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Review

Highlights on the appropriate use of fluoroquinolones in respiratory tract infections

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Abstract

The impact of respiratory infections on public health is increasing, and lower respiratory tract infections are a major cause of morbidity and mortality. Moreover, most antibiotic prescriptions are related to respiratory infections and this is probably one of the main determinants of the increasing rate of bacterial resistance in both community and hospital settings. This has been the catalyst for the development of new drugs, such as the new fluoroquinolones.

The new fluoroquinolones have an excellent spectrum providing cover for the most important respiratory pathogens, including atypical and "typical" pathogens. The pharmacokinetic and dynamic properties of the new fluoroquinolones have a significant impact on their clinical and bacteriological efficacy. They cause a concentration-dependent killing with a sustained post-antibiotic effect. Fluoroquinolones combine exceptional efficacy with cost-effectiveness. Not surprisingly, different guidelines have inserted these agents among the drugs of choice in the empirical therapy of LRTIs. This review discusses the most recent data on the bacteriological and clinical activity of the new fluoroquinolones and critically analyses the risks of a potential overuse of this valuable new class of drugs.

Keywords: Fluoroquinolones; Community-acquired respiratory infections; Antimicrobial resistance

Contents

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1. Introduction

Infections are still a major health problem worldwide, being associated with significant morbidity and mortality. Since the discovery of penicillin, the traditional approach to infections has been based on the development of novel compounds exerting microbicidal activity. The result is an impressive array of antibacterial, antifungal, antiviral and antiparasitic drugs currently at our disposal for clinical use in contrasting infections. However, antimicrobial treatments are hampered by the ever-increasing problem of resistant strains. The new fluoroquinolones have an excellent spectrum which covers the most important respiratory pathogens, including atypical and typical pathogens. The pharmacokinetic and dynamic properties of the new fluoroquinolones have a significant impact on their clinical and bacteriological efficacy. They cause concentration-dependent killing with a sustained post-antibiotic effect. Fluoroquinolones combine exceptional efficacy with cost-effectiveness. Not surprisingly, different guidelines have inserted these agents among the drugs of choice in the empirical therapy of community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB).

2. Mechanism of action

Ciprofloxacin presents a Gram-negative targeted spectrum of activity. The N-1 cyclopropyl group, which was originally described for ciprofloxacin, remains one of the most effective components for providing broad-spectrum activity against aerobic organisms. Enhanced bactericidal activity against *Streptococcus pneumoniae* has been attributed to the presence of a 2,4-difluorophenyl moiety at the N-1 position in an investigational series of compounds [1].

Compounds containing a combination of N-1 cyclopropyl with C8-methoxyl group (e.g. moxifloxacin and gatifloxacin) are particularly lethal, and incubation of wild-type *Staphylococcus aureus* cultures on agar containing C8-methoxyl fluoroquinolones produces no resistant mutant, whereas thousands arise during comparable treatment with control compounds lacking the C8 substituent [2].

The primary target for fluoroquinolones in most Gram-negative pathogens is the bacterial gyrase, which is encoded by *gyrA* and *gyrB* genes. In many Gram-positive bacteria, the primary target appears to be the corresponding subunit of topoisomerase IV encoded by *parC* and *parE* genes (or *grlA* and *grlB* for *S. aureus*). The development of a new generation of fluoroquinolones aims at targeting both *gyrA* and topoisomerase IV. The existence of two distinct targets and the characteristic stepwise accumulation of resistance implies that bacterial cells would require two distinct topoisomerase mutations before they can display resistance to these new fluoroquinolones.

