ROLE OF NEW FLUOROQUINOLONES IN THE TREATMENT OF LOWER RESPIRATORY TRACT INFECTIONS

Cristina Monica Popescu, Adriana Hristea, Ruxandra Moroti, Simona Fusca

[1]*Emergency County Hospital Slatina, Infectious Diseases*

[2]*National Institute for Infectious Diseases „Prof. Dr. Matei Bals“*

[3]*Emergency County Hospital Targoviste, Infectious Diseases*

ABSTRACT

Respiratory fluoroquinolones are important therapeutic options in the treatment of low respiratory tract infections because of the rising resistance to ß-lactams and other agents in Streptococcus pneumoniae, the most commonly bacterial pathogen identified in these infections.

These antibiotics offer some advantages that include excellent oral bioavailability, extensive penetration into sputum, bronchial and lung tissue and an elimination half-life that allows once-daily dosing.

Levofloxacin, moxifloxacin, ciprofloxacin are available in both intravenous and oral formula and are excellent candidates for early intravenous-to-oral switch therapy in hospitalized patients. The newer fluoroquinolones exibit concentration-dependent bacterial killing, offering coverage of the pathogens involved in lower respiratory tract infections and have been proved to be a safe and effective.

Resistance to fluoroquinolones in Streptococcus pneumoniae remains low but rational prescribing is needed to sustain their future clinical effectiveness.

Key words: respiratory fluoroquinolones, lower respiratory tract infections

Lower respiratory tract infections (LRTIs) are major causes of morbidity and mortality. These infections account for over two-third of antibiotic prescriptions and comprise approximately 80% of all infection presentations. Although the great majority of LRTIs are self-limiting viral infections, community-acquired pneumonia (CAP) is most of the times a bacterial disease with a substantial mortality, ranging from 0.2% for elderly people in the community to14% for those hospitalized with CAP.

LRTIs may be caused by Gram-positive organisms (predominantly *Streptococcus pneumoniae*), Gram-negative organisms (*Haemophilus influenzae* and *Moraxella catarrhalis*) and "atypical" bacteria (*Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae)*.

Identifying the causative pathogen is rarely possible before initiation of antibacterial treatment. Therefore, treatment of LRTIs is generally empiric.

TABLE 1. *Prevalence of major respiratory pathogens in lower respiratory tract infections*

Infection	Pathogen	Total isolates (%)
Acute exacerbation of chronic bronchitis (AECB)	*H. influenzae* *S. pneumoniae* *M. catarrhalis*	30-59 15-25 3-22
Community-acquired pneumonia CAP	*S. pneumoniae* *H.influenzae* *L. pneumophila* *C. pneumoniae* *M. catarrhalis*	8-46 2-11 1-16 6-15 2

Antimicrobials selected for the treatment of LRTIs should ideally possess activity against common and atypical pathogens and have optimal pharmacokinetic and pharmacodynamic parameters that facilitate convenient dosage schedules and good tissue penetration. Some key factors to consider when selecting the most appropriate antibacterial agent for LRTIs are summarized in table 2.

Adresa de corespondență:

Cristina Monica Popescu, Emergency County Hospital Slatina, Infectious Diseases, Crisan Street, No. 9-11, Slatina

TABLE 2. *Key Factors to Consider When Selecting Antibacterial Therapy for LRTIs*

• Disease-specific factors
Possible pathogens
Likelihood of resistant organisms
Severity of infections
Concomitant disease
• Antibacterial-specific factors
Spectrum of activity, including resistant strains
Proved clinical efficacy
Tolerability profile/ adverse effect
Convenience/ compliance
Cost

Emergence of antimicrobial resistance to commonly prescribed antimicrobial agents (ß-lactams, macrolides) has limited therapeutic options for treatment of LRTIs and newer fluoroquinolones (FQs) have been developed and are now recommended for the treatment of LRTIs.

