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NEW FRONTIERS IN COMMUNITY ACQUIRED PNEUMONIA: GARENOXACIN MESYLATE

Medicine

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ABSTRACT

Garenoxacin mesylate is a novel des-fluoro (6) quinolone with unique Pharmacokinetic profile that promises to cover a wide spectrum of sensitive and resistant organisms commonly encountered in community acquired infections including PRSP or BLNAR strains. Garenoxacin has been structurally designed to ensure high potency against Gm positive, Atypical & Anaerobic organisms with negligible potential for resistance development. Garenoxacin approved in the worldwide market since 2007 has been documented in over 10,000 patients with community acquired respiratory tract infections or Community-acquired Pneumonia when used as initial- or second-line therapy.

KEYWORDS

Garenoxacin, Community-acquired infections, Fluoroquinolones, Pneumonia, Beta-lactamases

INTRODUCTION

Community-acquired pneumonia (CAP) is a common infection that is potentially life threatening, especially in older adults and those with comorbid disease. The clinical definition of CAP that has been used in community studies has varied widely but has generally included a complex of symptoms and signs both from the respiratory tract and regarding the general health of the patients. Features such as fever (>38°C), pleural pain, dyspnea and tachypnoea and signs on physical examination of the chest (particularly when new and localising) seem most useful when compared with the gold standard of radiological diagnosis of CAP.

The Infectious Diseases Society of America (IDSA) defines CAP as "*an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized roles), in a patient not hospitalized or residing in a long-term care facility for more than 14 days before onset of symptoms*"1

Incidence

As per the CDC estimates, 1.1 million people gets hospitalized in US and more than 50,000 died due to pneumonia in 2009 (2). Though large studies are lacking at India on the incidence of CAP, the mortality data on the total number of deaths caused by "lower respiratory tract infections (LRTI)" are available. The number deaths due to LRTI was 35.1/1,00,000 population in 2008, for TB it was 35.8/1,00,000 population while it was 194.9/1,00,000 population for infectious and parasitic diseases. Thus around 20% of the mortality due to infectious diseases in India was caused by LRTI. The reported mortality of CAP from India is similar to that reported elsewhere in the world (3).

Several studies have shown that resistant pneumococcal infection in patients who require hospitalization is associated with increased length of stay mortality and cost of care.

Pathogenesis

There are several routes of pathogen acquisition involved in the pathophysiology of CAP. Aspiration of oropharyngeal contents is the most common route of acquisition but is often considered to be a subclinical aspiration. This should not be confused with aspiration pneumonia,which has an anaerobic etiology. The pathophysiology of90% of pneumonias involves organisms that descend from the oropharynx into the lower respiratory tract. Other routes of pathogen acquisition include inhalation and spread along mucous membranes (viruses), hematogenous spread (Staphylococcus), and contiguous spread.

Etiology & Classification

Many studies have examined the etiology of CAP. Virtually all studies in a compilation of 15 trials showed that *S. pneumoniae* was the most common pathogen (20%–60% of cases), followed by Haemophilus influenzae (3%–10%) (Table 1). The atypical pathogens (*Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila*) were variably implicated depending on the study, and viruses have become more appreciated as a common cause of pneumonia in adult patients. Other less common considerations (e.g., tuberculosis, Pneumocystis carinii, Q fever, fungi, and severe acute respiratory syndrome–associated coronavirus) exist, and clinicians should also consider these new and emerging pathogens as potential causes of pneumonia (4).

Table 1. Etiologic Agents in Community-Acquired Pneumonia*

Etiologic Agents	Cases (%)
Bacteria	
• *Streptococcus pneumoniae*	20-60
• *Haemophilusinfluenzae*	3-10
• *Moraxella catarrhalis*	1-2
• *Staphylococcus aureus*	3-5
• Other gram-negative species	3-10
Atypicals	
• *Mycoplasma spp*	1-6
• *Chlamydia spp*	4-6
• *Legionella spp*	2-8
Viruses	2-15
Aspiration pneumonia	6-10
No diagnosis	30-60

* Other considerations include tuberculosis, Pneumocystis carinii pneumonia, Q fever, and fungi.

The majority of studies that have evaluated the etiology of CAP have consisted of patients in the hospital, where laboratory processes are more likely to be available for diagnosis. However, half of these cases still did not have defined etiologies. When patients were stratified by disease severity (ambulatory, hospitalized [nonsevere], and intensive care unit [ICU] [severe]), S pneumoniae was the most common cause of CAP among patients in all settings (Table 2) followed by H. influenza and Legionella spp..