3. Pharmacokinetic dynamics

The pharmacokinetic characteristics of fluoroquinolones represent a crucial factor for their impact on clinical efficacy and safety. All fluoroquinolones have bactericidal activity with a post-antibiotic effect. They cause concentration-dependent bacterial killing. However, different bactericidal activity against different microorganisms has been demonstrated. Ciprofloxacin and prulifloxacin are less active against Gram-positive bacteria than against Gram negative [3,4]. Important parameters in the assessment of clinical response to fluoroquinolones are serum concentrations, expressed both as C_{max} and AUC, and C_{max}:MIC ratio or AUC_{24}:MIC (AUIC). C_{max} represents peak serum antibiotic concentration, while AUC is the area under the concentration–time curve. AUIC represents the ratio of the area under the concentration–time curve to the minimal inhibitory concentration (MIC) of the pathogen normalized to 24 h. C_{max}:MIC ratio values >10 and AUC_{24}:MIC (AUIC) ratio values >125 seem to prevent the emergence of antimicrobial resistant strains.

Fluoroquinolones are well absorbed by the gut, reaching peak concentrations in 1–2 h. Coingestion with food delays the time to peak serum concentration (C_{max}) but not the overall bioavailability (AUC). These compounds may therefore be given orally without regard to food intake. A number of multivalent metal cations (aluminium, magnesium, iron, zinc) can decrease the bioavailability of these drugs and C_{max} values may be decreased by approximately 60% with coingestion. As opposed to ciprofloxacin, newer compounds such as gatifloxacin, levofloxacin and moxifloxacin have not shown significant drug interactions with theophylline, warfarin, or digoxin, since they are not metabolized by P450 cytochrome. No significant alterations in pharmacokinetics and bioavailability have been found for prulifloxacin, levofloxacin, gatifloxacin, and moxifloxacin in the elderly [5–7].

4. Microbiology

The most commonly employed in vitro parameter for evaluating the microbiological activity of antibiotic agents is MIC. MIC measures the net drug effect when a standard bacterial inoculum is exposed to a fixed and constant drug concentration for 18–24 h. In order to approach the problem of resistance to antibiotics, microbiologists have identified the concentration at which selective proliferation of resistant mutants is expected to occur only rarely (mutant prevention concentration [MPC]). This measure is defined as the minimal antibiotic concentration required to prevent the growth of resistant mutants among 10^{10} colony forming units (CFU) of a heterogeneous-specific bacterial strain [8,9]. If drug concentrations are kept above MPC throughout the treatment period, few, if any, mutants would be selected since two simultaneous mutations would have to occur for cells to grow at this antibacterial concentration. Conversely, concentrations above MIC

but below MPC fall into a so-called 'mutant selection window', in which resistant mutants are selectively enriched. Studies on both laboratory and clinical isolates indicate that the agents with greatest activity against resistant mutants are moxifloxacin, sitafloxacin and gemifloxacin, followed by gatifloxacin, levofloxacin and ciprofloxacin.

Many new agents provide excellent coverage for *S. pneumoniae* in the following rank order: sitafloxacin > gemifloxacin > garenoxacin > moxifloxacin > gatifloxacin > levofloxacin > ciprofloxacin [10]. No significant differences were found between penicillin- or macrolide-resistant pneumococcal strains in terms of either MIC_{90} values or relative rank order [11]. The new fluoroquinolones generally retain the excellent Gram-negative activity displayed by ciprofloxacin. Against *Pseudomonas aeruginosa* ciprofloxacin continues to show activity equal or superior to newer compounds with the exception of sitafloxacin and prulifloxacin that show good in vitro activity [12,13].

Compared with ciprofloxacin, some newer agents provide significantly improved activity in relation to *anaerobes*. Overall, sitafloxacin appears to display the highest activity against anaerobic bacteria, higher even than gemifloxacin and garenoxacin.

Fluoroquinolones are also highly active against common respiratory pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*.

Increased use of new fluoroquinolone compounds for community- and hospital-acquired respiratory is and will be associated with increasing resistance. Fluoroquinolones resistance is related to two main mechanisms: alterations in target enzymes and alterations in drug permeation.

