

Newer antibiotics: Current concepts

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Abstract: Antibiotic resistance is a global problem. In the community, resistance can result from nosocomial acquisition of resistant bacteria, emergence of resistance consequent upon its use in the community or acquisition of resistant pathogens as a result of travel. Resistance can also occur as a result of using antimicrobial agents as 'growth promoters' in animals. Since resistance is often a result of the selective pressure exerted by the use or misuse of antibiotics, prudent and appropriate employment of these valuable agents is likely to reduce the emergence of resistance and prolong their usefulness. Besides prevention of selective pressure, physicians can also contribute to the control of spread of these infections by instituting appropriate isolation protocols. New agents can be developed to deal with resistance. In this review, various attributes of four new agents: linezolid for hospital-acquired infections, telithromycin for community-acquired respiratory tract infections, and moxifloxacin and gatifloxacin are described with the hope that a better understanding of their attributes would translate into appropriate deployment of these agents.

Oxazolidinones (Linezolid)

One way forward would be to discover and develop a new class of antimicrobials that are completely synthetic in nature. This would ensure that the target pathogens have no prior exposure and, therefore, no pre-existing resistance to the drug. The (S)-3-ary1-5-acetamidomethyl-2-oxazolidinones, first discovered and reported in 1987, are a novel class of synthetic antibacterial agents. Oxazolidinones have a number of intriguing attributes: (i) a unique mechanism of action that involves the inhibition of protein synthesis at a very early stage, providing a lack of cross-resistance with existing antimicrobials; (ii) a spectrum of activity that includes a number of important bacterial species; (iii) activity in animal models of human infection when administered by either the oral or parenteral routes; and (iv) sufficient structural latitude to allow for activity and/or toxicity modifications.

Linezolid is the first antibacterial drug of a new class, now available for the treatment of infections associated with vancomycin-resistant (VR) Gram-positive infections, e.g. *VREnterococcus faecium* (VREF). It is effluxed out of Gram-negative bacteria and consequently its activity is restricted to Gram-positive pathogens only (that lack these specific efflux pumps).

Spontaneous mutation occurs in 10^9 to 10^{11} generations for a few strains of staphylococci on exposure to sub-inhibitory concentrations of linezolid. In clinical settings, however, resistance develops and has been reported in enterococci and staphylococci.

In vitro activity¹

Minimum inhibitory concentrations (MIC) attained against

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various Gram-positive pathogen indicate that linezolid has MIC⁹⁰ against *Staphylococcus aureus*, *Staph. epidermidis* and *Staph. haemolyticus* of <4 µg/ml. The presence of β-lactam, glycopeptide or quinolone resistance does not effect the MIC. Similarly, the degree of penicillin, erythromycin or clindamycin resistance of *Streptococcus pneumoniae* isolates does not affect linezolid's activity. Linezolid also demonstrates excellent activity against enterococci (Table 1). MIC do not exceed 4 µg/ml even against vancomycin A and vancomycin B phenotypes of VR enterococci (VRE).

Table 1 Laboratory testing-interpretative breakpoints for linezolid

	Organisms	Susceptible	Intermediate	Resistant
MIC (µg/ml)	Staphylococci	<4	—	—
	Enterococci	<2	4	>8
	Pneumococci	<2	—	—
Zone size (mm)	Staphylococci	>21	—	—
	Enterococci	>23	21–22	<20
	Pneumococci	>21	—	—

Clinical utility

Preclinical investigation using animal models has indicated that linezolid is effective in systemic infection caused by penicillin-resistant *S. pneumoniae* (PRSP), endocarditis caused by methicillin-resistant (MRSA) or VRE, meningitis or otitis media caused by *S. pneumoniae* and soft tissue infection caused by MRSA or VRE.² The clinical and bacteriological success rate for all infections is equivalent to that of vancomycin, though patients treated with linezolid had a slightly shorter hospital stay. Linezolid has been approved for infections caused by VRE, pneumonia caused by Gram-positive bacteria, and skin and soft tissue infections caused by Gram-positive bacteria. Linezolid has also been approved for paediatric use and diabetic foot infections.³

