Fluoroquinolones, Oral Review

04/24/2008

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Comments and suggestions may be sent to Editor@providersynergies.com.

PROVIDER SYNERGIES L.L.C.
Together, we can do more.

FDA-Approved Indications

Drug	Mfr	Abdominal	AECB	Acute sinusitis	Bone and Joint	CAP	Nosocomial Pneumonia	Inhalational Anthrax	Diarrhea	Gonorrhea	LRTI	Febrile Neutropenia	PID	Prostatitis	Skin	Typhoid fever	UTI
ciprofloxacin (Cipro®)	generic	X*	X	X	X	-	X‡	X	X	X	X	X‡	-	X	X	X	X#
ciprofloxacin ER (Cipro XR®)	generic	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
ciprofloxacin ER (Proquin® XR)	Depomed	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X##
gemifloxacin (Factive®)	Oscient	-	X	-	-	X**	-	-	-	-	-	-	-	-	-	-	-
levofloxacin (Levaquin®)	Ortho McNeil	-	X	X	-	X**	X	X	-	-	-	-	-	X	X	-	X
moxifloxacin (Avelox®)	Schering	X	X	X	-	X**	-	-	-	-	-	-	-	-	X	-	-
norfloxacin (Noroxin®)	Merck	-	-	-	-	-	-	-	-	X	-	-	-	X	-	-	X
ofloxacin (Floxin®)	generic	-	X	-	-	X***	-	-	-	X	-	-	X	X	X	-	X

Abdominal = Intra-abdominal infections, AECB = Acute exacerbation of chronic bronchitis, CAP = Community acquired pneumonia, LRTI = Lower respiratory tract infections, PID = Pelvic inflammatory disease, UTI = Urinary tract infection.

‡ Ciprofloxacin (Cipro) IV only, not oral, is indicated and should be used in combination with other agents.[1] *Ciprofloxacin is indicated for abdominal infections in combination with metronidazole.

**Gemifloxacin (Factive), levofloxacin (Levaquin), and moxifloxacin (Avelox) are indicated for the treatment of CAP due to multi-drug resistant *Streptococcus pneumoniae*.

*** Ofloxacin is indicated for *Hemophilus influenza* and *S. pneumoniae* in CAP only.[2]

Ciprofloxacin is also indicated for complicated UTI and pyelonephritis caused by *Escherichia coli* in children ages one to 17 years; ciprofloxacin is not first line therapy for these infections.

Ciprofloxacin ER (Proquin XR) is only indicated in uncomplicated UTIs caused by *E. coli* or *Klebsiella pneumoniae*.

Overview

Several oral fluoroquinolone antibiotics with expanded spectrums are available. The older fluoroquinolones have a gram-negative spectrum of activity and have been very useful in the treatment of urological infections. Newer fluoroquinolones have broad spectrums of activity covering both gram-negative and gram-positive bacteria, and some agents are useful in the treatment of penicillin-resistant *Streptococcus pneumoniae*.

While the fluoroquinolones are effective choices for treatment of CAP, joint guidelines from the American Thoracic Society and Infectious Diseases Society of America recommend macrolides (e.g., erythromycin, clarithromycin, azithromycin – strong recommendation) or doxycycline (weak recommendation) for adult patients who are otherwise healthy without risk factors for multi-drug resistant *S. pneumoniae*.[3] For adult outpatients with co-morbidities including chronic heart, lung, renal, hepatic disorders, diabetes, alcoholism, malignancies, asplenia, immunosuppression, or use of any antibiotic within the last three months or other risk factors for multi-drug resistant *S. pneumoniae*, first line therapy may include a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin 750 mg) or a beta-lactam plus a macrolide as a strong recommendation. Beta-lactam selection may include one of the following: high dose amoxicillin 1 gm three times daily or amoxicillin/clavulanate. Other beta-lactam alternatives include ceftriaxone, cefpodoxime, or cefuroxime. Doxycycline may be used as an alternative to macrolides in combination with a beta-lactam. The fluoroquinolones should be used judiciously with appropriate dosing in an effort to avoid antibiotic resistance and therefore decreased effectiveness of this class of antibiotics.

For the treatment of pelvic inflammatory disease (PID), the CDC sexually transmitted diseases guidelines recommend oral therapy for patients with mild to moderately severe symptoms.[4,5] Oral regimens have been shown to provide outcomes similar to parenteral therapy. In April 2007, the CDC recommended cephalosporins be preferred agents for treatment of gonorrhea and PID due to increasing prevalence of fluoroquinolone-resistant gonorrhea throughout the US. Newly updated oral regimens include intramuscular ceftriaxone plus doxycycline with or without oral metronidazole. Intramuscular cefoxitin plus oral probenecid plus doxycycline with or without metronidazole may also be considered. Fluoroquinolones, levofloxacin or ofloxacin with or without metronidazole, may only be considered if the community prevalence and individual risk of gonorrhea is low. Tests for gonorrhea must be performed prior to initiating therapy. If the patient is positive for gonorrhea, antibiotic susceptibility may guide therapy or if the isolate is fluoroquinolone-resistant or susceptibility is unknown, parenteral cephalosporin therapy is recommended.

Current recommendations from Infectious Diseases Society of America (IDSA) do not list any fluoroquinolones as a treatment alternative for management of skin and skin structure infections.[6]

For management of acute sinusitis, adults with mild disease and no recent antimicrobial use should be treated with amoxicillin/clavulanate, cefpodoxime, cefdinir, or cefuroxime.[7] If patients fail to improve after three days, a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is considered appropriate therapy. For adults with mild disease and recent antimicrobial use or adults with moderate disease, consider a respiratory fluoroquinolone (levofloxacin or moxifloxacin), amoxicillin/clavulanate, or ceftriaxone as first line therapies.

