Iranian Journal of Microbiology
*Volume 14 Number 4 (August 2022) 458-465*

ORIGINAL ARTICLE

# Levofloxacin versus ceftriaxone and azithromycin for treating community-acquired pneumonia: a randomized clinical trial study

**Davood Yadegarynia[1], Shabnam Tehrani[1*], Fatemeh Maghsoudi Nejad[2], Fatemeh Shojaeian[3], Amirreza Keyvanfar[1]**

*[1]Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
*[2]Department of Infectious Diseases, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
*[3]Department of Surgical Pathology, Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University School of Medicine, Baltimore, US*

**Received:** March 2022**, Accepted:** June 2022

## ABSTRACT

**Background and Objectives:** We compared two common antibiotic regimens for the treatment of mild to moderate CAP: levofloxacin versus β-lactam and macrolide combination; in terms of their efficacy and side effects.
**Materials and Methods:** Patients with mild to moderate CAP were randomized into two groups. Group I received a combination of 1 gram ceftriaxone daily and 500 mg azithromycin daily for 5-7 days. Group II received levofloxacin 750 mg daily for five days. The signs and symptoms, hospitalization length, and the side effects were investigated.
**Results:** There were 77 and 74 patients in groups I and II. The vital signs of group II were significantly better on the 3rd day of admission, except for the temperature (P=0.09). The $O_2$ saturation of group II was markedly improved on the 5th day of admission (P=0.0061). In terms of clinical symptoms and hospitalization length, group II was considerably better. However, the rate of side effects in both groups was similar (P=0.885).
**Conclusion:** Hospitalized patients with mild to moderate CAP might take more advantage of fluoroquinolone administration. It could improve the patients' signs and symptoms and reduce hospitalization length, compared with the combination of macrolide and cephalosporin, with the same rate of side effects.

**Keywords:** Pneumonia; Community-acquired infections; Anti-bacterial agents; Levofloxacin; Ceftriaxone; Macrolides; Clinical trial

## INTRODUCTION

One of the most common respiratory diseases with potentially serious side effects is community-acquired pneumonia (CAP), which its annual prevalence in developed countries varies from 1.6-16 cases per 1000 (1, 2). Although a couple of antibiotic regimens are suggested for its treatment, it remains one of the leading causes of death from infectious diseases and is associated with considerable morbidity, mortality, and related costs. About 20% of the patients diagnosed with CAP will require hospitalization, and the rest will be treated in the outpatient setting (3-5). Following the diagnosis, an appropriate and fast initiation of antibiotic therapy is vital to properly manage and cure the patients (6). However,

*Corresponding author: Shabnam Tehrani, MD, Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: +98-2122439963 Fax: +98-2122439964 Email: Tehrani.shabnam89@yahoo.com

several factors could influence antibiotic selection, including drug resistance, numerous choices, route of consumption, long period of definite microbiological diagnosis, and side effects (6, 7). Considering both side effects and treatment failure, choosing the most appropriate drug regimen would prevent the costs and burdens of the disease on patients and the health systems (4).

The most recent guidelines suggest oral macrolide and beta-lactam/macrolide or a fluoroquinolone in the outpatient setting for patients with and without comorbidities and risk factors, respectively (7, 8). Although fluoroquinolone has been shown less treatment failure, it is associated with a range of side effects on muscles, tendons, joints, nerves, and central nervous system, in addition to QT prolongation (9, 10). Patients usually receive respiratory fluoroquinolones, such as levofloxacin or intravenous beta-lactam /macrolide in the inpatient setting. Notably, in the ward-based treatment, they are typically treated with either levofloxacin (750 mg) or azithromycin (500 mg) combined with ceftriaxone (1 g) (7, 11).

Macrolide resistance has been reported in over 25% of the cases (12). Moreover, the antimicrobial susceptibility testing of previous surveys in the region of this study, Tehran, showed that most of the isolates from nasopharyngeal specimens of healthcare workers were susceptible to levofloxacin (13). In another study, most *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were resistant to ceftriaxone, and *P. aeruginosa* was found to have low resistance-level to levofloxacin and ciprofloxacin (14). Regarding *S. pneumoniae* resistance, the susceptibility of the bacteria to the erythromycin, ceftriaxone, and levofloxacin were 23.8%, 90.4%, and 95.3%, respectively, in a previous study from Tehran (15). All the mentioned survey results favor a low resistance level to levofloxacin compared with the others.