Mechanism of action⁴

A number of marketed antibiotics control bacterial growth through the inhibition of prokaryotic RNA transcription and protein translation. Linezolid acts by inhibiting one of the first steps in the synthesis of bacterial proteins. By binding to the 50S subunit, it inhibits the formation of tertiary initiation complex and prevents translation (Fig. 1). This mechanism of action is unique to this class of agents and cross resistance, as seen with other inhibitors of protein synthesis, does not occur. Rifampicin is a potent inhibitor of bacterial RNA polymerase; macrolides, lincosamides, aminoglycosides, tetracyclines and oxazolidinones have protein translation as their site of action.

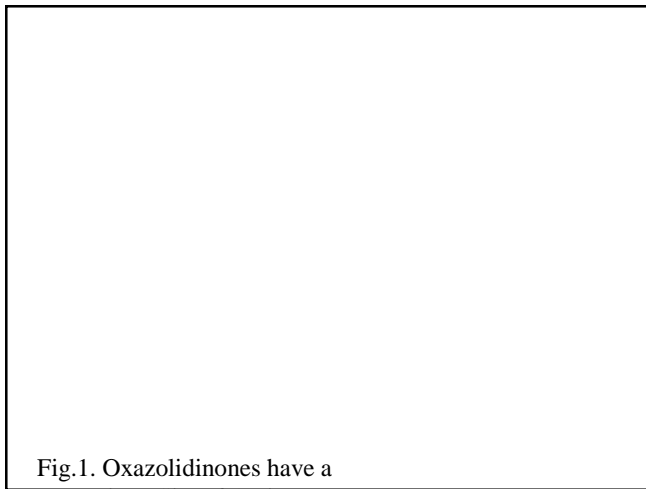


Fig.1. Oxazolidinones have a Unique Site of Action

Dose

The recommended dose of linezolid intravenous (i.v.) or oral (PO) is 600 mg every 12 hours. Linezolid should be administered separately because incompatibility has been observed with a few drugs: amphotericin B, ceftriaxone, cotrimoxazole, erythromycin, chloramphenicol, diazepam, pentamidine and phenytoin.

Adverse effects

In general, linezolid is well tolerated. Adverse side-effects include nausea, diarrhoea, headache, vomiting, oral candidiasis and pain at the infection site. Other serious side-effects are infrequent but may include elevated liver enzymes, atrial fibrillation, increased incidence of renal failure and thrombocytopenia. The last situation is frequent when linezolid is administered for more than 2 weeks. It is recommended that platelet counts be monitored weekly.⁵ Patients treated with linezolid should avoid consuming large quantities of food and beverages with a high tyramine content (e.g. aged cheese, fermented or air-dried meat, soy sauce, red wine).

Following oral administration, linezolid is rapidly and extensively absorbed. It may be administered irrespective of the timing of meals. Its absolute bioavailability is 100% and dosage adjustment is not necessary when switching from i.v. to oral

administration. Linezolid is not a substrate for any of the cytochrome P450 isoenzymes.

Place in therapy

Linezolid, being an oral agent active against all clinically important Gram-positive cocci, is likely to become the drug of choice for skin and soft tissue infections, and community acquired or nosocomial pneumonia. It is envisaged that linezolid therapy would be initiated (with the i.v. formulation) in the hospital, but oral administration would allow for early discharge. It appears appropriate to consider the use of linezolid in units and patients where multidrug-resistant enterococci or staphylococci are either documented or likely to be present, but not in units or patients where most staphylococci remain oxacillin-susceptible and most enterococci remain ampicillin-susceptible.^{4,6}

Ketolides (Telithromycin)

Antimicrobial resistance in community-acquired respiratory infections is an emerging problem. *S. pneumoniae*, major respiratory pathogen, is increasingly becoming resistant to penicillin, macrolides, trimethoprim-sulfamethaxazole (TMP-SMZ), tetracycline, quinolones and chloramphenicol. In the past, macrolides have been very effective in the empirical treatment of community-acquired respiratory infection as they not only provide coverage of the three key bacterial pathogens *S. pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae* but also extended coverage atypical pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* spp.

