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Patient stratification in the management of acute bacterial exacerbation of chronic bronchitis: the role of levofloxacin 750 mg

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ABSTRACT: This is the first prospective clinical trial in which patients with acute bacterial exacerbation of chronic bronchitis have been stratified by degree of underlying illness.

Uncomplicated patients were randomised to levofloxacin 750 mg once daily (*q.d.*) for 3 days or azithromycin *q.d.* for 5 days. Complicated patients were randomised to levofloxacin 750 mg *q.d.* for 5 days or amoxicillin 875 mg/clavulanate 125 mg twice daily for 10 days.

Regardless of therapy, complicated patients demonstrated lower clinical and microbiological success than uncomplicated patients. Clinical success for clinically evaluable patients was similar for levofloxacin and azithromycin (93.0 *versus* 90.1%, respectively), and levofloxacin and amoxicillin/clavulanate (79.2 *versus* 81.7%, respectively). For microbiologically evaluable patients, clinical response to levofloxacin for 3 days was superior to azithromycin for 5 days (96.3 *versus* 87.4%, respectively), and levofloxacin for 5 days was similar to amoxicillin/clavulanate for 10 days (81.4 *versus* 80.9%, respectively). Microbiological eradication was superior for levofloxacin for 3 days compared with azithromycin for 5 days (93.8 *versus* 82.8%, respectively), and similar for levofloxacin and amoxicillin/clavulanate for 10 days (81.4 *versus* 79.8%, respectively).

In conclusion, levofloxacin 750 mg for 3 days was comparable to azithromycin for 5 days for uncomplicated patients with acute bacterial exacerbation of chronic bronchitis, while 5 days of 750 mg levofloxacin was comparable to 10 days of amoxicillin/clavulanate for complicated acute bacterial exacerbation of chronic bronchitis.

KEYWORDS: Acute bacterial exacerbation of chronic bronchitis, amoxicillin/clavulanate, azithromycin, chronic bronchitis, levofloxacin, risk assessment

Chronic bronchitis is a slowly progressive disease punctuated by acute exacerbations [1]. These episodes contribute to morbidity, mortality and diminished quality of life (QoL) [2–5]. Failure to treat appropriately with an antibacterial that eradicates the pathogen quickly is associated with persistent airway inflammation, and can increase the requirement for hospitalisation and repeated courses of therapy [6, 7].

Underlying factors have been shown to influence treatment outcome in acute bacterial exacerbation of chronic bronchitis (ABECB). These include baseline lung function, the number of exacerbations from the preceding year and certain comorbidities [8–11]. Recent ABECB treatment guidelines [11] and published classification schemes are built upon the increasingly accepted premise [7, 8, 12–16] that patients should be grouped and antibacterial treatment appropriately selected according to these risk factors.

This study is the first large-scale prospective trial to stratify patients with ABECB into uncomplicated or complicated groups, based on the absence or presence of risk factors for treatment failure. Levofloxacin 750 mg was utilised for 3 (uncomplicated group) or 5 (complicated group) days. Comparator therapy was selected to match the anticipated microbiology and was in accordance with current treatment guidelines [11]. This study applies classification schemes proposed in ABECB treatment guidelines and helps to define the appropriate use of anti-infectives in ABECB *via* patient stratification.

MATERIALS AND METHODS

Study population

Outpatient males and females (aged ⩾18 yrs) with chronic bronchitis, as defined by the American Thoracic Society [17], and signs and symptoms consistent with type I or type II

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N. Zadeikis, A.C. Fisher, K. Walker, M.E. Ambruzs and A.M. Tennenberg were all full-time employees of Ortho-McNeil Pharmaceutical, Inc., at the time of this study. F.J. Martinez is a consultant for Pfizer, Aventis, Ortho-McNeil Pharmaceutical, Inc., and GlaxoSmithKline. R.F. Grossman is a consultant for Bayer, GlaxoSmithKline, Aventis and Abbott. This study was supported by Ortho-McNeil Pharmaceutical, Inc.

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(increased sputum volume and sputum purulence required) ABECB, as defined by ANTHONISEN *et al*. [18], were eligible for enrolment. Patients with calculated creatinine clearance <50 mL·min^{-1} were excluded.

Study design

This was a randomised, blinded, parallel-group, non-inferiority study conducted at 73 sites in the USA. The protocol was approved by the participating institutions' Institutional Review Boards and informed consent was obtained prior to any study procedures.

Prior to randomisation, patients were assigned to uncomplicated and complicated treatment groups, based on predetermined criteria (table 1). Patients were classified as current smokers, ex-smokers or nonsmokers. Uncomplicated patients were randomised to levofloxacin 750 mg once daily (*q.d.*) for 3 days or azithromycin 500 mg on day 1, followed by 250 mg *q.d.* for days 2–5. Complicated patients were randomised to levofloxacin 750 mg *q.d.* for 5 days or amoxicillin 875 mg/clavulanate 125 mg twice daily (*b.i.d.*) for 10 days. All treatment was orally administered. For uncomplicated patients, the treatment was double-blinded. For complicated patients, the large size of the amoxicillin/clavulanate tablets precluded over-encapsulation and blinding. A blister card was used to blind study personnel to the treatment, and patients were educated on the importance of maintaining the blind.