Developing a better understanding of the side effects, treatment guidelines, and the drugs' costs will improve our comprehension of the trade-offs associated with current treatments. As the drug resistance depends on the region, it is essential to investigate the efficacy of antibiotics for different diseases or organisms in each area. Here, we have investigated the efficacy, and side effects of two standard drug regimens, respiratory fluoroquinolone versus macrolide and beta-lactam, in patients admitted to the hospital with mild to moderate CAP.

## MATERIALS AND METHODS

This prospective parallel clinical trial was carried out on patients with community-acquired pneumonia (CAP) admitted to the Labbafinejad hospital from March 2019 to October 2020. Patients were randomized into two groups using a randomized block table to receive either ceftriaxone + macrolide or levofloxacin. The participants of both groups have been matched in terms of age, sex, and comorbidities such as hypertension (HTN), asthma, chronic obstructive pulmonary diseases (COPD), congestive heart failure (CHF), ischemic heart disease (IHD), and diabetes. Patients in arm I received the combination of ceftriaxone (third-generation cephalosporin) 1 gram daily intravenously and tablets of azithromycin (macrolide) 500 mg once daily for 5-7 days; arm II received levofloxacin (Tavanex) 750 mg orally once daily for total five days. All the patients were hospitalized during the trial.

Patients diagnosed with CAP (new infiltrates on a chest radiograph, in addition to two or more of the following symptoms: fever, pleuritic chest pain, dyspnea, leukocytosis, new-onset or exacerbated cough with or without sputum, and abnormal respiratory sound) were enrolled. In the following, patients whose severity of their disease was defined as mild to moderate based on the APACHE II score system were included in the study (16). Exclusion criteria were: infection with microorganisms resistant to the regimens used in this study, patients with cystic fibrosis, evidence in favor of empyema in the patient's radiography images, HIV/AIDS, patients with nosocomial pneumonia, a history of seizure, severe mental disorders, a history of allergy to drugs used in the study, pregnant or lactating woman, severe renal disease (creatinine clearance <30 mL/min), and a history of taking antibiotics in the last three months.

Patients were evaluated on the first, third, and fifth day of admission. To assess the efficacy of each regimen, we have followed the regression of the patients' clinical parameters (such as vital signs), duration of hospitalization, and the drugs' side effects and complications.

Evaluation indicators were as follows:

1. Changes in clinical signs and symptoms (improvement of vital signs, presence or absence of the cough and sputum),
2. Duration of hospitalization,

3. Safety profile (side effects) of all patients who received at least two doses of the drugs. (They have evaluated for side effects, such as skin, gastrointestinal, allergic, central nervous system, etc.)

SPSS 25.0v performed the data analysis, and the significance level was considered 0.05 (2-tailed). All data are presented as frequency (percentage) or mean ± standard deviation (SD). Student t-test and Chi-Square test used to compare the groups.

The Ethics Committee approved the study of Shahid Beheshti University of Medical Sciences (ID: IR.SBMU.MSP.REC.1395.292). Written informed consent was obtained from all participants before the study. Confidentiality of patients' data was maintained. Patients could exclude from the analysis whenever they want. Besides, the drugs would be discontinued by any side effects or complications that required intervention.

## RESULTS

During the study, 192 individuals were candidates for enrollment, and after assessing the inclusion and exclusion criteria, 160 patients were randomized. Finally, 77 individuals in group I and 74 individuals in group II continued to meet the requirements until the end of the study. The Consort Flow Diagram depicts the different stages of the clinical trial (Fig. 1).

Eventually, 151 patients were evaluated, 77 individuals (55.8% male) received ceftriaxone and azithromycin, and 74 (50% male) patients administrated levofloxacin. The mean age of the participants was 49.22 ± 7.51 and 51.04 ± 6.56 in groups I and II, respectively (P=0.115). 16 (20.7%) and 13 (17.5%) individuals were smokers among participants in groups I and II, respectively (P=0.674). Patients were matched in terms of sex, smoking, and past medical history. The patients in groups I and II not differed in terms of comorbidities (P>0.05). Moreover, the patients' vital signs in both groups have no observable differences. The baseline characteristics of patients are depicted in Table 1.

