

# Levofloxacin for the Treatment of Acute Exacerbation of Chronic Bronchitis: Position in Recent Guidelines

From left to right

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While the role of antimicrobial therapy for treatment of exacerbations of chronic obstructive pulmonary disease (COPD) remains controversial, most guidelines now include fluoroquinolones. This paper presents results of randomized clinical trials comparing levofloxacin with other commonly used agents in the management of acute exacerbations of chronic bronchitis (AECB) and the current treatment guidelines available. Results confirm that levofloxacin is as effective and well tolerated as cefuroxime axetil, azithromycin, gemifloxacin, and clarithromycin. Levofloxacin can be given in shorter durations of therapy, with a 5-day course achieving equivalent clinical and bacteriological success to the usual 7-day course (1). A higher dose of 750 mg levofloxacin, given for 3 days, has also been assessed in the management of AECB, and compared with azithromycin once daily (o.d.) for 5 days (uncomplicated patients) or amoxicillin 875 mg/clavulanate 125 mg twice daily (b.i.d.) for 10 days (complicated patients). The clinical success rate was 93.0% and 90.1% for levofloxacin and azithromycin, respectively and 79.2% for levofloxacin and 81.7% for amoxicillin/clavulanate, respectively. For microbiologically evaluable patients, the clinical response rate for levofloxacin for 3 days was superior to azithromycin for 5 days, while the 5-day course of levofloxacin (81.4%) was similar to 10-day amoxicillin/clavulanate (80.9%) (2).

Canadian guidelines for the management of AECB recommend fluoroquinolones including levofloxacin mostly for risk group II patients with AECB. A US consensus conference recommends the use of risk stratification, positioning the respiratory fluoroquinolones for the more severe AECB patients and for those having  $\geq 1$  risk factors. The 2004 Latin-American Thoracic Society (ALAT) recommendations on infectious exacerbations of COPD recommend respiratory fluoroquinolones for patients suffering mild COPD with risk factors, as well as in patients with moderate and severe COPD. 2005 German evidence-based guidelines for the treatment of AECB recommend fluoroquinolones for COPD patients suffering AECB with forced expiratory volume in one second ( $FEV_1$ )  $< 50\%$  of predicted values and no risk factors for *Pseudomonas aeruginosa*.

## Introduction

Exacerbations are a common cause of morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD). In the European Union, the annual number of consultations per 100,000 population averages 7,300 and accounts for €10.3 billion in health care costs. Despite aggressive medical treatment, approximately one-third of patients discharged from the emer-

gency department with acute exacerbations of COPD have recurrent symptoms within 14 days and 17% relapse and require hospitalization (3).

Conventional end-points for the efficacy of the pharmacological treatment of exacerbations of COPD include symptoms and bacteriological resolution at 2–4 weeks. These end-points have been used to evaluate new drugs and may have clinical relevance. Other end-points, such as the

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exacerbation-free interval, resource utilization (hospitalization, outpatient visits, medication use, lost of working days, etc.), and improved quality of life, may be more suitable end-points in these particular populations (4,5).

Exacerbation of COPD is a common event in the natural cause of the disease, characterized by changes in the patient baseline dyspnea, and cough and/or sputum beyond the level of day-to-day variability which is sufficient to result in a change of management.

There is no agreed classification of COPD exacerbations. The following working classification of severity can help to discriminate the clinical relevance of the episode and its outcome:

- Level I can be treated at home
- Level II requires hospitalization
- Level III leads to respiratory failure (6).

Major risk factors for COPD exacerbation are infectious processes of viral (rhinovirus, RSV, influenza) or bacterial origin (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Enterobacteriaceae*, *Pseudomonas* spp.), environmental conditions, air pollution, lack of compliance at long-term oxygen therapy, and failure to participate in pulmonary rehabilitation programs.

The role of antimicrobial therapy for the treatment of exacerbations of COPD is still a controversial issue. The new antimicrobials, particularly fluoroquinolones, have been included in most guidelines based on their excellent *in vitro* activity against respiratory pathogens, optimal bronchial penetration, and convenient administration. In this review, the role of levofloxacin, its indications, and its therapeutic results in controlled clinical studies are analyzed, as well the recognition of levofloxacin in different national and international treatment guidelines.

