Levofloxacin versus Ceftriaxone and Azithromycin Combination in the Treatment of Community Acquired Pneumonia in Hospitalized Patients

Mehran Izadi[1], Banafsheh Dadsetan[1], Zeinab Najafi[2], Sirous Jafari[2], Elham Mazaheri [2], Omid Dadras[3], Hajar Heidari[2] , Seyed A.S. Alinaghi[2] , Fabricio Voltarelli[4]

[1]Infectious Diseases Department, Ghaem Hospital, Karaj, Alborz, Iran

[2]Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Global Health and Socioepidemiology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[4]Graduation Program of Health Sciences, Faculty of Medicine, Federal University of Mato Grosso, Cuiabá, Brazil

Corresponding author: SeyedAhmad SeyedAlinaghi,
Address: Iranian Research Center for HIV/AIDS (IRCHA), Imam Khomeini Hospital, Tehran, Iran, Email: s_a_alinaghi@yahoo.com, Tel/Fax: +98 (21) 66947984

Abstract

Background: In Asia, an estimated of one million deaths caused by community-acquired pneumonia (CAP) each year. Despite the high mortality in elderly people, a large number of CAP patients have been treated and survived with optimal life expectancy. A few studies have been done on adult CAP therapeutic approaches in Asia. Moreover, differences have been noted between these studies and European data. We aimed to investigate the efficacy of oral Levofloxacin (TAVANEX), 750 mg, once daily for five days versus parenteral Ceftriaxone 1gr BD, plus oral Azithromycin (250 mg, once daily) for seven to ten days (standard regimen) in CAP treatment.

Materials and Methods: We conducted a prospective randomized trial among 150 patients with CAP in Qaem Hospital of Alborz city on December 2016 to June 2017. A group of CAP patients were randomized in two treatment groups. One group was treated with oral Levofloxacin (TAVANEX), 750 mg, once daily for five days and the other group with parenteral Ceftriaxone 1gr BD plus oral Azithromycin macrolide (250 mg, once daily) for seven to ten days (standard regimen). The efficacy and side effects of the assigned drugs were compared between two groups. The probability level for statistical significance was set at $P \leq 0.05$.

Results: The body temperature (P value=0.09), WBC count (P value=0.15), respiratory sounds (P value=0.18) and admission duration (P value=0.15) showed no significant differences after treatment between two group. There was no report of hospital mortality, clinical deterioration and antibiotic escalation during hospital admission in both groups of study. In standard regimen group, only two (2.7%) patients had skin rash while in Levofloxacin group one case (1.3%) had skin rash, two patients (2.7%) had gastrointestinal problems and three (4%) patients showed central nervous system (CNS) complications. In both groups, the reticulonodular pattern was more frequently observed in Chest X-ray. Although standard regimen group (n=27, 36%) showed more consolidation than patients in Levofloxacin group (n=22, 29.3%), the ground glass pattern was observed more in Levofloxacin group.

Conclusion: We concluded that monotherapy with oral Levofloxacin was as effective as treatment with Ceftriaxone plus Azithromycin combination in patients with CAP who required hospitalization.

Keywords: Community acquired pneumonia, levofloxacin, standard regimen, viruses, respiratory infection, fluoroquinolone.

1. Introduction

Community acquired pneumonia (CAP) is a common infectious disease, with high mortality rate worldwide, particularly, in developing countries. It accounts for most common infectious disease in children and cause of the serious morbidity and mortality in elderly patients [1, 2].

The most common cause of CAP are bacteria, amongst them the typical bacteria such as Streptococcus pneumonia and atypical bacteria such as Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella pneumophila, are the most prevalent germs [3, 4]. Twenty percent of CAPs caused by Viruses. The most common viruses are influenza, parainfluenza, human respiratory syncytial virus, human metapneumovirus and adenovirus [5].

Antibiotic treatment of CAP is rarely identified since commonly is the operant approach to fight against pathogens, even among hospitalized patients and patients never receive immediate treatment [6].

In Asia, an estimated of one million deaths caused by CAP each year. Despite the high mortality in elderly people, a large number of CAP patients have been treated and survived with optimal life expectancy [7]. A few studies have been done on adult CAP therapeutic approaches in Asia. Moreover, differences have been noted between these studies and European data [7-9].

In the United States, CAP is the sixth main cause of death [10]. The CAP-related mortality and morbidity have been reflected in the plethora of published studies. Current contradictions between national clinical guidelines reflect the variation in prevalence of target pathogens, pattern of drug resistance and clinical practice. Although there are several ongoing clinical trials that provide evidences for current practice and drug efficacy to identify the common etiologic pathogens and determine the appropriate clinical practice in order to achieve the optimal outcome, more epidemiological studies are required at the community level [10].

A number of studies endeavored for novel methods for respiratory infections treatment. Table **1** shows some recent patents for respiratory infection treatments as well as fluoroquinolone use.

