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Fluoroquinolones in Outpatient Infections: Friend or Foe?

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The fluoroquinolones are potent antimicrobials with a broad spectrum of coverage, concentration-dependent bactericidal activity, relatively low resistance rates among community-acquired pathogens and a favorable safety profile. Given these characteristics, the fluoroquinolones are regarded as antimicrobials with applicability to a wide variety of infections. However, concern regarding the development of fluoroquinolone resistance in certain key organisms has led most infectious disease experts to express caution regarding overuse of this class of drugs. This concern is the key factor supporting the utilization recommendations that follow.

SPECTRUM OF ACTIVITY

In general, the fluoroquinolones have a wide spectrum of antimicrobial activity, but individual differences do exist. Ciprofloxacin (Cipro®), norfloxacin (Noroxin®) and ofloxacin (Floxin®) were originally utilized for their activity against gram-negative pathogens. Development of the newer fluoroquinolones, levofloxacin (Levaquin®), gatifloxacin (Tequin®), and moxifloxacin (Avelox®), has focused on enhancement of gram-positive activity. All of the fluoroquinolones are active against most atypical pathogens including *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

RESISTANCE ISSUES

Since its description in 1967, penicillin resistance in *Streptococcus pneumoniae* has been steadily increasing and is an ongoing concern. Recent surveillance data shows penicillin resistance among respiratory tract isolates to be 6.8-17.8% worldwide, with the incidence in the United States noted to be 14%.[1] Of additional concern is the fact that penicillin resistance in *S. pneumoniae* implies diminished susceptibility to numerous additional antimicrobials; penicillin-resistant *S. pneumoniae* is thus referred to as drug resistant *S. pneumoniae* (DRSP).

It is in the context of the treatment of lower respiratory tract infections that the potential emergence of fluoroquinolone resistance becomes most important. The key concerns are: 1) overuse of fluoroquinolones in the era of DRSP, and 2) the question of whether certain fluoroquinolones should be favored over others for treatment of *S. pneumoniae*.

Although the fluoroquinolones generally retain good activity against DRSP, reports of increasing fluoroquinolone resistance have appeared since the observance of this phenomenon by Chen et al.[2] Ciprofloxacin is no longer used for this organism (regardless of penicillin resistance).

Gatifloxacin and moxifloxacin, which each possess a methoxy group at the 8-carbon position, are better able to prevent resistance than are fluoroquinolones with alternate C-8 moieties (e.g., levofloxacin).[3,4]

This phenomenon has gained greater notice as reports of levofloxacin resistance in *S. pneumoniae* have surfaced.[5] These structural differences, coupled with the apparent emergence of their clinical manifestation, has led some to propose that gatifloxacin and moxifloxacin be used in favor of levofloxacin for pneumococcal infections.[6] However, greater clinical data may be needed before such recommendations can be made. At the very least, the problem of fluoroquinolone resistance in *S. pneumoniae* highlights the need for judicious use of these agents.

ADVERSE EFFECTS AND DRUG INTERACTIONS

The fluoroquinolones have similar or improved adverse effect rates when compared with non-fluoroquinolone antibiotics.[7] Adverse effect rates are comparable between the fluoroquinolones, though minor differences do exist. Gastrointestinal effects were reported in 2-20% of patients, CNS effects averaged 1-2% and mild, reversible liver enzyme abnormalities were reported in 2-3% of patients.[7] Photosensitivity has been associated with the older fluoroquinolones, but the currently available fluoroquinolones have minimal phototoxicity potential.

The available fluoroquinolones have varying abilities to prolong the QTc interval, a condition associated with Torsades de Pointes.[7,8] Use of the fluoroquinolones with other drugs that increase the QTc interval or cause bradycardia (e.g., class Ia and III antiarrhythmics) should be monitored closely. Other antibiotics, including the macrolides, have been associated with greater degrees of cardiac toxicity than the fluoroquinolones.[8]

Tendon rupture and tendonitis have been reported with various fluoroquinolones, but the overall frequency of these events is quite low.[7] Additionally, chondrotoxicity has been suggested in children. Because of this concern, the fluoroquinolones are currently contraindicated in pediatrics.