Bacteria can develop resistance to these agents by chromosomal mutations in the target enzymes. These alterations arise from spontaneous mutations in the genes encoding enzyme subunits that may be present in small numbers (1 in 10^6 to 1 in 10^9 cells) in large bacterial populations. Genes encoding for DNA gyrase are identified as *gyrA* and *gyrB*, whereas genes encoding for topoisomerase IV are named *parC* and *parE*. Numerous reports indicate that mutations in *gyrA* or *parC* are associated with fluoroquinolone resistance, but the clinical significance of uncommon mutations in *gyrB* or *parE* is controversial.

The first step in mutational resistance usually involves amino acid changes in the primary enzyme target (DNA gyrase or topoisomerase IV) resulting in a rise in MIC values. A second mutation may confer additional resistance by causing amino acid changes in the secondary target enzyme [14]. Thus, increasing mutations lead to stepwise increases in resistance, and the increased prevalence of first-step mutants predisposes to selection of highly resistant second-step mutants. Selection of first-step mutants might be avoided by restricting use of less active agents in favour of newer compounds with better pharmacodynamic properties. Boswell et al. [15] showed different selective power of fluoroquinolones with *S. pneumoniae*. Agents that are highly potent are likely to prevent resistance emerging by killing both the parental organism and its less susceptible first-step mutant.

Recently, bacterial resistance to fluoroquinolones has shown to be also mediated by enhanced expression of efflux systems that actively pump the drug from the cytoplasm [16]. These pumps exist in both Gram-positive and Gram-negative bacteria.

A third mechanism of resistance has also been proposed, involving laboratory plasmid transmission of resistance from *Klebsiella pneumoniae* to *Escherichia coli* [17].

Recent reports indicate the presence of fluoroquinolone-resistant *S. pneumoniae* strains [18]. It has been documented that low-level fluoroquinolone resistance can occur through a single mutation in *gyrA* or *parC*, but that high-level resistance requires at least two different sequential mutations. The growing use of fluoroquinolones may contribute to the emergence of resistance. Resistant strains seem to be more common among elderly patients, who have the highest use of fluoroquinolones. On the other hand, the restricted use of these drugs in children may help to slow the rate of emerging fluoroquinolone resistance. The risk factors for infection or colonization with fluoroquinolone-resistant *S. pneumoniae* are age >65 years, nursing home residence, chronic obstructive pulmonary disease (COPD), recent and/or multiple hospitalizations, and previous exposure to antimicrobial agents (6 weeks prior hospitalization/12 months) [19–21].

Fluoroquinolone resistance particularly affects two other bacterial species: *S. aureus* and *P. aeruginosa*. Due to excellent intrinsic fluoroquinolone activity against *H. influenzae*, reports on resistance to this species are to date very rare.

5. Clinical studies

5.1. Acute exacerbations of chronic bronchitis

Chronic bronchitis is characterized by cough and excessive secretion of mucus and is diagnosed when patients report production of sputum on most days over at least 3 consecutive months for ⩾2 successive years [22]. The majority of patients with chronic bronchitis have some degree of underlying airflow obstruction and are thus classified as having COPD [23]. COPD is clinically characterized by abnormal tests of expiratory flow that do not change markedly over several months of observation. Chronic bronchitis is estimated to affect between 3.7% and 6.8% of the population in Europe [24], and prevalence increases with age [25]. Patients with chronic bronchitis are predisposed to recurrent attacks of bronchial inflammation—termed AECB—characterized by increased cough, worsening dyspnea and changes in sputum purulence and volume [26]. Bacterial agents are the predominant cause of AECB, accounting for 50–70% of episodes, and the acquisition of new strains of pathogenic bacterial

species to which the patient is susceptible has been linked with episodes of AECB [27].