Table 1. Some recent patents for respiratory infection treatments and fluoroquinolone use.

Patent Number	Current Assignee	Subject	References
US5686070A	Genentech Inc	Methods for treating bacterial pneumonia	[11]
US20050036951A1	Arizeke Pharmaceuticals Inc	Methods of treating lung diseases	[12]
US5290540A	Jackson Henry M Foundation for Advancement of Military Medicin	Method for treating infectious respiratory diseases	[13]
US20030012814A1	Shionogi Inc	Levofloxacin antibiotic product, use, and formulation	[14]
US6340689B1	LG Life Sciences Ltd	Methods of use of quinolone compounds against atypical upper respiratory pathogenic bacteria	[15]
US5756506A	Bayer HealthCare LLC	Single high dose fluoroquinolone treatment	[16]
US9795572B2	Institute For Clinical Pharmacodynamics Inc	Method for shortening anti-infective therapy duration in subjects with infection	[17]
US20150283120A1	The University of Chicago	Antibiotic methods and compositions for bacterial infections	[18]

To the best of our knowledge, there are just twenty-one studies that have been conducted on CAP in Iran. Eleven of these studies were conducted among children [19]. One study investigated and compared the clinical manifestations and laboratory abnormalities between elderly and younger age group in CAP patients. The results indicated more severe disease and higher mortality rate in elderly patients [20]. Despite these available epidemiological knowledge, limited evidences are present regarding the good clinical practice in adult CAP patients in Iran. Thus, in this study, we aimed to investigate and compare the main current antimicrobial treatment regimen and their outcomes in CAP, in situations similar to the general practice setting. The study compared the therapeutic effect of Levofloxacin, a fluoroquinolone given as a single first-line with a comparative arm of Ceftriaxone and Azithromycin combination (a beta-

lactam and a macrolide) as standard regimen in CAP patients admitted in Qaem Hospital, Karaj, 2017.

2. MATERIALS AND METHODS

2.1. Participants

Between December 2016 and June 2017, 150 CAP patients were recruited and randomized into two groups in Qaem hospital, Karaj, Alborz province, Iran. One group was treated with respiratory fluoroquinolone, oral Levofloxacin (TAVANEX), 750 mg, once daily for five days and the second one was treated with parenteral Ceftriaxone 1gr BD plus oral Azithromycin 250 mg, once daily for seven to ten days.

2.1.1. Inclusion and Exclusion Criteria

Patients who met the eligibility criteria were recruited and randomized into two treatment groups, using a simple random table to ensure the sound randomization and between the two arms of study (Fig. **1**). In terms of age, gender and accompanying diseases (high blood pressure and diabetes) both groups were matched. The eligibility criteria are described in Table **2**.

Table 2. Eligibility criteria for the study, Qaem Hospital, Karaj, December 2016 to June 2017.

Eligibility Criteria	**Factors**
Inclusion criteria	• Having informed written consent • All patients with initial diagnosis of CAP including patients with new pulmonary infiltration, two or more clinical symptoms of lower respiratory tract infection such as fever, new or intense dry or productive cough, abnormal pulmonary sounds (rales, wheezes) • All patients with mild to moderate pneumonia based on the APACHE score system • Age >14 years

Exclusion criteria	• Infection with microorganisms resistant to the regimens which are used in this study • Patients with cystic fibrosis • The presence of an empyema in the patient's graph • HIV positive patients • Patients with nosocomial pneumonia • Patients with Flu possibility • History of seizure or serious mental disorder • History of allergy to any of the medications • Pregnant or lactating women • Severe kidney disease (Cr Clearance <30 mg/dL) • History of taking an antibiotic course within the last three months • Patients in the APACHE score system in the severe pneumonia group

2.2. Measures and Procedures

Patient basic information and initial clinical features were extracted thorough interview and physical exam were performed by a team of physicians at the time of admission. The findings were recorded and kept in relevant patient sheets for further analysis. Radiologic and laboratory tests were conducted in Qaem hospital laboratories and the results were recorded for each patient in relevant forms. Furthermore, an electrocardiogram was done at the time of admission for all patients as the routine practice. To examine the efficacy and side effects of each treatment,

patients in each arm were evaluated at the time of admission, followed by daily visits until discharge and one time visit in office seven to ten days after treatment assignment. Table **3** indicates the items that were examined at each visit. In addition, we examined the patients for any possible side effect. The severity of side effects was classified into three groups: mild, moderate and severe. All the information collected in this study was recorded and kept in relevant documents for further analysis.

Table 3. Evaluation indices of the two groups of case and control, Qaem Hospital, Karaj, December 2016 to June 2017.