This review will compare and contrast the relative strengths, weaknesses, and distinguishing characteristics of the members of this class of antimicrobials. Few clinical trials directly compare the clinical efficacy and side effects of these agents. Trovafloxacin (Trovan®) is not included in the document. Due to safety issues, it is limited to treatment of severe, life-threatening infections in hospitalized patients.[8] Gatifloxacin (Tequin®) and lomefloxacin (Maxaquin®) have been discontinued by their respective manufacturers.

Pharmacology

Fluoroquinolones are synthetic, broad-spectrum antibacterial agents. The fluorine molecule provides increased potency against gram-negative organisms and broadens the spectrum to include gram-positive organisms; the piperazine moiety confers antipseudomonal activity. These agents are bactericidal. Fluoroquinolones promote cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase (associated with gram-negative activity) and type IV topoisomerase (associated with gram-positive activity), resulting in rapid bacterial death.[9] Mutations of the topoisomerase IV gene combined with gene mutations that alter DNA gyrase lead to high-level fluoroquinolone resistance in *S. pneumoniae.*

Pharmacokinetics[10,11]

Fluoroquinolones exhibit concentration-dependent (versus time-dependent) bacterial killing with more pronounced bactericidal activity as serum drug concentrations approach 30 times the minimum inhibitory concentration (MIC) or when the area-under-the-inhibitory-curve (AUIC) exceeds 250.[12,13] The exact level of the targeted AUIC varies in the literature.[14] Fluoroquinolones have a post-antibiotic effect of approximately one to two hours.[15]

Fluoroquinolones are well absorbed following oral administration, with bioavailability for most agents in excess of 85 percent. Exceptions are ciprofloxacin, which is 70 to 80 percent bioavailable, gemifloxacin (Factive), 71 percent bioavailable; and norfloxacin (Noroxin), which is 30 to 40 percent bioavailable.[16,17,18] Serum drug levels achieved after oral administration are comparable to those with intravenous (IV) dosing, which allows for early transition from IV to oral therapy and potential reduction of treatment costs.[19]

Fluoroquinolones are widely distributed throughout the body with tissue concentrations higher than achieved in plasma. The agents penetrate well into stool, bile, prostatic tissue, lung tissue, urine, and kidneys. Because cerebrospinal fluid concentrations are consistently low, the fluoroquinolones are inadequate for first-line treatment of meningitis.[20]

Below is a summary of the pharmacokinetic parameters.

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
ciprofloxacin (Cipro)[21]	~ 70	4	Four metabolites – less active than parent (15 percent of parent dose)	Urine: 40-50 Feces: 20-35
ciprofloxacin extended release (Cipro XR)[22]	--	6.3-6.6	Four metabolites – less active than parent (15 percent of parent dose)	Urine: 40-50 Feces: 20-35
ciprofloxacin extended release (Proquin XR)[23]	87	4.5	Four metabolites – less active than parent (15 percent of parent dose)	Urine: 41 Feces: 43
gemifloxacin (Factive)[24]	71	7	N-acetyl, E-isomer, and carbamyl glucuronide of gemifloxacin (<10 percent of oral dose)	Urine: 36 Feces: 61
levofloxacin (Levaquin)[25]	99	6-8	Desmethyl and N-oxide metabolites (little pharmacological activity)	Urine: 87 Feces: <4
moxifloxacin (Avelox)[26]	90	12	Two metabolites - sulfate and glucuronide conjugates	Urine: 34 Feces: 63
norfloxacin (Noroxin)[27]	30-40	3-4	Many metabolites, some active	Urine: 31-40 Feces: 30
ofloxacin (Floxin)[28]	98	9	Desmethyl and N-oxide metabolites (5 percent of parent)	Urine: 65-80 Feces: 4-8

Extended-release formulations of ciprofloxacin (Cipro XR, Proquin XR) are not interchangeable.[29]

Antimicrobial Activity

The older fluoroquinolones, ciprofloxacin and ofloxacin, have minimal gram-positive activity, but they are the most active against aerobic gram-negative bacilli. Limited microbial susceptibility and acquired resistance limit the usefulness of older agents in the treatment of staphylococcal, streptococcal, and enterococcal infections.[30] Ciprofloxacin remains the most potent of the fluoroquinolones against some strains of *Pseudomonas aeruginosa*.[31] Norfloxacin has a primarily gram-negative spectrum of activity.

Newer fluoroquinolones, gemifloxacin, levofloxacin, and moxifloxacin, have improved gram-positive coverage as compared to older agents. Newer agents have *in vitro* activity against *S. pneumoniae.* Gemifloxacin, levofloxacin, and moxifloxacin provide coverage for penicillin-resistant and multi-drug resistant strains of *S. pneumoniae.* However, levofloxacin- and fluoroquinolone-resistant *S. pneumoniae* isolates have been reported.[32,33] Compared with

levofloxacin, moxifloxacin is four to eight times more active against *S. pneumoniae in vitro.* Moxifloxacin also has shown greater *in vitro* activity against *Staphylococcus aureus* and some enterococcal strains.[34]