The treatment choice usually depends on a number of factors, including suspected or confirmed aetiology, clinical features and history, and local patterns of antibacterial resistance. Other relevant factors include the tolerability, convenience and cost of treatment. Two additional criteria for antibacterial selection have been identified in guidelines issued by the Société de Pneumologie de Langue Française [28]: the ability of the antibacterial to penetrate bronchial tissue and mucus, and low ecological risk (i.e. a low propensity to induce resistance).

Excellent tissue penetration, advantageous therapeutic ratios (mucosal concentration: MIC ratio often over 150) in addition to high potency against *H. influenzae* make fluoroquinolones an attractive antimicrobial choice in the treatment of AECB.

Clinical efficacy of levofloxacin in AECB has been evaluated in at least six clinical trials [29–34]. Overall, the use of levofloxacin is associated with a higher bacterial eradication rate. However, Lode et al. failed to demonstrate significant differences in the exacerbation-free interval, even if the results showed a trend towards a longer exacerbation-free interval in patients treated with levofloxacin in the population of patients with $FEV_1 < 50\%$ predicted [34].

Ramirez et al. analysed pooled data from two randomized, double-blind studies, and one non-blind study evaluating the efficacy of gatifloxacin (400 mg daily) in AECBs [35]. Gatifloxacin was generally associated with a higher bacterial eradication rate, and in one study also with a significantly better clinical cure rate compared to cefuroxime axetil [36].

Moxifloxacin (400 mg once daily) demonstrated better overall eradication rates compared to clarithromycin (500 mg bid) (77% versus 62%, respectively) in 750 patients with AECB, and clinical equivalence in terms of clinical cure rates [37]. The difference in eradication rates reached significance for *H. influenzae* (98% versus 67.5%) but not for *S. pneumoniae*. Other studies showed comparable clinical and bacteriologic efficacy of moxifloxacin compared to macrolide and betalactams [38–41]. However, an analysis of patient daily evaluations of AECB specific symptoms showed faster response rates for moxifloxacin compared to macrolides (azithromycin, clarithromycin, and roxithromycin) in 332 patients with AECBs [42]. A later study showed that moxifloxacin was equivalent to standard therapy for clinical success and showed superiority over standard therapy in clinical cure, bacteriologic eradication, and long-term outcomes [43].

Gemifloxacin activity was evaluated in two different studies, one in hospitalized patients [44], the other in outpatients [45].

Prulifloxacin compared to ciprofloxacin was evaluated in one randomized, double-blind, double-dummy study on the treatment of AECB [46]. The clinical response was determined by 4-point rating scores on cough, dyspnea, and expectoration (volume and appearance). Clinical success was observed in 84.7% and 85% of patients in the prulifloxacin and ciprofloxacin groups, respectively.

Table 1 summarizes AECB trials of new fluoroquinolones.

5.2. *Community-acquired pneumonia (CAP)*

Prospective, randomized studies on CAP have compared new fluoroquinolones to both macrolides and betalactam antibiotics [47–58]. In a large study, Finch et al. [56] analysed 628 pneumonia patients treated either with sequential intravenous-oral moxifloxacin or coamoxiclav (1.2 g tid intravenously, followed by 625 mg tid orally), with or without clarithromycin (500 mg bid intravenously or orally) for 7–14 days. The study showed statistically significant higher clinical success rates for moxifloxacin (93.4%) than for the comparator (85.4%, 95% CI, 2.91–13.19%; $p = 0.004$). Bacteriological success was likewise greater for the new fluoroquinolone (93.7%) than for the comparator (81.7%, delta 12.06%; 95% CI, 1.21–22.91%). This superiority was seen irrespective of the severity of the pneumonia and whether or not the combination therapy included a macrolide. Further indicators favouring moxifloxacin were time to resolution of fever, duration of hospital admission, and mortality. A recent open-label randomized study evaluated intravenous azithromycin plus ceftriaxone and intravenous levofloxacin with step-down oral therapy for hospitalized patients with moderate to severe CAP [57]. Favourable clinical outcomes in clinically evaluable patients were demonstrated in 91.5% of patients treated with ceftriaxone plus azithromycin and 89.3% (95% CI −7.1%, 11.4%) of patients treated with levofloxacin at the end of therapy visit and in 89.2% and 85.1% (95% CI −6.7%, 14.8%) patients, respectively, at the end of study visit. Bacteriological eradication rates for both treatments were equivalent with the exception of *S. pneumonia*, for which 44% of isolates were eradicated with levofloxacin compared to 100% of isolates with cetriaxone plus azithromycin.

