Original article

Efficacy and Safety of Levonadifloxacin in the Management of Community-Acquired Bacterial Pneumonia (CABP): Findings of a Retrospective, Real-World, Multi-centre Study

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Abstract

Background: Community-acquired bacterial pneumonia (CABP) remains a global public health threat and is a leading cause of hospitalization and infection-linked mortality. Levonadifloxacin is a novel benzoquinolizine antibiotic with a broad-spectrum activity including methicillin-resistant *Staphylococcus aureus* (MRSA) and CABP-pathogens. *Methods:* This multi-centre, retrospective, post-marketing, real-world study assessed the efficacy and safety of levonadifloxacin oral and/or intravenous therapy in the treatment of CABP. Data from 338 patients above 17 years-of-age who received levonadifloxacin (oral or intravenous or both) was collected from 89 healthcare facilities across India. Information on clinical condition, comorbidities, complications, and details of concurrent therapy (including antimicrobial agents) was also collected. Study outcomes were clinical and microbial success at the end of therapy while safety was assessed based on clinical and laboratory adverse events. *Results:* Of the 338 patients, 244 (72.2%) were male, 93 (27.5%) were female and 1 (0.43%) was a transgender. About 294 (87.0%) patients were hospital-treated and 44 (13%) received outpatient treatment. About 248 (73.4%) patients received intravenous levonadifloxacin treatment, 79 (23.4%) received oral and 11 (3.3%) received intravenous followed by oral levonadifloxacin therapy. The common comorbid conditions were diabetes (14.2%) and hypertension (8.6%). Mean duration of levonadifloxacin therapy was 6.4 days. Clinical and microbial success in levonadifloxacin-treated patients was 95.0% (321/388) and 96.8% (150/155), respectively. *Conclusions:* Levonadifloxacin showed promising clinical outcomes and safety when used as an intravenous and/or oral for the treatment of CABP, both in outpatients as well as hospitalized patients.

Keywords: Pneumonia, levonadifloxacin, clinical success, microbial success, CABP

Introduction

Lower respiratory tract infection (LRTI), particularly community-acquired bacterial pneumonia (CABP) causes substantial mortality, morbidity and economic burden worldwide [1]. Mortality due to respiratory infections remained unchanged from 2005 to 2015,

however in recent years, there is an increase in hospitalization rates indicating lack of safe and effective out-patient therapies [2].

Although *S. pneumoniae* is the most likely pathogen in all-cause pneumonia, other organisms like *H. influenzae* and atypical bacteria (*Mycoplasma, Chlamydia*, and *Legionella spp*.) are not uncommon [3]. Methicillin-resistant *Staphylococcus aureus*

(MRSA) has recently emerged as an important cause of CABP in previously healthy individuals exhibiting resistance to conventional Gram-positive antibiotics leading to extended hospital stay and higher mortality. Moreover, confirmed, or suspected involvement of MRSA in CABP, poses heightened therapeutic challenges in the community due to non-availability of safer oral anti-MRSA options.

Levonadifloxacin is a recently approved intravenous and oral, novel antibacterial agent for the treatment of acute bacterial skin and soft tissue infections (ABSSSI), diabetic foot infection (DFI) and concurrent bacteraemia in India. Reported to be highly active against Gram-positive organisms such as *S. aureus* (methicillin-resistant, methicillin-susceptible, quinolone-resistant, quinolone-susceptible isolates), *S. pyogenes, Enterococcus faecalis, S. dysgalactiae spp. dysgalactiae*, it also demonstrates activity against CABP-causing *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and atypical bacteria. Broad spectrum coverage, higher concentrations of levonadifloxacin in lung epithelial lining fluid (ELF) and intracellular compartments, accompanied by excellent safety profile offers the potential for a well-differentiated as well as empirical therapeutic option in community respiratory infections caused by extracellular and intracellular pathogens [4].

This study aimed to capture the results of oral and/or intravenous administration of levonadifloxacin for the treatment of CABP in hospital and out-patient settings.

