

The role of fluoroquinolones in the treatment of Tuberculosis

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SUMMARY. The need for new, more effective antituberculous drugs is pressing. The treatment of active disease needs to be shortened and simplified, the treatment given for latent tuberculosis (TB) also needs to be shortened and, most importantly, improved therapy for multi-drug resistant TB (MDR-TB) is needed. The fluoroquinolones are the first novel drugs since the rifamycins found to exert significant activity against *M. tuberculosis*. They are currently being used for the prophylactic treatment of individuals who have been exposed to MDR-TB, for the treatment of MDR-TB, for empirical treatment of TB in areas with high rates of MDR-TB and for patients who present severe adverse reactions to the conventional antituberculous regime. Conversely, their use is not recommended as a first-line drug for the routine treatment of TB. Fluoroquinolones are relatively safe antimicrobial compounds that bind to bacterial topoisomerases, resulting in cell death. They show strong bactericidal activity both in vitro and in vivo, and some, such as moxifloxacin, also exert sterilizing activity. Resistance to fluoroquinolones, associated with their previous use, is a significant issue. The emergence of resistance is far more likely when ciprofloxacin is included in the regime. In the case of community-acquired pneumonia the decision to administer a fluoroquinolone should be made with caution and the possibility of pulmonary TB should be considered. The appropriate use of fluoroquinolones both in the treatment of TB and for community-acquired pneumonia is of critical importance, since the emergence of resistance is becoming a significant problem. *Pneumon 2008; 21(4):395-401*

INTRODUCTION

Tuberculosis (TB) is a major public health issue world wide. One-third of the world's population has been infected with *Mycobacterium tuberculosis* and 2 million deaths are attributed to tuberculosis each year^{1,2}. In Greece, 10 cases per 100,000 inhabitants are reported every year, although the real

number may be twice as high³. The TB epidemic is fueled by the growing incidence of HIV infection and migration, and there appears to be an increase in multidrug-resistant TB (MDR-TB). MDR-TB is defined as TB resistant to at least isoniazid and rifampin, and extensively drug-resistant TB (XDR-TB) as disease caused by MDR strains that are also resistant to at least one fluoroquinolone and one or more injectable agents^{1,2,4}. It is estimated that in 2004 half a million new MDR-TB cases were diagnosed world wide⁴. In these cases cure is rarely achieved in more than 85% of patients initiating therapy, even when all antituberculous agents are available⁴. Although TB treatment is successful in 98% of cases in the developed world, 5-20% of MDR-TB patients and 66% of MDR-TB and HIV co-infected patients die during treatment⁴.

The currently recommended treatment for active pulmonary TB is lengthy and cumbersome and associated with severe adverse effects. It consists of 4 drugs (isoniazid, rifampin, pyrazinamide and ethambutol) given for the first 2 months, followed by 2 drugs (isoniazid and rifampin) administered for 4 additional months⁵. The initial phase duration of 2 months applies so long as the *M. tuberculosis* is proved to be susceptible, but it should be lengthened if susceptibility test results are not available. In the initial phase, combination treatment is given with the aim of killing the Mycobacteria in the exponential-phase growth and to prevent emergence of drug resistance. Isoniazid in adequate concentrations is the main bactericidal drug. During the continuation phase the target is to kill non-replicating, persistent *M. tuberculosis*. Drugs with strong bactericidal activity, such as isoniazid, are necessary for the initial phase, whereas those with sterilizing activity are most effective during the continuation phase^{6,7}. One additional difficulty with the currently available TB regime is the potential for drug interactions, primarily those between rifampin and the antiretroviral drugs used for the treatment of AIDS¹.

The treatment of MDR-TB includes relatively less effective, poorly tolerated and more expensive drugs that need to be administered for 18-24 months¹. Equally inadequate is the treatment of latent TB infection, which consists of isoniazid given for 6-9 months, for which the major problems are compliance and liver toxicity¹.

Despite these problems, the development of new drugs has been almost nonexistent since the introduction of rifampin in 1970⁸, and the need for new, more effective drugs that can achieve multiple goals in improving TB control is therefore urgent. The treatment of active disease needs to be shortened and simplified and the interac-

tions of TB regimens with other drugs to be minimized. Treatment of latent TB also needs to be shortened. Most importantly, improved therapy for MDR-TB and XDR-TB is absolutely necessary^{1,4}.