Variables	**Indicators**
Clinical symptoms and signs	• Reduction of respiratory distress (use of accessory muscles of respiration, respiratory rate) • Coughing • Confusion • Abnormal pulmonary sounds (Crackle and Wheeze)
Physical examinations	• Cutaneous • Gastrointestinal • Central Nervous System (CNS)
Laboratory	• Leukocytosis • Creatinine • Blood glucose

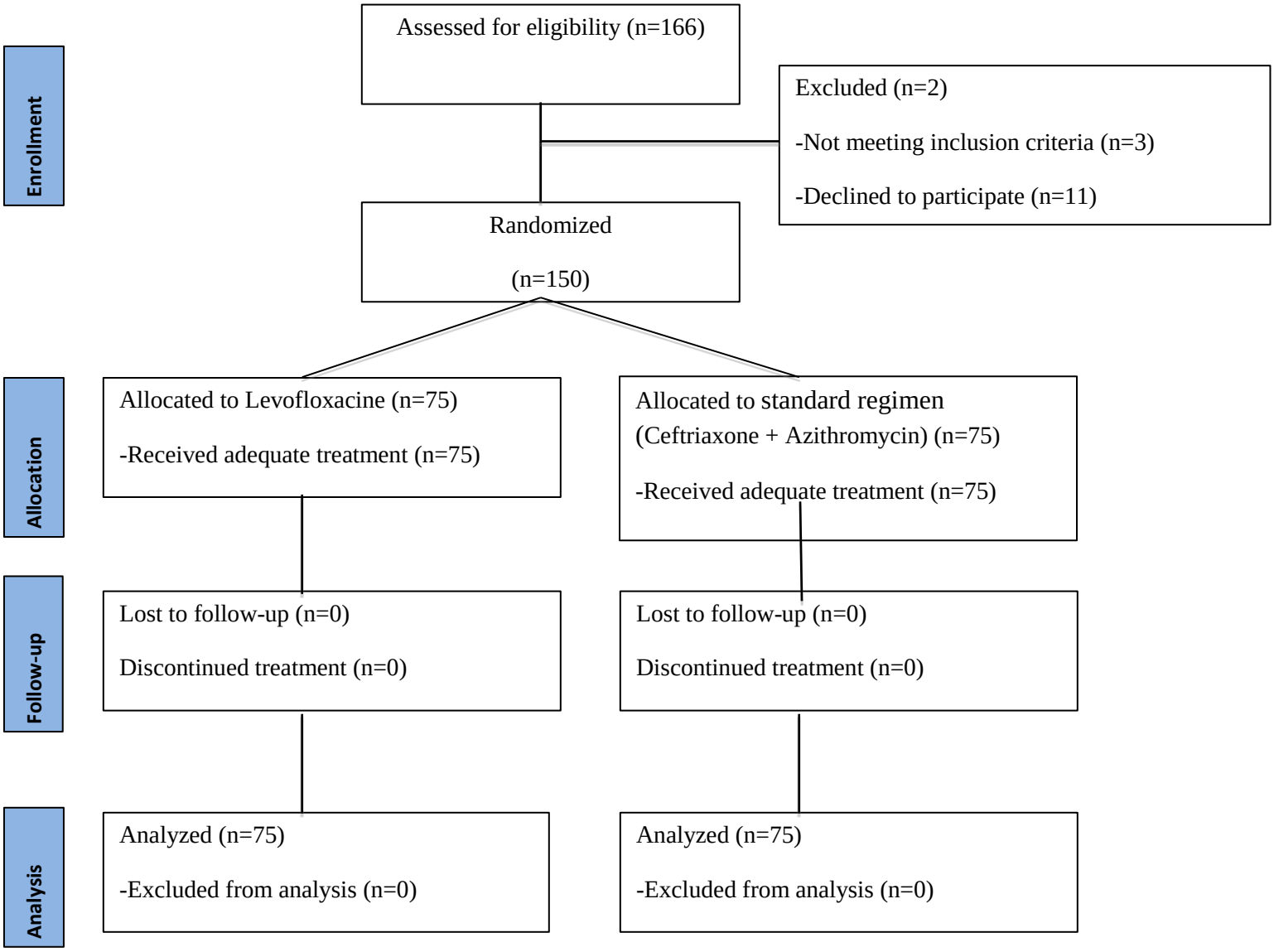

Fig. (1). Flow of participants through the study, Qaem Hospital, Karaj, December 2016 to June 2017.

2.3. Statistical Analysis

Applying the intention to treat analysis, patients in two groups were examined and compared in order to determine the efficacy and side effects of treatment. For the purpose of data analysis, we used SPSS software package (version 22). For measuring difference between groups, Independent-Samples T Test and Pearson Chi-Square Test were used and the probability level for statistical significance was set at $P \leq 0.05$.

3. RESULTS

3.1. Demographic Characteristics

In the present study, a total of 150 patients were recruited and assigned to two treatment groups. The mean age for Levofloxacin and standard regimen groups were 63.9 and 67.8 years, respectively. Before the intervention, demographic factors such as gender (P value=0.62) and age group (P value=0.28), in both study groups were recorded to have no significant differences between two arms (Table **4**).

