2-Day Versus 7-Day Course of Levofloxacin in Acute COPD Exacerbation

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Research Article

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Abstract

Introduction: Duration of antibiotic treatment in acute exacerbation of COPD (AECOPD) is most commonly based on expert opinion. Typical administration periods range from 5 to 7 days. A 2-day course with levofloxacin was not previously assessed. We performed a randomized clinical trial to evaluate the efficacy of 2-day versus 7-day treatment with levofloxacin in patients with AECOPD.

Methods: Patients with AECOPD were randomized to receive levofloxacin for 2 days and 5 days placebo (n=155) or levofloxacin for 7 days (n=155). The primary outcome measure was cure rate, and secondary outcome included need for additional antibiotics, ICU admission, reexacerbation rates and exacerbation free interval (EFI) within one year follow-up.

Results: In ITT analysis, cure rate was 79.3% (n=123) and 74.2% (n=115) respectively in 2-day and 7-day groups. In PP analysis, cure rate was 78% (n=92) and 69% (n=82) respectively in 2-day and 7-day groups. The difference between both groups was not significant. The need for additional antibiotics and ICU admission rates were not significantly different between both groups. One-year reexacerbation rate was 34.8% (n=54) in 2-day group versus 29% (n=45) in 7-day group (p=0.19); the EFI was 121 days (interquartile range, 99-149) versus 110 days (interquartile range, 89-132) in 2-day and 7-day treatment groups respectively (p=0.73). No difference in adverse effects was detected.

Conclusion: Levofloxacin once daily for 2 days is not inferior to 7 days with respect to cure rate and hospital readmission in COPD exacerbations. Our finings would improve patient compliance and reduce the incidence of bacterial resistance and adverse effects.

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as worsening of COPD symptoms characterised by a change in the patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management. [1] Exacerbations carry a major economic burden as they are responsible for the majority of health costs related to COPD. Most of these exacerbations are triggered by infectious agents and their treatment by antibiotics is a common practice. The use of antibiotics was shown to reduce short term mortality and significantly reduces the recurrence of exacerbations. [2, 3] However, widespread use of antibiotics for treatment and prevention of AECOPD, combined with the large number of individuals with COPD, may lead to increased levels of bacterial resistance. [4, 5] Reduction of unnecessary antibiotic use is one of the most important strategies to contain resistance. Shortening the duration of antimicrobial therapy has been advocated as a potentially effective measure for decreasing the emergence of antimicrobial resistance and minimizing the costs associated with various respiratory tract infections. [5] Available guidelines stated that antibiotic treatment should be maintained at an average of 7 to 10 days while the latest meta-analysis including 10 randomized controlled trials (Stolbrink 2018) showed no clinical inferiority of shorter courses. [6] While the shortest antibiotic treatment assessed was 3 days [7, 8], further reduction of the duration of

antibiotherapy warrants a consideration in order to reduce the risk of adverse events and the pressure that drives bacterial resistance. [9, 10] The aim of our study is to evaluate the efficacy of short course antibiotic therapy of 2 days compared to 7-day regimen in acute exacerbations of COPD.

Materials And Methods

Study design

This was a prospective, randomized, double blind controlled study including patients admitted to the emergency department (ED) with AECOPD. The study was carried out from Mars 2013 to January 2021. The study protocol has been prepared in accordance with the revised Helsinki Declaration for Biomedical Research Involving Human Subjects and Guidelines for Good Clinical Practice. The study was approved by ethics committees of all participating centers prior to implementation (Monastir and Sousse Universities), and all included patients provided their written informed consent. The study was registered at www.clinicaltrials.gov (NCT03698682), the first registration date of the study was in 09/10/2018.

Settings and Participants

This study included adult patients admitted to four EDs (Fattouma Bourguiba University Hospital Monastir, Sahloul University Hospital Sousse, Farhat Hached University Hospital Sousse and Taher Sfar University Hospital Mahdia). Patients were eligible for inclusion in the cohort if they were 45 years or older; had a smoking history of at least 10 pack-years; had a clinical diagnosis of mild-to-severe COPD, defined as a postbronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity ratio of 0·7 or lower and a postbronchodilator FEV1 of at least 30%, according to Global Initiative of Chronic Obstructive Lung Disease (GOLD). AECOPD was defined as a change in patients' baseline dyspnea, cough, or sputum beyond day-to-day variability, sufficient to warrant a change in management other than optimisation of bronchodilator therapy. Patients were excluded if they presented one of the following conditions: clinical evidence of hemodynamic compromise with need to vasoactive drugs, immediate need for endotracheal intubation, pneumonia, previous adverse reactions to study drug, antibiotic treatment in the previous days, pregnancy or lactation, severe renal (creatinine clearance < 40 mL/min) or hepatic impairment, and lung disease other than COPD that could affect the clinical evaluation of the treatments. Patients with active alcohol or drug abuse were also excluded.