Patients were evaluated on the third day of admission. The results show that the respiratory rate and $O_2$ saturation differed significantly among the groups (P=0.001 and <0.0001, respectively). According to the lower respiratory rate and higher $O_2$ saturation observed in group II, patients receiving levofloxacin had a better clinical condition on 3rd day of admission. However, the temperature of the patients not differed (P=0.09). Patients have been evaluated on the 5th day of admission similarly. As it is depicted in Table 2, the $O_2$ saturation of the participants in group II was significantly better than in group I; however, the temperature and respiratory rate not differed remarkably (P= 0.061 and 0.42, respectively). It presents that levofloxacin could improve the patients' clinical condition in less time than the combination of azithromycin and ceftriaxone.

Regarding patients' symptoms, the sputum of 58 and 69 patients in groups I and II was regressed on the 5th day, and the P-value of 0.004 shows a significant difference among the groups. In addition to the sputum, the cough improved in 48 and 60 patients on the 5th of admission, which favored a better impact of levofloxacin than the other regimen (P=0.01). The same results were observed on the 3rd day of admission, which might favor a better and faster response to therapy in group II.

Different side effects have been evaluated in patients during the treatment. Ten individuals in group I and 11 patients in group II complained of various symptoms, including nausea, skin rash, and headache. Hence, there was no significant difference in side effects between groups I and II (P=0.885). The average duration of hospitalization was 6.72 and 5.14 in groups I and II, demonstrating a notable difference (P-value <0.001).

## DISCUSSION

The current study evaluated two standard antibiotic regimens prescribed in CAP for patients admitted to the hospital. Our study demonstrated that hospitalized patients with mild to moderate pneumonia might benefit from respiratory fluoroquinolone compared to macrolide/beta-lactam. In particular, patients administered levofloxacin showed better and faster improvement of signs and symptoms (improvement of vital signs, coughs, and sputum), especially on 3rd day of admission, and lower duration of hospitalization, with the same rate of side effects, compared with the combination of azithromycin and ceftriaxone. As one of the most critical and common respiratory diseases, appropriate treatment of community-acquired pneumonia could reduce the disease's burden on the community and the patients. Hence, proper antibiotic selection and initiation, which could improve the patients' and healthcare systems' outcomes, are subject