Collection of clinical and microbiological data

At study entry, clinical signs and symptoms of ABECB were evaluated. Sputum samples were collected and assessed for adequacy ($\geqslant$25 polymorphonuclear neutrophils per low-powered field (LPF) and $\leqslant$10 squamous epithelial cells per LPF). A chest radiograph (to rule out pneumonia) and blood samples were obtained. Spirometry testing was performed if a historical baseline value was not available.

Clinical signs and symptoms were reassessed during on-therapy (days 3–6), post-therapy (days 10–19 uncomplicated or days 17–26 complicated patients) and post-study visits (days 35–40 uncomplicated/days 40–45 complicated patients).

Clinical and microbiological efficacy analyses

Post-therapy clinical response was classified as follows. Cure: all study entry criteria were met with resolution of acute signs and symptoms present at study entry (return to pre-exacerbation baseline) and no other antimicrobial therapy was administered. Improvement: all study entry criteria were met with clear, appreciable improvement in the acute signs and symptoms present at study entry, but with incomplete resolution of clinical evidence of infection (however, the infectious process was controlled and no further antimicrobials were required or were administered). Failure: persistence or worsening in the signs and symptoms of the ABECB process that indicated an inadequate response to treatment and resulted in additional nonstudy antimicrobial therapy for treatment of the original infection. Unable to evaluate: the clinical judgment of cure, improvement or failure could not be made due to the subject being lost to follow-up before the post-therapy visit.

Microbiological outcome was determined for patients who had a respiratory pathogen identified at admission. At post-therapy, microbiological response was classified as follows. Eradicated: absence of the study entry pathogen in a sputum culture obtained at the post-therapy visit in the absence of potentially effective systemic antimicrobials. Presumed eradicated: presumed absence of the study entry pathogen at the post-therapy visit for subjects deemed clinical successes (clinical cure or improvement) for whom no respiratory material was available for culture at the post-therapy visit. Persisted: continued presence of the original study entry pathogen in the post-therapy sputum culture. Presumed persisted: presumed presence of the study entry pathogen at the post-therapy visit for subjects who clinically failed and either had no post-therapy culture taken or had a negative post-therapy culture in the presence of potentially effective systemic antimicrobials. Unknown: no post-therapy culture obtained because subject was lost to follow-up, withdrew from therapy prematurely or had a sputum culture obtained in the presence of potentially effective systemic antimicrobials (except as noted previously for presumed persisted, which pertains to clinical failures).

Pharmacoeconomics and symptom resolution

A subset of patients volunteered to participate in a pharmacoeconomic sub-study. Patients were contacted monthly for up to 9 months in order to assess whether they used any acute (*i.e.* hospitalisation or emergency room), nonstudy, respiratory-related healthcare service and whether they used any additional antibacterials (respiratory healthcare utilisation questionnaire). These patients were additionally administered the transition dyspnoea index (TDI) questionnaire at each

TABLE 1 Chronic bronchitis severity classification

Group	Baseline clinical status	Criteria/risk factors	Enrolment decision
1	Acute tracheobronchitis	No underlying structural disease	Excluded
2	Uncomplicated chronic bronchitis	FEV_1 $\geqslant$50% pred with $<$4 exacerbations·yr^{-1}	Enrolled in uncomplicated strata
3	Complicated chronic bronchitis	FEV_1 $<$50% pred or FEV_1 50–65% pred and significant comorbidity[#]; or $\geqslant$4 exacerbations·yr^{-1}	Enrolled in complicated strata
4	Complicated chronic bronchitis (chronic bronchial infection)	Group 3 criteria + continuous sputum throughout the year	Enrolled in complicated strata

FEV_1: forced expiratory volume in one second; pred: predicted. [#]: *e.g.* diabetes mellitus, congestive heart failure, chronic renal or liver disease.

study visit and maintained a daily symptom diary (cough, breathlessness and sputum production). For the symptom diary, patients were asked to rate the severity of each symptom (cough, breathlessness or sputum production) on a four-point scale, ranging 0–3, as follows. 0: no symptoms; 1: ''mild symptoms''; 2: ''moderate symptoms''; and 3: ''severe symptoms''. The scores for each item were added to create an overall symptom score ranging 0–9. Improvement was predefined as the 1st day on which a one-point reduction in total symptom scores occurred from baseline. Kaplan-Meier estimates were used to analyse the data, giving the percentage of the total patients who experienced a one-point reduction in total symptom scores from baseline by day 3. Additionally, resolution of sputum volume, purulence and cough were rated by the investigator at each patient visit (including the on-therapy visit).

Statistical analyses

Efficacy analyses were performed separately for uncomplicated and complicated patients (smokers, ex-smokers and nonsmokers combined). The primary efficacy variable was clinical success (cured plus improved) in clinically evaluable (CE) patients at the post-therapy (test-of-cure) assessment.

To be CE, a patient had to meet the following requirements: confirmed diagnosis of ABECB; availability of post-therapy data; adequate therapy ($\geqslant$80% but $<$120% of protocol-specified doses taken); and no concurrent use of effective antibacterial agents within 72 h of study entry through to the post-therapy visit. To be microbiologically evaluable (ME), a patient had to be CE and have a pathogen identified at study entry. Microbiological response at the post-therapy visit was a secondary efficacy variable.