Randomization and intervention

After verification of inclusion and exclusion criteria as well the informed consent, demographic, clinical and biological data were collected at baseline. These included patient's comorbidities, number of exacerbations in the past year, physical examination findings, blood gas analysis, and standard laboratory tests results. Expectorated sputum samples were collected for pathogen culture. All data were recorded in standardized electronic case report forms (DACIMA Tunisia; https://www.dacimasoftware.com). Non-invasive ventilation (NIV) was performed for patients with an arterial carbon dioxide partial pressure > 45 mmHg and arterial pH < 7.35 with supplemental oxygen in

order to obtain a pulse oxygen saturation > 90%. Included patients were then randomized into two groups: short course group (2-Day group) in which patients received one tablet of 500 mg of levofloxacin per day for two days followed by one tablet of placebo per day for the subsequent five days; standard course group (control group) in which patients received one tablet of 500mg of levofloxacin per day for 7 days. The randomization list was provided by a software using a block size so that an equal number of patients were allocated to each treatment group in each block, and patients were assigned sequential ascending random numbers within each center and stratum. This randomization list was not accessible to any individual involved in the study conduct, and patient codes were only allowed to be broken in case of emergency. In order to ensure blinding, active drug as well as placebo tablets were encapsulated for identical appearance and placed in sealed envelopes. All patients who received at least one dose of study medication comprised the intent-to-treat (ITT) population. All patients received intravenous methylprednisolone (0.5 mg/kg every 6 hours), nebulized bronchodilator therapy, and fluid therapy. All other medication was prescribed at the attending physician's discretion. All patients were treated in the ED during the first 48 hours. After 48-hour ED stay, patients were discharged home if they improved; patients with marginal improvement were hospitalized in the ward or in the ICU if they required mechanical ventilation. All patients were monitored until hospital discharge. Adverse effects were reported and rated by the investigator as possibly, probably, or definitely related to the study treatment. Long-term follow-up was made with phone contact at months 1, 3, 6, and 12 after study treatment. If the patient was not reachable, the next of kin and/or the patient's general practitioner were contacted. Physicians who collected outcome data were not aware of treatment allocation. Vital status, the time to next acute exacerbation and the exacerbation-free interval (EFI) were also recorded.

Outcomes analysis

Outcome analysis were performed on the intent-to-treat and per-protocol (PP) populations. Clinical cure rate was considered as the primary outcome. It was defined as resolution of acute signs and symptoms of AECOPD to baseline level (non-exacerbated state), together resolution of fever if present at study entry and no reason for treatment failure. Secondary outcome included EFI, ICU admission rate, and need for additional antibiotics. The decision to initiate new antibiotics was left to the discretion of the treating physician. One-year reexacerbation and death rates were considered as secondary outcomes.

Safety assessment

Adverse events were evaluated in all patients who received at least one dose of the study medication and had one post-inclusion assessment. Adverse events were defined as treatment-emergent adverse events if they developed or worsened during the on-treatment period, defined as the time from the first drug intake up to 7 days after the last drug intake.

Statistical analysis

All statistical analysis were performed using SPSS software, version 20.0. The primary objective was to demonstrate that levofloxacin treatment for 2 days was non-inferior to 7 days of treatment. Analysis at follow-up for primary outcome was based on the ITT population and on per protocol population (PP). The

per-protocol population included the randomized patients included in the ITT population after excluding those with violated inclusion or exclusion criteria and those that did not get the allocated. Sample size calculation was based on non-inferiority testing for clinical cure in the PP population. The non-inferiority margin is 10%. Assuming an underlying clinical cure rate of 80% in the 7-day treatment group, 300 evaluable patients (150 per treatment group) were required to give a power of 80% to detect that the lower bound of the two-sided 95% CI for the difference in rates (2 day group minus 7 day group) was no less than − 10%. To account for a possible 10% patient loss to follow-up, we planned to enrol 330 patients. Qualitative data were described with frequencies and percentages; quantitative data were described with mean and standard error or with median, interquartile interval, and range. Baseline characteristics of patients were compared with the unpaired *t* test or the Wilcoxon rank sum test for continuous variables, depending on their distributions. Percentage differences were compared with the Fisher exact test (or the χ^2 test, when appropriate). In case of skewed distributions, continuous variables were logarithmically transformed for further analyses. Differences between both groups in cure rate and secondary outcomes were assessed with hazard ratio (HR). Comparisons of the incidence rates of AEs between the two study drug groups were performed descriptively. No interim analyses were planned or performed for this study. All statistical tests were two-sided and performed at the 0.05 significance level.