Of late, the efficacy of macrolides has been compromised with the emergence of resistance in *S. pneumoniae*. Macrolide resistance has two main mechanisms: modification of the target (the ribosome) and modification of antibiotic transport across the cell membrane. High-level resistance of *S. pneumoniae* and other Gram-positive organisms to 14 members of macrolides has been described as MLS_B (macrolide, lincosamide and streptogramin B) resistance. This resistance phenotype is further subdivided into two types: inducible and constitutive. The constitutive resistance (MLS_C) phenotype is highly resistant to all the three classes of antibiotics while the inducible phenotype (MLS_I) exhibits a high level of resistance to erythromycin and similar antibiotics but not to lincosamide and streptogramin. Resistance is mediated by methylation of the adenine residue at position 2058 in the ribosomal RNA (rRNA) resulting in markedly reduced binding of the antibiotic to its target. A family of genes called *erm* is the genetic determinant. The genes *erm A* and *erm C* are most common in *Staph. aureus* whereas *erm B* is the commonest in streptococci.⁷

The second mechanism by which bacteria become resistant to macrolides is efflux. The *mef* gene codes for the efflux pump.

These strains are clindamycin-susceptible, but erythromycin-resistant. They are also known as M phenotype strains.

Mechanism of action

Ketolides work by the inhibition of protein synthesis. They bind to the 23S rRNA subunit of the 50S rRNA of the bacterial ribosomes. Ketolides bind to A 2058 and A 2059 in domain V of 23S rRNA, the same site as erythromycin. In addition, ketolides bind to an additional site in domain II, A752. Ketolides also bind to L4 and L22 proteins in the ribosomes. This results in conformational change in the tunnel through which the nascent peptide passes.

Overall, the enhanced activity of ketolides compared to traditional macrolides is most likely derived from tighter binding of ketolides to the ribosome, additional ribosome binding sites, slow dissociation from the ribosome and rapid drug accumulation.

Spectrum of activity⁸

Similar to the macrolides, the spectrum of activity of telithromycin includes community-acquired respiratory tract pathogens. Owing to structural differences, telithromycin has demonstrated enhanced activity against erythromycin-resistant Gram-positive cocci (Table 2).

Table 2. NCCLS break-points of telithromycin (in µg/ml)

Against streptococci, staphylococci and enterococci		
S	I	R
<1	2	>4
Against <i>Hacmophilus influenzae</i>		
<2	4	>8

S: sensitive; I: intermediate; R: resistant; NCCLS: National Committee for clinical laboratory standards

Gram-negative bacteria : Telithromycin is active against *H. influenzae*, *M. catarrhalis*, *Neisseria gonorrhoeae* and *N. meningitidis*. It has no significant activity against *Enterobacteriaceae*, *Acinetobacter* and *Pseudomonas aeruginosa*.

Anaerobic bacteria : While telithromycin has some activity against the respiratory anaerobes: *Peptostreptococcus*, *Prevotella* and *Actinomyces*, it has modest, if any, activity against, *Clostridium*, *Fusobacterium* or *Bacteroides* spp.

Clinical utility^{9,10}

Ketolides have the potential to address the needs for an antibiotic with potent activity against multidrug resistant *S. pneumoniae* strains as well as to provide coverage against the major pathogens of the respiratory tract encountered in the outpatient setting. The ketolides are thus expected to be useful the treatment of community-acquired respiratory infection when resistant *S. pneumoniae* strains are considered.

Post-antibiotic effect

Similar to other macrolides, telithromycin has demonstrated a post-antibiotic effect (PAE) against most community-acquired pneumonia (CAP) pathogens. The duration of PAE appears to be dependent on the concentration with a rise in PAE seen with high concentrations.