Comparability of treatment groups for baseline characteristics was evaluated by Fisher's exact test for dichotomous variables, the Wilcoxon Mann-Whitney test for ordinal variables and the unpaired t-test for continuous variables. For efficacy analyses, two-sided 95% confidence intervals (CI) around the difference between treatment groups (comparator minus levofloxacin) were computed. To conclude that the levofloxacin regimen was at least as efficacious as the comparator, a 95% CI upper bound of $\leqslant$15% was used for clinical success $<$90%, and if clinical success rates in one of the treatment groups was $\geqslant$90%, the upper bound of the 95% CI had to be $\leqslant$10%. The 95% CI were computed with a continuity correction outlined by HAUCK and ANDERSON [19]. Superiority statistical assessment was, therefore, not prespecified.

The analyses of the difference in TDI score (levofloxacin minus comparator) were evaluated by the Wilcoxon rank-sum test. The respiratory healthcare utilisation questionnaire and symptom resolution analyses were evaluated using Fisher's exact test. Symptom resolution was defined as a one-point reduction in the total respiratory symptoms score.

RESULTS

Study population

A total of 763 ABECB patients were enrolled in the intent-to-treat (ITT) population (all randomised patients who took at least one dose of study drug), 394 uncomplicated and 369 complicated. In the uncomplicated population, 192 patients received levofloxacin and 202 patients received azithromycin. In the complicated patient population, 187 patients received levofloxacin and 182 received amoxicillin/clavulanate.

The most common reasons for clinical and microbiological nonevaluability were inappropriate post-therapy evaluation dates (*i.e.* the evaluation occurred outside the time window specified) and unconfirmed diagnosis (table 2).

Demographic and disease characteristics at baseline were different when comparing the uncomplicated and complicated CE populations (table 3). Within the uncomplicated population, patients receiving levofloxacin for 3 days had characteristics that were comparable to patients receiving azithromycin for 5 days. For the complicated population, patients receiving levofloxacin for 5 days had characteristics comparable to patients receiving amoxicillin/clavulanate for 10 days. For all treatment groups, the CE population was comparable to the ITT population. Both the uncomplicated and complicated groups contained some nonsmokers. Information regarding second-hand smoke or other environmental exposure among the nonsmokers was not specifically collected.

Clinical efficacy

For CE uncomplicated patients, clinical success at post-therapy was 93.0% for levofloxacin and 90.1% for azithromycin (fig. 1). When nonsmokers were excluded, the result of the analysis was 93.0% for levofloxacin and 89.4% for azithromycin. However, for ME patients, the clinical response for 3 days of levofloxacin was superior (95% CI upper limit $<$0) to 5 days of azithromycin (96.3 *versus* 87.4%). Clinical response rates by pathogen of interest (pathogens isolated from more than five patients) are presented in table 4. Post-study clinical success rates for the CE population of 92.2 and 92.5% were seen with levofloxacin and azithromycin, respectively.

Clinical success at post-therapy for the CE complicated patients was 79.2% for levofloxacin and 81.7% for amoxicillin/clavulanate (fig. 1). Levofloxacin 750 mg *q.d.* for 5 days was as effective as 10 days of amoxicillin/clavulanate *b.i.d.* When nonsmokers were excluded, the result of the analysis was 79.8% for levofloxacin and 81.5% for amoxicillin/clavulanate. For ME patients, the clinical response for 5 days of levofloxacin was similar to 10 days of amoxicillin/clavulanate (81.4 *versus* 80.9%, respectively). Clinical response rates between treatments by pathogen of primary interest are presented in table 4. Post-study clinical success rates of 80.4 and 82.7% were seen in levofloxacin and amoxicillin/clavulanate patients, respectively.

In vitro *susceptibility of bacterial isolates at study entry*

In the uncomplicated group, 318 study entry pathogens were isolated; 151 were isolated from 110 levofloxacin patients and 167 were isolated from 120 azithromycin patients. Of the pathogens with known susceptibilities, 140 out of 141 (99.3%) isolated from levofloxacin patients and 106 out of 114 (93.0%) isolated from azithromycin patients were susceptible to treatment.

Of the 23 *Streptococcus pneumoniae* isolates from uncomplicated patients, eight (34.8%) were resistant to azithromycin, whereas none was resistant to levofloxacin.

In the complicated group, 341 study entry pathogens were isolated; 172 were isolated from 125 levofloxacin patients and

TABLE 2 Evaluability for clinical and microbiological efficacy in the intent-to-treat population[#]

	Uncomplicated group		Complicated group	
	Levo.	Azithro.	Levo.	Amox./clav.
Subjects n	192	202	187	182
Total evaluable for clinical efficacy	143 (74.5)	151 (74.8)	120 (64.2)	126 (69.2)
Reasons for nonevaluability				
Unconfirmed clinical diagnosis	6 (3.1)	6 (3.0)	27 (14.4)	19 (10.4)
Lost to follow-up	2 (1.0)	7 (3.5)	4 (2.1)	5 (2.7)
Deviated from protocol dosing regimen	3 (1.6)	3 (1.5)	11 (5.9)	8 (4.4)
Inappropriate post-therapy evaluation date	12 (6.3)	9 (4.5)	13 (7.0)	8 (4.4)
Effective concomitant therapy	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Other protocol violation	1 (0.5)	1 (0.5)	1 (0.5)	8 (4.4)
Site disqualified[¶]	24 (12.5)	25 (12.4)	10 (5.3)	8 (4.4)
Total evaluable for microbiological efficacy	80 (41.7)	87 (43.1)	86 (46.0)	89 (48.9)
Reasons for nonevaluability				
Unconfirmed clinical diagnosis	6 (3.1)	6 (3.0)	27 (14.4)	19 (10.4)
Infection not bacteriologically proven	73 (38.0)	74 (36.6)	44 (23.5)	46 (25.3)
Lost to follow-up	0 (0.0)	3 (1.5)	3 (1.6)	3 (1.6)
Deviated from protocol dosing regimen	1 (0.5)	1 (0.5)	7 (3.7)	6 (3.3)
Inappropriate bacteriological culture	6 (3.1)	5 (2.5)	8 (4.3)	5 (2.7)
Effective concomitant therapy	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Other protocol violation	1 (0.5)	1 (0.5)	1 (0.5)	6 (3.3)
Site disqualified[¶]	24 (12.5)	25 (12.4)	10 (5.3)	8 (4.4)