3.2. Clinical and Paraclinical Findings

Table 5 illustrates the clinical features and laboratory findings of CAP patients at the admission time and after the treatments. There was no patient having confusion, cancer with neutropenia, history of transplantation, nasogastric (NG) tube and gastrointestinal (GI) intolerance. Moreover, the history of taking Quinolone and Macrolide was negative in previous 90 days for all the patients.

First day chest examination revealed that patients had more crackles than wheezing in both groups; 63 (84%) patients with crackles and 12 (16%) patients with wheezing were in Levofloxacin group and 67 (89.3%) patients with crackle, five (6.7%) with wheezing, two (2.7%) of unknown situation and one (1.3%) with normal chest exam were in the standard regimen group.

3.3. Outcomes

3.3.1. Primary Outcome

After the intervention, measuring body temperature (P value=0.09), WBC count (P value=0.15), respiratory sounds (P value=0.18) and admission duration (P value=0.15) showed no significant

differences between two groups (Table **5**). There was no report of hospital mortality, clinical deterioration and antibiotic escalation during hospital admission in both groups of study.

3.3.2. Radiologic Findings

In both groups, the reticulonodular pattern was more frequently than other patterns in Chest X-Ray, including 30 (40%) patients in Levofloxacin group and 32 (42.7%) cases in standard group. Although standard regimen group (n=27, 36%) showed more consolidation than patients treated with Levofloxacin (n=22, 29.3%), the ground glass pattern observed more in Levofloxacin group (n=23, 30.7% in standard regimen arm versus n=16, 21.3% in levofloxacin arm).

3.3.3. Side Effects

In standard regimen group, only two (2.7%) patients had skin rash, while in Levofloxacin group one case (1.3%) had skin rash, two patients (2.7%) had gastrointestinal problems and three (4%) patients showed central nervous system (CNS) complications. Table **6** briefly depicts the adverse reactions observed in each group.

Table 4. Demographic and basic clinical features of CAP patients, based on Levofloxacin and standard regimen at the admission time, Qaem Hospital, Karaj, Alborz province, December 2016 to June 2017.

Variables[1]	**Groups**		**P-value**
	Levofloxacin N (%)	**Standard regimen N (%)**	
Gender Male Female	46 (61.3) 29 (38.7)	43 (57.3) 32 (42.7)	0.62
Age group ≤35 36-50 51-70 ≥71	1 (1.3) 12 (16.0) 41 (54.7) 21 (28.0)	0 (0) 9 (12.0) 35 (46.7) 31 (41.3)	0.28
Diabetes	10 (13.3)	11 (14.7)	0.82
Hypertension	9 (12.0)	12 (16.0)	0.48
COPD[2]	16 (21.3)	20 (26.7)	0.45
Smoking	14 (18.7)	15 (20.0)	0.84

Fever	75 (100)	75 (100)	>0.9
Cough	74 (98.7)	75 (100)	0.32
Productive cough	60 (80)	55 (73.3)	0.34
Dyspnea	73 (97.3)	29 (38.7)	<0.001
Flu like syndrome	9 (12.0)	8 (10.7)	0.80
Hoarseness	23 (30.7)	0 (0)	<0.001
CXR finding Consolidation Reticulonodular Ground glass	 22 (29.3) 30 (40) 23 (30.7)	 27 (36) 32 (42.7) 16 (21.3)	0.40
CXR abnormality Unilateral Bilateral	 42 (56) 32 (42.7)	 48 (64) 27 (36)	0.37

[1]Subgroups do not always add up to total due to missing data, [2] Chronic Obstructive Pulmonary Disease

Table 5. Clinical and laboratory findings of CAP patients before and after intervention, based on treatment group, Qaem Hospital, Karaj, Alborz province, December 2016 to June 2017.

Characteristic	**Mean (SD*)**		**P-value**
	Levofloxacin	**Standard regimen**	
**First temperature (C)	38.4 (0.8)	38.5 (0.5)	0.87
First respiratory rate (per minute)	28.6 (3.1)	19.6 (1.9)	<0.001
First pulse rate (per minute)	96.7 (9.7)	105.3 (7.7)	<0.001
First systolic blood pressure (mmHg)	127.1 (20.1)	147.9 (148.3)	0.23
First diastolic blood pressure (mmHg)	76.0 (10.5)	77.8 (13.3)	0.36
First White Blood Cell (cells/ mcL)	12776.0 (3873.7)	12695.3 (3739.6)	0.90
First Platelet (cells/ mcL)	37315.1 (97202.4)	243.1 (75.4)	0.001