Pharmacokinetic activity

A single oral dose of 800 mg in a healthy volunteer achieved a maximum concentration (C_{max}) of 1.9-2.3 µg/ml at 1 hour (T_{max} [maximum time under the influence of antibiotic]). The t_{1/2} was 7.2-10.6 hour and area under curve (AUC) was 7.3-9.3 µg/hour/ml. A steady-state concentration is usually achieved in 2-3 days. Telithromycin can be taken without regard to food. Telithromycin experiences 33% first-pass metabolism and has a 57% absolute bioavailability. It shows 60%-80% protein binding ability, which is mild and should have minimal clinical significance. Telithromycin achieves high tissue concentration in respiratory fluids, saliva, alveolar macrophages, epithelial lining fluid and bronchial mucosa.

Elimination

Faecal elimination accounts for the majority (75.6%) of the dose of telithromycin, whereas urinary excretion accounts for the remainder (17.4%); only a small fraction is excreted uncharged in the urine and faeces.

Renal impairment

Plasma concentration and (AUC) were 1.4-1.5 times higher in patients with mild (creatinine... clearance 41-80 ml/min) or severe (<40 ml/min) renal impairment. No dosage adjustment is necessary.

Drug interaction

In vitro, telithromycin is a competitive inhibitor of CYP 3A4 and CYP2D6.

CYP 3A4 inhibitors: Co-administration of ketoconazole (a potent inhibitor of 3A4), results in a 100% and 50% increase in AUC and C_{max} of telithromycin, respectively.

CYP 3A4 substrate

Cisapride: Co-administration of telithromycin and cisapride caused a 2.4-2-fold increase in AUC and C_{max} of cisapride. Since cisapride causes increase in the QT interval on ECG, co-administration of these 2 drugs contraindicated.

Simvastatin: An 8-9-fold increase in AUC and 5.3-fold increase in C_{max} of simvastatin seen.

Midazolam: A 2-6-fold increase in AUC of midazolam was observed. Dosage adjustment is required to avoid prolonged sedation.

Dosage

The dosage of telithromycin is 800 mg orally once a day for 7 to 10 days for CAP and for 5 days for other respiratory tract infections. No intravenous formulation is available.

Adverse effects

Gastrointestinal adverse effects are the most commonly observed. The rate varies from 7.5% to 19.9% for diarrhoea and 2.4% to 11.7% for nausea. No *Clostridium difficile*-associated diarrhoea has been reported. Blurred vision (inability to focus) has been reported in young women (<40 year of age). The effect is mild and reversible with a peak incidence occurring within 2 hours of drug intake. The sole laboratory abnormality reported is elevated liver function tests. As with other available macrolides, telithromycin has the potential to lengthen the QT interval.

Place in therapy

When compared with the available macrolides, the main advantage of telithromycin is its activity against macrolide-resistant pneumococci. Its activity is comparable to that of clarithromycin and azithromycin for most other community-acquired pathogens. The primary use of telithromycin should be for those instances in which a resistant pathogen is isolated or highly suspected. An increasing awareness of local resistance pathogens will be necessary to optimize the use of telithromycin.

Gatifloxacin and moxifloxacin

Gatifloxacin (Tequin–Bristol Myers Squibb) and moxifloxacin (Avelox–Bayer) are the newest fluoroquinolone antibacterial agents, increasing the number of approved agents in this class to 10. They exhibit bactericidal action by inhibiting the enzymes DNA gyrase (topoisomerase II) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination. Both the new drugs contain a methoxy-substituent at position 8 of the molecule (Fig. 2), and this is thought to provide enhanced activity and lower selection of resistant mutants of Gram-positive bacteria.

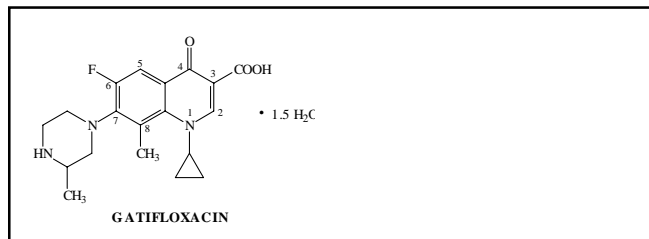


Fig. 2. Structures of gatifloxacin and moxifloxacin

Gatifloxacin Ras 1.5 molecules of H₂O entrapped indicating racemic mixture of R and S enantiomers which are equally active unlike levofloxacin. Gatifloxacin and moxifloxacin are active