The Tracking Resistance in the United States Today (TRUST) surveillance initiative evaluated over 3,000 gram-negative isolates from 26 hospital laboratories and tested the isolates for susceptibility to ciprofloxacin, levofloxacin, and seven other antibiotics in 2000.[35] The two tested fluoroquinolones were active against over 86.7 percent of all gram-negative isolates and had similar sensitivities to urinary isolates of *Escherichia coli*. *P. aeruginosa* susceptibilities were 73.5 for ciprofloxacin and 73 percent for levofloxacin. Other surveillance studies observed an increase in antimicrobial resistance among gram-negative organisms between 1994 and 2000 when fluoroquinolone use increased in settings such as intensive care units.[36]

Recently, fluoroquinolone-resistant *Neisseria gonorrhea* occurred in more than four percent of patients enrolled in a surveillance study evaluating the development of antibiotic resistance in the Untied States.[37] Cephalosporins (ceftriaxone, cefixime) are now the preferred agents for treatment of gonorrhea according to the Centers for Disease Control and Prevention (CDC).[38]

Spectrum of Activity

Drug	Gram-positive	Gram-negative	Anaerobic[a]	*Pseudomonas* species	Atypical	STD organisms
ciprofloxacin (Cipro, Cipro XR, Proquin XR)	+	++++	0	++++	++	++[b]
gemifloxacin (Factive)[c]	++[d]	+++	nr	++	+++	nr
levofloxacin (Levaquin)[c]	++[d]	+++	+	+++	+++	+++
moxifloxacin (Avelox)[39,40,41 c]	++[d]	+++	++	++	+++	+++
norfloxacin (Noroxin)	+	+++	0	+++	nr	++
ofloxacin (Floxin)	+	+++	0	++	+++	+++

nr = not reported
[a] Only moxifloxacin (Avelox) produces reliable anaerobic activity
[b] Ciprofloxacin does not provide reliable activity against *Chlamydia*
[c] Enhanced activity against streptococci; may be active against some isolates of methicillin-resistant *S. aureus* and enterococci
[d] Includes activity against penicillin-resistant and multi-drug resistant *S. pneumoniae* in the setting of CAP.

Contraindications/Warnings[42,43,44,45,46,47,48,49]

Fluoroquinolone prescribing information contains several warnings. Pseudomembranous colitis has been reported with nearly all antibacterial agents. Pseudomembranous colitis should be considered in patients who present with diarrhea after use of antibacterials.

Fluoroquinolones have also been associated with peripheral neuropathy and tendon disorders. Ruptures of the shoulder, hand, Achilles tendons, or other tendons requiring surgical repair or resulting in prolonged disability have been reported in patients receiving fluoroquinolones.

Reports of central nervous system stimulation, convulsions, tremors, toxic psychoses, and other CNS complaints in patients treated with at least one dose of a fluoroquinolone have been published. Serious hypersensitivity and/or anaphylactic reactions have been reported with fluoroquinolone use.

Fluoroquinolones are not effective therapies for syphilis.[50] Because treatment for gonorrhea may mask the symptoms of syphilis, patients receiving treatment for gonorrhea should have appropriate testing performed for syphilis.

Ciprofloxacin ER (Cipro XR) is contraindicated with coadministration of tizanidine (Zanaflex®).

Coadministration of ciprofloxacin and theophylline has resulted in serious and fatal reactions. Reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Rare reports of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias, and weakness have been reported in patients receiving fluoroquinolones. Fluoroquinolones should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, or motor strength in order to prevent the development of an irreversible condition.

Post-marketing reports of severe hepatotoxicity have occurred with levofloxacin (Levaquin) use. Use of levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis.

Dysglycemia

Hyperglycemia and hypoglycemia have been reported with gatifloxacin (Tequin) in both diabetic and non-diabetic patients.[51] Risk factors for dysglycemia include diabetes mellitus, older age, renal insufficiency, and concurrent glucose-altering medications such as hypoglycemic agents. If dysglycemia develops, fluoroquinolone therapy should be discontinued and proper management of dysglycemia should be initiated. Hypoglycemia has generally been associated with an increase in serum insulin with a decrease in serum glucose within three days of initiating therapy. Severe presentations of dysglycemia have included hyperosmolar non-ketotic hyperglycemic coma, diabetic ketoacidosis, hypoglycemic coma, convulsions, and mental status changes. Prompt management usually results in reversal of the events. Management of hyperglycemia should include insulin, if required. Precautions, rather than warnings, appear in the labeling for levofloxacin and ofloxacin (Floxin), as well.[52,53]

A retrospective review of 17,108 patients treated with fluoroquinolones and ceftriaxone in hospitalized settings demonstrated that two fluoroquinolones, levofloxacin (0.93 percent) and gatifloxacin (1.01 percent), had higher rates of dysglycemia than ceftriaxone (0.18 percent; RR 3.32, 95% CI, 2.31-4.78, $p<0.05$); however, there was not a significant difference between

levofloxacin and gatifloxacin (p=0.8).[54] No reports of dysglycemia were associated with ciprofloxacin. Other fluoroquinolones had a rate of 0.94 percent. Dysglycemia in the chart review was described by glucose over 200 mg/dL or less than 50 mg/dL within 72 hours of receiving an antibiotic. Many of the patients with hyperglycemia without a history of diabetes had other contributing factors to hyperglycemia including total parenteral nutrition, corticosteroids, sepsis, and renal insufficiency.