The fluoroquinolones have been variably reported to interact with cytochrome P450 enzymes (ciprofloxacin being most commonly referenced), though clinical implications are uncertain.[7] One of the most important interactions is the chelation of the fluoroquinolones with multivalent cation containing medications. Antacids, sucralfate, iron, magnesium, and zinc reduce the absorption of orally administered fluoroquinolones, decrease drug concentrations, and may lead to clinical failure. This effect is variable among the fluoroquinolones, but necessitates dosing the antibiotics 2 hours before or 4-6 hours after administration of multivalent cation containing products.[7] There have been reports of INR elevations in patients receiving concomitant warfarin and fluoroquinolone therapy, though the causality is questionable.[7]

OPTIMAL FLUOROQUINOLONE USE

The following are recommendations for proper use of the fluoroquinolones for each of the specified indications. Note that agents listed in Table 1 are potential alternatives according to established guidelines.

Community Acquired Pneumonia (CAP)

The fluoroquinolones are active against the most prevalent pathogens (*S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) responsible for CAP. They also possess activity against common atypical pathogens.

The American Thoracic Society guidelines include an antipneumococcal fluoroquinolone (i.e., gatifloxacin, levofloxacin, moxifloxacin) as an option in outpatients with cardiopulmonary disease and/or other modifying factors that may increase the risk of infection with DRSP (age >65 years, β–lactam therapy within the previous three months, alcoholism, immunosuppression, multiple medical co-morbidities and exposure to a child from a day care center).[9] An alternative to be used in this subset of patients is the combination of a β–lactam and either a macrolide or doxycycline.[9] Fluoroquinolones are not recommended for patients without cardiopulmonary disease or modifying factors. In comparison, the Infectious Diseases Society of America guidelines for outpatient management of CAP include β–lactams, macrolides, doxycycline or an antipneumococcal fluoroquinolone (in no particular hierarchy).[10]

Acute Bacterial Rhinosinusitis (ABRS)

Four recent guidelines for the management of ABRS all include the fluoroquinolones as an option, but their use is discouraged.[11-14] The Sinus and Allergy Health Partnership guidelines restrict fluoroquinolones to patients with moderate disease who have received antibiotics within the previous 4-6 weeks

or to patients with mild or moderate disease who are β–lactam allergic.[14] Other guidelines recommend that the fluoroquinolones be only in patients with moderate-to-severe infection or recent antibiotic failures.[11,12] Table 1 contains the recommendations of the Oregon Public Health Services.[13] It is important to note that a high percentage of cases of ABRS do not require antimicrobial treatment at all.

Acute Bacterial Exacerbations of Chronic Bronchitis (ABECB)

While gatifloxacin, levofloxacin, and moxifloxacin are all FDA-approved for the treatment of ABECB, formal guidelines for management of chronic bronchitis are lacking and controversy persists regarding optimal antimicrobial selection, as well as which patients require any antibiotic therapy. Some guidelines exclude the fluoroquinolones,[13] while others reserve the class as second-line agents in order to minimize the risk of resistance.[15]

Urinary Tract Infections (UTIs)

Urinary tract infections include cystitis, pyelonephritis, and prostatitis.[16-18] *Escherichia coli* is the most prevalent urinary pathogen.[17] Other gram-negatives (e.g., *Klebsiella pneumoniae*, *Proteus* spp., *Serratia* spp.) and gram-positives (e.g., enterococci and *Staphylococcus saprophyticus*) are also implicated. The fluoroquinolones have excellent activity against the common gram-negative urinary pathogens.[18] Fluoroquinolones concentrate in the urine and penetrate into renal tissues, making them attractive agents for both uncomplicated and complicated infections.[17] Because of concerns about poor urinary concentrations, moxifloxacin is not approved for treatment of UTIs.

Current guidelines for uncomplicated cystitis recommend empiric treatment with trimethoprim/sulfamethoxazole (TMP/SMX) in regions with low (<20%) *E. coli* resistance rates to this agent.[18] Restriction of fluoroquinolones to second-line status is recommended to minimize resistance and decrease costs.[19] The fluoroquinolones are suggested in regions where TMP/SMX resistance rates are increased.