Fluoroquinolones are sinthetic quinolone derivates that have a fluorine atom in the 6 position. The newer fluoroquinolones (or respiratory fluoroquinolones) levofloxacin, moxifloxacin, gatifloxacin and gemifloxacin show enhance activities against Gram-positive organism like *S pneumoniae* (including multiple drug-resistant *S pneumoniae*) in addition to their improved pharmacokinetic and pharmacodynamic properties compared to older agents such as ciprofloxacin. All new fluoroquinolones have high bioavailability, low protein binding and longer serum elimination half-life comparative with the earlier quinolones, thus permitting once-daily dosing. All of them penetrate phagocytic cells and have good activity against intracellular pathogens. The penetration into respiratory tissue is very high.

TABLE 3. *Concentrations of fluoroquinolones in serum and lung compartments*

Drug	Oral dosage (mg)	C max ss (µg/ml)	Alveolar macro-phages (µg/ml)	Epithelial lining fluid (µg/ml)
CIP	500 mg bid	2,9	34,9	1,87
LVX	500 mg od	5,7	98	10
LVX	750 mg od	8,6	105	22
GATI	400 mg od	4,2	77	6,16
MOXI	400 mg od	4,5	57	20,7
GEMI	320 mg od	1,8	107	2,69

Concentrations in lung tissue are generally higher than those in serum and remains above the MICs for the most susceptible organism (figure 1).

Levofloxacin, moxifloxacin, ciprofloxacin are currently available in both oral and intravenous formulations and the high bioavilability may allow flexible dosing and intravenous-to-oral switch therapy. Hospitalized patients may be switched more rapidly from intravenous to oral therapy, allowing them to be discharged from hospital earlier.

The newer fluoroquinolones combine good activity against Gram-negative and "atypical" organisms with extended Gram-positive activity and