### Clinical studies

In 1999, two comparative studies between levofloxacin and cefuroxime axetil for the treatment of acute exacerbations of chronic bronchitis (AECB) were published. The first was a randomized, double-blind, double-dummy, three-arm parallel, multicenter study that was conducted among adult patients with AECB in order to compare the efficacy and safety of two different doses of levofloxacin with cefuroxime axetil. A total of 832 patients were randomized to receive oral levofloxacin once daily (o.d.) 250 mg or 500 mg, or oral cefuroxime axetil 250 mg twice daily (b.i.d.) for 7–10 days. The primary efficacy analysis was based on the clinical response in patients with bacteriological confirmation of AECB, determined 5–14 days after the end of therapy, per-protocol (PP) population. Of 839 patients enrolled at 71

centers in 14 countries, seven were not treated, resulting in an intent-to-treat (ITT) population of 832. In total, 281 patients received levofloxacin 250 mg, 280 received levofloxacin 500 mg, and 271 received cefuroxime axetil. The cure rates in the ITT population were 70% (196/281) for levofloxacin 250 mg, 70% (195/280) for levofloxacin 500 mg, and 61% (166/271) for cefuroxime axetil. Rates in the PP population were 78% (121/156), 79% (108/137), and 66% (88/134), respectively. Both doses of levofloxacin were at least as effective as cefuroxime axetil and were active against the main pathogens of clinical relevance (*H. influenzae*, *S. pneumoniae*, *M. catarrhalis*). All three treatment regimens were equally well tolerated. The authors concluded that levofloxacin (250 mg and 500 mg) o.d. was effective and well tolerated in the treatment of AECB in adult patients (7).

A smaller study in the Netherlands (8) included a total of 124 patients that were treated for 7 days with oral levofloxacin 250 mg or 500 mg o.d., or cefuroxime axetil 250 mg b.i.d. The authors looked specifically at the clinical effectiveness of levofloxacin in patients with acute purulent exacerbations of chronic bronchitis in relation to the *in vitro* activity of isolated pathogens. The results demonstrated that levofloxacin eradicated a greater number of pathogens than cefuroxime axetil. The bacterial eradication rate was 68% for patients receiving the 500 mg dose and 63% for those receiving the 250 mg dose of levofloxacin, while it was only 48% for the comparator. The minimum inhibitory concentrations (MICs) of levofloxacin against all pre-treatment *S. pneumoniae* isolates ( $n = 39$ ) were 0.25–2 mg/L (geometric mean 0.95 mg/L); similar to the MICs of post-treatment strains ( $n = 32$ ; mean 1.11 mg/L). All except one of the *S. pneumoniae* isolates were susceptible to penicillin G (MIC  $\leq 0.06$  mg/L) and the remaining isolate was inhibited by 0.5 mg/L of penicillin G. It was fully susceptible to levofloxacin. The authors concluded that, although there were some failures in patients with *S. pneumoniae* and *Pseudomonas aeruginosa* infections, resistance to levofloxacin did not emerge rapidly among strains of *S. pneumoniae* during levofloxacin treatment. The natural resistance among pneumococci, *H. influenzae* and *M. catarrhalis* was rare.

Another randomized, double-blind, multicenter study was conducted in adult patients with AECB to compare the efficacy of a 5-day course of levofloxacin 500 mg o.d. with the standard 7-day regimen with the same dose (1). A total of 532 patients from 48 centers in 10 countries were randomized to receive levofloxacin: 268 received the 5-day course and 264 received the 7-day course. The primary efficacy analysis was

the clinical response at 7–10 days post-treatment in the PP population.

Clinical success rates in the primary PP analysis of 482 patients were 82.8% (197/238) for the 5-day group and 84.8% (207/244) for the 7-day group. The difference in success rate was -2.1% with a 95% confidence interval (CI): -9.1– 4.9. The bacterial eradication rates were 82.1% (92/112) and 83.2% (84/101) for the 5-day and 7-day groups, respectively. The results showed that for patients with AECB levofloxacin 500 mg o.d. for 5 days provided equivalent clinical and bacteriological success irrespective of the patient's age, the frequency of exacerbations, or the presence of co-existing cardiopulmonary or COPD (1).