against a wide range of Gram-positive and Gram-negative bacteria and also against *C. pneumoniae* and *M. pneumoniae*. They are more active than the early fluoroquinolones (e.g. ciprofloxacin and norfloxacin) and against Gram-positive bacteria such as *S. pneumoniae*. Gram-negative bacteria that are resistant to other fluoroquinolones may be susceptible to these new agents. Both agents have been shown to possess *in vitro* activity against PRSP. However, clinical data with infections caused by PRSP strains is limited and the US Food and Drug administration (FDA) has not approved these agents for this indication (only levofloxacin [Levaquin] has been approved by the FDA for CAP caused by PRSP strains). Gatifloxacin and moxifloxacin are less active against *P. aeruginosa* than agents such as ciprofloxacin, and thus are not indicated for the treatment of infections caused by *P. aeruginosa*.¹¹

Respiratory tract infections are the primary indication for gatifloxacin and moxifloxacin, although gatifloxacin is also indicated for urinary tract infections (UTI), pyelonephritis and gonorrhoea.

An important concern with the use of both gatifloxacin and moxifloxacin is the possibility of their prolonging the QT interval and an associated increased risk of ventricular arrhythmia including torsades de pointes. This has also been a concern with grepafloxacin (Raxar, GSK), which has been withdrawn from the market because of infrequent reports of adverse events of the cardiovascular system (CVS) adverse events.

Like other fluoroquinolones, gatifloxacin and moxifloxacin may cause dizziness, nervousness and central nervous system (CNS) stimulation. It should be used with caution in patients with known or suspected CNS disorders such as epilepsy.

When used in the recommended doses, Phototoxic reactions have not been observed with gatifloxacin and moxifloxacin, but patients should be advised to avoid excessive exposure to sunlight or artificial ultraviolet light on treatment.

Fluoroquinolones, including gatifloxacin or moxifloxacin, have shown erosion of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of several species.

As with other fluoroquinolones, the absorption and activity of gatifloxacin or moxifloxacin may be markedly reduced by metal-containing products. An appropriate interval of time must separate the administration of the two.

The cytochrome P450 system is not involved in the metabolism of gatifloxacin or moxifloxacin, nor is this system induced or inhibited by these new agents.

Moxifloxacin

The mean C_{max} and AUC values at steady state with a daily dosage regimen of 400 mg are:

C_{max}: 4.5 + 0.53 µg/ml

AUC: 48 + 2.7 µg.hr/ml

Time: 1 to 3 hours

t_{1/2}: 12 + 1.3 hours

Steady state is achieved after 3 days with a 400 mg once daily regimen.

Microbiology

Moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative bacteria.

Though moxifloxacin is active (MIC₉₀ < 2 µg/ml) against many Gram-negative facultative and true anaerobes, the significance of this has not been established in adequate and well-controlled clinical trials. The various breakpoints for testing *Enterobacteriaceae*, staphylococci, *H. influenzae*, *H. parainfluenzae*, *S. pneumoniae* and *N. gonorrhoeae* with 5 µg discs, are shown in Tables 3-6.

Table 3. Breakpoints for testing *Enterobacteriaceae* and staphylococci

	Moxifloxacin		Gatifloxacin	
	MIC (µg/ml)	Zone diameter (mm)	MIC (µg/ml)	Zone diameter (mm)
Susceptible	<2	>19	<2	>18
Intermediate	4	16-18	4	15-17
Resistant	>8	<15	>8	<14

Table 4. Breakpoints for testing *H. influenzae* and *H. parainfluenzae*.