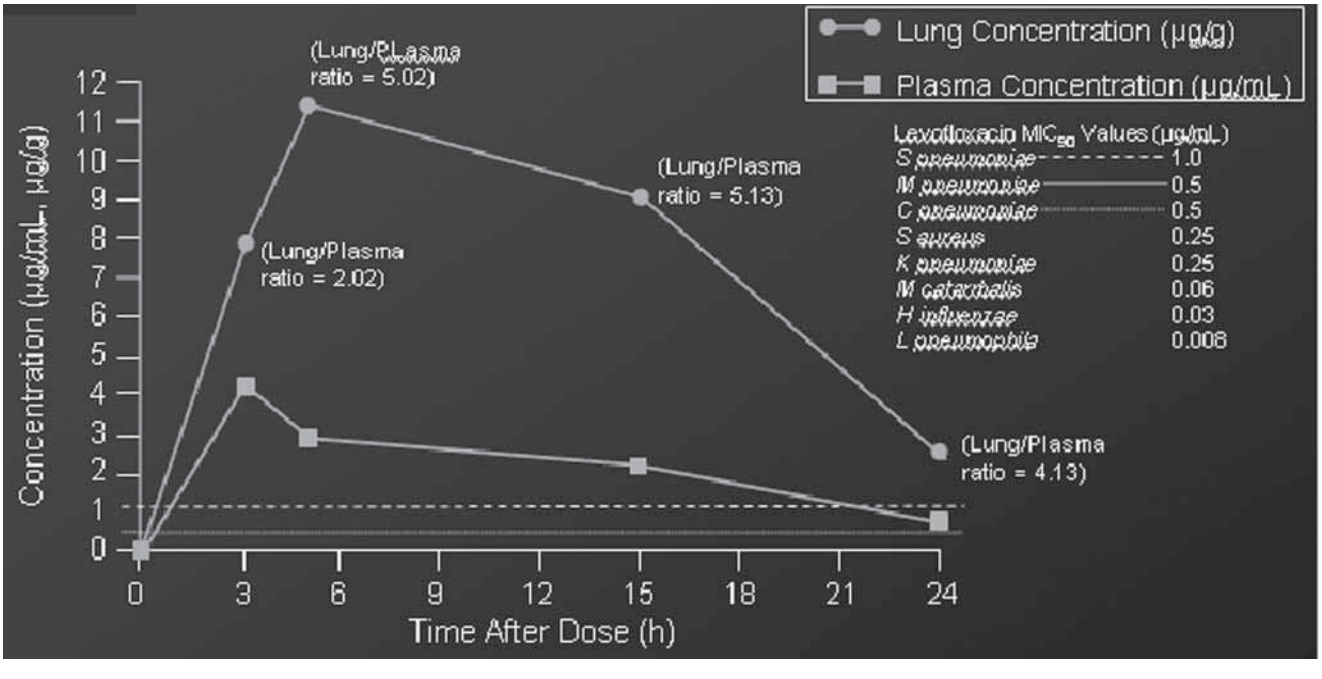

FIGURE 1. *Levofloxacin plasma and lung tissue concentrations vs. MCI90 values of key respiratory pathogens*

are unaffected by penicillin susceptibility status and beta-lactamase production.

TABLE 4. *In vitro activity of fluoroquinolones – percentage (%) of susceptible isolates according to NCCLS breakpoints (data collected from studies in North America evaluating clinical isolates collected between 1996 and 2003)*

Organism	LVX	CIP	MOX
Streptococcus pneumoniae			
penicillin-susceptible	99-100	66,9	N
penicillin-intermediate	100	76,7	N
penicillin-resistant	98-100	76,4	N
Staphylococcus aureus	96-100	98	98
Pseudomonas aeruginosa	62-74	63-80	43
Enterobacter cloacae	88-94	86-91	N
Escherichia coli	88-91	88-91	91
Klebsiella pneumoniae	94-95	93-94	92
Proteus mirabilis	85-87	77-79	74
Serratia marcescens	92-95	85-87	84

Fluoroquinolones exibit concentration-dependent bacterial killing and therefore Cmax/MIC and AUC/MIC ratio correlate with efficacy for these agents. For levofloxacin, Cmax/MIC ratio >10-12 and AUC/MIC >100-125 provide optimal bacterial eradication and reduce the development of resistance in infections caused by Gram-negative bacteria. In patients with infections caused by *Streptococcus pneumoniae* an AUC/MIC ratio >30-50 was associated with cure rates of 95-97%.

Comparative trials have confirmed the efficacy of fluoroquinolones in the treatment of LRTIs.

ACUTE EXACERBATION OF CHRONIC BRONCHITIS (AECB)

Bacterial infections are involved in 40%-60% of AECB. *Haemophilus influenzae* is the most frequently isolated bacterium, followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis*. *Enterobacteriaceae* and *Pseudomonas spp* are more frequently isolated in patients with the greatest degree of airflow obstruction (forced expiratory volume in one second-FEV1<50%). Atypical bacteria, such as *Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella spp* have also been implicated in 10% of AECB.

Martinez *et al.* stratify patients with AECB into uncomplicated or complicated groups based on the absence or the presence of risk factors for treatment failure.

Levofloxacin 750 mg for 3 days was comparable to azitromycin 500mg od for 5 days for uncomplicated patients with AECB, while 5 days of 750 mg levofloxacin were comparable to 10 days of amoxicillin/clavulanate 875/125mg twice daily for complicated AECB. Complicated patients had poorer clinical and microbiological outcomes than uncomplicated patients regardless of the therapeutic agent used. This study demonstrates that the short course of levofloxacin 750 mg is at least as effective as traditional courses of azitromycin and amoxicillin/clavulanate.