Methods

Setting
This data is a part of a large multi-centre, retrospective, post-marketing, real-world descriptive observational study (PIONEER study) conducted for the assessment of safety and efficacy of levonadifloxacin in bacterial pulmonary infections of community-origin. Data for clinical and microbial outcomes with levonadifloxacin use in pneumonia is included from 89 healthcare centres across India.

Informed consent and ethics
This prescription event monitoring study collected data of 338 patients who received treatment for pneumonia at respective hospitals. The study documents were reviewed and approved by the local Institutional Ethics Committee (IEC) of D Y Patil University School of Medicine, Navi Mumbai (DYP/IEC/06-019/2020). The study was conducted in accordance with the principles of Declaration of Helsinki (World Medical Association) and Good Clinical Practice (GCP) guidelines issued by the ICMR and CDSCO, Govt. of India. As this was a retrospective study, patient consent was obtained wherever possible, and strict confidentiality was maintained for patient's identity.

Study participants
Data of 338 male/female patients diagnosed with pneumonia based on clinical and diagnostic evaluation and who received levonadifloxacin (oral or injectable) was included in the study. The definition of pneumonia and LRTI was in accordance with the standard International Classification of Diseases (ICD-10) criteria [5]. Data was collected and recorded in a study specific data capture form from the participating sites. Patient information collected included their clinical condition on admission, comorbidities, complications, and details of concurrent therapy (including antimicrobial agents) received. Microbial testing data was collected wherever available. This being an observational study, there were no pre-defined study treatments and all treatments for the patients were at the discretion of the treating clinician.

Study outcomes
The study outcomes were the clinical and microbial success at the end of therapy. Clinical success is defined as resolution of all signs and symptoms of pneumonia (CABP), or improvement to such an extent that further antimicrobial therapy was not necessary. Clinical failure is defined as persistence or worsening of signs/symptoms, the need for additional antibiotic, new pulmonary infection, progression of the chest radiograph, or death due to pneumonia. Microbial success was defined as the absence of organism in the follow-up microbial testing in those patients where organisms were detected at baseline, or a negative follow-up microbial testing. Clinical improvement was defined as improvement in clinical signs and symptoms from the baseline.

Safety of the treatments was assessed using the clinical and laboratory adverse events documented. Global assessments were reported by the treating investigator for each patient for efficacy and safety based on a 5-point Likert scale of *excellent, very good, good, satisfactory,* and *poor*.

Statistical analysis
This being a descriptive observational study, there is no study hypothesis, and no statistical testing was carried out. The data was entered in Microsoft Office 365 Excel worksheet. Descriptives are presented for demography and study outcomes. Measurement data are presented as means and standard deviation (SD), whereas categorical data is presented as percentages.

Results

Demography and comorbid conditions
Of the 338 patients, 244 (72.2%) were male, 93 (27.5%) were female, and 1 (0.43%) was a transgender with a median age of 59.50 years (range 17 to 88 years). Table 1 presents the demography and duration of levonadifloxacin therapy received by the patients. 248 (73.4%) patients received intravenous levonadifloxacin, whereas 79 (23.4%) received oral therapy and 11 (3.3%) received intravenous therapy followed by oral levonadifloxacin. The mean duration of therapy was 6.09 days, 7.09 days, and 11.29 days with IV therapy, oral therapy and IV followed by oral therapy respectively. The common comorbid conditions were diabetes (14.2%) and hypertension (8.6%). Other comorbidities were ischemic heart disease (1.2%), thyroid disorders (1.2%), renal disorders (1.5%), malignancy (1.5%) and respiratory disorders (2.4%).

Renal impairment was reported in 51 (15.1%) patients, hepatic impairment in 19 (5.6%), and thrombocytopenia in 15 (4.4%) patients before initiation of antimicrobial therapy for LRTI (Table 2.). Concomitant drugs other than antimicrobial agents (AMA) used were oral hypoglycaemic agents (13.0%), oral anticoagulants (1.2%), heparin (1.2%), insulin (1.8%), corticosteroids (5.6%), antihypertensives (2.1%) and other drugs (14.2%).