Amsden, et al. conducted a randomized, double-blind, double-dummy, multicenter trial on the safety and efficacy of oral azithromycin versus levofloxacin in the treatment of outpatients with AECB. This study included 235 outpatients who received either azithromycin 500 mg on day 1 and 250 mg for days 2–5, or oral levofloxacin 500 mg o.d. for 7 days. In clinically evaluable patients, favorable outcomes were demonstrated in 89% of patients receiving azithromycin and 92% of patients receiving levofloxacin by day 4 of therapy. At day 24 on the post-therapy visit, favorable responses were approximately 82% and 86%, respectively. The bacterial eradication rates were 96% for azithromycin and 85% for levofloxacin. Both treatments were well tolerated; gastrointestinal symptoms were the most frequent adverse event (9).

In a randomized, double-blind, double-dummy, multicenter, parallel-group study in 60 different medical centers in the US, UK, and Germany, a 5-day treatment with oral gemifloxacin 320 mg o.d. was compared with a 7-day therapy with levofloxacin 500 mg o.d. In total, 335 out of 360 patients completed the study (93.1%). Clinical success rate in the PP population was 88.2% (134/152) and 85.1% (126/148), respectively. At long-term follow-up (days 28–35), the clinical success rates in the PP population were 83.7% (123/147) for gemifloxacin and 78.4% (109/139) for levofloxacin. The difference in clinical success rate was not statistically significant (10).

In Germany, a comparative study on levofloxacin versus clarithromycin in AECB focused on the exacerbation-free interval (11). The randomized, double-blind, multicenter study enrolled 511 patients and compared the exacerbation-free interval, efficacy and safety of 7-day levofloxacin 500 mg o.d. versus 10-day clarithromycin 250 mg b.i.d. in patients with AECB. Patients were monitored over a one-year period. A total of 434

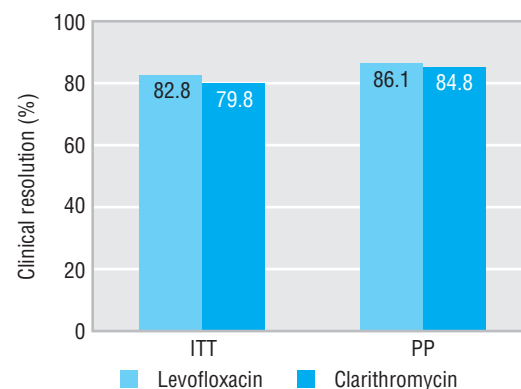
patients received the medication for  $\geq 5$  days (PP population).

In the microbiologically evaluable ITT (mITT) population, clinical success at the end of treatment was 82.8% of patients in the levofloxacin group and 79.8% in the clarithromycin group (Figure 1). Clinical success rates in the evaluable PP population ( $n = 365$ ) were 86.1% and 84.8%, respectively.

Potential pathogens responsible for the acute exacerbations were isolated in 125 (50%) patients in the levofloxacin group and in 131 (51.6%) in the clarithromycin group. The most frequently isolated strains were *H. influenzae* ( $n = 80$ ; 23.9%, levofloxacin; 25.8%, clarithromycin), *S. pneumoniae* ( $n = 50$ ; 14.5%, levofloxacin; 16.6%, clarithromycin), *M. catarrhalis* ( $n = 39$ ) and *Staphylococcus aureus* ( $n = 24$ ). Of the 322 strains isolated at baseline, 34.5% were resistant to clarithromycin and only one strain (*S. pneumoniae*) showed an intermediate level of resistance to levofloxacin. Of the *H. influenzae* strains, 35% were resistant to clarithromycin, whereas none were resistant to levofloxacin.

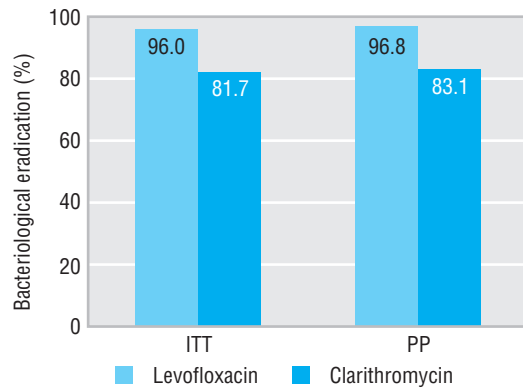
The bacterial eradication rate at the end of treatment in the evaluable mITT population with microbial etiology ( $n = 251$ ) was significantly higher in the levofloxacin group (96.0%) than in the clarithromycin group (81.7%) (14.3% difference; 95% CI: 6.7–21.8;  $p < 0.0001$ ) (Figure 2). Adverse events were reported by 49 patients; 24 (9.5%) in the levofloxacin group and 25 (9.7%) in the clarithromycin group. A total of 75 adverse events (31 and 44, respectively) were considered to be at least possibly drug-related. The most frequent adverse events were mild to moderate, although treatment was prematurely discontinued in 26 patients (14 in the levofloxacin group, 12 in the

**Figure 1. Clinical resolution rate at the end of therapy in the evaluable intent-to-treat (ITT) and per-protocol (PP) populations of AECB patients treated with levofloxacin or clarithromycin.**



Abbreviation: AECB = acute exacerbations of chronic bronchitis. Adapted from reference (11).