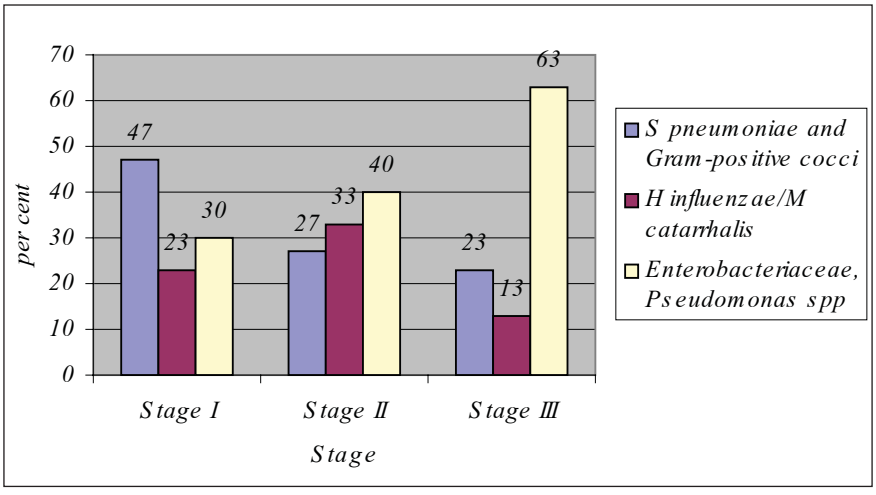

FIGURE 2. *Distribution of three groups of bacteria among patients wits three stages of severityof lung functions (stage I, FEV1 ≥50% of predicted value; stage II, FEV1 >35% to <50% of predicted value; stage III, FEV1 ≤35% of predicted value), in percentages.*

TABLE 5. *Levofloxacin vs comparators in AECB treatment*

	Uncomplicated group		Complicated group	
	levo	azithro	levo	amoxi/clav
Clinical success (%)	93	90,1	79,2	81,7
Microbiological success (%)	96,3	87,4	81,4	80,9

Another trial indicates that a 5 day course of moxifloxacin at a dose of 400 mg od is as effective as a 7 day course of macrolide antibiotic clarithromycin at a dose of 500 mg bd in the treatment of AECB. Both treatments gave high clinical success rates in the efficacy-evaluable population immediately after the end of treatment (94.4% for moxifloxacin and 93.8% for clarithromycin in day 7) and 7 days after the end of treatment (89.1% for moxifloxacin and 88.4% for clarithromycin).

This study has shown that a 5 day course of moxifloxacin given orally at 400 mg od is clinically equivalent and bacteriologically superior to a 7 day course of clarithromycin given orally at 500 mg bd for the treatment of patients with AECB.

COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Streptococcus pneumoniae is the most common causative pathogen of CAP. Other etiologic agents include *Haemophilus influenzae, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae*, *Legionella spp*, enteric Gram-negative bacteria. Some patients with CAP may have a mixed infection involving both typical and atypical pathogens and even a viral organism, although the incidence of such co-infection is not well-known. The causative pathogen cannot be identified in up to 50% of cases.

TABLE 6. *Most common etiologies of CAP*

Patient type	Etiology
Outpatient	*S. pneumoniae* *M. pneumoniae* *H. influenzae* *C. pneumoniae* respiratory viruses
Inpatient (non-ICU)	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella spp*
Inpatient ICU	*S. pneumoniae* *S. aureus* *Legionella spp* *Gram-negative bacili* *H. influenzae*

The choice of initial therapy is usually empirical.

In 2007, the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) released new guidelines for the management of care for adult patients with community-acquired pneumonia. In these guidelines, levofloxacin, gemifloxacin and moxifloxacin were reported to be equally effective as the combination of beta-lactam and macrolide and were proposed to be the preferred treatment for patients who require admission to hospital, as well as for patients with comorbidity who receive treatment as outpatients.

Comorbidities or recent antibiotic therapy increases the likelihood of infection with drug-resistant *Streptococcus pneumoniae (*DRSP) and enteric Gram-negative bacteria.

Hospitalisation is recommended in patients with PSI of IV or V and/or a CURB ≥2.