Results

A total of 712 patients were screened and 310 patients were randomized (ITT population) to receive 2-day course of levofloxacin (*n* = 155) or 7-day course (*n* = 155). The PP population comprised 246 patients at the end of follow-up (118 and 119 patients respectively in 2-day and 7-day groups) (Fig. 1). The main reason for withdrawing patients from the ITT analysis was incomplete end-of therapy evaluation (26 patients in 2-day course group and 22 patients in 7-day course group). An additional 10 patients were excluded from the ITT population as they had less than 7 days treatment in 7-day course group. Description of baseline characteristics of the patients is given in Table 1. Both treatment groups had similar baseline demographics and clinical findings (Table 1). They were also similar with respect to severity criteria of the episode assessed by the number of exacerbations during the previous year and Anthonisen classification. Adequate sputum sampling was obtained from 58.3% of the overall population. The two treatment groups were similar in the number of pathogens isolated at pre-therapy (44 *versus* 37 respectively in 2-day course and 7-day course groups). *S. pneumoniae*, the most common pathogen found, was isolated from 20 patients. The other most common pathogens identified at pre-therapy were *C. pneumoniae* (n = 18), and *Haemophilus influenzae* (n = 16) (Table 2).

Primary outcome

Clinical outcomes for the ITT and PP populations showed that a 2-day regimen of levofloxacin was non-inferior to a 7-day regimen (Table 3). In ITT population, cure rate was similar in the 2 groups [79.3% and 74.2% in the 2-day group and 7-day group respectively; HR 1.3; 95% CI, 0.87 to 1.93; p = 0.18]. In PP

population, cure rate was 78% and 69% in the 2-day group and 7-day group respectively (HR 1.00; 95% CI, 0.67 to 1.49; p = 0.98).

Secondary outcome

Data regarding secondary outcome in ITT population are shown in Table 3. Rate of additional antibiotic prescriptions was similar in both groups [3.2% and 1.9% in the 2-day group and 7-day group respectively; (p = 0.43)]. ICU admission rate was 5.1% in the 2-day group and 3.2% in the 7-day group (p = 0.65). One-year reexacerbation rate was not significantly different between the 2 groups (34.8% versus 29% in the 2-day group and 7-day group respectively; (p = 0.19). Median EFI was similar in both treatment groups [121 days (interquartile range 99–149) versus 110 days (interquartile range 89–132) in the 2-day and 7-day groups respectively; p = 0.73]. Survival curves for combined death and reexacerbation events did not differ significantly in the 2 groups when compared by the log-rank test (p = 0.78; Fig. 2). One-year death rate was not significantly different between the 2 groups (5.2% versus 7.1% in the 2-day group and 7-day group respectively; (p = 0.26).

Safety

The incidence of adverse events was low in this study [3 patients in the 2-day course group (1.9%) and 6 patients in the 7-day course group (3.9%); odds ratio 95% CI 0.5 (0.12–1.96)]. The most frequently reported treatment-related adverse event was gastrointestinal (2 patients in the 2-day group and 3 patients in the 7-day group). Most adverse events were mild and did not require discontinuation of the treatment study.

Discussion

Our results showed that in patients admitted with AECOPD, a 2-day course of Levofloxacin was not clinically inferior to a standard 7-day course in terms of cure rate, need for additional antibiotics or ICU admission, hospital readmissions rate, and exacerbation free interval.