Table 2 summarizes the CAP clinical trials data.

6. Rationale for fluoroquinolone use in the context of increasing antimicrobial resistance

The development of resistance has become an increasingly important concern not only among microbiologists but also now among clinicians. The dogma is that high levels of resistance in RTI pathogens should result in increased therapeutic failure rates, but the true extent of failure in CAP or AECB and its relation to resistance is not clear as yet. Only few case reports have documented true treatment failures that can be linked to bacterial resistance. In infections caused by drug-resistant *S. pneumoniae*, new quinolones such as moxifloxacin and gatifloxacin are more active in vitro compared to other new classes of antibiotics such as oxazolidinones, streptogramins, and ketolides.

Table 1
Comparative efficacy of new fluoroquinolones in AECB trials

Drug	Design/patients	Regimen	Duration	Results	Reference
Levofloxacin	R, db, dd, c/124	Levo 250 mg OD vs. 500 mg OD vs. cefuroxime axetil 250 mg bid	7 days	63% vs. 68% vs. 48% bacterial eradication	[29]
	R, nb, c/492	Levo 500 mg OD vs. cefuroxime axetil 250 mg bid	5–7 vs. 10 days	94.6% vs. 92.6% clinical success	[30]
	R, c, nb/373	Levo 500 mg OD vs. cefaclor 250 mg tid	5–7 vs. 7–10 days	92% vs. 92% clinical success	[31]
	R, db, dd, c/427	Levo 250 mg OD vs. L-500 mg OD vs. cefuroxime axetil 250 mg bid	7–10 days	78% vs. 79% vs. 66% clinical success	[32]
	R, c, nb/283	Levo 500 mg OD vs. cefuroxime axetil 250 mg bid vs. clarithromycin 500 mg bid	10 days	87.4% vs. 79.8% vs. 87.9% clinical success	[33]
	R, db, c/511	Levo 500 mg OD vs. clarithromycin 250 mg bid	7+3 placebo vs. 10 days	No difference in exacerbation-free interval. 82.8% vs. 79.8% clinical success; 96% vs. 81.7% bacterial eradication ($p<0.01$)	[34]
Moxifloxacin	R, db, c/745	Moxi 400 mg OD vs. clarithromycin 500 mg bid	5 vs. 7 days	89% vs. 88% clinical success; 77% vs. 62% bacterial eradication	[37]
	R, db, c/926	Moxi 400 mg OD vs. moxi 400 mg OD vs. clarithromycin 500 mg bid	5 vs. 10 days vs. 10 days	95% vs. 95% vs. 94% clinical success	[38]
	R, nb, c/401	Moxi 400 mg OD vs. azithromycin 500 mg OD × 1 day + 250 mg × 4 days	5 days	85% vs. 81% clinical success	[39]
	R, db, c/567	Moxi 400 mg OD vs. azithromycin 500 mg OD × 1 day + 250 mg × 4 days	5 days	88% vs. 88% clinical success; 89 vs. 86% bacterial eradication	[40]
	R, nb, c/575	Moxi 400/mg OD vs. co-amoxiclav 625 mg tid	5 vs. 7 days	96.2% vs. 91.6% clinical success; 87.7% vs. 89.6% bacterial eradication	[41]
	R, db, c/733	Moxi 400 mg OD vs. clarithromycin 500 mg bid vs. amoxicillin 500 mg id vs. cefuroxime axetil 250 mg bid	5 vs.7 days	87.6% vs. 83% clinical success; 76.8% vs. 67.5% bacterial eradication. Superiority of M regarding need for additional antimicrobial treatment of AECB, rate of bacteriologic eradication, and time to next	[43]
Gatifloxacin	R, db, dd, c/211	Gati 400 mg OD vs. cefuroxime axetil 250 mg bid	7–10 days	89% vs. 77% clinical success ($p<0.04$)	[35]
	Pooled results of two studies (r, db, c) and one trial (nb, nc). Includes data from 19./907	Gati 400 mg OD vs. levofloxacin 500 mg OD vs. cefuroxime axetil 250 mg bid	7–10 days	93% vs. 88% bacterial eradication (G vs. comparators, respectively)	[36]
Gemifloxacin	R, db, dd, c/274	Gemi 320 mg OD vs. ceftriaxone 1 g OD IV (1–3 days) + oral cefuroxime axetil 500 mg BID po (max 7 days)	5 vs. 5–10 days	86.8% vs. 81.3% clinical success	[44]