For patients admitted in the ICU in whom *P aeruginosa* is suspected, the first-line recommendation is for an antipneumococcal antipseudo-

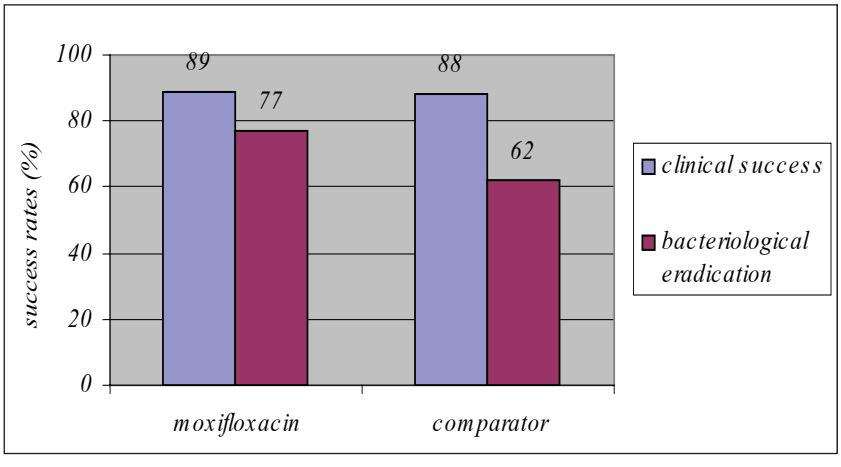

FIGURE 3. *Moxifloxacin vs comparator in AECB treatment*

monal ß-lactam plus either ciprofloxacin or levofloxacin (750 mg).

Monotherapy with moxifloxacin (400 mg i.v. once daily followed by oral moxifloxacin 400 mg for 7 to 14 days) is superior to the one with a standard combination regimen of a ß-lactam and a ß-lactamase inhibitor, co-amoxiclav (1,2 g administrated by i.v. infusion three times a day followed by oral co-amoxiclav 625 mg three times a day), with or without a macrolide, clarithromycin (500 mg twice daily iv or orally), in the treatment of patients with CAP admitted to a hospital. The duration for fever to go down was faster for patients who received moxifloxacin (2 vs 3 days), and the duration of hospital admission was approximately 1 day less for patients who were administered moxifloxacin.

Legionella infections account for up to 16% of cases of CAP and in numerous observational studies, Legionella is among the four microbial causes of hospitalization.

Ofloxacin and levofloxacin have been successfully used in the treatment of Legionnaires disease.

Levofloxacin has excellent *in vitro* activity against *Legionella spp*. and is effective in intracellular killing of various strains of Legionella. In addition, levofloxacin concentrates in the intrapulmonary compartments at levels well above the MCI. Unlike the macrolides which are bacteriostatic for Legionella, levofloxacin is bactericidal.

Fluoroquinolones were as effective as erytromycin in the treatment of Legionnaires disease and duration to apyrexia was significantly longer in the macrolide group (77,1 h vs 48 h).

NOSOCOMIAL PNEUMONIA

Hospital-acquiredpneumonia(HAP),healthcare-acquired pneumonia (HCAP) and ventilator-associated pneumonia (VAP) may be caused by a wide spectrum of bacterial pathogens.

Early-onset HAP and VAP (occuring in the first 4 days of hospitalization) are often caused by community-acquired pathogens such as *S. pneumoniae, H influenzae* or methicillin-susceptible *S aureus (MSSA*).

In contrast, late-onset HAP and VAP (5 days or more) are more likely to be caused by multidrug-resistant (MDR) pathogens: *P aeruginosa, Enterobacteriacaes, Acinetobacter spp*, methicillin-resistant *S aureus* (MRSA) or *Legionella spp.*

Monotherapy with fluoroquinolones (levofloxacin, moxifloxacin, ciprofloxacin) is an appropriate choice for treatment in patients with early-onset HAP, HCAP or VAP and no risk factors for MDR pathogens. For patients with late-onset HAP, HCAP or VAP or risk factors for MDR pathogens, the initial empiric antibiotic therapy should be started with a broad-spectrum antipseudomonasß-lactam plus a fluoroquinolone antipseudomonas (ciprofloxacin or levofloxacin) or an aminoglicoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin if MRSA risk factors are present or there is a high incidence locally.