Two nested-case control studies involving elderly patients in Canada evaluated the incidence of emergency department or inpatient treatment for hyperglycemia and hypoglycemia associated with outpatient treatment using macrolides, second-generation cephalosporins, or respiratory fluoroquinolones.[55] In the two-year study, gatifloxacin was associated with an increased risk of hypoglycemia compared to macrolides (adjusted odds ratio 4.3; 95% CI, 2.9-6.3). Levofloxacin had a slightly increased risk (adjusted odds ratio 1.5; 95% CI, 1.2-2.0) whereas the other antibiotics, ciprofloxacin included, did not have any increased risk. For hyperglycemia, only gatifloxacin was associated with an increased risk (adjusted odds ratio 16.7; 95% CI, 10.4-26.8).

QTc interval prolongation

As a class, fluoroquinolones have been associated with QTc interval prolongation. Fluoroquinolones, with the exception of ciprofloxacin and norfloxacin (Noroxin), now have warnings in the product labeling to avoid use of these drugs in patients with pre-existing prolonged QTc interval, in those receiving agents concurrently known to prolong the QTc interval, in patients with uncorrected hypokalemia, or those receiving Class IA or III antiarrhythmics.[56,57,58,59,60,61,62] QTc interval prolongation appears to be a dose-related effect; recommended dosages should not be exceeded. Reduce the dosage for patients with renal insufficiency to avoid excessively high serum levels.

In 787 patients in Phase III clinical trials, the mean effect of moxifloxacin (Avelox) on the QTc interval was 6±26 msec; however, the rate was similar in a comparator group of 702 patients who were receiving drugs known to prolong the QTc interval.[63] The magnitude of QTc prolongation may increase with increasing concentrations of the drug. No cardiovascular morbidity or mortality has been reported in over 7,900 patients receiving IV therapy or 18,000 patients receiving oral moxifloxacin in post-marketing trials where no ECGs were monitored.[64]

In the double-blind CAPRIE trial, moxifloxacin IV/oral and levofloxacin IV/oral were compared for cardiac rhythm safety in 394 elderly hospitalized patients for the treatment of community acquired pneumonia (CAP).[65] Holter monitoring for at least three days revealed a ventricular arrhythmia rate of 8.3 and 5.1 percent for moxifloxacin and levofloxacin; this difference was not statistically significant. Nonsustained ventricular tachycardia occurred in 7.3 percent of patients receiving moxifloxacin and 5.1 percent of patients receiving levofloxacin. One case of sustained monomorphic ventricular tachycardia occurred in the moxifloxacin group. One patient on levofloxacin developed torsades de pointes.

A retrospective database analysis evaluated the reported crude rates of torsades de pointes in patients who received a fluoroquinolone (ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin) between 1996 and 2001. Ciprofloxacin was associated with a significantly lower rate of torsades de pointes than other fluoroquinolones.[66]

QTc Warnings

Drug	Cases of TdP per 10 million Rx (95% CI)[67]	QT guidance	Guidance for patients at high risk
ciprofloxacin (Cipro)[68,69]	0.3 (0-1.1)	None	None
gemifloxacin (Factive)[70]	no data	"Fluoroquinolones may prolong the QT interval in some patients."	Gemifloxacin "should be avoided in patients with a history of prolongation of the QTc interval, patients with uncorrected electrolyte disorders (hypokalemia or hypomagnesemia), and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents. Pharmacokinetic studies between gemifloxacin and drugs that prolong the QTc interval such as erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Factive should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with Factive treatment in over 8,119 patients, including 707 patients concurrently receiving drugs known to prolong the QTc interval and 7 patients with hypokalemia."
levofloxacin (Levaquin) [71]	5.4 (2.9-9.3)	"Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the ECG and infrequent cases of arrhythmia."	"Rare cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving quinolones, including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide) and class III (sotalol, amiodarone) antiarrhythmic agents."
moxifloxacin (Avelox)[72]	0 (0-26)	"Moxifloxacin has been shown to prolong the QT interval of the ECG in some patients."	"Moxifloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA or Class III antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations. Pharmacokinetic studies between moxifloxacin and other drugs that prolong the QT interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. An additive effect of moxifloxacin and these drugs cannot be excluded; therefore moxifloxacin should be used with caution when given concurrently with these drugs."
norfloxacin (Noroxin)[73]	no data	None	None
ofloxacin (Floxin) [74]	2.1 (0.3-7.6)	"Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on the ECG and infrequent cases of arrhythmia."	"Ofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA or Class III antiarrhythmic agents."

Drug Interactions

Drug	theophylline	phenytoin	cyclosporine	warfarin	digoxin	Class IA and III antiarrhythmics
ciprofloxacin (Cipro, Cipro XR, Proquin XR)[75,76,77]	X	X	X	X	-	-
gemifloxacin (Factive)[78]	-	not studied	not studied	-	-	X
levofloxacin (Levaquin)[79]	-	-	-	possible	-	X
moxifloxacin (Avelox)[80]	-	-	-	-	-	X
norfloxacin (Noroxin)[81]	X	-	X	possible	-	X
ofloxacin (Floxin)[82]	X	-	-	-	-	-

A fluoroquinolone should not be administered at the same time (more than two hours before and at least six hours after) as antacids, multi-valent cation drugs including sucralfate, chewable/buffered didanosine, metal cations such as iron and calcium, and multivitamins containing zinc due to reduced bioavailability of the fluoroquinolone.