**Figure 2. Bacteriological eradication rate at the end of therapy in the evaluable intent-to-treat (ITT)<sup>a</sup> and per-protocol (PP)<sup>b</sup> populations of AECB patients treated with levofloxacin or clarithromycin.**



<sup>a</sup> Difference in the ITT population,  $p < 0.0001$ .

<sup>b</sup> Difference in the PP population,  $p = 0.01$ .

Abbreviation: AECB = acute exacerbations of chronic bronchitis. Adapted from reference (11).

clarithromycin group) due to one or more adverse events, mostly due to gastrointestinal symptoms.

Martinez et al analyzed the role of levofloxacin 750 mg in the management of AECB (2). The ITT population was 763 patients, who were stratified by degree of underlying illness. Uncomplicated patients were randomized to levofloxacin 750 mg o.d. for 3 days or azithromycin o.d. for 5 days. Complicated patients were randomized to levofloxacin 750 mg o.d. for 5 days or amoxicillin 875 mg/clavulanate 125 mg b.i.d. for 10 days. Regardless of therapy, complicated patients demonstrated lower clinical and microbiological success rates than uncomplicated patients.

The clinical success rate for clinically evaluable patients was similar for levofloxacin (93.0%)

and azithromycin (90.1%), and levofloxacin (79.2%) and amoxicillin/clavulanate (81.7%). For microbiologically evaluable patients, the clinical response rate for levofloxacin for 3 days was superior to azithromycin for 5 days (96.3% and 87.4%, respectively), while the 5-day course of levofloxacin (81.4%) was similar to 10-day amoxicillin/clavulanate (80.9%) (Figure 3). Microbiological eradication was superior for levofloxacin 3-day therapy (93.8%) compared with azithromycin 5-day therapy (82.8%) and similar for levofloxacin for 5 days (81.4%) and amoxicillin/clavulanate for 10 days (79.8%). The conclusion of this study was that levofloxacin 750 mg for 3 days was comparable to azithromycin for 5 days for uncomplicated patients with AECB, while 5 days of 750 mg levofloxacin was comparable to 10 days of amoxicillin/clavulanate for complicated AECB (2).

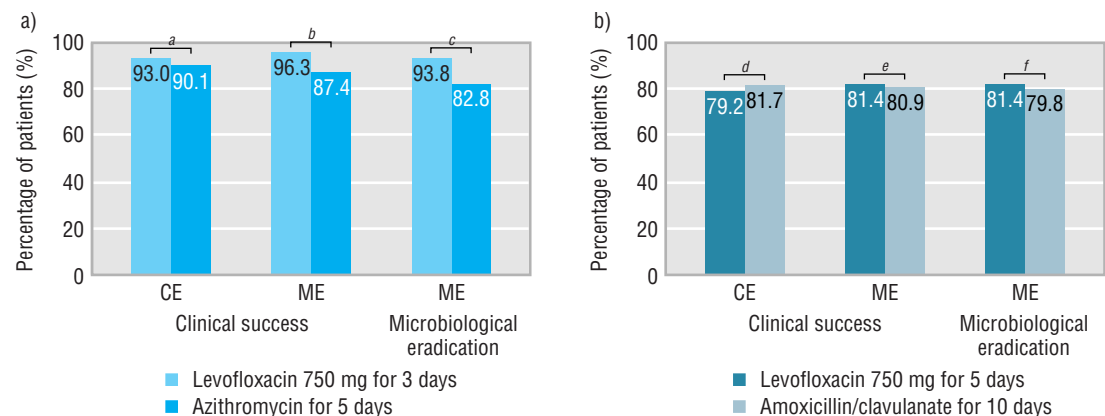
### Role of levofloxacin in recent treatment guidelines

Five guidelines or consensus conferences on the antimicrobial treatment of AECB are available from different countries.