TABLE 7. *Modifying factors that increase the risk of infection with specific pathogens*

Pathogen	Modifying Factors
Penicillin resistant and drug-resistant pneumococci	Age> 65 yr ß-lactam therapy within the past 3 mo Alcoholism Imunosuppresive illness (including therapy with corticosteroids) Multiple medical comorbidities Exposure to a child in a day care center
Enteric Gram-negative organism	Residence in a nursing home Underlying cardiopulmonary disease Multiple medical comorbidities Recent antibiotic therapy
P. aeruginosa	Structural lung disease (bronchiectasis) Monotherapy with moxifloxacin (400 mg i.v. once daily followed by oral moxifloxacin 400 mg for 7 to 14 days) is superior to the one with a standard combination regimen of a ß-lactam and a ß-lactamase inhibitor, co-amoxiclav (1,2 g administrated by i.v. infusion three times a day followed by oral co-amoxiclav 625 mg three times a day), with or without a macrolide, clarithromycin (500 mg twice daily iv or orally), in the treatment of patients with CAP admitted to a hospital. The duration for fever to go down was faster for patients who received moxifloxacin (2 vs 3 days), and the duration of hospital admission was approximately 1 day less for patients who were administered moxifloxacin. Corticosteroid therapy Broad-spectrum antibiotic therapy for 7 d in the past months Malnutrition

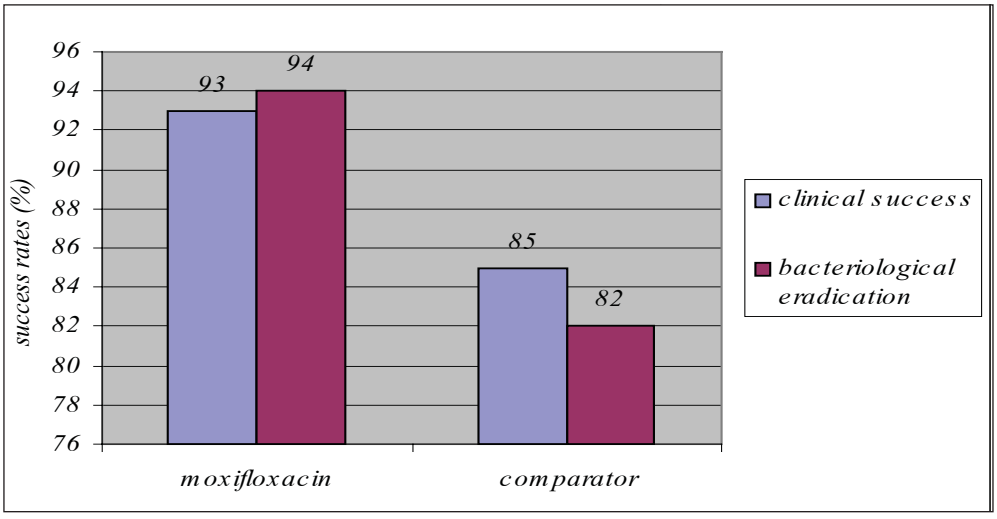

FIGURE 4. *Moxifloxacin vs comparator in CAP treatment*

TABLE 8. *Risk factors for multidrug-resistant pathogens causing HAP, HCAP and VAP*

Antimicrobial therapy in preceding 90 days
Current hospitalization of 5 days or more
High frequency of antibiotic resistance in the community or in the specific medical unit
Presence of risk factors for HCAP:
Hospitalization for 2 days or more in the preceding 90 days
Residence in a nursing home or extended care facility
Home infusion therapy (including antibiotics)
Chronic dialysis within 30 days
Home wound care
Family member with multidrug-resistant pathogen
Immunosuppressive disease and/or therapy

West *et al* compared the efficacy and safety of levofloxacin (750mg od given iv and then orraly for 7 to15 days) and imipenem/cilastatin (500mg to 1g iv every 6 to 8 hours) followed by oral ciprofloxacin (750mg every 12 hours) 7-15 days in adult patients with nosocomial pneumonia. The clinical cure rates and the microbiological eradication rates were similar.