Data are presented as n (%). Levo.: levofloxacin; azithro.: azithromycin; amox.: amoxicillin; clav.: clavulanate. [#]: patients were counted only once; [¶]: one clinical site enrolled 67 subjects; after an audit of this site and review of the data collected, there were outstanding questions about the site's determination of disease severity and clinical assessment of the subjects; the subjects enrolled at this site were disqualified from the clinical, microbiological and pharmacoeconomic populations, but remained in the safety populations; the disqualification of these subjects occurred during the course of the study and before closure of the database and subsequent unblinding of the treatment of the subjects.

169 were isolated from 123 amoxicillin/clavulanate patients. Of the pathogens with known susceptibilities, 149 out of 156 (95.5%) isolated from levofloxacin patients and 114 out of 127 (89.8%) isolated from amoxicillin/clavulanate patients were susceptible to treatment.

Microbiological efficacy

Post-therapy microbiological eradication rates are summarised in figure 1 and table 5. For uncomplicated patients, microbiological eradication was 93.8% for 3 days of levofloxacin and 82.8% for 5 days of azithromycin. The 95% CI was <0, indicating that levofloxacin 750 mg *q.d.* for 3 days was statistically superior to azithromycin administered for 5 days.

For complicated patients, the microbiological eradication rates were 81.4% for 5 days levofloxacin and 79.8% for 10 days amoxicillin/clavulanate. For *Haemophilus influenzae*, amoxicillin/clavulanate eradicated 100%, while levofloxacin eradicated 83.3%. All of the *H. influenzae* isolates were susceptible to levofloxacin with minimal inhibitory concentrations of 0.03 $\mu g \cdot mL^{-1}$, and none of the patients had documented persistence of the pathogen at post-therapy.

Concomitant steroid use

To examine the relationship between outcome and concomitant steroid use, a sub-analysis was performed by grouping patients into categories of either acute or chronic concomitant steroid use. For all populations, there was no evidence that acute steroid use impacted upon the clinical success or microbiological eradication rates (table 6).

Pharmacoeconomics and symptom resolution

Results of key assessments are summarised in table 7. In the CE complicated population, levofloxacin demonstrated a greater improvement ($p=0.036$) in TDI score by days 3–6 compared with amoxicillin/clavulanate. A similar improvement in TDI score was found between treatment groups among the uncomplicated patients.

Patient-recorded diary entries indicated that respiratory symptoms were significantly improved by day 3 ($p=0.015$) in the uncomplicated ME levofloxacin group compared with azithromycin. For CE complicated patients, by the on-therapy physician visit, more levofloxacin than amoxicillin/clavulanate patients experienced resolution of their cough (56.3 and 43.2%, respectively; $p=0.019$) as well as reduction of sputum volume (63.0 and 48.3%, respectively; $p=0.01$) and sputum purulence (54.3 and 37.7%, respectively; $p=0.003$), as assessed by the study investigator. Similar improvement at the on-therapy visit was found between treatment groups among the uncomplicated patients.

TABLE 3 Baseline characteristics for the clinically evaluable uncomplicated and complicated patients