In the Lille consensus conference on the treatment of AECB, modern fluoroquinolones including levofloxacin were not recommended as first-line treatment. However, in the more severe bronchitis patients the consensus conference allowed the use of modern fluoroquinolones (12).

The Canadian guidelines for the management of AECB were published in July–August 2003. These guidelines were based on relevant articles published between 1966 and July 2002. The treatment recommendations were graded on the strength of evidence and modern fluoro-

**Figure 3. Clinical success rates and microbiological eradication rates at post-therapy visits, by a) uncomplicated and b) complicated treatment.**



Note: The 95% confidence intervals around the difference between treatment groups, comparator minus levofloxacin, are indicated (<sup>a</sup> -9.6–3.8; <sup>b</sup> -17.6–-0.1; <sup>c</sup> -21.2–-0.8; <sup>d</sup> -7.8–12.9; <sup>e</sup> -12.7–11.7; <sup>f</sup> -13.9–10.7).

Abbreviations: CE = clinically evaluable, ME = microbiologically evaluable.

Adapted from reference (2).

quinolones including levofloxacin were recommended mostly for risk group II patients with AEBC. These patients have treatment failure risk factors such as poor underlying lung function (forced expiratory volume in one second [FEV<sub>1</sub>] < 50% of predicted values) or those with moderate impairment of lung function (FEV<sub>1</sub> 50–65% of predicted value) but with significant comorbidities (ischemic heart disease, congestive heart failure, diabetes, etc.) and/or experiencing ≥ 4 exacerbations a year (Table 1).

*H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* continue to be the predominant microorganisms, although enteric Gram-negative organisms may be also isolated from pulmonary secretions. Treatment should focus on resistant organisms and antimicrobials such as fluoroquinolones are preferred to amoxicillin or other traditional first-line agents. The Canadian guidelines also point out that a number of studies have demonstrated significantly superior bacterial eradication rates with fluoroquinolones compared with cefuroxime or clarithromycin. In addition, there may be some evidence to suggest that the enhanced bacterial eradication associated with fluoroquinolones leads

to faster symptom resolution and a prolonged exacerbation-free interval when compared to cephalosporins and extended spectrum macrolides (level II of evidence) (13). This preliminary evidence, however, does not warrant fluoroquinolone use in all cases of AEBC.

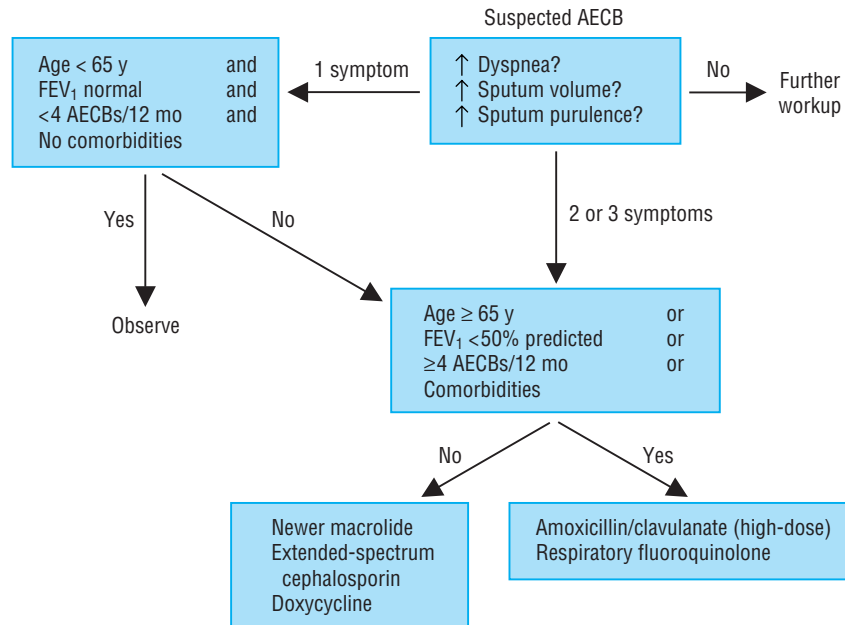
A consensus conference in the US published as a primary care consensus guideline for the treatment of AEBC, which was released in 2004. These guidelines stress that *S. pneumoniae* resistance to penicillin, azithromycin and other macrolides, trimethoprim–sulfamethoxazole (TMP–SMX) and cefuroxime continues to be a problem in the US. On the other hand, resistance to amoxicillin/clavulanate, ceftriaxone, levofloxacin, and vancomycin remains low. The consensus conference suggested a simplified risk stratification and an antibacterial management algorithm which is shown in Figure 4. The authors positioned the modern respiratory fluoroquinolones for the more severe AEBC patients and for those having ≥ 1 risk factors (age ≥ 65 years, FEV<sub>1</sub> < 50% of predicted value, ≥ 4 exacerbations in 12 months, or comorbidities) (14).

