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EDITORIAL COMMENTARY

Fluoroquinolones for Treatment of Community-Acquired Pneumonia and Tuberculosis: Putting the Risk of Resistance into Perspective

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(See the article by Long et al. on pages 1354–60)

Community-acquired pneumonia (CAP) is a common and important disease that occurs in all age groups worldwide. *Streptococcus pneumoniae* is the most common cause of CAP and is the pathogen associated with the greatest morbidity and mortality [1]. High-level penicillin-resistant and drug-resistant *S. pneumoniae* infections are now a global problem; thus, the number of therapeutic options for the empirical treatment of CAP is limited. The fluoroquinolones for treatment of respiratory diseases, including gatifloxacin, moxifloxacin, and levofloxacin, have an excellent spectrum, providing coverage for the most important respiratory pathogens, including drug-resistant *S. pneumoniae* and atypical pathogens. The rate of fluoroquinolone-resistant pneumococcus infection is <3% in most countries [2–4]. As a result, the fluoroquinolones for treatment of respiratory diseases have been recommended and are increasingly being used as preferred or alternative therapy for the treatment of CAP [1, 5].

Given that an estimated one-third of the world's population is infected with *Mycobacterium tuberculosis* and ~1.6 million deaths worldwide in 2006 were attributable to tuberculosis (TB), TB remains a major public health concern. Fluoroquinolones have excellent in vitro activity against *M. tuberculosis*. They are one of the most important drug classes for the treatment of multidrug-resistant TB and of patients who experience severe adverse effects of first-line anti-TB therapy [6, 7]. Furthermore, fluoroquinolone-containing regimens are likely to be proved to be effective for shortening the treatment duration for drug-susceptible disease [6].

Depending on the prevalence of TB in a specific region, a percentage of patients with CAP who are empirically treated with a fluoroquinolone will actually have pulmonary TB with or without infection due to a copathogen. In a study of CAP in adult patients in Asian countries, Song et al. [8] found that the etiology was *M. tuberculosis* in 3.3% of cases. There's the rub. Monotherapy with a fluoroquinolone may temporarily improve the patient's symptoms and, therefore, delay diagnosis [9–12] and/or may select for fluoroquinolone-resistant *M. tuberculosis* strains. In this issue of *Clinical Infectious Diseases,* Long et al. [13] put the threat of the emergence of fluoroquinolone resistance into perspective. With access to 2 large provincial TB registries with linkages to corresponding prescription drug plans, the authors found that, although outpatient fluoroquinolone use (ostensibly for CAP) was not uncommon among patients with pulmonary TB, fluoroquinolone-resistant *M. tuberculosis* was identified infrequently; only 3 of 74 patients who had been treated with a fluoroquinolone prior to the diagnosis of pulmonary TB were infected with a fluoroquinolone-resistant strain. All 3 patients had received >1 fluoroquinolone prescription during the 3 months before the diagnosis of TB. Ginsburg et al. [14, 15] performed a retrospective cohort study that involved patients with newly diagnosed, culture-confirmed TB. Fifty-five patients were included in the study, 19 of whom had previous fluoroquinolone exposure and 36 of whom did not. Two of the 19 patients, both of whom had AIDS, had isolates of *M. tuberculosis* that demonstrated decreased fluoroquinolone susceptibility, compared with 0 of 36 patients who did not have previous fluoroquinolone exposure. Both patients had AIDS, and 1 of these patients, who has been described previously elsewhere [12], had received >1 course of fluoroquinolone therapy. Huang et al. [16] performed a