The purpose behind shortening antibiotherapy duration was mainly to limit bacterial resistance and reduce healthcare cost provided that their clinical efficacy is not impaired.[11] A systematic review of many common infections, including acute respiratory and urinary infections found that, in general, shorter treatments of antibiotics were as effective as longer [12]. In AECOPD, numerous studies have been performed to evaluate this possibility particularly with fluoroquinolones. They showed that short course fluoroquinolone therapy was as effective as the standard course and, in some studies, it was associated with faster recovery, fewer relapses, prolonged duration between episodes, and less hospitalization.[13] The recent meta-analysis conducted by Stolbrink et al. [6] included 10 randomized controlled trials evaluating short and standard antibiotic course with the same antibiotic classes. The total number of patients in this study was 3979 patients, of which 1990 patients received an antibiotic course of 6 days or fewer, and 1989 received that of 7 days or more. Three of the studies involving fluoroquinolones were

in favour of short course treatment and all of them defined the short course regimen as 5-day duration.[14–16] In a prospective trial stratifying patients with AECOPD into uncomplicated or complicated groups, Martinez et al advocated the use of high dose levofloxacin (750 mg) for 3 days in uncomplicated group and for 5 days in complicated group.[17] In our study, we reduced the course to two days which is the shortest antibiotic duration so far in acute exacerbations of COPD but without patients' stratification and without increasing the dose of levofloxacin. The main strengths of our trial were that it was large, double blind, and multicentre and was conducted over more than three years covering all four seasons with a minimal loss to follow up and good adherence to treatment.

How can an antibiotherapy as short as two days be as effective as a longer one? The fact that some acute bacterial infections are cured with 1 day of antibiotics would support the principle that, if antibiotics are useful, their positive effects are mainly observed within the early infection period.[18] This implies that the effect of antibiotics are particularly important in the acute phase of infection; it accelerates the decrease of the bacterial growth rate allowing the immune system to acquire an enhanced ability to fight the microorganism.[19] Except in a few key circumstances, sterility of the infection site is not necessary for clinical healing. In addition, the dogma that stopping antibiotic treatment early encourages resistance to antibiotics is not evidence based. [6, 9] On the contrary, reducing the exposure of patients to antibiotics will reduce the risk of selective pressure that drives bacterial resistance.[20] Furthermore, besides antibiotic treatment duration, timing of treatment is an important factor of success. In a recent study using a mathematical model of a generic bacterial infection, Paupério et al showed that the difference between the short and the standard treatments strongly depends on the timing of treatment.[21] Another important consideration in pharmacodynamics is the presence of post antibiotic effect (PAE), which refers to the ability to suppress bacterial growth after a scripted exposure to an antibiotic. Similar to the aminoglycosides, fluoroquinolones have concentration-dependent bactericidal activity and a prolonged PAE against gram positive and gram-negative bacteria.[22, 23]

One could further investigate the optimal antibiotic duration using the kinetics of serum inflammatory markers. Many studies assessed the effects of implementation of procalcitonin guidelines on antibiotic prescription in cases of AECOPD. However, it seems that procalcitonin-guided antibiotic strategy could reduce antibiotic prescriptions, but is unable to diminish antibiotic exposure duration compared to standard course.[24, 25]

The findings of the present study must be interpreted in the context of several potential limitations. First, we excluded patients with hemodynamic or respiratory instability requiring intensive care unit and mechanical ventilation upon their admission. Therefore, our findings cannot be extrapolated to unstable patients with such severe COPD exacerbations. Second, while we advocate shortening courses of fluoroquinolones therapy, particularly in light of their concentration dependent killing activity, extrapolating these results to other antibiotic classes is presumptive. Third, it may be argued that shorter course was found to be as effective as longer one because antibiotics are largely ineffective at any dose. This could be true; however, in our study we only included patients belonging to type 1 and 2 of

Anthonisen classification and most of our patients had a high level of C-reactive protein which is an accepted marker for antibiotic treatment.

As a conclusion, our study showed that a 2-day course of levofloxacin was as effective as 7-day course in AECOPD. Our findings should probably be considered if we want to avoid antibiotic overuse and antibiotic resistance.

Abbreviations

AECOPD: acute exacerbation of chronic obstructive pulmonary disease

EFI: exacerbation free interval

ED: emergency department

ITT: intent-to-treat

Declarations

Acknowledgments

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Ethics approval and consent to participate

This study was conducted in accordance with the 'Declaration of Helsinki' as a statement of ethical principles for medical research involving human subjects, including the study of identifiable human substances and data. This study was approved by the Institutional Review Board of Monastir and Sousse Universities. And all included patients provided their written informed consent.

Consent to publication

Not applicable..

Author Contributions Statement

SM and IT wrote the protocol. MAM, AS, MT, LB, KBHA and RR drafted this manuscript and performed the statistical analyses and interpretation of the findings. The statistical analyses were confirmed by RR, IT, YBD, MHG, AB, KB and HB. NS, AB, MM, ZM, WB and RB contributed to the preparation of the manuscript. AA and SN approved the final manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and analysed during the current study are available from Semir Nouira (email: semir.nouira.urg@gmail.com) on reasonable request.