Of the new compounds being tested for their efficacy in TB treatment, the fluoroquinolones are the first novel drugs since the development of rifamycins to have been shown to have significant activity against *M. tuberculosis*⁹. Fluoroquinolones are fluorine-containing derivatives of older quinolones, such as nalidixic acid. As they have a broad-spectrum antimicrobial activity, they have been widely used for the treatment of bacterial infections of the respiratory, gastrointestinal and urinary tracts for the last 30 years². Fluoroquinolones are the only antibiotics that directly inhibit DNA synthesis. They target bacterial topoisomerases II and IV, enzymes which control DNA topology^{2,10}. Different fluoroquinolones appear to favour different enzyme; ciprofloxacin binds preferentially to topoisomerase IV, whereas moxifloxacin has a predilection for topoisomerase II. Fluoroquinolone binding to topoisomerases leads to bacterial death by mechanisms that have not been fully elucidated, although strand-breakage, autolysis, and blockade of replication by the topoisomerase-fluoroquinolone complex have all been proposed^{2,11}. Fluoroquinolones have been shown to penetrate into macrophages where they also exert bactericidal activity².

IN VITRO ACTIVITY

The newer fluoroquinolones sparfloxacin, gatifloxacin and moxifloxacin have lower minimum inhibitory concentrations (MIC) for *M. tuberculosis* than the older levofloxacin, ciprofloxacin and ofloxacin² (Table 1). Of all the fluoroquinolones tested against rifampin-tolerant *M. tuberculosis*, gatifloxacin and moxifloxacin exert the greatest bactericidal activity². When combined with various first-line antituberculous drugs, these compounds have been shown to cause greater reduction in colony forming units (CFU) of intramacrophage *M. tuberculosis* than the other drugs alone². The in vitro activity of the various fluoroquinolones on *M. tuberculosis* is ranked in the order: lomefloxacin < ciprofloxacin < or = ofloxacin < sparfloxacin < moxifloxacin = gatifloxacin¹². Gatifloxacin and moxifloxacin showed low MIC for both ofloxacin resistant and ofloxacin susceptible strains, although some cross resistances was observed¹². Moxifloxacin appears to exert both bactericidal and sterilizing activity, maintained

TABLE 1. Minimum inhibitory concentration (MIC) of fluoroquinolones against *Mycobacterium tuberculosis*².

Fluoroquinolone	MIC ($\mu\text{g/mL}$)
Ciprofloxacin	0.5-4
Ofloxacin	1-2
Levofloxacin	1
Sparfloxacin	0.2-0.5
Gatifloxacin	0.2-0.25
Moxifloxacin	0.12-0.5

against persistent *M. tuberculosis* tolerant to high rifampin concentrations⁶. It has been shown that the number of viable counts for 100-day cultures of *M. tuberculosis* exposed to various concentrations of ciprofloxacin is significantly higher than that of those exposed to other fluoroquinolones, such as moxifloxacin and gatifloxacin; in other words, ciprofloxacin has a significantly lower bactericidal activity than the other fluoroquinolones⁶.

IN VIVO ACTIVITY

The in vivo activity of fluoroquinolones is concentration-dependent. One in vivo comparison found that gatifloxacin, moxifloxacin and isoniazid had similar activity against *M. tuberculosis*. According to several studies in mice, moxifloxacin is the most strongly bactericidal (possibly more than isoniazid) followed, in order of decreasing activity, by sparfloxacin, levofloxacin and ofloxacin. Moxifloxacin also appears to exert a degree of sterilizing activity that may enable achievement of the goals of a shortened therapy regime and improved treatment of latent TB². In a mouse model the combination of rifampin, pyrazinamide, and moxifloxacin showed sterilizing activity that exceeded substantially not only that of the standard regime but also that of the standard regime with the addition of moxifloxacin¹³. Moxifloxacin has been dem-

onstrated to be able to kill mycobacteria in the absence of ongoing protein synthesis, which might explain its efficacy against *M. tuberculosis* in a dormant state¹⁴.