With the widely use of fluoroquinolones in the clinical practice, the potential for developing resistance has become a concern. Clinical isolates of *S pneumoniae* that are not susceptible to fluoroquinolones have emerged. Surveillance programs in USA have found that resistance to the fluoroquinolones in *S pneumoniae* remains low (1% in 2000) with higher rates in Hong Kong 14,3%, South Koreea 2,9%, USA 1,8%, Mexico 1,5%, Canada 1,4% and Japan 1,3%. Resistance to levofloxacin regulary confers resistance to other quinolones (63% and 29% of levofloxacin-resistant isolates were also resistant and intermediate to moxifloxacin in this study). Resistance to fluorquinolones in pneumococci occurs in a step- wise fashion, with mutation observed in either parC or gyrA (depending on the selecting fluoroquinolone) or both, leading to decreased fluorquinolone susceptibility. Strains usually become fully fluoroquinolone resistant with the addition of a mutation in the other target gene (either gyrA or parC). Mutations in parE or gyrB and antimicrobial drugs efflux also contribute to fluoroquinolone resistance but usually to a lower degree.

Respiratory fluoroquinolones offer some advantages for the treatment of LRTIs because they are highly active against penicillin-resistant strains of *S pneumoniae*, are active against all of the other respiratory pathogens, are active against Legionella and the other atypical pulmonary pathogens and have the great advantage of favourable pharmacokinetic profile. Fluoroquinolones exibit excellent penetration into sputum, bronchial and lung tissues and have proven excellent clinical and bacteriological efficacy in the treatment of LRTIs. In addition, fluoroquinolones can be used in penicillin-alergic patients and erythromycin-intolerant patients. Rational prescribing is needed to sustain their future clinical efficacy.

REFERENCES

1. **American Thoracic Society Documents Gudelines for the Managemrnt of Adults with Hospital-acquired,** Ventilator-associated and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388-416.
2. **Canton R, Morosini M et al** – Worldwide incidence, molecular epidemiology and mutations implicated in fluoroquinolones-resistant *Streptococcus pneumoniae* data from the global PROTEKT surveillance programme. *Journal of Antimicrobial Chemotherapy* 2003; 52: 944-952.
3. **Croom KF, Goa KL** – Levofloxacin A Review of its Use in the Treatment of Bacterial Infections in the Unite States. *Drugs* 2003; 63(24): 2769-2802.
4. **Eller J, Ede A et al** – Infective Exacerbations of Chronic Bronchitis Chest 1998; 113:1542-1548.
5. **Finch R, Schurmann D et al** – Randomized Controlled Trial of Sequential intravenous (i.v.) and Oral Moxifloxacin Compared with Sequential i.v. and Oral Co-amoxiclav with or without Clarithromycin in Patients with Community-Acquired Pneumonia Requiring Initial Parenteral Treatment. *Antimicrob Agents Chemother* 2002; 46(6): 1746-1754.
6. **Guthrie R** – Community-Acquired Lower Respiratory Tract Infections. *Chest* 2001; 120: 2021-2034.
7. **Mandell LA, Wunderink RG et al** – Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clinical Infectious Diseases* 2007; 44: S27-72.
8. **Martinez FJ, Grossman RF et al** – Patient stratification in the management of acute bacterial exacerbation of chronic bronchitis: the role of levofloxacin 750mg *Eur Respir J* 2005; 25: 1001-1010.
9. **Sabria M, Pedro-Botet ML et al** – Fluoroquinolones vs Macrolide in the treatment of Legionnaires Disease. *Chest* 2005; 128: 1401-1405.
10. **Wilson R, Kubin R et al** – Five daymoxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis. *Journal of Antimicrobial Chemotherapy* 1999; 44: 501-513.