

Should fluoroquinolones be first-line antibiotics in the treatment of community-acquired pneumonia in areas with high incidence of tuberculosis?

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The current Taiwanese guidelines on antimicrobial therapy of pneumonia in adults by the Infectious Diseases Society of Taiwan recommended that newer fluoroquinolones (FQs) [moxifloxacin and levofloxacin] can be the drug of choice in the treatment of community-acquired pneumonia (CAP), but emphasize that “when newer FQs are used, pulmonary TB should be considered and aggressive microbiological evaluation for *Mycobacterium tuberculosis* should be performed” [1]. Recent guidelines established by the Infectious Diseases Society of America and the American Thoracic Society advocate the use of newer FQs (moxifloxacin, levofloxacin, or gemifloxacin) as empirical therapy for patients with CAP [2]. Interestingly, Singh [3] indicated that this implementation in endemic areas would increase the potential for masking active tuberculosis (TB) and emergence of an epidemic of extensively drug-resistant *M. tuberculosis* (XDRTB). On this basis, Singh advocated that the newer FQs should not be used as first-line antibiotics for the treatment of CAP in areas of TB endemicity, such as in India where TB accounts for 7% of CAP [3].

In Taiwan, the annual incidence of TB has remained persistently high, ranging from 62.7 per 100,000 population in 2000 to 70.0 per 100,000 population in 2006, according to the Centers for Disease Control in Taiwan [4]. During this period, the annual prevalence of combined multidrug-resistant *M. tuberculosis* (MDRTB) at the National Taiwan University Hospital (NTUH) was

3.0% in 2000, 7.7% in 2004, and 3.3% in 2006 (data from annual reports of NTUH). Because of the potent in vitro and in vivo activity of FQs, as well as their excellent safety profiles in long-term therapy, FQs continue to be used for the treatment of TB primarily in cases involving resistance or intolerance to first-line antituberculous drugs and are also candidates for use as new first-line drugs in Taiwan [5]. Furthermore, FQ susceptibility should be routinely assessed for clinical isolates of *M. tuberculosis*, especially for multidrug-resistant *Mycobacterium* isolates, and when patients have a prior history of TB or prior use of antituberculous drugs.

Data from Taiwan suggest the need for further study of the applicability of these consensus criteria on FQ use in endemic areas. Studies have shown that the empirical use of FQs in pulmonary TB patients who initially present with a clinical picture of CAP is associated with temporary improvement in pulmonary and systemic symptoms and signs [6,7]. Unfortunately, these effects also led to delayed diagnosis and prolonged infectivity, greater morbidity and mortality, and ultimately increased the risk of spread of *M. tuberculosis* in the community [6,7]. A recent analysis of 520 TB patients in Taiwan found that 14.4% had received FQs prior to diagnosis. This empiric FQ therapy was associated with a mean delay of 34 days before initiating antituberculous treatment, more frequent coexistence of underlying disease and hypoalbuminemia, and a poor outcome. Interestingly, a subsequent isolate from one of the 9 patients who had paired isolates of *M. tuberculosis* for evaluation developed ofloxacin resistance (by the modified proportional method, no minimal inhibitory concentration data were provided) within 1 week of FQ treatment [7].

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There is a paucity of clinical evidence to support the emergence of FQ resistance among *M. tuberculosis*, particularly in the multidrug-resistant strains, MDRTB and potentially XDRTB, due to prior use of FQs for treatment of CAP or other clinical infections in areas with TB endemicity. A recent study in Taiwan by Wang et al, including 420 clinical isolates of *M. tuberculosis* from 420 patients (2004-2005), demonstrated susceptibility rates to ofloxacin, ciprofloxacin, levofloxacin, and moxifloxacin of 98.3%, 98.6%, 98.6%, and 97.6%, respectively, with an overall resistance rate of 3.3% to any FQ tested [8]. They found that 45 patients had previous FQ exposure >1 week and 63 patients had previous FQ exposure ≤1 week. However, neither the previous exposure to FQs (4.6%) nor the duration of FQ exposure (≤1 week, 4.8%; >1 week, 4.4%) was correlated with the FQ resistance of *M. tuberculosis* isolates. First-line anti-TB drug resistance (8.5% vs 2.3%), especially multidrug resistance (19% vs 2.5%), and prior antituberculous treatment (7.9% vs 2.5%) were significantly associated with FQ resistance of *M. tuberculosis* isolates [8]. Huang et al also suggested that FQ resistance among *M. tuberculosis* strains was the result of treatment of patients with MDRTB strains rather than the use of the drugs in the community [9].

More studies are needed to elucidate the relationship between prior FQ use and subsequent emergence of FQ resistance in *M. tuberculosis*. Gemifloxacin, a newer FQ with poor activity against *M. tuberculosis* compared with levofloxacin and moxifloxacin, might be a promising FQ to solve this problem [10]. However, further clinical study is required to support its beneficial role in unmasking TB diagnosis and treatment when it is widely used for empirical treatment of CAP.

FQs could be the alternative agents for the treatment of CAP in adults in Taiwan but “pulmonary TB should be always considered and aggressive microbiological evaluation for *M. tuberculosis* should be performed” prior to prescribing FQs for patients with CAP.

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