The ratios of two pharmacokinetic parameters, the peak serum concentration (C_{max}) and the 24-hour area-under-the-curve (AUC_{24}), to the MIC are generally accepted as pharmacodynamic correlates of fluoroquinolone efficacy. The greatest bactericidal effect with a decreased probability of resistance to fluoroquinolones against various bacterial pathogens occurs at $C_{\text{max}}/\text{MIC}$ ratios of >8-10 and $\text{AUC}_{24}/\text{MIC}$ ratios of >100-125. It is evident that moxifloxacin at the recommended daily dose of 400mg would be the most active fluoroquinolone against tuberculosis, while ciprofloxacin is the least effective² (Table 2).

ACTIVITY AND SAFETY IN HUMANS

It has been shown in humans that fluoroquinolones are absorbed readily after oral administration and achieve effective tissue penetration and distribution into the lungs and alveolar macrophages (Table 2)². The early bactericidal activity, i.e. the log fall in the CFU count in sputum during the first 48 hours of therapy, of ciprofloxacin and ofloxacin is lower than that of isoniazid. Apparently this is not the case with moxifloxacin, since two studies have demonstrated that its early bactericidal activity is superior to that of rifampin and perhaps comparable to that of isoniazid^{2,15,16}.

Severe adverse effects of fluoroquinolones include tendonitis, photosensitivity, seizures, and QT interval prolongation. Gastrointestinal and central nervous system reactions, hepatitis, renal dysfunction and hypoglycaemia have also been reported. Fluoroquinolones are restricted for use in children due to the possibility of mutagenesis and cartilage abnormalities, and they are not recommended during pregnancy, except as second-line therapy

TABLE 2. Pharmacokinetic and pharmacodynamic parameters of fluoroquinolones².

Fluoroquinolone	C_{max} ($\mu\text{g/mL}/70\text{kg}$)	AUC_{24} ($\mu\text{g}^*\text{h/mL}/70\text{Kg}$)	$C_{\text{max}}/\text{MIC}$	$\text{AUC}_{24}/\text{MIC}$
Ciprofloxacin (250 mg)	1,5	5.75	1-2	10-20
Ofloxacin (400mg)	4	48	2	24
Levofloxacin (500mg)	6.21	44.8	5-7	40-50
Sparfloxacin (400mg)	1.18	33	2	40
Gatifloxacin (400mg)	3.42	30	8.4	68
Moxifloxacin (400mg)	4.34	39.3	9	96

C_{max} : maximum concentration in serum, AUC: area under curve, MIC: minimum inhibitory concentration.

for MDR-TB in that setting².

Drug interactions between fluoroquinolones and other antituberculous drugs are infrequent, although a recent study has shown potentially serious interactions affecting gatifloxacin and rifampin concentrations. When these drugs are administered together gatifloxacin levels increase and rifampin levels decrease¹⁷. Fluoroquinolone absorption may be reduced when co-administered with antacids. Older fluoroquinolones have an excellent safety record in long-term therapy, as has also been suggested for moxifloxacin².

CLINICAL TRIALS

Clinical trials on the use of fluoroquinolones in the treatment of TB have focused on shortening the first-line therapy regime and on improvement of MDR-TB treatment. In a clinical trial in India, which evaluated the possibility of treatment shortening, patients with TB were assigned to four treatment groups all of which received ofloxacin. As no standard therapy group was included in the study, the interpretation of the results was limited. However, the rate of sputum conversion at 2 months ranged from 92 to 98%, which is superior to that achieved by the classical regime. Even more impressive was the very low relapse rate. Patients who received daily isoniazid, rifampin, pyrazinamide, and ofloxacin for 3 months, followed by twice-weekly isoniazid and rifampin for 1 or 2 months, experienced a 2-4% relapse rate in the first 2 years after the completion of treatment. No increased incidence of adverse reactions was observed¹⁸.

Several clinical trials have been reported in the literature concerning the role of fluoroquinolones in the treatment of TB¹⁹⁻²². According to a recent meta-analysis of 11 randomized controlled trials comprising a total of 1,514 patients, no statistically significant difference was observed in relation to cure, treatment failure and clinical or radiological improvement when first-line drugs were replaced by a fluoroquinolone (ciprofloxacin, ofloxacin or moxifloxacin). The substitution of ciprofloxacin into first-line regimes was associated with a higher incidence of relapse and longer time to sputum conversion^{19,23}. Addition of levofloxacin to the classic regime had no effect. Based on these findings, there is currently no justification for the substitution of a fluoroquinolone for first-line drugs or the addition of a fluoroquinolone to the standard regime¹⁹.