Adverse Effects

Drug	Nausea	Diarrhea	Dizziness	Vomiting	Abdominal pain	Headache	Phototoxicity
ciprofloxacin (Cipro)[83] n=49,038	2.5	1.6	<1	1	<1	<1	<1
ciprofloxacin ER (Cipro XR)[84] n=961	4	2	2	2	<1	3	<1
ciprofloxacin ER (Proquin XR)[85] n=547	<1	<1	<1	<1	<1	2.4	nr
gemifloxacin (Factive)[86] n=8,119	3.7	5	1.7	1.6	2.2	4.2	reported
levofloxacin (Levaquin)[87]	6.8	5.4	2.4	2.4	2.5	5.8	reported
moxifloxacin (Avelox)[88] n= >8,600	6	5	2	0.1-2	0.1-2	0.1-2	reported
norfloxacin (Noroxin)[89]	2.6	0.3-1	2.6	0.3-1	0.3-1	2.8	reported
ofloxacin (Floxin)[90]	10	4	5	4	1-3	9	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Photosensitivity/phototoxicity cautions have been added to the prescribing information for all products in this class. Patients taking a fluoroquinolone are advised to avoid excessive exposure to sunlight or artificial ultraviolet light to prevent skin eruptions or sunburns.

Rash has been reported in 1.2 to 5.3 percent of patients receiving gemifloxacin (Factive) with the highest occurrence seen in women less than 40 years old taking gemifloxacin for seven (12 percent of women less than 40 years old) or ten days (15.3 percent of women less than 40 years old).[91] Postmenopausal women taking hormone replacement therapy and gemifloxacin were also observed to have a higher rate of rash than men. Gemifloxacin therapy is not recommended to exceed seven days. Longer duration of treatment is associated with a higher incidence of rash in all patients except men over 40 years of age. Gemifloxacin should be discontinued when a rash appears.

Special Populations

Pediatrics

In initial studies of fluoroquinolones, bone and joint abnormalities (osteochondrosis) were seen in young dogs. Permanent damage to cartilage in weight-bearing joints was concerning. Adverse effects in tendons have been reported. Benefits of systemic fluoroquinolone use versus risks associated with use in pediatrics must be considered.[92] The American Academy of Pediatrics stated fluoroquinolone use in children should only be considered when there are no other safe or effective alternatives to treatment of an infection caused by multi-drug resistant bacteria or to provide oral therapy when parenteral treatment is not feasible, and no other oral agent is effective.[93]

Very limited data are available regarding the use of fluoroquinolones in children. Some of the literature is from foreign countries where the use of the fluoroquinolones is for infections not typically seen in the United States. Foreign trials have investigated the use of ciprofloxacin in febrile neutropenia associated with chemotherapy in children. During the 1990s, use of ciprofloxacin in cystic fibrosis patients was prominent as a new alternative for the treatment of respiratory tract infections with *P. aeruginosa* and other multi-drug resistant gram-negative pathogens.

Ciprofloxacin is the only fluoroquinolone with indications for patients younger than 18 years of age. Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis in children ages one to 17 years.[94] Ciprofloxacin is also indicated in the treatment of inhalational anthrax for children. Ciprofloxacin ER (Cipro XR, Proquin XR) has not been studied in children.[95,96]

Pregnancy[97,98,99,100,101,102,103,104]

Fluoroquinolones are all Pregnancy Category C.

Renal Insufficiency

All fluoroquinolones except moxifloxacin (Avelox) require adjustment of dose and/or interval for patients with renal insufficiency.

Dosages

Drug and Availability	AECB/Lower respiratory tract infection	Duration (days)	CAP	Duration (days)	Acute Sinusitis	Duration (days)	UTI (regimen selected based on the severity of infection)
ciprofloxacin (Cipro) 250, 500, 750 mg tablets, 250 mg/5 mL (5%) and 500 mg/5 mL (10%) suspension	500-750 mg every 12 hours	7-14	--	--	500 mg every 12 hours	10	250 mg every 12 hours for three days; 250-500 mg every 12 hours for seven to 14 days Pediatrics: 10-20 mg/kg every eight to 12 hours (not to exceed 750 mg) for 10 to 21 days
ciprofloxacin ER (Cipro XR) 500, 1,000 mg tablets	--	--	--	--	--	--	500 mg daily for three days; 1,000 mg daily for seven to 14 days
ciprofloxacin ER (Proquin XR) 500 mg tablets	--	--	--	--	--	--	500 mg daily for three days with the main meal of the day
gemifloxacin (Factive) 320 mg tablets	320 mg daily	5	320 mg daily	5-7	--	--	--
levofloxacin (Levaquin) 250, 500, 750 mg tablets 25 mg/mL oral solution	500 mg daily	7	500 mg daily	7-14	500 mg daily	10-14	250 mg daily for three to 10 days
			750 mg daily	5	750 mg daily	5	
moxifloxacin (Avelox) 400 mg tablets	400 mg daily	5	400 mg daily	7-14	400 mg daily	10	--
norfloxacin (Noroxin) 400 mg tablets	--	--	--	--	--	--	400 mg every 12 hours for three to 21 days
ofloxacin (Floxin) 200, 300, 400 mg tablets	400 mg every 12 hours	10	400 mg every 12 hours	10	--	--	200 mg every 12 hours for three to 10 days

All fluoroquinolones except moxifloxacin (Avelox) require dosage adjustment in patients with renal impairment.
Ciprofloxacin ER (Cipro XR and Proquin XR) tablets should not be crushed, chewed or split.
Gemifloxacin (Factive) tablet should be swallowed whole with plenty of liquid and may be taken without regard for food.
Levaquin solution should be given one hour before or two hours after a meal.