Table 1 (*continued*)

Drug	Design/patients	Regimen	Duration	Results	Reference
	R, db, dd, c/360	Gemi 320 mg OD vs. levofloxacin 500 mg OD	5 vs. 7 days	(ITT population) 85.2% vs. 78.1% (PP population), 88.2% vs. 85.1% clinical success. Significant difference in study withdrawals (Gem vs. Levo)	[45]
Prulifloxacin	R, db, dd, c/235	Pruli 600 mg OD vs. cipro 500 mg bid	10 days	84.7% vs. 85% clinical success	[46]

R = randomized; db = double-blind; dd = double-dummy; c = comparative; nb = nonblind; nc = noncomparative.

Table 2
Comparative efficacy of new fluoroquinolones in CAP trials

Drug	Design/patients	Regimen	Duration	Results	Reference
Levofloxacin	R, nb, c/590	Levo 500 mg iv/oral OD vs. ceftriaxone 1–2 g iv OD or bid or cefuroxime axetil 500 mg oral bid, ± erythromycin 500 mg–1 g every 6 h) or doxycycline if atypicals suspected	7–14 days	96% vs. 90% clinical success	[47]
Moxifloxacin	R,db, c/474	Moxi 400 mg OD vs. clarythromycin 500 mg bid	10 days	95% vs. 95% clinical success	[53]
	R, db, c	Moxi 200 mg OD vs. M-400 mg OD vs. clarithromycin 500 mg bid	10 days	90.7% vs. 92.8% vs. 92.2% clinical success	[54]
	R, db, c/411	Moxi 400 mg OD vs. amoxicillin 1 g tid	10 days	91.5% vs. 89.7% clinical success	[55]
	R, c/628	Moxi 400 mg iv/os OD vs. co-amoxiclav iv (1.2 g tid)/ os 625 mg tid) ± clarithromycin 500 mg bid iv/os	7–14 days	93.4% vs. 85.4% clinical success ($p<0.05$); 93.7% vs. 81.7% bacteriological success	[56]
Gatifloxacin	R,db,dd, c/418	Gati 400 mg iv/os OD vs. levofloxacin 500 mg iv/os OD	7–14 days	96% vs. 94% clinical success	[49]
	R, db, dd, c/432	Gati 400 mg OD vs. clarithromycin 500 mg bid	7–14 days	95% vs. 93% clinical success	[50]
	R,db, c/283	Gati 400 mg iv OD switch to gati 400 mg oral OD vs. ceftriaxone 1–2 g iv ± erythromycin 500 mg–1 g iv qid step down to oral clarithromycin 500 mg bid	7–14 days	97% vs. 91% overall clinical success; 96% vs. 90% in severe pneumonia	[51]
Gemifloxacin	R, nb, c/345	Gemi 320 mg OD vs. cefriaxone iv/oral cefuroxime ± macrolide	⩽14 days	92.2% vs. 93.4% clinical success 90.6% vs. 87.3% bacterial eradication	[58]

R = randomized; db = double-blind; dd = double-dummy; c = comparative; nb = nonblind; nc = noncomparative.