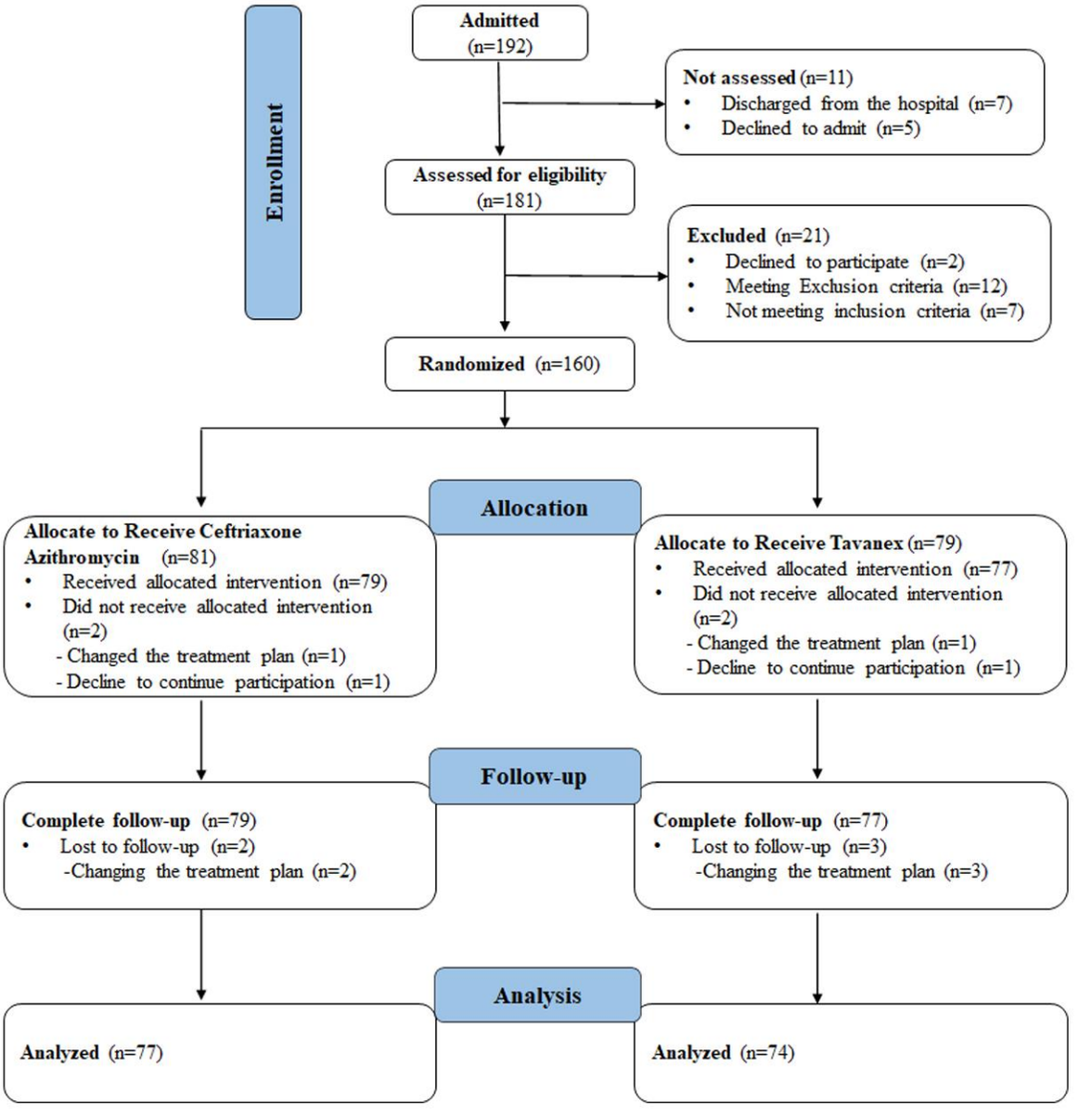


**Fig. 1.** The CONSORT Flow Diagram of the study

to significant trade-offs. In particular, a regimen associated with a lower retreatment frequency might be related to a higher rate of side effects (10).

For both inpatients' and outpatients' settings, the most common pathogens associated with CAP include *Streptococcus pneumoniae, Hemophilus influenzae,* and *Moraxella catarrhalis.* Gram-negative Bacilli, methicillin-resistant *Staphylococcus aureus* (MRSA), and viruses are also known to be less common causes of CAP. Despite the availability of antimicrobial therapies, the recent emergence of drug-resistant pneumococcal and staphylococcal isolates has limited the effectiveness of currently available regimens and made the antibiotic resistance study important and crucial (5).

*Streptococcus pneumoniae* is a common commensal and opportunistic pathogen. Suspected pneumococcal upper respiratory infections and pneumonia are often treated with macrolide antibiotics. Macrolides are bacteriostatic antibiotics and inhibit protein synthesis by binding to the 50S ribosomal subunit. The widespread use of macrolides could be associated with increased macrolide resistance in *S. pneumoniae,* and the treatment of pneumococcal infections with macrolides may result in treatment failures (17). Moreover, macrolide resistance among *Streptococ-*

**Table 1.** Comparing the baseline characteristics of patients in Group I and Group II

| Variables | Group I (n=77) | Group II (n=74) | P-Value |
|---|---|---|---|
| Gender | | | |
| Male | 43 (55.8%) | 37 (50%) | 0.424 |
| Female | 34 (44.1%) | 37 (50%) | |
| Age (Mean) | 49.22 ± 7.51 | 51.04 ± 6.56 | 0.115 |
| Smokers | 16 (20.7%) | 13 (17.5%) | 0.674 |
| Comorbid Diseases | | | |
| COPD | 15 (19.4%) | 13 (17.5%) | 0.636 |
| HTN | 20 (25.9%) | 11 (14.8%) | 0.20 |
| CHF | 8 (10.3%) | 5 (6.7%) | 0.28 |
| Asthma | 13 (16.8%) | 15 (20.2%) | 0.634 |
| IHD | 10 (12.9%) | 9 (12.1%) | 0.86 |
| DM | 15 (19.4%) | 13 (17.5%) | 0.091 |
| Presenting Vital Signs | | | |
| Temperature (c) | 38.54 ± 1.26 | 38.46 ± 1.89 | 0.05 |
| Respiratory Rate (/min) | 26.24 ± 4.32 | 25.91 ± 4.18 | 0.697 |
| Saturation | | | |
| WO Supplementary $O_2$ (%) | 87 ± 5.35 | 87 ± 4.89 | 0.299 |
| With Supplementary $O_2$ (%) | 95 ± 6.12 | 95 ± 4.19 | |