First Creatinine (mg/dL)	1.3 (0.3)	1.2 (0.4)	0.21
First blood sugar (mg/dL)	151.1 (48. 3)	118.1 (51.6)	<0.001
**Last systolic blood pressure	119.7 (10.8)	123.3 (15.5)	0.11
Last diastolic blood pressure	73.6 (5.1)	75.0 (10.2)	0.29
Last temperature	37.2 (0.1)	37.1 (0.3)	0.09
Last respiratory rate (per minute)	20.5 (1.8)	14.1 (1.6)	<0.001
Last pulse rate (per minute)	82.6 (4.3)	85.5 (6.0)	0.001
Last White Blood Cell (cells/ mcL)	9098.7 (2025.6)	8655.7 (1717.7)	0.15
Last Platelet (cells/ mcL)	31105.3 (79677.1)	241.7 (74.2)	0.001
Last Creatinine (mg/dL)	1.1 (0.2)	1.1 (0.3)	0.40
Last blood sugar (mg/dL)	131.5 (25.2)	94.6 (20.7)	<0.001
Defeverness (day)	1.4 (0.6)	1.4 (0.6)	>0.9
Admission duration (day)	3.3 (0.70)	3.4 (0.6)	0.15

*Standard Deviation ** the "First" means at the admission time and the "Last" was measured after the treatment.

Table 6. Adverse drug reactions among CAP patients receiving Levofloxacin versus standard regimen, Qaem Hospital, Karaj, Alborz province, December 2016 to June 2017.

Variables	Group	Adverse reactions	N (%)
Type of antibiotic side effect	Levofloxacin	GI[1]	2 (2.7)
		Skin rash	1 (1.3)
		CNS[2]	3 (4.0)
	Standard regimen	Skin rash	2 (2.7)
Severity of antibiotic side effects	Levofloxacin	Mild	3 (4.0)
		Moderate	1 (1.3)
		None	69 (92.0)
		Unknown	2 (2.7)
	Standard regimen	Mild	2 (2.7)
		None	73 (97.3)

[1]Gastrointestinal, [2] Central Nervous System

DISCUSSION

In the present study, 750 mg oral Levofloxacin proved as an effective treatment as standard combination therapy. In fact, the results suggest that quinolones for CAP patients may yield the same level of efficacy as beta-lactams and macrolides. Furthermore, since levofloxacin is prescribed as a single, oral, daily dose, patient compliance is much better and would be a better choice compared to standard regimen which contains Ceftriaxone as an injectable drug prescribed twice daily. Measurement of important factors such as fever, cough, COPD, hoarseness, dyspnea and CXR findings in both groups showed similar clinical features at the time of admission. In addition, measuring the CAP-related factors such as body temperature, WBC count, defeverness and admission duration at the end of the study, showed no significant differences between the groups. Therefore, it seems reasonable to assume that the Levofloxacin can act as effective as the Ceftriaxone and Azithromycin Combination therapy in CAP treatment.

Levofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against gram-positive and gram-negative bacteria and atypical respiratory pathogens. It is active against both penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae*. The prevalence of *S. pneumoniae* resistance to Levofloxacin is less than 1% in the US populations [21].

A number of randomized comparative trials in the United States have shown high efficacy of Levofloxacin in treatment of respiratory and genitourinary tract, skin and skin structures infections. Sequential intravenous or oral Levofloxacin 750 mg once daily for 7-14 days was as effective as intravenous Imipenem/Cilastatin 500-1000 mg which is prescribed every six-eight hours followed by oral Ciprofloxacin 750 mg twice daily in nosocomial pneumonia. In some patients with mild to severe CAP symptoms, intravenous and/or oral Levofloxacin, 500 mg once daily for 7-14 days, achieved good clinical and bacteriological response rates similar to those with comparator agents, such as Amoxicillin/Clavulanic acid, Clarithromycin, Azithromycin, Ceftriaxone and/or Cefuroxime and Gatifloxacin. A recent study indicates that in treatment of mild to severe CAP, giving daily 750 mg intravenous or oral Levofloxacin for five days can be as effective as giving daily 500 mg for ten days. Exacerbations of chronic bronchitis and acute maxillary sinusitis responded well to treatment with 500 mg oral Levofloxacin once daily for 7 and 10-14 days, respectively [22, 23].

Similar studies have demonstrated that Levofloxacin is associated with clinical improvement equal to combination therapy with Ceftriaxone and Azithromycin as the standard regimen in CAP treatment. Moreover, duration of patient admission was approximately the same [24].