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Yosra Ben Daya is employed by Medis Laboratories. Medis Laboratories did not play a role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript and did not provide financial support in the form of authors' salaries. Medis Laboratories provided support in the form of study treatments (levofloxacin and placebo) as well as laboratory tests. The specific roles of these authors are detailed in the 'author contributions' section. The funder did not provide support in the form of salaries for authors and did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section.

References

1. B.R. Celli, W. MacNee, A. Agusti, A. Anzueto, B. Berg, A.S. Buist, P.M.A. Calverley, N. Chavannes, T. Dillard, B. Fahy, A. Fein, J. Heffner, S. Lareau, P. Meek, F. Martinez, W. McNicholas, J. Muris, E. Austegard, R. Pauwels, S. Rennard, A. Rossi, N. Siafa. "Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper." European Respiratory Journal. 2004; 2004; 23:932 – 46
2. Jacobs DM[1], Pandit U, Sethi S. Acute Exacerbations in Chronic Obstructive Pulmonary Disease: Should We Use Antibiotics and if So, Which Ones? Curr Opin Infect Dis. 2019; 32:143–151.
3. Roede, B M. "Antibiotic treatment is associated with reduced risk of a subsequent exacerbation in obstructive lung." Thorax. 2008; 63:968–73.
4. Desai H, Richter S, Doern G, et al. Antibiotic resistance in sputum isolates of Streptococcus pneumoniae in chronic obstructive pulmonary disease is related to antibiotic exposure. COPD. 2010; 7:337–44.
5. Pérez-Trallero E, Marimón JM, González A, Ercibengoa M, Larruskain J. In vivo development of high-level fluoroquinolone resistance in Streptococcus pneumoniae in chronic obstructive pulmonary disease. Clin Infect Dis. 2005; 41:560–4.
6. Marie Stolbrink, Jack Amiry, and John D Blakey. Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A systematic review. Chron Respir Dis. 2018 Aug; 15(3): 225–240.
7. Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. BMJ. 2017;358:j3418.
8. Bennett JB, Crook SJ, Shaw EJ, et al. A randomized double blind controlled trial comparing two amoxycillin regimens in the treatment of acute exacerbations of chronic bronchitis. J Antimicrob Chemother 1988. 21: 225–232.

9. Roede BM, Bresser P, El R, et al. Three vs. 10 days of amoxycillin-clavulanic acid for type 1 acute exacerbations of chronic obstructive pulmonary disease: a randomised, double-blind study. Clin Microbiol Infect. 2007; 13:284–290.
10. Spellberg B The New Antibiotic Mantra-"Shorter Is Better." JAMA Intern Med. 2016; 176:1254–1255.
11. Rice LB. The Maxwell Finland Lecture: for the duration-rational antibiotic administration in an era of antimicrobial resistance and clostridium difficile. Clin Infect Dis. 2008; 46:491–496.
12. Thorpe KE, Joski P, Johnston KJ. Antibiotic-Resistant Infection Treatment Costs Have Doubled Since 2002, Now Exceeding $2 Billion Annually. Health Aff (Millwood). 2018; 37:662–669.
13. Hanretty AM, Gallagher JC. Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials. Pharmacotherapy. 2018; 38:674–687.
14. Anzueto A, Miravitlles M. Short-course fluoroquinolone therapy in exacerbations of chronic bronchitis and COPD. Resp Med. 2010; 104:1396–403.
15. Chodosh S, Deabate CA, Haverstock D, Aneiro L, Church D. "Short course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis." Resp Med. 2000; 94:18–27.
16. Langan CE, Zuck P, Vogel F, et al. "Randomized double-blind study of short-course (5 day) grepafloxacin versus 10 day clarithromycin in patients with acute bacterial exacerbations of chronic bronchitis." J Antimicrob Chemoth. 1999; 44:515–23.
17. Masterton RG, Burley C.J, The Study Group. "Randomized, double-blind study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis." Intern J Antimicrob Agents. 2001; 18:503–12.
18. Martinez FJ, Grossman RF, Zadeikis N, Fisher AC, Walker K, Ambruzs ME, Tennenberg AM. Patient stratification in the management of acute bacterial exacerbation of chronic bronchitis: the role of levofloxacin 750 mg. Eur Respir J. 2005; 25:1001–10.
19. Wald-Dickler N, Spellberg B. Short-course Antibiotic Therapy—Replacing Constantine Units With "Shorter Is Better". Clin Infect Dis. 2019; 69:1446–1449.
20. Ankomah P, Levin BR. 2014 Exploring the collaboration between antibiotics and the immune response in the treatment of acute, self-limiting infections. Proceedings of the National Academy of Sciences U S A. 2014; 10;111:8331-8.
21. Pauperio FFS, Ganusov VV, Gjini E. Mathematical modeling links benefits of short and long antibiotic treatment to details of infection bioRxiv 555334 [Preprint] August 14, 2019.; Available from: https://doi.org/10.1101/555334.
22. Cunha CB, Opal SM. Antibiotic Stewardship: Strategies to Minimize Antibiotic Resistance While Maximizing Antibiotic Effectiveness. Med Clin North Am. 2018; 102:831–843.
23. Lode H, Borner K, Koeppe P. Pharmacodynamics of fluoroquinolones. Clin Infect Dis. 1998; 27:33–9.
24. Turnidge J. Pharmacokinetics and pharmacodynamics of fluoroquinolones. Drugs 1999; 58(suppl 2):29–36.

25. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, Wootton M, Hood K, Phillips R, Melbye H, Llor C, Cals JWL, Naik G, Kirby N, Gal M, Riga E, Francis NA. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. N Engl J Med. 2019; 381:111–120.
26. Li Z, Yuan X, Yu L, Wang B, Gao F, Ma J. Procalcitonin-guided antibiotic therapy in acute exacerbation of chronic obstructive pulmonary disease: An updated meta-analysis. Medicine (Baltimore). 2019; 98:e16775.

Tables

Table 1. Patients' demographic and clinical characteristics at admission*

	2-day group n=155	7-day group n=155	p
Age years, mean (SD)	68.2(10.5)	67.1(10.0)	0.34
Sex ratio M/F	132/23	136/19	0.51
Smoking (pack-years), mean (SD)	42.8(15.9)	44.6(15.7)	0.39
Peak Expiratory Flow (L/min), mean (SD)	54(72.7)	41.5(60.8)	0.33
Body mass index (kg / m^2), mean (SD)	26.5(4.3)	26.5(5.8)	0.91
Exacerbations within the past year, mean (SD)	2.4(1.5)	2.1(0.9)	0.17
Past medical history n (%)			
Hypertension	42 (27)	50 (32.2)	0.39
Heart failure	5 (3.2)	5 (3.2)	0.96
Diabetes	29 (18.7)	36 (32.2)	0.37
Anthonisen classification n (%)			0.74
Type 1	69 (44.5)	66 (42.5)	
Type 2	74 (47.6)	82 (57.5)	
Blood pressure			
Systolic mmHg, mean (SD)	142(25)	138(22)	0.71
Diastolic mmHg, mean (SD)	71(21)	73(22)	0.63
Temperature (°C), mean (SD)	37.1(0.5)	37.1(0.6)	0.99
Pulse rate (b/min), mean (SD)	104(26)	110(20)	0.97
Respiratory rate (c/min), mean (SD)	27(10)	29(11)	0.87
Blood gas			
pH, median (IQR)	7.35(7.30-7.42)	7.34(7.29-7.40)	0.18
$PaCO_2$ (mmHg), median (IQR)	42 (37-49)	43 (37-50)	0.39
White blood cells (x10^3/mm^3)	13.8±8.8	13.9±8.8	0.93
C reactive protein (mg/L), median (IQR)	43 (21-95)	47 (24-101)	0.62

* intent-to-treat population; IQR, interquartile range

Table 2. Bacteriologic results

	2-day group	7-day group
Branhamella catarrhalis	2	4
Haemophilus influenzae	9	7
Klebsiella pneumoniae	1	2
Pseudomonas aeruginosa	5	4
Staphylococcus aureus	2	0
Streptococcus pneumoniae	11	9
Chlamydophila pneumonia	8	10
Mycoplasma pneumoniae	4	2
Coxiella burnetii	2	1
Total	**44**	**37**