Table 2. Etiology of Community-Acquired Pneumonia by Disease Severity (Descending Order of Incidence)

Ambulatory Patients	Hospitalized (Non-ICU)	ICU (Severe)
Streptococcus pneumoniae	*S pneumoniae*	*S pneumoniae*
Mycoplasma pneumoniae	*M pneumoniae*	*Legionella spp*

Haemophilusinfluenzae	*C pneumoniae*	*H influenzae*
Chlamydia pneumoniae	*H influenzae*	Other gram-negative bacilli
Respiratory viruses	*Legionella spp*	*Staphylococcus aureus*
Aspiration		
Respiratory viruses		

Atypical organisms or Mycoplasma was most common for patients 50 years and without significant comorbid conditions or abnormality of vital signs, whereas S pneumoniae was the most common pathogen for older patients or those with significant underlying disease.

Antibiotic Resistance

- **Strep. pneumoniae -** Worldwide there has been a steady rise in the prevalence of Pencillin resistant Strep. pneumoniae (PRSP) strains. Surveillance studies conducted worldwide have shown rising MICs for Amoxy-clav combinations with ≈4 to 7% strains demonstrating MICs of 4 mg/L [5,6]. These strains are not covered with classical dosage administration of 625 mg for the combination given three times a day and require further higher dose supplementation [2]. Ho (2000) et al[7], demonstrated Fluoroquinolone resistance emerging in South East Asian Countries including Hong Kong where the resistance rates have been 13.3% & 8.9% for Levofloxacin & Moxifloxacin respectively.
- **H. influenza –** In elderly individuals, particularly those with underlying lung disease, H. influenzae can cause severe pneumonia. The development of Beta-lactamase negative ampicillin resistance strains (BLNAR) has been considered as an important advance in the evolution of these organism species since there is associated alteration of PBP binding site. Prevalence of BLNAR among H. influenzae has been increasing in various countries including Asia (18.2%) (8).
- **Atypical pathogens -** Similarly in Asian population the high prevalence of Atypical pathogens (23.5%) amongst CAP patients presents a unique challenge in empirical management [9]. However the high rates of macrolide-resistant M. pneumoniae reported in China (>90%) and Japan (87.1%) 10,11 **h**as limited the available therapeutic options while managing CAP empirically

Guidelines for management of CAP

Observations of antimicrobial resistance and the increase in the number of likely causative pathogens have led to challenges in the management of CAP, and clinicians should consider these factors when selecting empiric therapy. Because the differences in clinical signs and symptoms for bacterial and viral etiologies are not clear, clinicians may have difficulty distinguishing between bacterial and viral causes of infection and determining whether antimicrobial therapy is warranted. Obtaining uncontaminated specimens from the suspected infection site to determine whether the etiology is bacterial is difficult and rarely done. Even when specimens are obtained, microbiological results are inconclusive approximately 50% of the time.

Several guidelines for the treatment of CAP have been developed to aid physicians in selection of appropriate therapy (Table 4)

Table 4. Empiric Antimicrobial Therapy Recommendations for Outpatient Community- Acquired Pneumonia in Immunocompetent Adults from the 2003 Updated Guidelines of the Infectious Diseases Society of America (12)

Patient Variable	Preferred Treatment Options
Previously healthy	
• No recent antibiotic therapy	A macrolide* or doxycycline
• Recent antibiotic therapy†	A respiratory fluoroquinolone‡ alone or an advanced macrolide§ plus either high-dose amoxicillin_ or high-dose amoxicillin clavulanate_
Comorbidities (COPD, diabetes mellitus, renal failure, congestive heart failure, or malignancy) No recent antibiotic therapy	An advanced macrolide§ or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a beta- lactam¶

COPD _ chronic obstructive pulmonary disease.
* Erythromycin, azithromycin, or clarithromycin.

† The patient was given a course of antibiotic(s) for any infection within the past 3 months. Depending on the class of antibiotics recently given, a selection may be made from among the suggested options.

‡ Moxifloxacin, gatifloxacin, levofloxacin, or gemifloxacin.
§ Azithromycin or clarithromycin.

_ Dosage for amoxicillin, 1 g orally t.i.d.; for amoxicillin-clavulanate, 2 g b.i.d.