COPD: Chronic Obstructive Pulmonary Disease; HTN: Hypertension; CHF: Congestive Heart Failure; IHD: Ischemic Heart Disease; DM: Diabetes Mellitus; WO: Without

Data are presented as mean ± standard deviation (SD) or frequency (%)

**Table 2.** Comparing clinical findings of the participants in both groups after initiation of the treatment.

| Characteristics | Group I (n=77) | Group II (n=74) | P-Value |
|---|---|---|---|
| Vital Signs | | | |
| 3rd day of admission | 37.18 ± 1.56 | 37.1 ± 1.78 | 0.09 |
| Temperature (c) | 22.84 ± 4.12 | 21.14 ± 3.95 | 0.001 |
| Respiratory Rate (/min) | 88 ± 3.96 | 90 ± 4.25 | <0.001 |
| Saturation $O_2$ (%) | | | |
| 5th day of admission | 36.96 ± 1.70 | 36.87 ± 1.53 | 0.061 |
| Temperature (c) | 17.6 ± 2.76 | 18.1 ± 3.1 | 0.42 |
| Respiratory Rate (/min) | 92 ± 3.80 | 93 ± 4.12 | 0.006 |
| Saturation $O_2$ (%) | | | |
| Symptoms | | | |
| 3rd day of admission | 19 (24.6%) | 41 (55.4%) | <0.001 |
| Absence of Sputum | 19 (24.6%) | 35 (47.2%) | 0.003 |
| Improvement of Cough | | | |
| 5th day of admission | 58 (75.3%) | 69 (93.2%) | 0.004 |
| Absence of Sputum | 48 (62.3%) | 60 (81%) | 0.01 |
| Improvement of Cough | | | |
| Side Effects | 10 (12.9%) | 11 (14.8%) | 0.885 |
| Nausea | 3 (3.8%) | 5 (6.7%) | 0.158 |
| Rash | 6 (7.7%) | 5 (6.7%) | |
| Headache | 0 | 1 (1.3%) | |
| Others | 1 (1.2%) | 0 | |
| Days of Hospitalization | 6.72 ± 3.12 | 5.14 ± 2.67 | <0.001 |

Data are presented as mean ± standard deviation (SD) or frequency (%)

*cus pneumoniae*, the most common cause of community-acquired pneumonia, increases in the United States. This increasing resistance might turn into a critical problem in the near future (18). It is noteworthy that the risk of antibiotic resistance could be exacerbated by multiple drug class usage, beta-lactam, and macrolide (19). On the other hand, levofloxacin belongs to the respiratory fluoroquinolones family and is considered a broad-spectrum antibiotic. Today, due to the increased resistance to beta-lactams and macrolides, their usage has also been recommended. Levofloxacin is a concentration-dependent antibiotic, and higher doses maximize its bactericidal effects in a short time. This drug also promotes good tissue penetration and proper concentration (20-22).

The Infectious Disease Society of America (IDSA) guidelines recommend doxycycline, macrolides, or fluoroquinolones as the preferred antimicrobial agents for empiric therapy of most outpatient CAP cases. In addition, patients admitted to the general medical wards with CAP diagnosis could receive either monotherapy of respiratory fluoroquinolone or a combination of a third-generation cephalosporin and a macrolide (20, 23). Different studies investigated these two standard regimens. A survey conducted in the US demonstrated that patients who received levofloxacin have lower hospitalization duration, which is consistent with the current study (24). A couple of other investigations have approved levofloxacin's superiority over macrolide/beta-lactam based on clinical symptoms and duration of stay (25, 26). We also concluded that the patients who received levofloxacin have a faster and more appropriate response to therapy based on their clinical signs and symptoms. Moreover, in previous studies, respiratory fluoroquinolones have shown less treatment failure than beta-lactams (27).