Microbial and clinical outcomes
Table 3 presents the results of microbial testing done in 238 patients. Culture report was positive in 85.7% patients (204/238) including 53.8% (128/238) Gram-positive and 21.8% (52/238) Gram-negative. About 233 (68.9%) patients received additional AMAs with 223 (66.0%) receiving only one AMA along with levonadifloxacin, whereas 9 (2.7%) patients received two additional AMAs. The common AMAs used along with levonadifloxacin were meropenem/ imipenem/ carbapenem (37.3%), beta-lactams (10.7%), remdesivir (4.7%),

aminoglycosides (1.8%), polypeptides (0.9%), macrolides (0.9%), antifungals (3.9%) and 11.5% received other AMAs.

Table 4 presents the clinical success (95.0%) and microbial success (96.8%) at the end of therapy. Data of 155 patients was available for microbial evaluation. Clinical improvement on day 4 was 84.31% (285/338) as shown in Table 5.

Figure 1 presents global assessments for efficacy and safety at end of therapy.

Table 1: Demography and duration of levonadifloxacin therapy

Levonadifloxacin route of administration		Age (yrs.)	BMI (Kg/m2)	Duration of therapy (days)
Intravenous (n=248)	Mean	59.10	25.46	6.09
	SD	12.22	4.40	1.960
	Median	59.50	25.20	6.00
	Range	22 – 88	13.11 – 44.39	1 – 15
Oral (n=79)	Mean	55.66	26.31	7.09
	SD	14.075	4.24	2.97
	Median	57.00	26.03	6.00
	Range	17 – 88	18.29 – 38.40	4 – 17
Intravenous followed by oral (n=11)	Mean	64.55	26.66	11.29
	SD	9.913	2.94	3.30
	Median	65.00	26.64	10.00
	Range	50 – 78	23.53 – 33/87	8 – 17
All patients (n=338)	Mean	58.47	25.69	6.45
	SD	12.712	4.33	2.54
	Median	59.50	25.39	6.00
	Range	17 – 88	13.11 – 44.39	1 – 17
BMI: body mass index; SD: standard deviation				

Table 1- Demographic details of age, body mass index (BMI) and Duration of levonadifloxacin therapy in days are mentioned for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients.

Table 2: Comorbidities at the time of admission for LRTI (n=338)

Comorbidities	No.	% (n=338)
Bacteraemia	96	28.4%
Sepsis	65	19.23%
Renal impairment	51	15.1%
Hepatic impairment	19	5.6%
Thrombocytopenia	15	4.4%
Other complications	8	2.4%

Table 2- Comorbidities at the time of admission are mentioned in numbers and percentage of n=338.

Table 3: Microbial testing results at baseline (n=238)

Organisms detected	No. of isolates	% (n=238)
Gram-positive organisms	128	53.8%
Gram-negative organisms	52	21.8%
Atypical organisms	20	8.4%
Anaerobic organisms	10	4.2%
Mixed bacterial infections	35	14.3%
Negative bacterial culture	34	14.3%

Table 3- Microbial data is mentioned as organism detected at baseline in numbers and percentage of n=238.

Table 4 Study outcomes at the end of levonadifloxacin therapy

Levonadifloxacin route of administration	Clinical outcome			Microbial outcome		
	Total	success	%	Total	success	%
Intravenous	248	232	93.5%	117	112	95.7%
Oral	79	78	98.7%	32	32	100.0%
Intravenous followed by oral	11	11	100.0%	6	6	100.0%
All patients	338	321	95.0%	155	150	96.8%

Table 4- Study outcomes at the end of therapy are mentioned in Clinical outcome and Microbial outcome as numbers and percentage for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients.