Current guidelines for CAP management in adults recommended both monotherapy (a new macrolide or a beta-lactam which usually is a high dose Aminopenicillin) and combination therapy (macrolide and beta-lactam) as the first-line drugs in non-hospitalized and hospitalized CAP patients [10, 25-27]. Recently, newer fluoroquinolones such as Moxifloxacin, Gatifloxacin or Levofloxacin have been recommended as first-line antibiotics in CAP [28-31].
Several studies have compared new fluoroquinolones with Amoxicillin, second and third generation cephalosporin [32-34] or macrolide, such as Clarithromycin [35-40].
According to recent American Thoracic Society (ATS) guidelines [41], these findings suggest that new quinolones have the same efficacy as beta-lactams alone or in combination with macrolides for treatment of hospitalized and non-hospitalized CAP patients [37].
Likewise, In a double-blind clinical trial study by A. Torres et al. the oral Moxifloxacin as a first-line option for CAP proved to be as effective as an alternative of mono- or combination therapy (Amoxicillin 1g t.i.d. or Clarithromycin 500 mg BD alone or in combination) [37].
In another study by Ching-Chi Lee *et al.* [42], demographics and clinical characteristics of 733 adults with poly-microbial or mono-microbial community-onset bacteremia empirically treated by an appropriate fluoroquinolone (n=87) or third-generation cephalosporin (n=646) were compared. A critical illness, an initial syndrome with severe sepsis or a fatal outcome at 28 days was less common in the fluoroquinolone group. A total of 645 (88.0%) patients were febrile at initial presentation and the fluoroquinolone group with/without a critical illness had a shorter time to defervescence than the third-generation cephalosporin group. By the propensity scores, 87 patients with appropriate fluoroquinolone therapy were matched with 435 treated by third-generation cephalosporin therapy at a ratio of 1:5 and there were no significant differences in terms of bacteremia severity, comorbidity severity, major comorbidities, causative microorganisms and bacteremia sources between groups. Moreover, crude mortality rates at 28 days did not differ significantly. However, the time to defervescence was shorter in the fluoroquinolone group [42].

In another study, 31 patients with CAP entered to the study and used the previous guidelines of the American Infectious Disease Association, the American Thoracic Society and the latest IDSA/ATS related to CAP for patients' management with this clinical syndrome. Only 0.2% of ٣٢ patients had hospital admissions based on the guidelines and standardized guideline management was performed in only 18 (58%) of patients. The authors of present article finally put emphasis on adherence to standardized guidelines and evidence-based care [43].
In Mikaeilli H et al. study that calculated the patients identified by CAP with Pneumonia Severity Index (PSI) scores, on-admission level of serum d-dimer may predict the severity of community-acquired pneumonia [44] and a similar study by Saleh P et al. revealed that on-admission serum qCRP is well-correlated with PSI in the hospitalized patients with pneumonia and, it can be used as a predicting marker of short-term prognosis [45]. Another study by Naini SE et al. about PSI scoring suggests this scoring system as an index to assess the prognosis of death [46].

The duration of antibiotic therapy for patients with CAP is recommended to be 7-10 days or even longer [25, 47-50]. In a study of CAP caused by atypical pathogens, 5 day therapy with a new fluoroquinolone was as effective as 10 day therapy [51]. The fast resolution of clinical symptoms in our study support the hypothesis that for patients with mild to moderate disease, short-term treatment could be a feasible and safe therapy option.

CONCLUSION

Even though Levofloxacin could be a reasonable alternative for empirical treatment of community-onset bacteremia in the hospital setting, our finding may not be generalized to other regions where fluoroquinolone resistance is substantial. Furthermore, we only investigated short-term benefits of fluoroquinolone therapy during four weeks after disease onset and the long-term effects of fluoroquinolone therapy remained obscure.
The present study proved that oral monotherapy with Levofloxacin is as effective as the standard regimen for mild to moderate CAP treatment in hospitalized patients.
The results advanced the existent knowledge regarding the CAP treatment and could guide the future practices and clinical decisions. In addition, it could assist the physician in formulating an appropriate therapeutic plan in similar settings when resistance Streptococcus species are suspected in CAP patients.

CURRENT & FUTURE DEVELOPMENTS

Substitution of monotherapy instead of using multi drugs in the treatment of infectious diseases is considered more pleasant for patients, cost-effective and less invasive so it has stimulated the research activity in this field. Therefore, many new monotherapy regimens have been made and patented, but still, there are new aspects to explore and work on.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical necessities are achieved based on Institutional Review Board (IRB) of Alborz University of Medical Sciences. Moreover, a written informed consent was obtained for each patient. All data were kept confidential as nameless and coded at a standard.

HUMAN AND ANIMAL RIGHTS

No Animals were used for studies that are the basis of this research.

Consent for publication

Not applicable.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

We thank all the staff in Qaem Hospital for their help.

References

[1] Falade AG, Ayede AI. Epidemiology, aetiology and management of childhood acute community-acquired pneumonia in developing countries-A review. Afr J Med Med Sci 2011; 40(4): 293-308.

[2] Jain S, Self WH, Wunderink RG, Richard GW, Sherene F, Robert B, *et al.* Community-acquired pneumonia requiring hospitalization among US adults. N Engl J Med 2015; 373(5): 415-27.