	Uncomplicated			Complicated		
	Levo.	Azithro.	p-value	Levo.	Amox./clav.	p-value
Subjects n	143	151		120	126	
Sex						
Male	71 (49.7)	65 (43.0)	0.293	66 (55.0)	64 (50.8)	0.525
Female	72 (50.3)	86 (57.0)		54 (45.0)	62 (49.2)	
Age yrs						
18–24	7 (4.9)	8 (5.3)		1 (0.8)	1 (0.8)	
25–34	13 (9.1)	11 (7.3)		1 (0.8)	1 (0.8)	
35–39	13 (9.1)	21 (13.9)		5 (4.2)	4 (3.2)	
40–45	27 (18.9)	19 (12.6)		13 (10.8)	10 (7.9)	
46–64	51 (35.7)	62 (41.1)		56 (46.7)	68 (54.0)	
⩾65	32 (22.4)	30 (19.9)		44 (36.7)	42 (33.3)	
Mean	50.7±15.04	51.0±15.87	0.869	59.0±13.09	59.3±12.23	0.853
Weight lbs	177.7±41.15	181.9±48.36	0.424	185.8±56.30	173.6±44.47	0.060
Race						
Caucasian	84 (58.7)	93 (61.6)	0.601	93 (77.5)	96 (76.2)	0.905
Black	44 (30.8)	44 (29.1)		22 (18.3)	28 (22.2)	
Asian	2 (1.4)	3 (2.0)		1 (0.8)	1 (0.8)	
Hispanic	12 (8.4)	9 (6.0)		3 (2.5)	1 (0.8)	
Other#	1 (0.7)	2 (1.3)		1 (0.8)	0 (0.0)	
Smoking history						
Nonsmoker	28 (19.6)	28 (18.5)	0.439	6 (5.0)	7 (5.6)	0.469
Current smoker	77 (53.8)	93 (61.6)		56 (46.7)	64 (50.8)	
Ex-smoker	38 (26.6)	30 (19.9)		58 (48.3)	55 (43.7)	
Pack-yrs n	28.7±26.0 (115)	27.4±22.8 (121)	0.683	41.4±31.5 (113)	47.8±37.4 (116)	0.163
FEV_1 % pred						
<50%	4 (2.8)	1 (0.7)	0.493	60 (50.0)	68 (54.0)	0.534
50–65%	31 (21.7)	33 (21.9)		32 (26.6)	32 (25.4)	
66–80%	45 (31.5)	45 (29.8)		14 (11.7)	12 (9.5)	
⩾80%	63 (44.0)	72 (47.6)		14 (11.7)	14 (11.1)	
Corticosteroid usage						
Acute steroids						
Systemic	8 (5.6)	5 (3.3)	0.403	5 (4.2)	6 (4.8)	1.000
Inhaled	1 (0.7)	1 (0.7)	1.000	2 (1.7)	2 (1.6)	1.000
Chronic steroids						
Systemic	16 (11.2)	15 (9.9)	0.850	20 (16.7)	17 (13.5)	0.593
Inhaled	17 (11.9)	12 (7.9)	0.341	25 (20.8)	22 (17.5)	0.521
Exacerbation frequency past 12 months						
0	4 (2.8)	8 (5.3)	0.189	7 (5.8)	5 (4.0)	0.150
1–3	138 (96.5)	143 (94.7)		44 (36.7)	35 (27.8)	
4–6	1 (0.7)	0 (0.0)		60 (50.0)	78 (61.9)	
⩾7	0 (0.0)	0 (0.0)		9 (7.5)	8 (6.3)	
Continuous sputum						
Yes	89 (62.2)	94 (62.3)	1.000	88 (73.7)	83 (65.9)	0.215
No	54 (37.8)	57 (37.7)		32 (26.7)	43 (34.1)	

Data are presented as n (%) or mean±SD, unless otherwise stated. Levo.: levofloxacin; azithro.: azithromycin; amox.: amoxicillin; clav.: clavulanate; FEV_1: forced expiratory volume in one second; % pred: % predicted. #: other includes Puerto Rican, Latino and Native American.

Safety

Of the 394 ITT uncomplicated patients, 389 (190 levofloxacin/199 azithromycin) were safety evaluable (all randomised patients who took at least one dose of study drug and had available safety information). Similarly, of 369 ITT complicated patients, 362 (183 levofloxacin/179 amoxicillin) were evaluable for safety. Within-group reporting rates for at least one treatment-emergent adverse event were 34.7% for levofloxacin

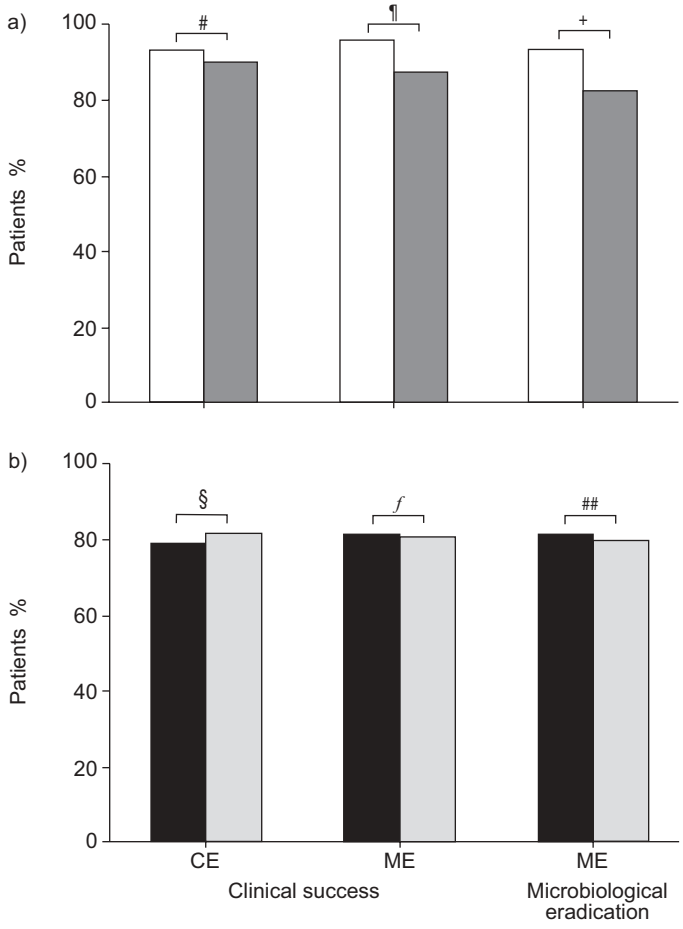

FIGURE 1. Clinical success rates and microbiological eradication rates at the post-therapy visit. Results are shown for the a) uncomplicated and b) complicated treatment groups. CE: clinically evaluable; ME: microbiologically evaluable. □: levofloxacin 750 mg for 3 days; ■: azithromycin for 5 days; ■: levofloxacin 750 mg for 5 days; ■: amoxicillin/clavulanate for 10 days. The 95% confidence intervals around the difference between treatment groups, comparator minus levofloxacin, are indicated ([#]: -9.6–3.8; [¶]: -17.6– -0.1; [+]: -21.2– -0.8; [§]: -7.8–12.9; [f]: -12.7–11.7; [##]: -13.9–10.7).

when compared with 36.7% for azithromycin (95% CI -7.8–11.7) and, in the complicated, 42.1% for levofloxacin when compared with 48.6% for amoxicillin/clavulanate (95% CI -4.0–17.0).