It is evident that new, well planned clinical trials are needed to assess the role of fluoroquinolones in the treatment of TB. Gatifloxacin and moxifloxacin are being studied in phase II and/or III trials on the shortening of treatment duration for active, drug-susceptible pulmonary TB. These compounds are being examined more closely than any other drug in the treatment of TB and are being tested in combination regimes in which they replace ethambutol or isoniazid¹. In a completed phase II study the sputum of patients who received gatifloxacin or moxifloxacin instead of ethambutol cleared more quickly than that of patients receiving conventional therapy or a regime that included ofloxacin, although the overall rate of sputum conversion at 2 months was not improved²¹. These results were confirmed by another study with moxifloxacin²². The ability of gatifloxacin or moxifloxacin to substitute ethambutol, or to shorten the duration of treatment to 4 months is now being tested in phase III trials¹. It has been shown that substitution of moxifloxacin for isoniazid shortens the duration of therapy much more effectively than does substitution of moxifloxacin for ethambutol¹³. Moreover the combination of moxifloxacin and isoniazid is not antagonistic and there is even a suggestion that moxifloxacin might increase the activity of isoniazid²⁰.

Concerning MDR-TB, in a retrospective study improvement of the cure rate (75% vs 56%) and reduction of the mortality rate (12% vs 22%) were observed in the period 1984-1998 in comparison with the period 1973-1983. This improvement was attributed to the implementation of surgical methods and the use of fluoroquinolones in the treatment of MDR-TB, especially in older patients²⁴. Fluoroquinolone use was associated with significant improvement in survival²⁴. In a comparative study between ofloxacin and its active S(-) enantiomer, levofloxacin, the latter was found to be more efficacious than the former when incorporated into MDR-TB regimes²⁵. It is evident that the role of fluoroquinolones is much better established in MDR-TB than for susceptible TB. According to the ATS/CDC guidelines of 2003⁵ fluoroquinolones should be used for:

- Prophylactic treatment of individuals who have been exposed to MDR-TB
- Treatment of MDR-TB
- Empirical treatment of TB in areas with high rates of MDR-TB, and
- Patients receiving the conventional regime who present severe adverse reactions^{2,19}.

FLUOROQUINOLONE RESISTANCE

As mentioned above, fluoroquinolones target bacterial topoisomerases II and IV. Unlike most other bacterial species, *M. tuberculosis* includes only topoisomerase II and lacks topoisomerase IV. Moxifloxacin has a predilection for topoisomerase II, which may explain, at least in part, the stronger bactericidal activity of moxifloxacin compared with ciprofloxacin, which binds preferentially to topoisomerase IV^{2,26}. Topoisomerase II or gyrase is a tetramer that consists of two A and two B subunits which include areas of interaction with the fluoroquinolones. These areas are encoded by the DNA regions QRDR. Mutations within the QRDR have been identified that are associated with fluoroquinolone resistance. The most common mutation is a substitution at codon 94 of the subunit A gene. Many mutations have been reported and it appears that different substitutions cause different levels of resistance². Resistance level appears to be related to the number of mutations since single mutations are associated with low-level fluoroquinolone resistance whereas bacteria with high-level resistance generally have two mutations^{2,27}. Thus, high-level resistance to fluoroquinolones appears to be generated in a stepwise process of additive mutations^{2,11}. Mutations in the same area have also been associated with hypersusceptibility to fluoroquinolones²⁷.

It is apparent that *M. tuberculosis* resistance to fluoroquinolones occurs primarily due to mutations in the QRDR of gyrase A gene. However such mutations are not found in all patients with fluoroquinolone resistance. In fact only 42-85% of resistant *M. tuberculosis* isolates have mutations in gyrase A QRDR and to date, no isolates have been associated with gyrase B QRDR mutations. Other mechanisms that may account for fluoroquinolone resistance include mutations in areas other than QRDR, decreased cell wall permeability to the drug, drug inactivation, or an active drug efflux pump^{2,28}.