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study to determine the frequency of the emergence of fluoroquinolone-resistant strains in Taiwan and to assess whether such resistance might be attributable to use of fluoroquinolones for treatment of patients with multidrug-resistant TB or to the increased use of fluoroquinolones in the community. The authors found an increase in the rates of resistance to ciprofloxacin, ofloxacin, and levofloxacin only in the group of patients with mulitdrug-resistant TB, which suggests that fluoroquinolone resistance was likely the result of treatment of patients with multidrug-resistant TB rather than of use in the general community. In a study performed in Taiwan by Wang et al. [17], a total of 420 clinical isolates of *M. tuberculosis* from 420 patients (2004–2005) had rates of susceptibility to levofloxacin and moxifloxacin of 98.6%, and 97.6%, respectively, with an overall resistance rate of 3.3% to any fluoroquinolone tested. The authors found that 45 patients had previous fluoroquinolone exposure for >1 week and that 63 patients had previous fluoroquinolone exposure for ⩽1 week. However, neither the previous exposure to fluoroquinolones nor the duration of fluoroquinolone exposure was correlated with the fluoroquinolone resistance of *M. tuberculosis* isolates. First-line anti-TB drug resistance and prior anti-TB treatment were significantly associated with fluoroquinolone resistance of *M. tuberculosis* isolates.

Although the rates are low, are they likely to increase in the future with the increasing use of the fluoroquinolones for the empirical treatment of CAP and other infections treated with fluoroquinolones in the community [18]? Not necessarily, if the right fluoroquinolones are used at the right dosage and for the right duration.

Fluoroquinolones exert their effects by trapping a DNA-drug-enzyme complex and specifically inhibiting ATP-dependent enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. In *M. tuberculosis,* there is only 1 target, DNA gyrase, because topoisomerase IV is absent. DNA gyrase consists of 2 components encoded by the *gyrA* and *gyrB* genes. Most mutations conferring changes in drug susceptibility occur in a quinolone-resistant–determining region in *gyrA* and, more rarely, in *gyrB.* Reduced susceptibility can also occur as a result of changes in drug efflux [19]. However, these 2 mechanisms only account for ~50% of the resistance described in clinical isolates [14]. Alterations in DNA gyrase that result in reduced susceptibility occur through selection of spontaneously preexisting mutants in the quinolone-resistant–determining region. The wild-type bacillary population in the lung of an infected patient is $>1 \times 10^8$. Preexisting mutants with reduced susceptibility to the fluoroquinolones are present at a predictable frequency of 1×10^{-6}–1×10^{-8}. The usual approach for prevention of the emergence of these preexisting mutants is to use combination therapy. This is effective because of the rule of independence of mutation; each drug is active on preexisting mutants that are resistant to other drugs [20]. Another approach proposed by Drlica and Zhao [21] is to administer the drug at doses that produce blood concentrations that continuously exceed the resistance level of all spontaneous mutants and, thereby, prevent the selective amplification of any mutant population. The greater the activity of the agent, the less likely they will select for mutants that have reduced susceptibility [22]. The newer fluoroquinolones, including moxifloxacin, levofloxacin, and gatifloxacin, have better in vitro and bactericidal activity and more favorable pharmacokinetic properties, compared with the older fluoroquinolones, ciprofloxacin and ofloxacin [22–26]. The duration of exposure of the *M. tuberculosis* infecting organisms to the fluoroquinolone may also be a risk factor for the development of resistance. During the past decade, results from clinical trials have supported a reduction in the duration of therapy with the newer fluoroquinolones for CAP to 5 days [1]. Although most of the information regarding the time to emergence of resistance to therapy has been for older, less-active agents, the information available suggests that resistance is unlikely to emerge with a short duration of therapy with an active agent [14].

At the end of the day, the most important strategy to reduce the risk of a mistaken diagnosis of CAP in a patient with pulmonary TB is to always consider the "great mimicker" as a possible cause and, when suspected, to perform the relevant diagnostic tests before prescribing fluoroquinolones [27].