[3] File TM Jr. Community-acquired pneumonia. Lancet 2003; 362(9400): 1991-2001.

[4] Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax, 2010; p. thx. 2009. 129502.

[5] Johnstone J, Majumdar SR, Fox JD, Marrie TJ. Viral infection in adults hospitalized with community-acquired pneumonia: Prevalence, pathogens, and presentation. Chest 2008; 134(6): 1141-8.

[6] Nascimento-Carvalho CM, Ribeiro CT, Cardoso MR, Barral A, Araújo-Neto CA, Oliveira JR, *et al.* The role of respiratory viral infections among children hospitalized for community-acquired pneumonia in a developing country. Pediatr Infect Dis J 2008; 27(10): 939-41.

[7] Liam CK, Pang YK, Poosparajah S, Chua KT. Community-acquired pneumonia: an Asia Pacific perspective. Respirology 2007; 12(2): 162-4.
[8] Brown JS. Geography and the aetiology of community-acquired pneumonia. Respirology 2009; 14(8): 1068-71.
[9] Song J-H, Thamlikitkul V, Hsueh P-R. Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. Int J Antimicrob Agents 2011; 38(2): 108-17.
[10] Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Clin Infect Dis 2000; 31(2): 383-421.
[11] Doerschuk CM, *et al.* Methods for treating bacterial pneumonia. Google Patents 1997.
[12] Henderson D. Methods of treating lung diseases. Google Patents 2004.
[13] Prince GA, Hemming VG. Method for treating infectious respiratory diseases. Google Patents 1994.
[14] Rudnic EM, *et al.* Levofloxacin antibiotic product, use and formulation thereof. Google Patents 2003.
[15] Dubois J, St-Pierre C. Methods of use of quinolone compounds against atypical upper respiratory pathogenic bacteria. Google Patents 2002.
[16] Copeland DD, Ewert KM, Wollen TS. Single high dose fluoroquinolone treatment. Google Patents 1998.
[17] Ambrose PG. Method for shortening anti-infective therapy duration in subjects with infection. Google Patents 2017.
[18] Daum RS, Boyle-Vavra S. Antibiotic methods and compositions for bacteria infections. Google Patents 2013.
[19] Sheibani F, Shahverdi MJG, Naderi H. A survey of the common etiologic agents of community-acquired pneumonia in Iran. Medical Journal of Mashhad University of Medical Sciences 2015; 57(9): 1002-15.
[20] Jafari S, Soltanpour F , Soudbakhsh A , Safavi E , Rokni YH , Navipour R, *et al.* Community-Acquired Pneumonia: A Comparison between elderly and nonelderly patients. Tehran University Medical Journal TUMS Publications 2006; 64(8): 74-80.
[21] Anderson VR, Perry CM. Levofloxacin : A review of its use as a high-dose, short-course treatment for bacterial infection. Drugs 2008; 68(4): 535-65.
[22] Deshpande LM, Jones RN. Antimicrobial activity of advanced-spectrum fluoroquinolones tested against more than 2000 contemporary bacterial isolates of species causing community-acquired respiratory tract infections in the United States (1999). Diagn Microbiol Infect Dis 2000; 37(2): 139-42.
[23] Biedenbach DJ, Barrett MS, Croco MA, Jones RN. BAY 12-8039, a novel fluoroquinolone. Activity against important respiratory tract pathogens. Diagn Microbiol Infect Dis 1998; 32(1): 45-50.
[24] Biedenbach DJ, Jones RN. The comparative antimicrobial activity of levofloxacin tested against 350 clinical isolates of streptococci. Diagn Microbiol Infect Dis 1996; 25(1): 47-51.
[25] Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000; 31(2): 347-82.