When *M. tuberculosis* is sequentially challenged with increasing concentrations of fluoroquinolones, stepwise resistance occurs and these mutations appear to map the gyrase gene. However, eventually a concentration is reached at which no mutant is recovered. The term "mutant prevention concentration" (MPC) has been proposed as a new measure of antibiotic activity that is indicative of the drug concentration above which resistant colonies are no longer recoverable when over 10^{10} cell are plated². Of the first-line antituberculosis agents, none achieves human C_{max} levels that exceed the MPC, in contrast to

moxifloxacin and gatifloxacin. According to MPC, ciprofloxacin is the least active fluoroquinolone with a very low AUC/MPC ratio (Table 3)²⁹, which is clinically significant as the emergence of resistance is far more likely when ciprofloxacin is included in the regimen rather than the other fluoroquinolones.

As fluoroquinolone susceptibility is not assessed routinely, the prevalence of fluoroquinolone resistance in *M. tuberculosis* is unknown, but several recent studies are concerned with the emergence of resistant clinical isolates^{2,30,31}. The significance of *M. tuberculosis* resistance to fluoroquinolones is underlined by the fact that ciprofloxacin failure does not appear to be due to poor bactericidal activity but to rapid emergence of resistance at the doses used clinically³². In the Philippines, ciprofloxacin resistance increased from 13.3% in 1989 to 1994 to 51.4% in 1995 to 2000, mainly because ciprofloxacin was often the only effective drug in the regimen used for the treatment of MDR-TB³³. Emergence of fluoroquinolone resistance in MDR *M. tuberculosis* strains is possible, and decisions concerning the treatment regime in these cases should be made with caution^{2,31,33}. Concerning moxifloxacin, the currently recommended dose of 400mg is likely to suppress the emergence of resistance in 60% of patients, whereas a much higher percentage (86-93%) would achieve this goal with 600-800mg/day. Whether these doses are well tolerated remains to be seen⁷.

While there have been no reports of cross-resistance between fluoroquinolones and other classes of antituberculous agents, cross-resistance is observed within the fluoroquinolone class. Fluoroquinolone resistance is primarily seen as a result of in vivo selection of a fluoroquinolone-resistant mutant subpopulation, and therefore emergence of resistance is associated with their previous use. The time needed for acquisition of resistance

TABLE 3. Area under the curve (AUC)/mutant prevention concentration (MPC) ratio of fluoroquinolones against *Mycobacterium tuberculosis*²⁹.

Fluoroquinolone	AUC _{tot} /MPC ₅₀	AUC _{tot} /MPC ₉₀
Ciprofloxacin	6-38.5	2.4-15.4
Levofloxacin	74.7	29.9
Gatifloxacin	75	30
Moxifloxacin	98.2	32.7

AUC_{tot}: total area under the curve, MPC₅₀: mutant prevention concentration when 50% of the strains were considered, MPC₉₀: mutant prevention concentration when 90% of the strains were considered.

varies, but it has been suggested the resistant strains can develop after courses of treatment shorter than 2 weeks^{2,34}. Because of this, the decision to administer a fluoroquinolone for community-acquired pneumonia when there is a possibility of TB is critical. Recent studies have demonstrated that initial empirical therapy with a fluoroquinolone in presumed bacterial pneumonia which was finally diagnosed as TB was associated with delay in the diagnosis and a worse outcome of the TB^{35,36}. After empirical use of fluoroquinolones (mainly ciprofloxacin) for 1-3 weeks, 11% of *M. tuberculosis* isolates became resistant³⁵. In areas with high TB incidence, therefore, when fluoroquinolones are to be used, pulmonary TB should be considered and careful microbiological evaluation for *M. tuberculosis* should be performed³⁷.

CONCLUSIONS

Fluoroquinolones are a new and important alternative drug category for the treatment of TB. In order for them to be used appropriately the following points should be kept in mind:

- Currently fluoroquinolones are used as antituberculous agents in MDR-TB and, to a lesser extent, in the case of severe adverse reactions to the conventional antituberculous regime.
- In the majority of cases of TB the current conventional treatment regime is successful. Fluoroquinolones are not included at present in the first-line treatment of TB, although that might change in the future, in order to shorten treatment duration.
- The newer fluoroquinolones moxifloxacin and gatifloxacin have been shown to exert better activity and are associated with a lower probability of emergence of resistance.
- Ciprofloxacin should not be included in the treatment of TB because emergence of resistance is probable, due to pharmacokinetic and pharmacodynamic parameters.
- The appropriate use of fluoroquinolones in the treatment of TB and for community-acquired pneumonia is of critical significance, since with uncontrolled use the emergence of resistance might render this important group of antimicrobial compounds useless.