¶ High-dose amoxicillin or high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime.

Similarly, the guidelines from the **American Thoracic Society (13)** suggest empiric therapy based on the likely infecting pathogens. Combination therapy with oralβ-lactams, such as cefpodoxime, cefuroxime, high-dose amoxicillin, or amoxicillin- clavulanate, plus a macrolide or doxycycline for "atypical" coverage, or monotherapy with a respiratory fluoroquinolone are indicated in outpatients with cardiopulmonary disease (congestive heart failure or COPD) and/or other modifying factors that place them at risk for infection with DRSP or gram-negative pathogens.

British Thoracic Society (14) suggests empirical therapy based on severity of infection. The CURB-65 recommended by the British Thoracic Society provides a complimentary guide for identification of more severely ill. The guidelines support the use of more traditional β-lactam antibiotics as first line therapy. For patients treated in community, amoxicillin remains the preferred agent while doxycycline or clarithromycin are appropriate as alternative choices. Oral therapy with amoxicillin and a macrolide is preferred for patients with moderate severity CAP. Monotherapy with a macrolide may be suitable for patients who have failed to respond to an adequate course of amoxicillin prior to admission. When oral therapy is contraindicated, the preferred parental choice includes intravenous amoxicillin or benzylpenicillin together with clarithromycin. For those intolerant of penicillins or macrolides, oral doxycycline is main alternative along with oral levofloaxacin & oral moxifloxacin.

When a change in empirical antibiotic therapy is considered necessary those with moderate severity pneumonia in hospital on combination therapy, changing to doxycycline or a fluoroquinolone with effective pneumococcal cover are alternative options. Adding a fluoroquinolone is an option for those with high severity pneumonia not responding to combination β-lactam/macrolide antibiotic regimen. Fluoroquinolone is also recommended for the management of moderate and high severity or life threatening legionella pneumonia.

The **Joint ICS/NCCP (I) recommendations**, 2012 (3) suggests following factor while choosing the initial empiric treatment:

a) The most likely pathogen
b) Knowledge of local susceptibility patterns
c) Pharmacokinetic and pharmacodynamics (PK/PD) of antibiotics
d) Compliance, safety and cost of the drugs and
e) Recently administered drugs

Primary aim of the treatment is choose an empiric antibiotic which aims at most common pathogen involved which in most cases is *Streptococcus pneumoniae, H. influenza or Atypicals*.

Antibiotics should be started as early as possible after the diagnosis of CAP is established. In severe CAP, antibiotics should be administered as soon as possible preferably within 1 hour (200 Gupta). Most non-severe infections would settle within 3-5 days. In cases where oral therapy is not possible then intravenous route should be preferred. Patients may be switched over to oral medications as soon as they improve clinically and are able to ingest orally. **Most cases respond within 3-7 days; longer durations are not required routinely** (3).

Garenoxacin

Garenoxacinmesylate is novel des-fluoro quinolone that lacks classical C-6 fluorine and has a difluormethoxy substituent at position 8, instead of a methoxy group. This has improved the bacteriostatic and bactericidal activity and decrease the selection of resistant mutants. Garenoxacin has exceptional activity against gram positive cocci

including *Staphylococcus aureus*. It is the most active quinolone against methicillin-susceptible and resistant staphylococci, being more active than moxifloxacin, levofloxacin, ofloxacin and ciprofloxacin and it is 16 to 64 fold more active than ciprofloxacin against quinolone resistant *Staphylococcus aureus* (15).

The table on the comparative MIC_{90} suggests the superiority of garenoxacin over moxifloxacin, levofloxacin and amoxicillin-clavulanate

Table 1: MIC_{90} (µg/ml) of various anti-infectives against common pathogens (16,17)

Pathogens	GRN	AMC	LVX	MFX
Methicillin-susceptible S. aureus	0.03	0.5	0.25	0.06
Methicillin-resistance S. aureus	1	> 128	2	8
Penicillin-susceptible S. pneumoniae	0.12	≤ 0.25	2	0.25
H. influenza	≤ 0.03	2	0.03	0.06
M. catarrhalis	≤ 0.03	0.25	0.06	0.12
S. pyogenes	0.25	≤ 0.015	1	0.25
Klebsiella	0.5	32	0.25	0.5
P. aeruginosa	16	> 128	4	8
Mycoplasma	0.06	NT	0.5	0.12
Leigonella	0.06	NT	0.03	0.06
E. coli	0.06	4 to 16	0.06	0.06
Enterobacter spp.	0.25	4	0.12	0.25
Acinetobacter baumannii	0.25	NT	1	1
Bacteriodes fragilis	0.5	4	2	0.5
Peptostreptococci	0.25	4	4	1