	Moxifloxacin		Gatifloxacin	
	MIC (µg/ml)	Zone diameter (mm)	MIC (µg/ml)	Zone diameter (mm)
Susceptible	<1	>18	<0.5	>18

Table 5. Breakpoints for testing *Streptococcus pneumoniae*

	Moxifloxacin		Gatifloxacin	
	MIC (µg/ml)	Zone diameter (mm)	MIC (µg/ml)	Zone diameter (mm)
Susceptible	<1	>18	<1	>18
Intermediate	2	15-17	2	15-17
Resistant	>4	<14	>4	<14

Table 6. Breakpoints for testing *Neisseria gonorrhoeae* with gatifloxacin only

	MIC (µg/ml)	Zone diameter
Susceptible	<0.125	>38
Intermediate	0.25	34-37
Resistant	>0.5	<33

Tequin (Gatifloxacin)

Following oral administration, gatifloxacin is well absorbed and its absorption is not affected by food. Its absolute

bioavailability is 96% and it is not necessary to adjust this dose when switching from i.v. to oral route. It is excreted unchanged via the kidneys. In patients with creatinine clearance <40 mL/minute, an initial dose of 400 mg is given on the first day and the dosage is reduced to 200 mg once a day on subsequent days. Gatifloxacin is available as 200 mg and 400 mg tablets. The i.v. formulation includes a single use vials containing a concentrated solution of 200 mg (10 mg/ml, 20 ml) and 400 mg (10 mg/ml, 40 ml) of gatifloxacin in 5% dextrose injection over a period of 60 minutes. It should not be administered by rapid or bolus i.v. infusion. The single use vials must be further diluted to a concentration of 2 mg/ml with a compatible solution (e.g. 5% dextrose, 0.9% sodium chloride) prior to administration. Additives or other medication should not be added to the gatifloxacin solution or infused simultaneously through the same i.v. line. The dosing of gatifloxacin for various indications are shown in Table 7.

Table 7. Food and Drug Administration (USA)-approved dosage regimens for gatifloxacin

Indications of gatifloxacin	Daily dose (mg)	Duration
ABECB	400	7-10 days
Acute sinusitis	400	10 days
community-acquired pneumoiae (CAP)	400	7-14 days
Uncomplicated urinary tract infection (UTI) Single dose	400	3
	or 200	
Complicated UTI	400	7-10 days
Acute pyelonephritis	400	7-10 days
Gonorrhoea	400	Single dose

The pharmacokinetics of Gatifloxacin are linear and depend on doses ranging from 200 to 800 mg administered over a period of up to 14 days. Steady-state concentrations are achieved by the 3rd day. A comparison of *in vitro* activity¹² of the four quinolones is shown in Table 8.

Table 8. Comparison of pharmacokinetic/Pharmacodynamic parameters for four fluoroquinolones and selected targets.

Fluoroquinolone	Dose (mg)	C _{max}	AUC	<i>Streptococcus pneumoniae</i>			<i>Pseudomonas aeruginosa</i>		
				MIC µg/ml	C _{max} /MIC	AUC/MIC	MIC µg/ml	C _{max} /MIC	AUC/MIC
Cipro	500	3	28	2	1.5	14	4	0.75	7
	750	3.6	32	2	1.8	16	4	0.9	8
Levo	500	5.7	48	1	5.7	48	16	0.36	3
Moxi	400	4.5	48	0.25	18	192	8	0.56	6
Gati	400	4.2	34	0.5	8.4	68	8	0.52	4.25

Place in therapy

In the guidelines of CAP and acute maxillary sinusitis, moxifloxacin, gatifloxacin and levofloxacin are either first-line or alternative treatment options. Gatifloxacin and moxifloxacin should not be used to treat *Pseudomonas* infection.

Mutant prevention concentration

Mutant prevention concentration (MPC)^{12,13} is a novel concept

that has been employed in the evaluation of antibiotics' ability to minimize or limit the development of resistant organisms. MPC has been defined as the MIC of the least susceptible single-step mutant. By definition, cell growth in the presence of antibiotic concentrations greater than MPC requires an organism to have developed two or more resistant causing spontaneous chromosomal point mutation.

Table 9 : Mutant prevention concentration (MPC).

Fluoroquinolone	Daily dose	C _{max}	<i>Pseudomonas</i>	<i>Streptococcus aeruginosa</i>
			MPC	MPC
Ciprofloxacin	500 bid	3	2	NR
	750 bid	3.6	2	NR
Levofloxacin	500 bid	5.7	8	8
Moxifloxacin	400 bid	4.5	NR	2
Gatifloxacin	400 bid	4.2	NR	4

A strategy for restricting the development of resistance is to find compounds that have narrow mutant selective windows (MPC/MIC=1) (Table 9).