Table 5: Clinical improvement on day 4 with levonadifloxacin therapy (N=338)

Route of administration	Not improved	Improved	Total
Intravenous	37	211	248

Oral	15	64	79
Intravenous followed by Oral	1	10	11
Total	53	285	338

Table 5- Clinical improvement on day 4 with levonadifloxacin therapy is mentioned as numbers for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients.
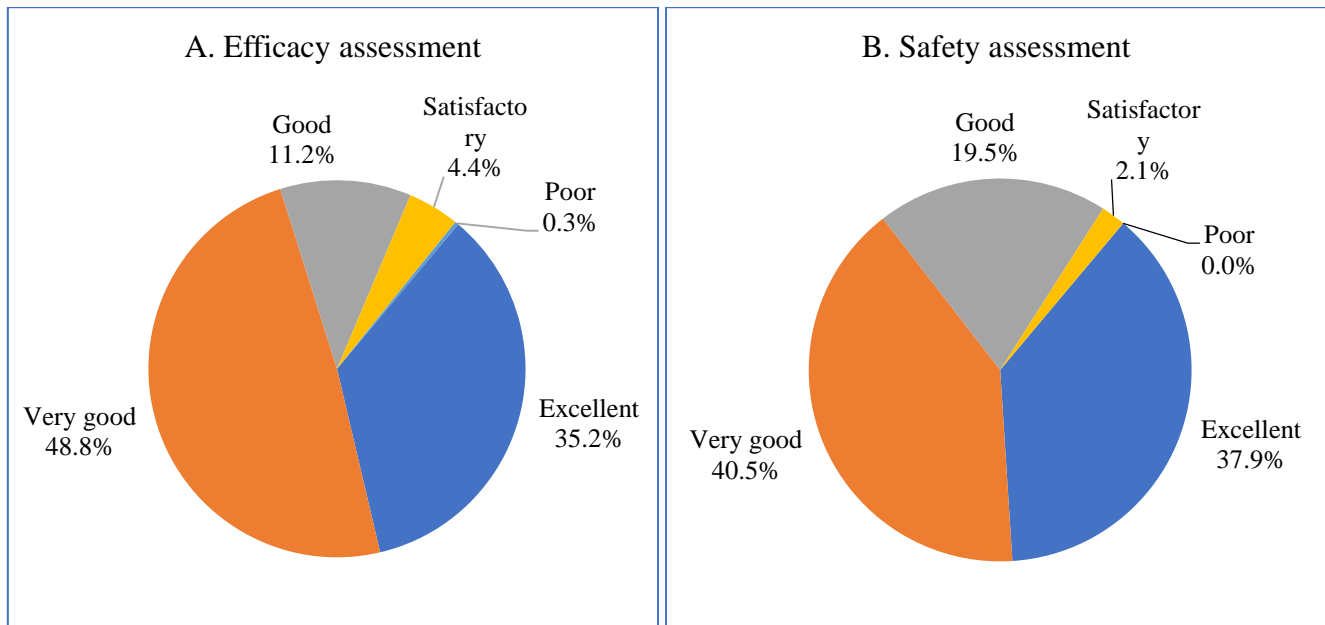

Figure 1: Global assessment at the end of therapy (%, n=338)

Figure 1- (A) Efficacy assessment at end of therapy made by treating investigator for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients based on five point scale of excellent, very good, good, satisfactory and poor. (B) Safety assessment at end of therapy made by treating investigator for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients based on five point scale of excellent, very good, good, satisfactory and poor.

Safety

Of the 338 patients who received levonadifloxacin, adverse events were documented for only 4 (1.2%) patients and a total of 5 (1.5%) adverse events were reported. Nausea was reported for three patients, diarrhoea for 1 (0.3%) patient and fatigue for 1 (0.3%) patient. All events were mild in severity.

Discussion

Community-acquired bacterial pneumonia is the third leading cause of death worldwide and the leading cause of death in low-income countries [6]. Bacterial pneumonia causes significant short-term and long-term mortality. The factors contributing to long-term mortality may be older age, comorbidities, frailty, cardiovascular complications, inflammation, and the severity of the initial infection [7]. In the absence of reliable therapy, patients treated on outpatient basis need frequent follow-up evaluation (every 72 hrs.) to detect clinical failure early [8]. If delayed, CABP can worsen leading to clinical failure and severe cases require hospitalization [9].