It should be noted that oral levofloxacin is rapidly absorbed and bioequivalent to the intravenous formulation. The patients can switch between these formulations, which results in more options for the therapeutic regimens (28). In a study conducted by Belforty on the route of fluoroquinolones administration in hospitalized patients, oral treatment was associated with lower mortality rates and shorter hospital stays. Patients in this group also experienced fewer changes in treatment regimens. But there was no significant difference between hospital mortality and ICU transfer between the groups. Hence, hospitalized patients can be safely treated with an oral respiratory fluoroquinolone (29). The studies have shown that the conversion of intravenous drugs to oral ones decreased the length of hospital stays and produced significant cost savings, both on medication and the total inpatient expenditures (30). Economic pressures on healthcare delivery have necessitated a focus on reducing costs while maintaining and improving the quality of care. A growing consensus holds that switching from intravenous to oral therapy is cost-effective (31, 32); hence, we used oral fluoroquinolones in our survey.

However, serious side effects of levofloxacin have been reported (33). Some studies stated that fluoroquinolones are more associated with severe side effects than macrolides and cephalosporins (34). In this study, the rate of early side effects in both groups was not significantly different, contrasting with some other tasks (10, 34). It might be due to the patients' short follow-up in our study or the differences in fluoroquinolone usage (inpatients setting). However, most previous studies demonstrated the same rate of side effects in both regimens (35). In the current study, patients were hospitalized, and we encountered fewer safety-related issues observed in the outpatient population. Although, more studies with higher participants, longer follow-ups, and more indicators are needed to determine fluoroquinolone effectiveness and side effects accurately.

## CONCLUSION

Levofloxacin showed improvement of clinical signs and symptoms in more patients and in less time, rather than the combination of azithromycin and ceftriaxone, with a shorter duration of hospitalization and the same rate of side effects. Hence, this study demonstrated that hospitalized patients with mild to moderate CAP might benefit from respiratory fluoroquinolones such as levofloxacin compared with the combination of beta-lactam and macrolide.

## REFERENCES

1. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med* 2014; 371: 1619-1628.
2. Capelastegui A, España PP, Bilbao A, Gamazo J, Medel F, Salgado J, et al. Study of community-acquired