For the uncomplicated group, 12 (6.3%) levofloxacin patients and 16 (8.0%) azithromycin patients reported drug-related adverse events. The most common drug-related adverse events in uncomplicated patients were nausea (four levofloxacin and three azithromycin patients) and diarrhoea (three levofloxacin and 10 azithromycin patients). Adverse events resulting in discontinuation of treatment (four in levofloxacin and one in azithromycin) were considered probably or very likely to be related to the study drug. Four (2.1%) levofloxacin patients experienced treatment-emergent serious adverse events (SAEs) compared to one (0.5%) patient in the azithromycin group. None of the SAEs in either treatment group was assessed by the investigator as being related to the study drug.

For complicated patients, 16 (8.7%) levofloxacin patients and 16 (8.9%) amoxicillin/clavulanate patients reported drug-related adverse events. The most common drug-related adverse event was diarrhoea (four levofloxacin and five amoxicillin/clavulanate patients). Adverse events resulting in discontinuation of treatment (five in levofloxacin and one in amoxicillin/clavulanate) were considered probably or very likely to be related to the study drug. Eleven (6.0%) levofloxacin patients experienced treatment-emergent SAEs compared with 13 (7.3%) amoxicillin/clavulanate patients. The only SAE assessed by the investigator to have a possible relationship to the study drug in either treatment group was aggravated depression in an amoxicillin/clavulanate-treated subject.

The rates of all drug-related adverse events, SAEs, events resulting in discontinuation of treatment and markedly abnormal laboratory findings were not notably different between levofloxacin and comparator. No deaths occurred, and no unusual or unexpected safety problems were reported.

TABLE 4 Clinical success rates summarised for pathogens of primary interest[#] at the post-therapy visit in clinically evaluable patients

Pathogen	Uncomplicated		Complicated	
	Levo.	Azithro.	Levo.	Amox./clav.
Haemophilus influenzae	27/27 (100)	22/24 (91.7)	25/30 (83.3)	19/20 (95.0)
Haemophilus parainfluenzae	19/20 (95.0)	22/23 (95.7)	17/20 (85.0)	15/18 (83.3)
Moraxella catarrhalis	14/14 (100)	18/20 (90.0)	11/12 (91.7)	16/19 (84.2)
Streptococcus pneumoniae	12/12 (100)	9/11 (81.8)	16/18 (88.9)	9/13 (69.2)
Pseudomonas aeruginosa	3/3 (100)	5/6 (83.3)	2/5 (40.0)	4/5 (80.0)
Staphylococcus aureus	7/7 (100)	1/2 (50.0)	4/5 (80.0)	3/5 (60.0)
Klebsiella pneumoniae	2/2 (100)	5/6 (83.3)	1/2 (50.0)	4/5 (80.0)
Enterobacter cloacae	1/1 (100)	3/5 (60.0)	0/0 (0.0)	0/0 (0.0)

Data are presented as n/N patients who had the pathogen alone or in combination with other pathogens at study entry (%), unless otherwise stated. Levo.: levofloxacin; azithro.: azithromycin; amox.: amoxicillin; clav.: clavulanate. [#]: isolated from at least five patients.

DISCUSSION

The major goals of therapy for ABECB should be to provide rapid clinical resolution, eradicate the causative pathogen and return respiratory function to pre-exacerbation baseline as quickly as possible [16]. The selection of antibacterial therapy is generally made empirically, based on probable pathogens and local susceptibility patterns. Recent guidelines now additionally recommend choosing antibacterial therapy based on patient risk factors [7, 8, 11–16, 20]. The recommended antibacterial therapy reflects the spectrum of potential pathogens and the contribution of risk factors to outcomes.

TABLE 5 Microbiological eradication[#] rates at the post-therapy visit in the microbiologically evaluable population