Although the AUC/MIC and C_{max}/MIC ratios are useful for predicting the potential for developing drug resistance, it is suggested that the AUC/MIC should exceed 100 for Gram-positive and gram-negative species to prevent selection of resistant strains. Alternatively, Zhao *et al.* have suggested that rate at which resistance develops to a fluoroquinolone is related to its MIC and MPC.¹³

Moxifloxacin exceeds the MPC for *S. pneumoniae* and ciprofloxacin exceeds the MPC for *P. aeruginosa* (both 2 µg/ml) by achieving a C_{max} of 4.5 µg/ml and 3 µg/ml, respectively.

Evidence is emerging that suggests a link between appropriate fluoroquinolone use, development of resistance against the entire fluoroquinolone class and clinical failure. The major factors associated with increasing resistance to fluoroquinolone include:

- Under-dosing, i.e. use of a marginally potent agent whose-MIC is largely reached in the serum or infected tissue
- Overuse of agents known to encourage resistant mutants

- Inability to readily detect and respond to changes in antimicrobial susceptibility.

Ciprofloxacin, levofloxacin and gatifloxacin achieve a high concentration in urine, thus, they are appropriate choices for treating UTI in the community.

For infections in which *S. pneumoniae* is anticipated to be the most likely pathogen (CAP), moxifloxacin, which currently has the best anti-pneumococcal pharmacodynamic activity and the lowest MPC against this agent, would represent a prudent therapeutic choice.

Expecting a single fluoroquinolone to be suitable for all infections is unreasonable and excessive use of any single fluoroquinolone for all indications will lead to resistance that adversely affect the entire class.¹⁴

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Literature Review

Compiled by Dr. Pradeep Chatterjee

Antimicrobial treatment in Diabetic women with Asymptomatic Bacteriuria. Godfrey K, Harding MD, Nicoble MD *et al* (*N. Eng J. Med.* 2002;**347**:1576–83)

Asymptomatic bacteriuria is common among women with diabetes, and the treatment of such infections has been recommended to prevent complications related to symptomatic urinary tract infection. Thus the study in women (>16 years of age) with diabetes, bacteriuria (>10 colony-forming units of an organism per milliliter in cultures of two consecutive urine specimens) were enrolled with no urinary symptoms. 50 were randomly assigned to receive placebo and 55 to receive antimicrobial therapy. For the first six weeks which included the initial course of treatment, the study was placebo-controlled and double blind. Subsequently, the women were screened for bacteriuria every three months for up to three years, antimicrobial therapy was provided to women in the antimicrobial therapy group who had asymptomatic bacteriuria.

Four weeks after the end of the initial course of therapy 78% of placebo

recipients had bacteriuria, as compared with 20% of women who received antimicrobial agents (p<0.001). During a mean follow up of 27 months, 20 of 50 women in the placebo group (40%) and 23 of 55 women in the antimicrobial therapy group (42%) had at least one episode of symptomatic urinary tract infection. The time to a first symptomatic episode was similar in the placebo group and the antimicrobial therapy group. P=0.67 by the long rank test), as were the (ISD) rates of any symptomatic urinary tract infection (1.10+0.17) and 0.93+0.14 per 1000 days of follow up respectively; relative risk, 1.19; 95% confidence interval 0.28 to 1.81). Pyelonephritis (0.28+0.08) and 0.13±0.05 per 1000 days of follow up; relative risk, 1.93; 95% confidence interval 0.47 to 7.89). The women in the antimicrobial therapy group had almost five times as many days of antibiotic use for urinary tract infection as did the women in placebo group. (158.2+1.7 yrs 33.7+0.91/1000 days of follow up.

Treatment of asymptomatic bacteriuria in women with diabetes does not appear to reduce complications. Diabetes itself should not be an indication for screening for or treatment of asymptomatic bacteriuria.