NT – Not tested; AMC-Amoxicillin clavulanate; LVX – Levofloxacin; MOX- Moxafloxacin

The consistency in the susceptibility pattern of the above organisms to Garenoxacin was once again highlighted by recent publication by Yamagishi (2017) highlighting higher propensity for Garenoxacin to achieve target systemic or site concentrations when compared with Moxifloxacin or Levofloxacin. The JSC suggested susceptibility breakpoints of 0.5 & 0.125 mcg/ml were within the 'ideal' free AUC/MIC values calculated for Strep. pneumoniae and H. influenza pathogens (18)

Similarly the unfavorable PK-PD ratio for mycobacterium tuberculosis as suggested by Vora et al (19) with literature reported MIC90 as 4 µg/ml probably limits its role in High-risk cases with probable overlapping symptoms unless however ruled out by sputum culture for AFB or Genxpert analyses

Clinical studies

Clinical efficacy of Garenoxacin has been evaluated in 20 Phase II/III/IV clinical trials involving ≈ 10,000 patients for various therapeutic indications including RTIs

Bacterial pneumonia: A double-blind study was conducted comparing GARENOXACIN 400 mg qd with LVFX 100 mg three times a day for 10 days in patients with bacterial pneumonia. Though the efficacy rates were comparable, PRSP were less effectively eradicated by Levofloxacin (20).

Description	Daily dose and duration	Patients (n)	Results
Clinical phase III comparative study of oral GARENOXACIN versus LVFX in patients with bacterial pneumonia	GARENOXACIN 400 mg, 10 days LVFX 300 mg, 10 days	135 118	**Clinical Efficacy rate** • GARENOXACIN – 94.9% • LVFX – 92.8% **Bacterial eradication rate** • GARENOXACIN – 100% • LVFX – 87.8%

Atypical pneumonia: In a postmarketing surveillance study to determine the efficacy and safety of the oral quinolone antibacterial agent garenoxacin (Geninax® Tablets 200 mg) against atypical pneumonia, 105 patients were evaluated. The efficacy rates among patients suspected of having atypical pneumonia and those with a confirmed diagnosis of atypical pneumonia were 94.8% (55/58 patients) and 92.3% (12/13 patients), respectively. The incidence of adverse drug reactions (including abnormal laboratory tests) was 4.8% (5/105 patients). Among the adverse drug reactions, gastrointestinal disorders, infection and infestation, nervous system disorder, and skin and subcutaneous tissue disorder were observed in 2.9% of patients (3/105), 1.0% (1/105), 1.0% (1/105), and 1.0% (1/105), respectively. (21)

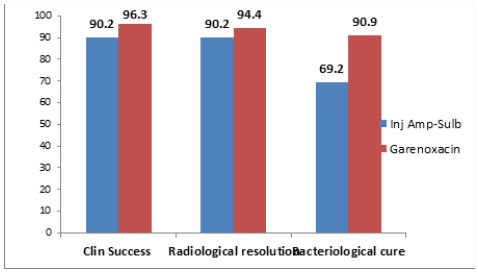
Post-marketing Surveillance study:

- A Retrospective observational study was conducted between 2008 and 2010 by Hori et al (22) . 6412 patients (15 to 103 yrs) with Pharyngitis/laryngitis; Tonsilitis; Acute bronchitis; Pneumonia; AECB; Otitis media; Sinusitis infections were included in analysis. Garenoxacin mean dose of 400 mg was administered for 5 days. High clinical efficacy rates were observed based on causative organism

Indication	Efficacy rate (%)
1. S. pneumoniae (PRSP)	100 %
2. M. catarrhalis	95.8 %
3. H. Influenzae (BLNAR)	100 %
4. C. pneumoniae	92.5%
5. M. pneumoniae	100 %

Switch therapy: Garenoxacin shows superior Pharmacokinetic profile as suggested by high AUC/MIC ratio of ≥30, ≥60, ≥80 against S. pneumoniae, S. aureus and Enterobacteriacae. CHMP has therefore advised use of Garenoxacin 400 mg as "Switch therapy" in community or outpatient settings where the use of injectable antibiotics involving cephalosporins or beta lactams may be deemed appropriate. The consequent benefits with Garenoxacin have been well highlighted by Hori (22) and Kohona (23) where clinical efficacy rates following 'Switch' from Injectable penicillin or cephalosporins ranged from 94.2 to 96.3% respectively.