This study was conducted to identify the clinical and microbiological outcomes during the treatment of CABP with levonadifloxacin (oral and/or intravenous). The prescription event monitoring study included patients who received oral and/or intravenous levonadifloxacin for the treatment of CABP. Since most patients were hospitalized for their respiratory condition, they had an intravenous line and received intravenous levonadifloxacin, of which some were switched to oral therapy after a few days. Data for microbial success was available for 155 patients and these were used to estimate the microbial success rate. Levonadifloxacin

therapy was rated by investigators as '*excellent to good*' for efficacy in 95.2% patients and safety in 97.9% patients.

For most patients receiving treatment in hospital for pneumonia, treatment is usually initiated with an intravenous antibiotic within 4-8 hours of hospitalization to achieve high plasma and pulmonary concentrations for rapid antibacterial effect [10]. However, a switchover to oral therapy should always be considered for patients after clinical stability [11]. Two randomized controlled trials have shown significant reductions in the duration of hospital stay and adverse drug reactions, in patients who switch to oral therapy early [11,12]. Our study also included few patients (3.2%) who were switched over from intravenous to oral therapy. Several studies report that 5 days of treatment should be given for mild to moderately severe pneumonia with clinical stability after 3 days of treatment, and 7 days for severe cases of pneumonia [22,13]. However, for a novel antibiotic with high potency, coverage of all the potential respiratory pathogens, high lung and intracellular penetration which was found to be better than that of other fluoroquinolones (levofloxacin and moxifloxacin),[14] a short-course of therapy could be adequate in rendering a favourable clinical outcome. In this context, the mean duration of levonadifloxacin therapy for the treatment of CABP observed in this study was just 6-7 days, suggesting a favourable PK/PD and activity profile.

In this study, all patients received levonadifloxacin as empirical therapy. Despite this, the microbiological success rate observed in this study was 96.8% (150/155). Levonadifloxacin demonstrated the clinical success rates of 93.5% with intravenous therapy, 98.7% with oral therapy and 100.0% with intravenous followed by oral therapy. Choice of empirical antibiotic can pose

challenges to the treating clinician due to availability of varied group of antimicrobials. A meta-analysis of currently used antibiotics for community-acquired pneumonia in adult outpatients concluded that it is not possible to make strong evidence-based recommendations regarding the choice of antibiotic to be used for the treatment of CABP in ambulatory outpatients. As stated by the author, under such circumstances, other factors such as tolerability, duration and frequency of treatment and cost will take on more importance in determining the choice of treatment. The 2018 guidelines by '*The Korean Society of Infectious Diseases and Korean Society for Chemotherapy*' strongly recommends use of respiratory fluoroquinolones as empirical therapy with a very high level of evidence [13].

Levonadifloxacin is a broad-spectrum benzoquinolizine subclass of quinolones, has bactericidal activity against both Gram-positive and Gram-negative bacteria due to dual action through inhibition of DNA gyrase and topoisomerase-IV [15]. High rates of clinical efficacy with levonadifloxacin treatment is an outcome of its high intrapulmonary concentrations with penetration ratios in ELF and alveolar macrophages (AM) being 7.66 and 1.58, respectively (taking into account unbound plasma concentrations) [16]. Moreover, potent activity of levonadifloxacin against both extracellular and intracellular organisms might have also contributed in microbiological cure [4]. Further, observed safety of levonadifloxacin in 'real-world' patients, specifically in those with multiple co-morbidities points towards its favourable disposition profile.