[26] Schaberg T, Torres A. ERS Task Force Report. Guidelines for management of adult community-acquired lower respiratory tract infections. Eur Respir J 1998; 11(4): 986-91.
[27] Heffelfinger JD, Dowell SF, Jorgensen JH, Klugman KP, Mabry LR, Musher DM, *et al.* Management of community-acquired pneumonia in the era of pneumococcal resistance: A report from the Drug-Resistant Streptococcus pneumoniae therapeutic working group. Arch Intern Med 2000; 160(10): 1399-408.
[28] Petitpretz P, Arvis P, Marel M, Moita J, Urueta J. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. Chest 2001; 119(1): 185-95.
[29] Aubier M, Verster R, Regamey C, Geslin P, Vercken JB. Once-daily sparfloxacin versus high-dosage amoxicillin in the treatment of community-acquired, suspected pneumococcal pneumonia in adults. Clin Infect Dis 1998; 26(6): 1312-20.
[30] O'Doherty B, Dutchman DA, Pettit R, Maroli A. Randomized, double-blind, comparative study of grepafloxacin and amoxycillin in the treatment of patients with community-acquired pneumonia. J Antimicro Chemot 1997; 40(suppl-1): 73-81.
[31] Trémolières F, de Kock F, Pluck N, Daniel R. Trovafloxacin versus high-dose amoxicillin (1 g three times daily) in the treatment of community-acquired bacterial pneumonia. Eur J Clin Microbiol Infect Dis 1998; 17(6): 447-53.
[32] File TM Jr, 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(9): 1965-72.
[33] Norrby SR, Petermann W, Willcox PA, Vetter N, Salewski E. A comparative study of levofloxacin and ceftriaxone in the treatment of hospitalized patients with pneumonia. Scand J Infect Dis 1998; 30(4): 397-404.
[34] Traub SL, *et al.* 94e. A double-blind, randomized, multicenter, global study in hospitalized community acquired pneumonia patients comparing trovafloxacin with ceftriaxone and optional erythromycin. J Human Pharmacol Drug Ther 1997; 17(5): 1095.
[35] Hoeffken G, Meyer HP, Winter J, Verhoef L. The efficacy and safety of two oral moxifloxacin regimens compared to oral clarithromycin in the treatment of community-acquired pneumonia. Respir Med 2001; 95(7): 553-64.
[36] Moola S, Hagberg L, Churchyard GA, Dylewski JS, Sedani S, Staley H. Comparison of grepafloxacin with clarithromycin in the treatment of community-acquired pneumonia (CAP). In Program and Abstracts of the 38th International Conference on Antimicrobial Agents and Chemotherapy San Diego, American Society for Microbiology 1998.
[37] Torres A, Muir JF, Corris P, Kubin R, Duprat-Lomon I, Sagnier P-P., Höffken G. *et al.* Effectiveness of oral moxifloxacin in standard first-line therapy in community-acquired pneumonia. Eur Respir J 2003; 21(1): 135-43.
[38] Mathers DL, Hassman J, Tellier G. Efficacy and tolerability of once-daily oral telithromycin compared with clarithromycin for the treatment of community-acquired pneumonia in adults. Clin Ther 2004; 26(1): 48-62.
[39] Ramirez J, Unowsky J, Talbot GH, Zhang H, Townsend L. Sparfloxacin versus clarithromycin in the treatment of community-acquired pneumonia. Clin Ther 1999; 21(1): 103-17.

[40] Chien S-M, Pichotta P, Siepman N, Chan CK. Treatment of community-acquired pneumonia. A multicenter, double-blind, randomized study comparing clarithromycin with erythromycin. Chest 1993; 103(3): 697-701.
[41] 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(7): 1730-54.
[42 Lee CC, Wang JL, Lee CH, Hsieh CC, Hung YP, Hong MY *et al.* Clinical benefit of appropriate empirical fluoroquinolone therapy for adults with community-onset bacteremia in comparison with third-generation cephalosporin therapy. Antimicrobial Agents Chemother 2016; e02174-16.
[43] Fahimi F, Mandana M, Tahereh S, Rocsanna N. Management of community acquired pneumonia in a teaching hospital: The role of established guidelines. Tanaffos 2007; 6(2): 32-7.
[44] Mikaeilli H, Zarghami N, Yazdchi M, Mardani M, Ansarin K. On-admission level of serum d-dimer and the severity of community-acquired pneumonia. Pak J Biol Sci 2009; 12(6): 514-7.
[45] Saleh P, Azari-Yam S, Naghavi-Behzad M. The correspondence between pneumonia severity index (PSI) and quantitative C-Reactive protein in patients with pneumonia. Tabriz U Med Sci Health Serv 2013; 35(2): 56-63.
[46] Naini, S.E., Naini A.E., Shirani K, Bagheri A. Assessment of pneumonia severity index in patients with community-acquired pneumonia admitted to alzahra hospital, Isfahan, Iran. J Isfahan Medical School 2012; 30(182).
[47] Marston BJ, Plouffe JF, File TM Jr, Hackman BA, Salstrom SJ, Lipman HB, *et al.* Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance Study in Ohio. Arch Intern Med 1997; 157(15): 1709-18.
[48] Niederman MS, McCombs JS, Unger AN, Kumar A, Popovian R. The cost of treating community-acquired pneumonia. Clin Ther 1998; 20(4): 820-37.
[49] Fine MJ, Auble TE, Yealy DM, Barbara H.H, Lisa AW, Daniel ES, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336(4): 243-50.
[50] Fine MJ, Pratt HM, Obrosky DS, Lave JR, McIntosh LJ, Singer DE, *et al.* Relation between length of hospital stay and costs of care for patients with community-acquired pneumonia. Am J Med 2000; 109(5): 378-85.
[51] Dunbar LM, Khashab MM, Kahn JB, Zadeikis N, Xiang JX, Tennenberg AM. Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. Curr Med Res Opin 2004; 20(4): 555-63.