Clinical Trials

Search Strategies

Studies were identified through searches performed on PubMed and http://www.ifpma.org/clinicaltrials.html and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled trials performed in the United States comparing oral agents within this class within the last seven years in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Numerous clinical trials were published comparing the fluoroquinolones in both inpatient and outpatient settings in the 1990s. Little evidence exists that shows one fluoroquinolone is superior to others for the approved indications when given in equivalent dosages. Due to changes in susceptibility of *Pseudomonas* and other organisms to fluoroquinolones since the 1990s, only studies published since 2000 are included.[105] Nationwide and regional variances in pathogen susceptibility and resistance rates must be taken into consideration when evaluating studies. Many short-term clinical trials in outpatients with minor infections lose a significant portion of patients due to lack of follow-up. Losses are greater than 25 percent of enrolled patients in some trials.

Many trials performed with the fluoroquinolones compare the agents to other broad-spectrum antibiotics such as macrolides, cephalosporins, and extended-spectrum penicillins. While relative efficacy is important, the comparisons lend little insight into relative efficacy and safety of agents within this class. Studies comparing available fluoroquinolones to trovafloxacin (Trovan), gatifloxacin (Tequin), and lomefloxacin (Maxaquin) were not included as these fluoroquinolones are no longer available in the United States.

ciprofloxacin ER (Cipro XR) and ciprofloxacin (Cipro)

In a multicenter, randomized, double-blind, double-dummy Phase III trial consisting of 891 women with acute cystitis, ciprofloxacin ER 500 mg daily for three days was compared to ciprofloxacin 250 mg twice daily for three days for bacterial eradication.[106] Clinical response rates were 95.5 and 92.7 percent for ciprofloxacin ER and ciprofloxacin, respectively (95% CI, -1.6 to 7.1). Bacterial eradication rates were 94.5 and 93.7 percent for ciprofloxacin ER and ciprofloxacin, respectively (95% CI, -3.5 to 5.1). The most common pathogens were *E. coli, Enterococcus faecalis, Proteus mirabilis*, and *Staphylococcus saprophyticus*.

Ciprofloxacin ER 1,000 mg once daily and ciprofloxacin 500 mg twice daily were compared in 1,035 patients with complicated urinary tract infections or acute uncomplicated pyelonephritis.[107] Treatment continued for seven to 14 days. In the randomized, double-blind, North American trial, patients were enrolled if they had a positive pre-treatment urine culture and pyuria in the preceding 48 hours. Bacteriologic efficacy determined between five and 11 days after treatment

initiation were 89 percent and 85 percent for ciprofloxacin ER and ciprofloxacin, respectively (95% CI, -2.4 to 10.3). Clinical cure rates were similar with 97 percent for ciprofloxacin ER and 94 percent for ciprofloxacin (95% CI, -1.2 to 6.9). Late follow-up was done 28 to 42 days after therapy initiation; similar cure rates were observed. *E. coli* was the most common organism identified in urine cultures. Similar rates of adverse events were reported.

The efficacy and safety of ciprofloxacin ER and ciprofloxacin were compared in 523 adult women with acute uncomplicated UTI.[108] In a multicenter, randomized, double-blind study, patients with a positive pre-treatment urine culture were randomized to ciprofloxacin ER 500 mg once daily or ciprofloxacin 250 mg twice daily. Treatment duration was three days. At the test of cure visit (days four to 11 after therapy), microbiological eradication rates were 93.4 and 89.6 percent for ciprofloxacin ER and ciprofloxacin, respectively. Clinical cure rates were 85.7 for ciprofloxacin ER and 86.1 percent for ciprofloxacin. After four to six weeks, microbiological and clinical outcomes were similar between the groups. Nausea (0.6 vs. 2.2 percent) and diarrhea (0.2 vs. 1.4 percent) were lower in the ciprofloxacin ER group.

gemifloxacin (Factive) and levofloxacin (Levaquin)

In a randomized, double-blind, double dummy, multicenter, parallel-group study, a total of 360 adults with acute exacerbation of chronic bronchitis (AECB) were randomly assigned to receive gemifloxacin 320 mg daily for five days or levofloxacin 500 mg daily for seven days.[109] A total of 335 patients completed the study. In the intent-to-treat population, clinical success rate at follow-up was 85.2 percent with gemifloxacin and 78.1 percent for levofloxacin. The clinical efficacy of gemifloxacin for five days in AECB was at least as good as levofloxacin for seven days. Fewer patients withdrew from the gemifloxacin arm of the trial. (p=0.02).

levofloxacin (Levaquin) and ciprofloxacin (Cipro)

In a multicenter, randomized, double-blind trial, levofloxacin 500 mg daily and ciprofloxacin 500 mg twice daily were compared for efficacy and safety in the treatment of chronic bacterial prostatitis in 377 patients.[110] Treatment duration was 28 days. Clinical success rates, which included both cured and improved patients, were similar between the two drugs (levofloxacin 75 percent; ciprofloxacin 72.8 percent). Bacteriological eradication rates were similar with 75 and 76.8 percent for levofloxacin and ciprofloxacin, respectively. The most common pathogens were *E. faecalis* and *E. coli*. Six-month relapse rates were also similar. Both drugs were well tolerated.

Summary

Fluoroquinolones provide gram-negative, gram-positive, and atypical pathogen coverage for the treatment of CAP and AECB. Serum concentrations with use of oral formulations are often similar to those produced by IV administration of these agents. With once daily dosing, excellent serum concentrations, and the ability to reliably cover most common respiratory pathogens, levofloxacin (Levaquin), gemifloxacin (Factive), and moxifloxacin (Avelox) are effective choices for the treatment of CAP.

