation episodes that warrant treatment, and to reduce the likelihood of resistance development. CB patients with a prior history of more than four acute exacerbation episodes requiring antibiotic treatment over a 1-year period have a high risk for *P. aeruginosa* colonisation. In those cases, it is recommended that a sputum sample for culture and antibiotic susceptibility testing always be obtained, because the

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P. aeruginosa resistance rate to FQ in some areas is high [138]. Until the results become available, if oral antibiotic treatment is considered, ciprofloxacin or levofloxacin should be used.

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