- In a randomized, double-blind, multicentric study, switch therapy to oral Garenoxacin was bacteriologically and clinically evaluated in 108 patients with mild to moderate severe CAP requiring hospitalization. Patients were randomized to receive continous Ampicillin-sulbactam injection for 7 days or Oral Garenoxacin after 3 days. The active control arm received additionally Clarithromycin. Garenoxacin therapy showed comparable clinical and radiological resolution rates to the control arm receiving Injection Amp-Sulbactam with Clarithromycin (23)



Clinical safety

Garenoxacin mesylate has been well tolerated in above clinical trials with its true character revealed in 'Real world clinic settings' or post marketing surveillance studies.

Hori et al (22) reported negligible incidence of Diarrhea/vomiting (0.6%), Dizziness (0.05%), Somnolence (0.06%) or Hypotension (0.05%) thus offering a unique safety profile that is unparalleled amongst Fluoroquinolones or Beta-lactams

Garenoxacin is a well tolerated drug with its safety profile well differentiated due to the lack of Fluorine atom at C6 position **(24) that probably translates to its least potential for QTc prolongation compared to other Fluoroquinolones when administered at** therapeutic dosages of 400 mg (25). In a prospective, observational, open-label, safety study involving analyses of 12498 prescriptions for Garenoxacin across India, adverse events were reported in 159 patients that included 0.5% cases with nausea/vomiting, 0.1% cases with diarrhea & 0.02% cases for drowsiness or dizziness were reported with none involving QTc prolongation or cardiac side effects. In a lone case of serious adverse event observed, the causality assessment ruled out the association with Clinical use of the drug (26)

Similarly in an observational, open-label, single-arm, prospective, clinical study conducted in Post-approval outpatient settings of India,

again highlighted the relative safety of Garenoxacin amongst the 468 pts with respiratory tract infections with no reports of any QTc prolongation or Torsades pointes (27)

Dosage and Administration

Infection	*Garenoxacin*	*Levofloxacin*	*Moxifloxacin*	*Amox-clavulanate*
CAP	400mg OD 5-14 days	500 mg OD 7-14 days	400 mg OD 7-14 days	625 mg TID/ 1000 mg BD for 7 to 14 days
AECB	400mg OD 5 days	500 mg OD 7days	400 mg OD 5 days	625 mg TID/ 1000 mg BD for 7 -14 days

Summary

Clinical management of Community-acquired pneumonia remains a major therapeutic challenge due to lack of expertise for timely intervention and diagnostic limitations for identification of causative organisms

Garenoxacin with its unique chemical structure offers differentiated yet potent activity against major CAP pathogens including ***Strep. pneumoniae, H. influenza, Legionella spp, Mycoplasma besides Enterobacteriacae or Anaerobes***. It has a favourable pharmacokinetic profile, a good clinical response rate and is well tolerated while offering once a day dosage convenience against Pencillin/Quinolone Resistant Strep pneumoniae and/or BLNAR strains causing Severe LRTIs

Garenoxacin would therefore be a welcome addition to the therapeutic armamentarium of the clinicians while treating some of these severe infections in their 'real world' clinic settings.