Table 3. Clinical Outcomes

Patient Outcomes	2-day group n= 155	7- day group n= 155	P Value	OR (95% CI)
Primary Outcome at 12 months				
Mortality n (%)				
ITT	8 (5.2)	11 (7.1)	0.26	0.61(0.26-1.44)
PP	8 (6.6)	10 (8.1)	0.65	1.25 (0.47-3.28)
Reexacerbations n (%)				
ITT	54 (34.8)	45(29.0)	0.27	0.76 (0.47-1.23)
PP	48 (39.3)	40 (32.2)	0.24	0.73 (0.43-1.23)
Combined Events n(%)				
ITT	62 (40.0)	56(36.1)	0.48	0.84 (0.53-1.34)
PP	56 (45.9)	50 (40.3)	0.37	1.13 (0.87-1.5)
Secondary Outcome*				
Need for additional antibiotic therapy n(%)	5 (3.2)	3 (1.9)	0.43	1.72 (0.43-6.89)
ICU Admissions n(%)	8 (5.1)	5 (3.2)	0.32	1.68 (0.58-4.84)
Exacerbation free interval days; median (IQR)	121 (99-149)	110(89-132)	0.51	1.02 (0.98-1.06)

Figures

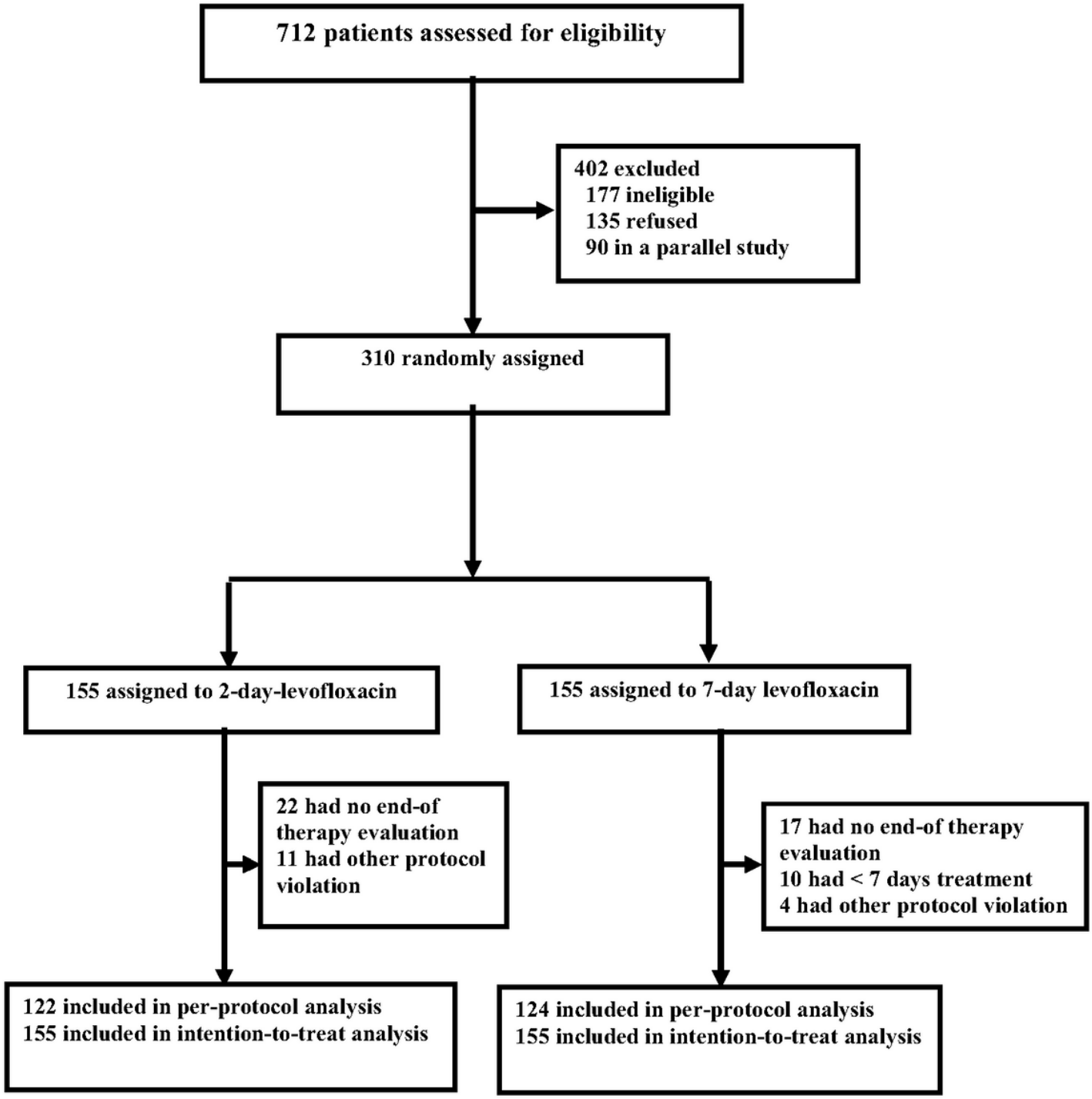

Figure 1

Trial profile.