	Uncomplicated group			Complicated group		
	Levo.	Azithro.	95% CI[¶]	Levo.	Amox./clav.	95% CI[¶]
Pathogen category						
Gram-positive aerobic pathogens	20/22 (90.9)	12/15 (80.0)	-37.8–16.0	21/24 (87.5)	14/19 (73.7)	-40.3–12.6
Gram-negative aerobic pathogens	76/81 (93.8)	88/105 (83.8)	-19.4–0.6	75/93 (80.6)	88/106 (83.0)	-8.9–13.7
Total by pathogen	96/103 (93.2)	100/120 (83.3)	-18.6– -1.1	96/117 (82.1)	102/125 (81.6)	-10.6–9.7
Total by patient[+]	75/80 (93.8)	72/87 (82.8)	-21.2– -0.8	70/86 (81.4)	71/89 (79.8)	-13.9–10.7
Pathogen						
Enterobacter cloacae	1/1 (100.0)	3/5 (60.0)		0/0 (0.0)	0/0 (0.0)	
Haemophilus influenzae	26/27 (96.3)	21/24 (87.5)	-25.9–8.3	25/30[§] (83.3)	20/20 (100.0)	0.8–32.5
Haemophilus parainfluenzae	18/20 (90.0)	20/23 (87.0)	-24.6–18.5	18/20 (90.0)	15/18 (83.3)	-31.1–17.8
Klebsiella pneumoniae	2/2 (100.0)	5/6 (83.3)		1/2 (50.0)	4/5 (80.0)	
Moraxella catarrhalis	14/14 (100.0)	18/20 (90.0)	-26.7–6.7	10/12 (83.3)	16/19 (84.2)	-30.0–31.8
Pseudomonas aeruginosa	3/3 (100.0)	4/6 (66.7)		3/5 (60.0)	4/5 (80.0)	
Staphylococcus aureus	7/7 (100.0)	0/2 (0.0)		4/5 (80.0)	3/5 (60.0)	
Streptococcus pneumoniae	11/12 (91.7)	10/11 (90.9)	-28.4–26.9	16/18 (88.9)	10/13 (76.9)	-42.9–19.0

Data are presented as n/N (%), unless otherwise stated. Levo.: levofloxacin; azithro.: azithromycin; CI: confidence interval; amox.: amoxicillin; clav.: clavulanate. [#]: eradication plus presumed eradication; [¶]: two-sided 95% CI around the difference of comparator minus levofloxacin; [+]: eradication of all pathogens identified at study entry for a patient; [§]: one patient was inappropriately assessed as a failure by the investigator, even though all of the patient's baseline symptoms were resolved and *H. influenzae* had been eradicated.

This is the first large-scale, prospective trial in ABECB to use risk stratification of patients to guide the selection of antibacterial regimens, in accordance with recently published treatment guidelines. Only patients with well-defined exacerbations were enrolled, and care was taken to exclude patients who were likely to have viral infections. Prior to randomisation, patients were stratified into uncomplicated and complicated groups. Different durations of levofloxacin, either 3 days for uncomplicated patients or 5 days for complicated patients, were studied. Different comparators were employed for uncomplicated (azithromycin) and complicated (amoxicillin/clavulanate) patients, as the guidelines recommend [11, 16, 20].

This study demonstrated, in a prospective fashion, that complicated patients, regardless of the therapeutic agent employed, had poorer clinical and microbiological outcomes

TABLE 6 Distribution of concomitant steroid use: clinical successes and microbiological eradications

	Uncomplicated group			Complicated group		
	Levo.	Azithro.	p-value	Levo.	Amox.	p-value
Clinical success						
Clinically evaluable						
Acute steroid use	12/15 (80.0)	6/9 (66.7)	0.635	12/22 (54.5)	12/20 (60.0)	0.764
No acute steroid use	121/128 (94.5)	130/142 (91.5)	0.476	83/98 (84.7)	91/106 (85.8)	0.845
Microbiologically evaluable						
Acute steroid use	5/5 (100)	4/5 (80.0)	1.000	4/10 (40.0)	6/13 (46.2)	1.000
No acute steroid use	72/75 (96.0)	72/82 (87.8)	0.083	66/76 (86.8)	66/76 (86.8)	1.000
Microbiological eradication						
Microbiologically evaluable						
Acute steroid use	4/5 (80.0)	3/5 (60.0)	1.000	5/10 (50.0)	7/13 (53.8)	1.000
No acute steroid use	71/75 (94.7)	69/82 (84.1)	0.041	65/76 (85.5)	64/76 (84.2)	1.000

Data are presented as n/N (%), unless otherwise stated. Levo.: levofloxacin; azithro.: azithromycin; amox.: amoxicillin.

TABLE 7 Pharmacoeconomic and symptom resolution assessments: clinically and microbiologically evaluable populations

	Uncomplicated group			Complicated group		
	Levo.	Azithro.	p-value	Levo.	Amox./clav.	p-value
Total TDI[#,¶]						
Clinically evaluable[+]	1.3±2.4 (120)	1.3±2.5 (22)	0.891[f]	0.9±2.2 (107)	0.5±1.9 (113)	0.036
Microbiologically evaluable[+]	1.5±2.6 (66)	1.0±2.5 (69)	0.800	0.9±2.3 (75)	0.7±1.8 (79)	0.099
Patients with improvement in respiratory symptoms by day 3[§] %						
Clinically evaluable	63.8 (116)	50.4 (121)	0.049[##]	57.0 (109)	62.2 (110)	0.465
Microbiologically evaluable	70.3 (64)	49.3 (73)	0.015	58.8 (78)	65.7 (77)	0.483
Respiratory healthcare utilisation[##]						
Clinically evaluable n	143	151		120	126	
Hospitalisation %	0	1	1.000[##]	0	2	0.247
Nonstudy medical visits %	3	1	0.203	3	6	0.335
Additional antibacterial use %	8	15	0.047	31	33	0.685
Microbiologically evaluable n	80	87		86	89	
Hospitalisation %	0	1	1.000	0	3	0.246
Nonstudy medical visits %	1	1	1.000	0	6	0.060
Additional antibacterial use %	6	16	0.053	29	35	0.424