Ciprofloxacin (Cipro) has a slightly different spectrum of activity (more gram-negative activity) and different indications (including bone and joint infections) than other fluoroquinolones. Ciprofloxacin and levofloxacin have the greatest activity against *P. aeruginosa*.

Norfloxacin (Noroxin) is indicated only for infections related to the urinary tract. For the management of acute and non-severe prostatitis, ciprofloxacin or levofloxacin may be

considered.[111] For chronic prostatitis, ciprofloxacin or levofloxacin or trimethoprim-sulfamethoxazole for four to 12 weeks may be considered.

Many factors must be considered when choosing the most appropriate fluoroquinolone for a particular patient. Little evidence suggesting clinical outcomes differ among the fluoroquinolones when administered for appropriate indications exists.

References

[1] Cipro I.V. [package insert]. West Haven, CT; Bayer Corporation; March 2004.
[2] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[3] Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis. 2007; 44(Suppl 2):S27-S72.
[4] Center for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2006. MMWR. 2006; 55(RR-11);1-100.
[5] CDC. Available at: http://www.cdc.gov/std/treatment/2006/updated-regimens.htm. Accessed April 24, 2008
[6] Stevens DL, Bisno AL, Chambers HF, et al for the Infectious Diseases Society of America. Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections. Clin Infect Dis. 2005; 41:1373-406.
[7] Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryng Head Neck Surg. 2004; 130(1):1-45.
[8] Food and Drug Administration. Public health advisory: Trovan. June 9, 1999.
[9] Hooper D, Quinolones. In: Mandell GL, Bennett JE, Mandell DR. Douglas and Bennett's Principles and Practice of Infectious Disease. 5th ed. Philadelphia: Churchill Livingstone; 2000; 404-23.
[10] Pickerill KE, et al. Comparison of the fluoroquinolones based on pharmacokinetic and pharmacodynamic parameters. Pharmacotherapy. 2000; 20(4):417-428.
[11] Hooper D, Quinolones. In: Mandell GL, Bennett JE, Mandell DR. Douglas and Bennett's Principles and Practice of Infectious Disease. 5th ed. Philadelphia: Churchill Livingstone; 2000; 404-423.
[12] Turnidge J. Pharmacokinetics and pharmacodynamics of fluoroquinolones. Drugs. 1999; 58(suppl 2):29-36.
[13] Schentag JJ, Meagher AK, Forrest A. Fluoroquinolone AUIC break points and the link to bacterial killing rates. Part 2: human trials. Ann Pharmacother. 2003; 37(10):1478-88.
[14] Wise R. Maximizing efficacy and reducing the emergence of resistance. J Antimicrob Chemother. 2003; 51(suppl 1):37-42.
[15] Hooper D, Quinolones. In: Mandell GL, Bennett JE, Mandell DR. Douglas and Bennett's Principles and Practice of Infectious Disease. 5th ed. Philadelphia: Churchill Livingstone; 2000; 404-423.
[16] Wolfson JS, Hooper DC. Comparative Pharmacokinetics of ofloxacin and ciprofloxacin. Am J Med. 1989; 87(suppl 6C):31-36.
[17] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[18] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006
[19] Walker RC. The fluoroquinolones. Mayo Clin Proc. 1999; 74:1030-7.
[20] Hooper D, Quinolones. In: Mandell GL, Bennett JE, Mandell DR. Douglas and Bennett's Principles and Practice of Infectious Disease. 5th ed. Philadelphia: Churchill Livingstone; 2000; 404-423.
[21] Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[22] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[23] Proquin XR [package insert]. Menlo Park, CA; Depomed; September 2007.
[24] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[25] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[26] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[27] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006.
[28] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[29] Proquin XR [package insert]. Menlo Park, CA; Depomed; September 2007.
[30] Hooper DC. New uses for new and old quinolones and the challenge of resistance. Clin Infect Dis. 2000; 30:243-254.
[31] Hooper DC. New uses for new and old quinolones and the challenge of resistance. Clin Infect Dis. 2000; 30:243-254.
[32] Pletz MW, McGee L, Jorgensen J, et al. Levofloxacin-resistant invasive Streptococcus pneumoniae in the United States: evidence for clonal spread and the impact of conjugate pneumococcal vaccine. Antimicrob Agents Chemother. 2004; 48(9):3491-7.
[33] Doern GV, Brown SD. Antimicrobial susceptibility among community-acquired respiratory tract pathogens in the USA: data from PROTEKT US 2000-01. J Infect. 2004; 48(1):56-65.
[34] Eliopoulos GM. Activity of newer fluoroquinolones in vitro against gram-positive bacteria. Drugs. 1999; 58(suppl 2):23-28.
[35] Karlowsky JA, Kelly LJ, Thornsberry C, et al. Susceptibility to fluoroquinolones among commonly isolated gram-negative bacilli in 2000: TRUST and TSN data for the United States. Tracking Resistance in the United States today. The Surveillance Network. Int J Antimicrob Agents. 2002; 19(1):21-31.
[36] Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA. 2003; 289 (7):885-8.
[37] Wang SA, Harvey AB, Conner SM, et al. Antimicrobial resistance for Neisseria gonorrhoeae in the United States, 1988 to 2003: the spread of fluoroquinolone resistance. Ann Intern Med. 2007 ; 147(2):81-8.
[38] CDC. Available at: http://www.cdc.gov/std/treatment/2006/updated-regimens.htm. Accessed April 24, 2008.
[39] Behra-Miellet J, Dubreuil L, Jumas-Bilak E. Antianaerobic activity of moxifloxacin compared with that of ofloxacin, ciprofloxacin, clindamycin, metronidazole and beta-lactams. Int J Antimicrob Agents. 2002; 20(5):366-74.