There is, however, some concern regarding continual use of fluoroquinolones with modest antipneumococcal potency which may select pneumococcal-resistant strains with high MIC values.

In one study comparing gatifloxacin and levofloxacin in the treatment of CAP, the more active quinolone (gatifloxacin) eradicated all pneumococci, whereas the less-active drug (levofloxacin) failed to eradicate 22% of

these organisms [49]. The use of less-active drugs may then induce resistance to more active agent [19,20,59–61], since within-class cross-resistance is very common [20,21].

In all clinical guidelines, available fluoroquinolone agents are discussed, although no clinical distinction is made between agents with greater or lesser activity against pneumococci. One consideration in choosing among these agents is to select the drug that has lowest MIC values against *S. pneumoniae*, and the order of activity (least to most active) for these agents is levofloxacin (MIC 1.0–2.0 mg/L), gatifloxacin (MIC 0.25–0.5 mg/L), and moxifloxacin (MIC 0.25 mg/L). Does greater in vitro potency translate into greater clinical efficacy? Future guidelines will need to address the issue of whether the choice of more active antipneumococcal quinolones will prevent the development of even higher rates of quinolone-resistant pneumococci [62].

Another important issue is the activity against *P. aeruginosa* particularly in acute exacerbations of more severe chronic bronchitis and in hospital-acquired pneumonia. The recent ATS-IDSA guidelines for hospital-acquired pneumonia suggest the use of high-dose ciprofloxacin (400 mg iv tid) or levofloxacin (750 mg iv od) as active agents in combination therapy [63]. However, fluoroquinolones, as all other agents, should be used only if local susceptibility data show that these agents are effective. This remains a problem, because a significant fall in *P. aeruginosa* sensitivity to quinolones resulted with widespread use of these agents in hospital [64].

7. Discussion

Currently available fluoroquinolones have an excellent spectrum that provides coverage for the most important respiratory pathogens, including atypical and "typical" pathogens. However, the coverage for Gram-negative, highly resistant *S. pneumoniae* strains, anaerobic bacteria, and *Pseudomonas* spp. differs, sometimes significantly, in old and new quinolones. For most of these drugs, excellent absorption and minimal toxicity permit comparable oral and iv therapy for the treatment of serious infection. Rapid switch therapy reduces the cost of hospitalization by reducing drug cost and, potentially, the length of stay in hospital. New compounds can be administered once daily, which increases the level of treatment compliance. The availability of these agents in oral dosage form offers the option of outpatient treatment in situations where patients may have traditionally received inpatient intravenous therapy. Fluoroquinolones, therefore, combine exceptional efficacy with cost-effectiveness. Not surprisingly, different guidelines have inserted these agents among the drugs of choice in the empirical therapy of CAP.

When a new fluoroquinolone is selected for the treatment of CAP or AECB, differences in these agents merit some consideration. General consensus is that targeted therapy of the agent with maximal potency and optimal pharmacodynamic properties will give the best clinical, bacteriological and economic outcomes in specific infections, as well as slow the inevitable emergence of resistance. For infections where *S. pneumoniae* is involved, the new fluoroquinolones moxifloxacin, gatifloxacin or gemifloxacin should be used in preference to older agents so as to reduce selection of drug-resistant isolates. Where infections are caused by organisms such as *H. influenzae* or *Moraxella catarrhalis*, the selection of resistant mutants is less likely with any of the fluoroquinolones. Compared to moxifloxacin, gatifloxacin and gemifloxacin, ciprofloxacin, levofloxacin and prulifloxacin are more active against *Pseudomonas* species.

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