Skin and Skin-Structure Infections

Staphylococcus aureus, *Streptococcus pyogenes*, and other streptococci are the common pathogens associated with skin and skin-structure infections in immunocompetent patients.[19] While the fluoroquinolones have been favorably evaluated for uncomplicated (i.e., cellulitis) and complicated skin infections, these infections are more appropriately treated with narrow spectrum β-lactams such as dicloxacillin and cephalexin.[19] The use of fluoroquinolones in skin infections should be reserved for more severe infections where gram-negative pathogens are suspected, as in diabetic patients.

Conclusions

The fluoroquinolones possess activity against a broad spectrum of bacteria and are considered generally well tolerated. However, the latest evidence of emerging resistance in *S. pneumoniae* isolates has prompted a re-evaluation of fluoroquinolone use, especially for treatment of infections for which there are many effective alternatives. In conclusion, there are few indications for which fluoroquinolones should be considered as first-line antibiotics.

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Table 1 - Selected Options for Management of Common Outpatient Infections

First-Line	Cost# ($)	Second-Line	Cost# ($)
CAP; patients not at risk for DRSP [9,10] (Usual duration 7-14 days)			
doxycycline (100 mg q12h)	1.40	Tequin (400 mg q24h)	54.05
Zithromax (250 mg q24h)^	37.15	Avelox (400 mg q24h)	56.00
Biaxin (500 mg q12h)	50.40	Levaquin (500 mg q24h)	58.30
CAP; patients at risk for DRSP [9,10] (Usual duration 7-14 days)			
One of the following:		Listed agents are acceptable 1st line therapies	
amoxicillin (1000 mg q8h)	5.05		
Vantin (200 mg q12h)	53.20		
amox/clav* (500 mg q8h)	75.20		
cefuroxime* (500 mg q12h)	89.90		
Plus, one of the following:			
doxycycline (100 mg q12h)	1.40		
Zithromax (250 mg q24h)^	37.15		
Biaxin (500 mg q12h)	50.40		
Tequin (400 mg q24h)	54.05		
Avelox (400 mg q24h)	56.00		
Levaquin (500 mg q24h)	58.30		
ABRS [11-14] (Usual duration 7-14 days) Antibiotics NOT indicated unless severe symptoms or mucopurulent discharge present for >10 days.			
amoxicillin (500 mg q8h)	2.50	TMP/SMX (1 DS q12h)	2.25
		Zithromax (250 mg q24h)^	37.15
		Biaxin (500 mg q12h)	50.40
		Vantin (200 mg q12h)	53.20
		cefuroxime* (500 mg q12h)	89.90
		Tequin (400 mg q24h)	54.05
		Avelox (400 mg q24h)	56.00
		Levaquin (500 mg q24h)	58.30
ABECB [13,15] (Usual duration 7-14 days) Antibiotics NOT indicated in otherwise healthy adults without clinical signs of pneumonia unless cough persists >21 days and other causes are ruled out.			
doxycycline (100 mg q12h)	1.40	Zithromax (250 mg q24h)^	37.15
TMP/SMX (1 DS q12h)	2.25	Biaxin (500 mg q12h)	50.40
amoxicillin (500 mg q8h)	2.50	Avelox (400 mg q24h)^^	40.00
		Tequin (400 mg q24h)	54.05
		Levaquin (500 mg q24h)	58.30
Uncomplicated UTI [19] (Usual duration 3 days)			
TMP/SMX (1 DS q12h)	1.00	Noroxin (400 mg q12h)	20.90
		Levaquin (250 mg q24h)	21.40
		Tequin (200 mg q24h)	23.40
		nitrofurantoin (100 mg q6h)	14.90
Complicated UTI/Pyelonephritis [18,19] (Usual duration 7-14 days)			
Noroxin (400 mg q12h)	20.90	TMP/SMX (1 DS q12h)	2.25
Levaquin (250 mg q24h)	21.40		
Tequin (400 mg q24h)	54.05		
Cipro (500 mg q12h)	61.30		
Acute Prostatitis [17] (Usual duration 4 weeks)			
TMP/SMX (1 DS q12h)	9.00	Listed agents are acceptable 1st line therapies	
Noroxin (400 mg q12h)	83.60		
Cipro (500 mg q12h)	245.20		

^500 mg q24h *1 day, followed by 250 mg q24h *4 days
^^FDA approved for 5 day therapy
#Cost for shortest treatment course using AWP-13 or MAC on July 15, 2002
*Newly available generic and price is expected to drop over time.

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