Editorial

How Are We Creating Fluoroquinolone-resistant Tuberculosis?

Fluoroquinolones display excellent antimicrobial and clinical activity against *Mycobacterium tuberculosis*. Their high oral bioavailability, generally good tolerability, and low-to-moderate cost have earned them a place in second-line antituberculosis regimens for patients who are intolerant of first-line drugs or for treating drug-resistant disease (1, 2). Several recent studies in humans have suggested a potential role for fluoroquinolones in the initial treatment phase of drug-susceptible tuberculosis (TB) (3–5). At the same time, however, fluoroquinolone-resistant TB is being widely recognized in the world, and its incidence appears to be increasing (6). Fluoroquinolone resistance is one of the major defining characteristics of extensively drug-resistant TB and is generally associated with a poor outcome in patients (7).

One rather important mechanism for the development of fluoroquinolone-resistant TB is the suboptimal use of second-line drug regimens, especially in the presence of a poorly functioning program in the treatment of multidrug-resistant TB (8–10). Indeed, such a phenomenon is a harbinger of extensively drug-resistant TB.

Fluoroquinolones enjoy a unique position among anti-TB drugs in that they are also the most widely prescribed class of antibiotics in the world today. Their broad spectrum of antibacterial activities and convenient dosing, in combination with those features listed above, make them frequent choices for treating a variety of infections caused by susceptible organisms and for empiric therapy of common infections, such as pneumonia or sinusitis, where a causative organism has not been identified. Herein lies a potentially serious problem: administration of a fluoroquinolone as a single agent to a patient with a suspected bacterial infection who really has unsuspected TB can induce bacillary resistance to the entire class of drugs. Because the patient may feel better with initiation of this treatment, there may be a delay in the diagnosis of TB, promoting the spread of TB within the community (11).

Fluoroquinolone resistance has been described with recurrent courses of treatment (12) but not after brief courses administered in inpatient settings close to the time of TB diagnosis (9). In their case-control study of a cohort of Tennessee Medicaid outpatients published in this issue of the *Journal* (pp. 365–370), Devasia and colleagues (13) refine our understanding of this phenomenon by showing that fluoroquinolone-resistant TB was most closely associated with prolonged or recurrent use of these antibiotics for infections where TB initially was not suspected. This practice apparently is widespread because in a subset of Medicaid patients enrolled more than 300 days before TB diagnosis, of those for whom determination of outpatient fluoroquinolone exposure was most complete, 37% had received a fluoroquinolone. Resistance to fluoroquinolones in *M. tuberculosis* was substantially higher among persons who received more than 10 days of fluoroquinolones, particularly if this occurred more than 60 days before the TB diagnosis. Although Devasia and coworkers did not speculate on the underlying reasons, it is plausible that these findings are related to the organism taking advantage of time-course issues in masking TB while selection of drug-resistant mycobacterial mutants occurs.

Few providers today knowingly will prescribe a single agent for the treatment of active TB. However, they are often guided by published expert recommendations, including clinical guidelines, which also may be used to inform institutional treatment protocols. As an example, the 2007 Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines for the management of community-acquired pneumonia recommends empiric therapy with a fluoroquinolone as a first-line selection in several clinical situations, including those involving comorbidities such as "renal disease, diabetes mellitus, alcoholism, malignancies" or "immunosuppressed conditions" (14). These also are conditions that may increase one's risk for developing active TB. Although the statement indicates the need to perform specific diagnostic testing in situations where TB risks may exist, the recommendation for using fluoroquinolones is not qualified; that is, the statement does not indicate when it may be inappropriate to use these drugs. In some settings, such as emergency departments or outpatient clinics, pressure to initiate antibiotics early may drive the clinician to start such therapy without rigorously considering the specific diagnosis that would make a fluoroquinolone an inappropriate treatment choice.

It may be possible to minimize the induction of bacillary resistance to fluoroquinolones by using higher doses of fluoroquinolones with better activity against *M. tuberculosis* in empiric antiinfective regimens (15, 16), but concerns of safety and tolerance, and of cost, make this possibility rather unlikely. For now, we all need to be more careful when considering the use of these drugs in the community setting and limit the use of prolonged or repeated courses of fluoroquinolones, or even avoid them altogether, in patients who are at risk of having active TB.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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DOI: 10.1164/rccm.200906-0863ED