[40] Edmiston CE, Krepel CJ, Seabrook GR, et al. In vitro activities of moxifloxacin against 900 aerobic and anaerobic surgical isolates from patients with intra-abdominal and diabetic foot infections. Antimicrob Agents Chemother. 2004; 48(3):1012-6.
[41] Goldstein EJC, Citron DM, Warren YM, et al. In vitro activity of moxifloxacin against 923 anaerobes isolated from human intra-abdominal infections. Antimicrob Agents Chemother, 2006; 50(1):148-155).
[42]Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[43] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[44] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[45] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[46] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[47] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[48] Proquin XR [package insert]. Menlo Park, CA; Depomed; September 2007.
[49] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006.
[50] Center for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2006. MMWR. 2006; 55(RR-11);1-100.
[51] Tequin [package insert]. Princeton, NJ; Bristol-Myers Squibb; January 2006.
[52] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[53] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[54] Mohr JF, McKinnon PS, Peymann PJ, et al. A retrospective, comparative evaluation of dysglycemias in hospitalized patients receiving gatifloxacin, levofloxacin, ciprofloxacin and ceftriaxone. Pharmacotherapy. 2005; 25(10):1303-9.
[55] Park-Wyllie L, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. N Engl J Med. 2006; 354:
[56]Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[57] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[58] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[59] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[60] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[61] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[62] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006.
[63] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[64] Faich GA, Morganroth J, Whitehouse AB, et al. Clinical experience with moxifloxacin in patients with respiratory tract infections. Ann Pharmacother. 2004; 38(5):749-54.
[65] Morganroth J, Dimarco JP, Anzueto A, et al for the CAPRIE Study Group. A randomized trial comparing the cardiac rhythm safety of moxifloxacin vs. levofloxacin in elderly patients hospitalized with community-acquired pneumonia. Chest. 2005; 128(5):3398-406.
[66] Frothingham R. Rates of Torsades de Pointes Associated with Ciprofloxacin, Ofloxacin, Levofloxacin, Gatifloxacin, and Moxifloxacin. Pharmacotherapy. 2001; 21(12):1468-1472.
[67] Frothingham R. Rates of Torsades de Pointes Associated with Ciprofloxacin, Ofloxacin, Levofloxacin, Gatifloxacin, and Moxifloxacin. Pharmacotherapy. 2001; 21(12):1468-1472.
[68] Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[69] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[70] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[71] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[72] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[73] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006.
[74].Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[75] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[76] Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[77] Proquin XR [package insert]. Menlo Park, CA; Depomed; September 2007.
[78] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[79] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[80] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[81] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006.
[82] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[83] Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[84] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[85] Proquin XR [package insert]. Menlo Park, CA; Depomed; September 2007.
[86] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[87] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[88] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[89] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006.
[90] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[91] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[92] Committee on Infectious Diseases. The use of systemic fluoroquinolones. Pediatrics. 2006; 118(3):1287-92.
[93] The Committee on Infectious Diseases. The use of systemic fluoroquinolones: a policy statement. Pediatrics. 2006; 188(3):1287-1292.
[94] Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[95] Proquin XR [package insert]. Menlo Park, CA; Depomed; September 2007.
[96] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[97]Cipro oral [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.

[98] Cipro XR [package insert]. West Haven, CT; Bayer Corporation/Schering; October 2007.
[99] Levaquin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; February 2008.
[100] Avelox [package insert]. West Haven, CT; Bayer Corporation/Schering; February 2008.
[101] Floxin [package insert]. Raritan, NJ; Ortho-McNeil Pharmaceutical; April 2007.
[102] Factive [package insert]. Waltham, MA; Oscient Pharmaceuticals; May 2007.
[103] Proquin XR [package insert]. Menlo Park, CA; Depomed; September 2007.
[104] Noroxin [package insert]. Whitehouse Station, NJ; Merck; December 2006.
[105] Bhavnani SM, Hammel JP, Jones RN, et al. Relationship between increased levofloxacin use and decreased susceptibility of Streptococcus pneumoniae in the United States. Diagn Microbiol Infect Dis. 2005; 51(1):31-7.
[106] Henry DC, Bettis RB, Riffer E, et al. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. Clin Ther. 2002; 24(12):2088-104.
[107] Talan DA, Klimberg IW, Nicolle LE, et al. Once daily, extended release ciprofloxacin for complicated urinary tract infections and acute uncomplicated pyelonephritis. J Urol. 2004; 171(2 Pt 1):734-9.
[108] Fourcroy JL, Berner B, Chiang YK , et al. Efficacy and safety of a novel once-daily extended-release ciprofloxacin tablet formulation for treatment of uncomplicated urinary tract infection in women. Antimicrob Agents Chemother. 2005; 49(10):4137-43.
[109] Sethi S, Fogarty C, Fulambarker A. A randomized, double-blind study comparing 5 days oral gemifloxacin with 7 days oral levofloxacin in patients with acute exacerbation of chronic bronchitis. Respir Med. 2004; 98(8):697-707.
[110] Bundrick W, Heron SP, Ray P, et al. Levofloxacin versus ciprofloxacin in the treatment of chronic bacterial prostatitis: a randomized double-blind multicenter study. Urology. 2003; 62(3):537-41.
[111] The Medical Letter. Treatment Guidelines: Choice of Antibacterial Drugs. Med Ltr. 2004; 2(19):13-26.