REFERENCES

1. Spigelman MK. New tuberculosis therapeutics: a growing pipeline. *J Infect Dis* 2007; 196:S28-34.

2. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. *Lancet Infect Dis* 2003; 3:432-42.
3. Κέντρο Ελέγχου και Πρόληψης Νοσημάτων, Γραφείο Φυματίωσης. Οδηγίες για την αντιμετώπιση της Φυματίωσης. Αθήνα 2006.
4. Mitnick CD, Castro GC, Harrington M, Sacks LV, Burman W. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. *PLOS medicine* 2007;4:1730-34.
5. American Thoracic Society/Centers for Disease Control and prevention/Infectious Diseases Society of America. Treatment of Tuberculosis. *Am J Resp Crit Care Med* 2003;167:603-62.
6. Hu Y, Coates ARM, Mitchison DA. Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2003; 47:653-57.
7. Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modeling. *J Infect Dis* 2004; 190:1642-51.
8. Seaworth BJ. Multidrug-resistant tuberculosis. *Infect Dis Clin North Am* 2002; 16:73-105.
9. Iseman MD. Tuberculosis therapy: (past), present and future. *Eur Respir J* 2002; 36:S87-94.
10. Chen CR, Malik M, Snyder M, Drlica K. DNA Gyrase and Topoisomerase IV on the bacterial Chromosome: Quinolone-induced DNA Cleavage. *J Mol Biol* 1996; 258:627-37.
11. Zhao X, Xu C, Domagala J, Drlica K. DNA topoisomerase targets of the fluoroquinolones: A strategy for avoiding bacterial resistance. *Rpoc Natl Acad Sci USA* 1997; 94:13991-96.
12. Sulochana S, Rahman F, Paramasivan CN. In vitro activity of fluoroquinolones against *Mycobacterium tuberculosis*. *J Chemother* 2005; 17:169-73.
13. Nuernberger EL, Yoshimatsu T, Tyagi S, et al. Moxifloxacin-containing regimens of reduced duration produce a stable cure in murine tuberculosis. *Am J Respir Crit Care Med* 2004; 170:1131-4.
14. Malik M, Drlica K. Moxifloxacin Lethality against *Mycobacterium tuberculosis* in the Presence and Absence of Chloramphenicol. *Antimicrob Agent Chemother* 2006; 50:2842-44.
15. Gosling RD, Uiso LO, Sam NE, et al. The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 2003; 168:1342-5.
16. Pletz MW, Deroux A, Roth A, Neumann KH, Mauch H, Lode H. Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. *Antimicrob Agents Chemother* 2004; 48:780-2.
17. McIlleron H, Norman J, Kanyok TP, Fourie PB, Horton J, Smith PJ. Elevated gatifloxacin and reduced rifampicin concentrations in a single-dose interaction study amongst healthy volunteers. *J Antimicrob Chemother* 2007; 60: 1398-401.
18. Tuberculosis Research Centre (Indian Council of Medical Research), Chennai. Shortening short course chemotherapy. A randomised clinical trial for treatment of smear positive pulmonary tuberculosis with regimens using ofloxacin in the