pneumonia: incidence, patterns of care, and outcomes in primary and hospital care. *J Infect* 2010; 61: 364-371.
3. Brar NK, Niederman MS. Management of community-acquired pneumonia: a review and update. *Ther Adv Respir Dis* 2011; 5: 61-78.
4. Ott SR, Hauptmeier BM, Ernen C, Lepper PM, Nüesch E, Pletz MW, et al. Treatment failure in pneumonia: impact of antibiotic treatment and cost analysis. *Eur Respir J* 2012; 39: 611-618.
5. Ramirez JA, Anzueto AR. Changing needs of community-acquired pneumonia. *J Antimicrob Chemother* 2011; 66 Suppl 3(Suppl 3): iii3-9.
6. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections--Full version. *Clin Microbiol Infect* 2011; 17 Suppl 6(Suppl 6): E1-59.
7. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44 Suppl 2 (Suppl 2): S27-72.
8. Watkins RR, Lemonovich TL. Diagnosis and management of community-acquired pneumonia in adults. *Am Fam Physician* 2011; 83: 1299-1306.
9. Rubinstein E, Camm J. Cardiotoxicity of fluoroquinolones. *J Antimicrob Chemother* 2002; 49: 593-596.
10. Llop CJ, Tuttle E, Tillotson GS, LaPlante K, File Jr TM. Antibiotic treatment patterns, costs, and resource utilization among patients with community acquired pneumonia: a US cohort study. *Hosp Pract (1995)* 2017; 45: 1-8.
11. Armitage K, Woodhead M. New guidelines for the management of adult community-acquired pneumonia. *Curr Opin Infect Dis* 2007; 20: 170-176.
12. Klugman KP, Lonks JR. Hidden epidemic of macrolide-resistant pneumococci. *Emerg Infect Dis* 2005; 11: 802-807.
13. Samadpanah M, Gachkar L, Salarian S, Hadavand F. Nasopharyngeal Colonization and levofloxacin Susceptibility of *Streptococcus pneumoniae* among Healthcare Workers in a Teaching Hospital in Tehran, Iran. *Nov Biomed* 2020; 8: 129-134.
14. Azimi T, Maham S, Fallah F, Azimi L, Gholinejad Z. Evaluating the antimicrobial resistance patterns among major bacterial pathogens isolated from clinical specimens taken from patients in Mofid Children's Hospital, Tehran, Iran: 2013-2018. *Infect Drug Resist* 2019; 12: 2089-2102.
15. Houri H, Tabatabaei SR, Saee Y, Fallah F, Rahbar M, Karimi A. Distribution of capsular types and drug resistance patterns of invasive pediatric *Streptococcus pneumoniae* isolates in Teheran, Iran. *Int J Infect Dis* 2017; 57: 21-26.
16. Richards G, Levy H, Laterre P-F, Feldman C, Woodward B, Bates BM, et al. CURB-65, PSI, and APACHE II to assess mortality risk in patients with severe sepsis and community acquired pneumonia in PROWESS. *J Intensive Care Med* 2011; 26: 34-40.
17. Schroeder MR, Stephens DS. Macrolide resistance in *Streptococcus pneumoniae*. *Front Cell Infect Microbiol* 2016; 6: 98.
18. Hyde TB, Gay K, Stephens DS, Vugia DJ, Pass M, Johnson S, et al. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA* 2001; 286: 1857-1862.
19. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf* 2014; 5: 229-241.
20. Bartlett JG, Dowell SF, Mandell LA, File Jr TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious diseases Society of America. *Clin Infect Dis* 2000; 31: 347-382.
21. Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* 2008; 68: 535-565.
22. Hurst M, Lamb HM, Scott LJ, Figgitt DP. Levofloxacin: an updated review of its use in the treatment of bacterial infections. *Drugs* 2002; 62: 2127-2167.
23. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163: 1730-1754.
24. Frei CR, Jaso TC, Mortensen EM, Restrepo MI, Raut MK, Oramasionwu CU, et al. Medical resource utilization among community-acquired pneumonia patients initially treated with levofloxacin 750 mg daily versus ceftriaxone 1000 mg plus azithromycin 500 mg daily: a US-based study. *Curr Med Res Opin* 2009; 25: 859-868.
25. Torres A, Liapikou A. Levofloxacin for the treatment of respiratory tract infections. *Expert Opin Pharmacother* 2012; 13: 1203-1212.
26. Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, et al. High-dose, short-course levofloxacin for community-acquired Pneumonia: a new treatment paradig. *Clin Infect Dis* 2003; 37: 752-760.
27. File Jr TM, Segreti J, Dunbar L, Player R, Kohler R, Williams RR, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrob Agents Chemother* 1997; 41: 1965-1972.

28. Noreddin AM, Elkhatib WF. Levofloxacin in the treatment of community-acquired pneumonia. *Expert Rev Anti Infect Ther* 2010; 8: 505-514.
29. Belforti RK, Lagu T, Haessler S, Lindenauer PK, Pekow PS, Priya A, et al. Association between initial route of fluoroquinolone administration and outcomes in patients hospitalized for community-acquired pneumonia. *Clin Infect Dis* 2016; 63: 1-9.
30. Yen Y-H, Chen H-Y, Wuan-Jin L, Lin Y-M, Shen WC, Cheng K-J. Clinical and economic impact of a pharmacist-managed i.v-to-p.o conversion service for levofloxacin in Taiwan. *Int J Clin Pharmacol Ther* 2012; 50: 136-141.
31. Rebuck JA, Fish DN, Abraham E. Pharmacokinetics of intravenous and oral levofloxacin in critically ill adults in a medical intensive care unit. *Pharmacotherapy* 2002; 22: 1216-1225.
32. Milkovich G. Intravenous-to-oral transition therapy in community-acquired pneumonia: The INOVA health system experience. *Pharmacotherapy* 2001; 21: 83S-88S.
33. Zambon A, Polo Friz FH, Contiero P, Corrao G. Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs. *Drug Saf* 2009; 32: 159-167.
34. Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. *Chest* 2007; 131: 466-473.
35. Raz-Pasteur A, Shasha D, Paul M. Fluoroquinolones or macrolides alone versus combined with β-lactams for adults with community-acquired pneumonia: systematic review and meta-analysis. *Int J Antimicrob Agents* 2015; 46: 242-248.