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References

1. 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):S27–72.
2. Davies TA, Yee YC, Goldschmidt R, et al. Decline in the prevalence of pandemic clones Spain23F-1 and Spain9V-3 among US fluoroquinolone-resistant *Streptococcus pneumoniae* TRUST Surveillance isolates since 2001. Postgrad Med **2008**; 120:39–45.
3. Low DE. Fluoroquinolone-resistant pneumococci: maybe resistance isn't futile? Clin Infect Dis **2005**; 40:236–8.
4. Song JH, Ko KS, Lee MY, et al. In vitro activities of ertapenem against drug-resistant *Streptococcus pneumoniae* and other respiratory pathogens from 12 Asian countries. Diagn Microbiol Infect Dis **2006**; 56:445–50.
5. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J **2005**; 26:1138–80.
6. Spigelman MK. New tuberculosis therapeutics: a growing pipeline. J Infect Dis **2007**; 196(Suppl 1):S28–34.
7. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med **2003**; 167: 603–62.
8. Song JH, Oh WS, Kang CI, et al. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. Int J Antimicrob Agents **2008**; 31:107–14.
9. Yoon YS, Lee HJ, Yoon HI, et al. Impact of fluoroquinolones on the diagnosis of pul-

monary tuberculosis initially treated as bacterial pneumonia. Int J Tuberc Lung Dis **2005**; 9:1215–9.
10. Wang JY, Hsueh PR, Jan IS, et al. 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.
11. Dooley KE, Golub J, Goes FS, et al. Empiric treatment of community-acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis. Clin Infect Dis **2002**; 34:1607–12.
12. Ginsburg AS, Woolwine SC, Hooper N, et al. The rapid development of fluoroquinolone resistance in *M. tuberculosis.* N Engl J Med **2003**; 349:1977–8.
13. Long R, Chong H, Hoeppner V, et al. Empirical treatment of community-acquired pneumonia and the development of fluoroquinolone-resistant tuberculosis. Clin Infect Dis **2009**; 48:1354–60 (in this issue).
14. Ginsburg AS, Hooper N, Parrish N, et al. Fluoroquinolone resistance in patients with newly diagnosed tuberculosis. Clin Infect Dis **2003**; 37:1448–52.
15. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. Lancet Infect Dis **2003**; 3:432–42.
16. Huang TS, Kunin CM, Shin-Jung LS, et al. Trends in fluoroquinolone resistance of *Mycobacterium tuberculosis* complex in a Taiwanese medical centre: 1995–2003. J Antimicrob Chemother **2005**; 56:1058–62.
17. Wang JY, Lee LN, Lai HC, et al. Fluoroquinolone resistance in *Mycobacterium tuberculosis* isolates: associated genetic mutations and relationship to antimicrobial exposure. J Antimicrob Chemother **2007**; 59:860–5.
18. Gaba PD, Haley C, Griffin MR, et al. Increasing outpatient fluoroquinolone exposure before tuberculosis diagnosis and impact on culture-negative disease. Arch Intern Med **2007**; 167:2317–22.
19. Escribano I, Rodriguez JC, Llorca B, et al. Importance of the efflux pump systems in the resistance of *Mycobacterium tuberculosis* to fluoroquinolones and linezolid. Chemotherapy **2007**; 53:397–401.
20. Iseman MD. Evolution of drug-resistant tuberculosis: a tale of two species. Proc Natl Acad Sci U S A **1994**; 91:2428–9.
21. Drlica K, Zhao X. Mutant selection window hypothesis updated. Clin Infect Dis **2007**; 44: 681–8.
22. Almeida D, Nuermberger E, Tyagi S, et al. In vivo validation of the mutant selection window hypothesis with moxifloxacin in a murine model of tuberculosis. Antimicrob Agents Chemother **2007**; 51:4261–6.
23. Levofloxacin. Tuberculosis **2008**; 88:119–21.
24. Moxifloxacin. Tuberculosis **2008**; 88:127–31.
25. Johnson JL, Hadad DJ, Boom WH, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis **2006**; 10:605–12.
26. Ji B, Lounis N, Maslo C, et al. In vitro and in vivo activities of moxifloxacin and clinafloxacin against *Mycobacterium tuberculosis.* Antimicrob Agents Chemother **1998**; 42:2066–9.
27. 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.