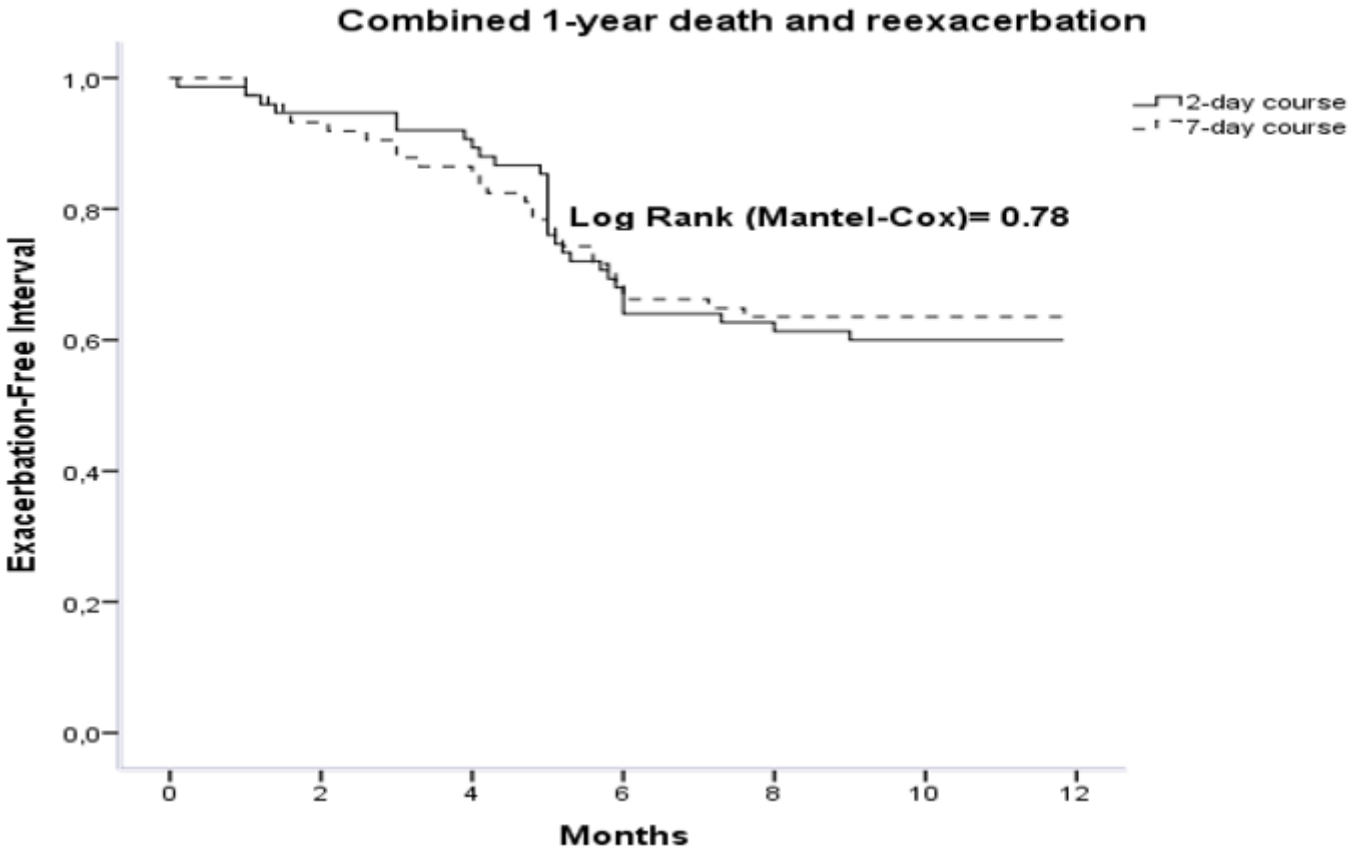

Figure 2

Survival curves in 2-day and 7-day regimen groups. Both groups did not differ significantly when compared by the log-rank test (p=0.78).