The favourable safety and efficacy of levonadifloxacin in patients who were on other medications such as anti-diabetics, anti-hypertensive etc. suggests minimal drug-drug interaction which is an outcome of levonadifloxacin's lack of CYP interaction. In addition to direct antibacterial action, levonadifloxacin has also been demonstrated to significantly reduce the inflammatory responses as seen in human whole-blood assay through inhibition of pro-inflammatory cytokines and in the acute lung injury model by lowering lung total white blood cell count, myeloperoxidase, and pro-inflammatory cytokine levels (TNF-alpha, IL-6, and IL-1). This immunomodulatory finding was corroborated using histopathological evidence that suggested minimal infiltration of neutrophils into the lung tissue by levonadifloxacin after a lipopolysaccharide challenge. This feature may play a role in augmenting the clinical efficacy [17]. Levonadifloxacin has comparable antibacterial activity with other quinolones against *Haemophilus influenzae, Klebsiella pneumoniae, and Pseudomonas aeruginosa*. Its activity against multidrug resistant Gram-positive, quinolone sensitive Gram-negative, atypical bacteria and anaerobes offers a great advantage of using a single agent for the treatment of polymicrobial infections. Additionally, as compared to other fluoroquinolones, levonadifloxacin had lower MIC (0.5 mg/L and 2.0 mg/L) for anaerobic organisms (*B. fragilis, Prevotella, Porphyromona, ß-lactamase-producing Fusobacteria, C. perfringens, and C. difficile*) [4].

Levonadifloxacin is not a substrate for *NorA* efflux pump, hence development of antimicrobial resistance by efflux mechanisms by Gram-positive bacteria is minimized [18]. Further, it has activity against slow-growing staphylococci and has improved activity in acidic pH. The excellent oral bioavailability of levonadifloxacin not affected by food, coupled with favourable pharmacokinetic and pharmacodynamics profile makes it a preferred antibiotic for varied infections including anaerobic infections. Non-clinical and clinical studies have established an excellent safety profile of levonadifloxacin with lack of potential adverse effects, such as phototoxicity, prolongation of QT

interval,[19] hepatotoxicity, and nephrotoxicity, thus potentially offering a better option for the treatment of bacterial CABP. Levonadifloxacin could be a preferred antibiotic of choice for empirical therapy, which enables the clinician for easy switch-over from injectable to oral therapy.

The main strength of our study is that it includes data based on the real-word scenario for CABP management from hospitals across the country and thus this study provides insights of the therapeutic utility of levonadifloxacin in CABP management. Also, very few studies are reported from India regarding use of empirical antibiotic use in pneumonia. The strength of our study lies in the fact that in addition to the clinical and microbial outcomes in pneumonia, data on extent of infections and common organisms isolated is available. The study, however, has a few limitations. Due to the retrospective study design, there was no study monitoring and there is no control on the different confounding factors. Also, there could be a possible under-reporting of data on treatments, and adverse events due to lack of adequate documentation. Also, our study is restricted to a short-term follow-up limited till the patients were discharged from hospital.

Conclusion

Immunomodulatory and antibacterial activity of levonadifloxacin is expected to provide clinical benefits in the treatment of community-acquired bacterial pneumonia. Levonadifloxacin could be a preferred antibacterial agent in the management of CABP which also enables the clinicians for easy switch-over from injectable to oral formulation.

Declaration

Ethics approval and consent to participate

Included above in the section of Informed consent and Ethics under Methods

List of abbreviations

CABP: Community-Acquired Bacterial Pneumonia
MRSA: Methicillin-Resistant Staphylococcus aureus
IV: Intravenous
LRTI: Lower Respiratory Tract Infection
ABSSSI: Acute Bacterial Skin and Soft Tissue Infections
DFI: Diabetic Foot Infection
ELF: Epithelial Lining Fluid
IEC: Institutional Ethics Committee
GCP: Good Clinical Practice
ICD-10: International Classification of Diseases
SD: Standard Deviation
AMA: Antimicrobial Agents
BMI: Body Mass Index
AM: Alveolar Macrophages

Trial registration

Trial registration no.: CTRI/2020/09/028152 [Registered on: 30/09/2020]

Data Availability

All the quantitative and qualitative data used in writing the article are included in this manuscript.

Conflicts of Interest

Funding Statement

Authors' contributions

PP conceived the research idea and collected all the relevant data. KM, SB & PS conducted the literature review and wrote the manuscript. BT performed the data analysis and helped with the manuscript writing.   All authors thoroughly reviewed the manuscript and approved its content for publication.