Data are presented as mean±SD (n) or % (n), unless otherwise stated. Levo.: levofloxacin; azithro.: azithromycin; amox.: amoxicillin; clav.: clavulanate; TDI: transition dyspnoea index. [#]: the TDI total change score is scored on a scale from -9 to +9, where a positive number indicates improvement; [¶]: clinically evaluable; [+]: based on patients who completed assessment; [§]: daily diary entries (cough, breathlessness and sputum production), where improvement is defined as a one-point reduction in the total symptom score; [f]: based on the Wilcoxon rank-sum test, two-sided; [##]: based on the Fisher's exact test.

than uncomplicated patients. For CE patients, clinical success rates were similar for levofloxacin and azithromycin in the uncomplicated group, and for levofloxacin and amoxicillin/clavulanate in the complicated group. Coupled with the 750-mg dose, a shortened course of levofloxacin therapy (3–5 days) did not limit clinical efficacy. In fact, for microbiologically confirmed cases, clinical success and microbiological eradication were superior with 3 days of levofloxacin 750 mg when compared to 5 days of azithromycin, while only 5 days of levofloxacin 750 mg were similar to 10 days of amoxicillin/clavulanate. Additionally, patients treated with levofloxacin 750 mg were more likely to experience an improvement in TDI score and earlier resolution of respiratory symptoms, such as increased sputum production, sputum purulence and cough, than their amoxicillin/clavulanate-treated counterparts in the complicated group. Similar findings were noted in a recent study of levofloxacin 750 mg for 5 days for community-acquired pneumonia [21].

These data confirm that the selection of antibiotics can influence the clinical and bacteriological outcome in ABECB. The difference in success rates seen among ME patients in the uncomplicated group who received different treatments supports the position that antibacterial therapy can improve outcomes in selected patients with ABECB [4], and confirms that the choice of agent or class of agents is, in fact, clinically meaningful. In this clinical trial, among the uncomplicated patients, no *S. pneumoniae* isolates were resistant to levofloxacin. However, 34.8% were resistant to azithromycin. This concurs with national surveillance studies, such as Tracking Resistance in the United States Today (TRUST), which continues to demonstrate 99% susceptibility to levofloxacin, but with resistance to macrolides of ~28% [22].

This study has confirmed the importance of evaluating additional outcome measures in ABECB trials [23, 24]. As ABECB is known to diminish QoL [2–5] and increase the likelihood of hospitalisation and repeated antibacterial courses [7, 25, 26], results from a daily diary and a respiratory healthcare utilisation questionnaire were utilised to demonstrate the rapid resolution of symptoms in both uncomplicated and complicated levofloxacin patients. Others have also suggested improved symptom resolution, health status and healthcare utilisation with quinolones in selected ABECB patients [27–29].

The optimal duration of therapy in ABECB remains to be established [11]. Recently, investigators have cogently argued for using the shortest duration of antibacterials possible to achieve multiple goals, including improved compliance, lower cost and a reduced frequency of potential adverse events.

As a concentration-dependent agent [28–33], therapeutic outcome with levofloxacin is most closely linked to area under the concentration–time curve/minimum inhibitory concentration (MIC) or maximum concentration/MIC ratios. This pharmacodynamic principle, paired with levofloxacin's favourable safety index (which allows flexible dosing), supports the approach of using higher doses, such as the 750-mg dose, to achieve rapid microbiological eradication, rapid resolution of the clinical signs and symptoms of infection, and to allow for a shorter duration of therapy. Levofloxacin's excellent clinical efficacy in pulmonary

infections and its rapidly bactericidal action suggest that a higher daily dose, coupled with a shorter treatment duration, could optimise ABECB therapy.

There were several challenges and limitations of this study. First, therapy in the complicated group could not be blinded due to the large size of the amoxicillin/clavulanate tablets. However, investigators were blinded to treatment, and patients were instructed not to reveal the study medication to blinded study personnel. This study could not definitively exclude patients that may have experienced an acute exacerbation for a reason other than bacterial infection. Additionally, ~13% (39 patients) of the uncomplicated ABECB group were aged <35 yrs, and 10 of these patients were also nonsmokers, which may indicate a respiratory condition other than chronic bronchitis. Yet, the small percentage of these patients, as well as equal distribution between treatment groups (six in the levofloxacin group and four in the azithromycin group), should limit their effects on the overall conclusions from the current study. A minority of randomised patients did not report a smoking history. The results of analyses, however, were similar when these putative nonsmokers were excluded. Steroid therapy was not standardised [24], although administration was not associated with differential response rates by antibacterial agents. Interestingly, as others have noted [28], response rates were lower when acute steroids were administered. Spirometry was obtained at the time of exacerbation in some of the patients. This should be of limited concern as forced expiratory volume in one second changes little during outpatient exacerbations [34]; this approach would also be of greater applicability in clinical practice where baseline spirometry may not be available. Sputum cultures were used to detect the presence of persistent pathogens at post-therapy, although this method may underestimate the presence of colonisation, particularly by *H. influenzae* [35].

In conclusion, patient stratification may be a worthwhile approach in the management of patients with acute bacterial exacerbation of chronic bronchitis. Additional prospective clinical trials would be valuable to validate antimicrobial selection based on patient stratification by severity of illness. Underlying risk factors that influence the likelihood of treatment failure may guide the choice of an appropriate antibacterial agent. This study demonstrates that short courses of levofloxacin 750 mg are at least as effective as traditional courses of azithromycin and amoxicillin/clavulanate for the spectrum of patients with acute bacterial exacerbation of chronic bronchitis.

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