The update to the Latin–American Thoracic

**Table 1. Empiric therapy in patients with acute exacerbations of chronic bronchitis (AEBC)**

Risk group	Basic clinical state	Symptoms and risk factors	Probable pathogens	First choice	Alternatives for treatment failure
0	Acute tracheobronchitis	Cough and sputum without previous pulmonary disease	Usually viral	None unless symptoms persist for > 10–14 days	Macrolide or tetracycline
I	Chronic bronchitis without risk factors (simple)	Increased cough and sputum, sputum purulence, and increased dyspnea	<i>Haemophilus influenzae</i> , <i>Haemophilus</i> species, <i>Moraxella catarrhalis</i> , <i>Streptococcus pneumoniae</i>	2 <sup>nd</sup> generation macrolide, 2 <sup>nd</sup> or 3 <sup>rd</sup> generation cephalosporin, amoxicillin, doxycycline, TMP–SMX	Fluoroquinolone, β-lactam/β-lactamase inhibitor
II	Chronic bronchitis with risk factors (complicated)	As in group I plus ≥ 1 of the following: • FEV <sub>1</sub> < 50% predicted • ≥ 4 exacerbations/year • Cardiac disease • Use of home oxygen • Chronic oral steroid use • Antibiotic use in the past 3 months	As in group I plus <i>Klebsiella</i> species plus other Gram-negative pathogens Increased probability of β-lactam resistance	Fluoroquinolone or β-lactam/β-lactamase inhibitor	May require parenteral therapy Consider referral to a specialist or hospital
III	Chronic suppurative bronchitis	As in group II with constant purulent sputum • Some have bronchiectasis • FEV <sub>1</sub> < 35% predicted • Multiple risk factors (e.g. frequent exacerbations and FEV <sub>1</sub> < 50% predicted)	As in group II plus <i>Pseudomonas aeruginosa</i> and multi-resistant <i>Enterobacteriaceae</i>	Ambulatory patients: tailor treatment to airway pathogen, <i>P. aeruginosa</i> common (ciprofloxacin) Hospitalized patients: parenteral therapy usually required	—

Abbreviations: FEV<sub>1</sub> = forced expiratory volume in 1 second, TMP–SMX = trimethoprim–sulfamethoxazole. Adapted from reference (13).

**Figure 4. Risk stratification and antibacterial management algorithm.**

Abbreviations: AECB = acute exacerbations of chronic bronchitis, FEV<sub>1</sub> = forced expiratory volume in 1 second.

Adapted from reference (14).

Society (ALAT) recommendations on infectious exacerbations of COPD published in 2004 is very similar to the Canadian guidelines. Modern respiratory fluoroquinolones including gatifloxacin, levofloxacin, and moxifloxacin were recommended for patients suffering mild COPD with risk factors, as well as in patients with moderate and severe COPD. However, in severity group III, ciprofloxacin is the fluoroquinolone of choice if *Pseudomonas* colonization or infection is suspected (15).

The German guidelines for the treatment of AECB were recently published in 2005. In these very strong evidence-based guidelines, modern fluoroquinolones including moxifloxacin and levofloxacin are recommended for COPD patients suffering AECB with FEV<sub>1</sub> < 50% of predicted values and no risk factors for *P. aeruginosa*. In general, these guidelines are very similar to the already

mentioned Canadian recommendations (16).

Considering the current guidelines, it can be summarized that in North and South America, as well as in Europe, modern fluoroquinolones like levofloxacin have a very well-defined indication in the treatment of AECB. Based on the severity criteria of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definitions, patients falling in GOLD group III are the appropriate group to receive treatment with modern respiratory fluoroquinolones as empirical therapy or as pathogen-specific treatment. The usual dose of levofloxacin is 500 mg o.d. for 5–7 days, however there are strong data to suggest that in most patients the daily dose of levofloxacin 750 mg o.d. for 3–5 days is also effective. Levofloxacin has minimal side effects, which are mostly gastrointestinal or the transient elevation of hepatic enzymes.

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