REFERENCES

1. Lionel A et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults: CID 2007:44 (Suppl 2)
2. Marston BJ, et al, for the Community- Based Pneumonia Incidence Study Group. Incidence of community-acquired pneumonia requiring hospitalization. Arch Intern Med. 1997;157:1709–1718.
3. Gupta D. National Pneumonia Guidelines Lung India 2012; 2:S27-S62
4. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med. 1995;333:1618–1624.
5. Felmingham D, Reinert RR, Hirakata Y, et al. Increasing prevalence of antimicrobial resistance among isolates of Streptococcus pneumoniae from the PROTEKT surveillance study, and comparative in vitro activity of the ketolide, telithromycin. J Antimicrob Chemother 2002;50 Suppl. S1:25S-37S .
6. White AR. Augmentin® (amoxicillin/clavulanate) in the treatment of community-acquired respiratory tract infection: a review of the continuing development of an innovative antimicrobial agent. Journal of Antimicrobial Chemotherapy 2004; 53 Suppl(S1): i3–i20
7. Ho PL, Tse WS, Tsang KWT et al. Risk factor for acquisition of levofloxacin-resistant Streptococcus pneumoniae: a case control study. Clin Infect Dis 2001; 347:65-6.
8. Lulitanond A. Jpn J Infect Dis 2002;65: 122-125
9. Ngeow YF et al. An Asian study on the prevalence of atypical respiratory pathogens in community-acquired pneumonia. International journal of infectious diseases. 2005;9(3):144-53.
10. Okada T, Morozumi M, Tajima T, Hasegawa M, Saskata H, Ohnari S, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant Mycoplasma pneumoniae infection in a 2011 outbreak among Japanese children. Clin Infect Dis. 2012;55:1642–9.
11. Cao B, Zhao CJ, Yin YD, Zhao F, Song SF, Bai L, et al. High prevalence of macrolide resistance in Mycoplasma pnemoniae isolates from adult and adolescent patients with respiratory tract infection in China. Clin Infect Dis. 2010;51:189–94
12. Mandell LA, for the Infectious Diseases Society of America. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis. 2003;37:1405–1433.
13. American Thoracic Society. 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.
14. BTS Guidelines
15. Ince D, Zhang X, Silver LC, Hooper DC. Dual targeting of DNA gyrase and topoisomerase IV: target interactions of garenoxacin (BMS-284756, T-3811ME), a new desfluoroquinolone. Antimicrobial agents and chemotherapy. 2002;46(11):3370-80.
16. Andersson & MacGowan. Development of the quinolones. J of Antimicrobial Chemo 2003 ; 51, Suppl. S1 : 1–11
17. Weller TMA. The in vitro activity of BMS 284756, a new des fluorinated quinolone. J Antimicrob Chemother 2002; 49 : 177-184
18. Yamagishi Y, Shibata T, Nakagawa S, Nomura N, Mitsuyama J, Mikamo H. Proposed Pharmacokinetic-Pharmacodynamic Breakpoint of Garenoxacin and Other QuinolonesJpn J Infect Dis 2017; 70, 616–620
19. Vora A, Krishnaprasad K. Guiding Principles for the use of Fluroquinolones in Out-patient Community Settings of India: Panel Consensus. Journal of The Association of Physicians of India,2017; 65: 51-54
20. Kobayashi H. Clinical phase III comparative study on garenoxacin versus levofloxacin in patients with bacterial pneumonia. Nippon Kagaku Ryoho Gakkai Zasshi 2007;55(Suppl. 1):127–43.
21. Koichi Izumikawa a, *, Akira Watanabe b, Naoyuki Miyashita c, Tadashi Ishida d,Hiroaki Hosono e, Satoru Kushimoto e, Shigeru Kohno. Efficacy and safety of garenoxacin tablets on clinically diagnosed atypical pneumonia: Postmarketing surveillance in Japan. J Infect Chemother. 2014 Sep;20(9):541-8
22. Hori S, Maki N. Survey on the usage results of Garenoxacin tablets. Post marketing surveillance report. 2011;59(5).
23. Kohno S. Clinical phase III open-labeled study of oral garenoxacin in patients with respiratory tract infection by penicillin-resistant Streptococcus pneumoniae. Nippon Kagaku Ryoho Gakkai Zasshi 2007;55 (Suppl 1): 185-93
24. Shams WE, Evans ME. Guide to Selection of Fluoroquinolones in Patients with Lower Respiratory Tract Infections. Drugs 2005; 65 (7): 949-991
25. Takagi H. Clinical studies of Garenoxacin. Int J of Antimicrobial Agents 2008; 32: 468–474
26. Anoop Hajare, Amandeep Gupta, Saiprasad Patil, K Krishnaprasad, Amit Bhargava. A prescription event monitoring study on the utility of garenoxacin, a newer fluoroquinolone in IndiaInternational Journal of Applied and Basic Medical Research, 2015; 5(2):87-91
27. Garg H, Katke P, Krishnaprasad K. Post-Approval Assessment on Clinical Utility and Safety Profile of Garenoxacin Mesylate in Patients with Community Acquired Respiratory Tract Infections. Journal of Clinical Diagnostic Research 2018;12(1): OC05-OC09