Acknowledgments

References

[1] Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. Lancet 2015;386 (9998):1097-108.

[2] Ramirez JA, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, et al. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. Clin Infect Dis 2017;65(11):1806-12.

[3] Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect 2014;20 Suppl 5:45–51.

[4] Bhagwat SS, Nandanwar M, Kansagara A, Patel A, Takalkar S, Chavan R, et al. Levonadifloxacin, a Novel Broad-Spectrum Anti-MRSA Benzoquinolizine Quinolone Agent: Review of Current Evidence. Drug Design, Development and Therapy 2019;13:4351–65.

[5] World Health Organization. International Statistical Classification of Diseases and Related Health Problems.[Internet].Geneva:WHO;[updated2019]. Available from: https://icd.who.int/browse10/2019/en

[6] Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. Cochrane Database Syst Rev 2014;2014(10):CD002109.

[7] Restrepo MI, Faverio P, Anzueto A. Long-term prognosis in community-acquired pneumonia. Curr Opin Infect Dis 2013;26:151–8.

[8] 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(3):611–8.

[9]   Aliberti S, Blasi F. Clinical stability versus clinical failure in patients with community-acquired pneumonia. Semin Respir Crit Care Med 2012;33(3):284–91.

[10] Barlow G, Nathwani D, Williams F, Ogston S, Winter J, Jones M, et al. Reducing door-to antibiotic time in community-acquired pneumonia: controlled before-and-after evaluation and cost-effectiveness analysis. Thorax 2007;62(1): 67–74.

[11] Oosterheert JJ, Bonten MJ, Schneider MM, Buskens E, Lammers JJ, Hustinx WMN, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ 2006;333(7580):1193.

[12] Carratalà J, Garcia-Vidal C, Ortega L, Fernández-Sabé N, Clemente M, Albero G, et al. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. Arch Intern Med 2012;172(12):922–8.

[13] Lee MS, Oh JY, Kang CI, Kim ES, Park S, Rhee CK, et al. Guideline for Antibiotic Use in Adults with Community-acquired Pneumonia. Infect Chemother 2018;50(2):160-198

[14] Barcia- Macay M, Seral C, Mingeot- Leclercq M- P, Tulkens PM, Van Bambeke F. Pharmacodynamic evaluation of the intracellular activities of antibiotics against Staphylococcus aureus in a model of THP-1 macrophages. Antimicrob Agents Chemother 2006;50(3):841–851.

[15] Bhagwat SS, Mundkur LA, Gupte SV, Patel MV, Khorakiwala HF. The anti-methicillin-resistant Staphylococcus aureus quinolone WCK 771 has potent activity against sequentially selected mutants, has a narrow mutant selection window against quinolone-resistant Staphylococcus aureus, and preferentially targets DNA gyrase. Antimicrob Agents Chemother 2006;50(11):3568–79.

[16] Rodvold KA, Gotfried MH, Chugh R, Gupta M, Yeole R, Patel A, et al. Intrapulmonary pharmacokinetics of levonadifloxacin following oral administration of alalevonadifloxacin to healthy adult subjects. Antimicrob Agents Chemother 2018;62(3):e02297–17.

[17] Patel A, Sangle GV, Trivedi J, Shengule SA, Thorve D, Patil M, et al. Levonadifloxacin, a Novel Benzoquinolizine Fluoroquinolone, Modulates Lipopolysaccharide-Induced Inflammatory Responses in Human Whole-Blood Assay and Murine Acute Lung Injury Model. Antimicrob Agents Chemother 2020;64(5):e00084-20.

[18] Jacobs MR, Bajaksouzian S, Windau A, Appelbaum PC, Patel MV, Gupte SV, et al. In vitro activity of the new quinolone WCK 771 against staphylococci. Antimicrob Agents Chemother. 2004;48(9):3338–42.

[19] Mason JW, Chugh R, Patel A, Gutte R, Bhatia A. Electrocardiographic effects of a supratherapeutic dose of WCK 2349, a benzoquinolizine fluoroquinolone. Clin Transl Sci 2019;12(1):47–52.