- intensive phase. *Int J Tub* 2002; 49: 27–38.
19. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD004795. DOI: 10.1002/14651858.CD004795.pub3.
 20. Gillespie SH, Gosling RD, Uiso L, Sam NE, Kanduma EG, McHugh TD. Early bactericidal activity of a moxifloxacin and isoniazid combination in smear-positive pulmonary tuberculosis. *J Antimicrob Chemother* 2005; 56: 1169–71.
 21. Lienhardt C, Rustomjee R, Allen J, et al. Comparison of 2-months sterilizing activities of several quinolone-containing regimens: preliminary results of a phase II trial in South Africa [abstract LB2-13]. In: Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). Washington DC: American Society for Microbiology, 2005:205.
 22. Burman WJ, Johnson J, Goldberg S, et al. Moxifloxacin vs. Ethambutol in multidrug treatment of pulmonary tuberculosis—final results of a randomized double-blind trial [abstract LB-31]. In: Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington, DC). Washington, DC: American Society for Microbiology, 2005:203.
 23. Moadebi S, Harder CK, Fitzgerald MJ, Elwood KR, Marra F. Fluoroquinolones for the treatment of pulmonary tuberculosis. *Drugs* 2007; 67:2077-99.
 24. Chan ED, Laurel V, Strand MJ, Chan JF, Huynh MLN, Goble M, Iseman MD. Treatment and Outcome Analysis of 205 Patients with Multidrug-resistant Tuberculosis. *Am J Respir Crit Care Med* 2004; 169:1103–9.
 25. Yew WW, Chan CK, Leung CC, et al. Comparative Roles of Levofloxacin and Ofloxacin in the Treatment of Multidrug-Resistant Tuberculosis. *CHEST* 2003; 124:1476–81.
 26. Matrat S, Veziris N, Mayer C, et al. Functional Analysis of DNA Gyrase Mutant Enzymes Carrying Mutations at Position 88 in the A Subunit Found in Clinical Strains of *Mycobacterium tuberculosis* Resistant to Fluoroquinolones. *Antimicrob Agents Chemother* 2006; 50:4170-73.
 27. Aubry A, Veziris N, Cambau E, Truffot-Pernot C, Jarlier V, Fisher M. Novel Gyrase Mutations in Quinolone-Resistant and –Hyposusceptible Clinical Isolates of *Mycobacterium tuberculosis*: Functional Analysis of Mutant Enzymes. *Antimicrob Agents Chemother* 2006; 50:104-12.
 28. Pasca MR, Gugliera P, Aresi F, Bellinzoni M, De Rossi A, Riccardi G. Rv2686c-Rv2687c-Rv2688c, an ABC Fluoroquinolone Efflux Pump in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2004; 48:3175-78.
 29. Rodriguez JC, Cebrian L, Lopez M, Ruiz M, Jimenez I, Royo G. Mutant prevention concentration: comparison of fluoroquinolones and linezolid with *Mycobacterium tuberculosis*. *J Antimicrob Chemother* 2004; 53:441-44.
 30. Shi R, Zhang J, Li C, Kazumi Y, Sugawara I. Emergence of Ofloxacin Resistance in *Mycobacterium tuberculosis* Clinical Isolates from China as Determined by *gyrA* Mutation Analysis Using Denaturing High-Pressure Liquid Chromatography and DNA Sequencing. *J Clin Microb* 2006; 44:4566-68.
 31. Huang TS, Kunin CM, Lee SSJ, Chen YS, Tu HZ, Liu YC. Trends in fluoroquinolone resistance of *Mycobacterium tuberculosis* complex in a Taiwanese medical centre: 1995–2003. *J Antimicrob Chemother* 2005; 56: 1058-62.
 32. Gumbo T, Louie A, Deziel MR, Drusano GL. Pharmacodynamic Evidence that Ciprofloxacin Failure against Tuberculosis Is Not Due to Poor Microbial Kill but to Rapid Emergence of Resistance. *Antimicrob Agents Chemother* 2005; 49: 3178-81.
 33. Grimaldo ER, Tupasi TE, Rivera AB, et al. Increased resistance to ciprofloxacin and ofloxacin in multidrug-resistant *Mycobacterium tuberculosis* isolates from patients seen at a tertiary hospital in the Philippines. *Int J Tuberc Lung Dis* 2001; 5:546-50.
 34. Ginsburg AS, Woolwine SC, Hooper N. The rapid development of fluoroquinolone resistance in M tuberculosis. *N Engl J Med* 2003; 349:1977–8.
 35. Wang JY, Hsueh PR, Jan IS, Liaw YS, Yang PC, Luh KT. Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas. *Thorax* 2006; 61:903-8.
 36. Dooley KE, Golub J, Goes FS, Merz WG, Sterling TR. Empirical treatment of community-acquired pneumonia with fluoroquinolones and delays in the treatment of tuberculosis. *Clin Infect Dis* 2002; 34:1607-12.
 37. Hsueh PR. Should fluoroquinolones be first-line antibiotics in the treatment of community-acquired pneumonia in areas with high incidence of tuberculosis? *J Microbiol Immunol Infect* 2007; 40:386-7.