Empiric Treatment of Community-Acquired Pneumonia with Fluoroquinolones, and Delays in the Treatment of Tuberculosis


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Fluoroquinolones, which are widely used to treat community-acquired pneumonia, also have excellent in vitro activity against *Mycobacterium tuberculosis*. A retrospective cohort study was conducted among adults with culture-confirmed tuberculosis to assess the effect of empiric fluoroquinolone therapy on delays in the treatment of tuberculosis. Sixteen (48%) of 33 patients received fluoroquinolones for presumed bacterial pneumonia before tuberculosis was diagnosed and treated. There were no differences between the group who did and the group who did not receive fluoroquinolones, except that patients who received fluoroquinolones were more likely to present with shortness of breath. Among patients treated empirically with fluoroquinolones, the median time between presentation to the hospital and initiation of antituberculosis treatment was 21 days (interquartile range, 5–32 days); among those who were not, it was 5 days (interquartile range, 1–16 days; \( P = .04 \)). Initial empiric therapy with a fluoroquinolone was associated with a delay in the initiation of appropriate antituberculosis treatment.

Fluoroquinolones have broad-spectrum antimicrobial activity against pulmonary pathogens and are therefore recommended as first-line therapy for the treatment of community-acquired pneumonia in adults [1, 2]. This class of antibiotics is used extensively for this indication. A study of prescriptions written for outpatient treatment of community-acquired pneumonia in the United States from November 2000 through January 2001 found that, of the nearly 1 million prescriptions for the 5 antibiotics routinely used for this indication (i.e., amoxicillin-clavulanic acid, azithromycin, clarithromycin, gatifloxacin, and levofloxacin), fluoroquinolones accounted for 43% [3]. Fluoroquinolones are also widely used in developing countries [4].

In contrast to the other antibiotics used to treat community-acquired pneumonia, the fluoroquinolones have excellent in vitro activity against *Mycobacterium tuberculosis* [5–7]. Ciprofloxacin has good activity in vivo in the first 2–7 days of treatment, although its activity is slightly less than that of isoniazid [8, 9]. We hypothesized that a relatively short (≤2-week) course of such potent monotherapy could delay the diagnosis of tuberculosis without curing the disease. Delays in the diagnosis and treatment of tuberculosis are associated with increased morbidity and mortality, as well as continued transmission of *M. tuberculosis* [10, 11]. To our knowledge, the effect of empiric fluoroquinolone therapy on possible delays in the initiation of anti-tuberculosis therapy has not been assessed previously.

**PATIENTS AND METHODS**

**Patient population.** At the Johns Hopkins Hospital (Baltimore, MD), fluoroquinolones have been recom
mended for use as first-line therapy for inpatient and outpatient community-acquired pneumonia in adults since January 1998. We reviewed the Johns Hopkins Hospital microbiology laboratory log of all cases of culture-confirmed tuberculosis diagnosed from January 1998 through April 2001. Inpatient and outpatient medical records from all adult patients (age, ≥18 years) were then reviewed; all persons with newly diagnosed tuberculosis were included in the study. Patients were excluded from the study if they did not have respiratory symptoms at clinical presentation or if information regarding antibiotic use was not available. Restriction fragment–length polymorphism (RFLP) analysis (also known as “DNA fingerprinting”) of M. tuberculosis isolates has been performed for all culture-confirmed cases of tuberculosis in Maryland since 1996. The study was approved by the Johns Hopkins Hospital Joint Committee on Clinical Investigation.

Definitions. Respiratory symptoms were defined as ≥1 of the following: cough, shortness of breath, and pleuritic chest pain, with or without fever. Improvement of symptoms was defined as improvement of ≥1 of the following: cough, shortness of breath or need for oxygenation, pleuritic chest pain, and fever. Patients were considered to have pulmonary tuberculosis if cultures of specimens of sputum, bronchoalveolar lavage fluid, or pulmonary parenchyma (obtained via transbronchial biopsy) were positive for M. tuberculosis. Extrapulmonary tuberculosis sites were defined as those sites outside the pulmonary parenchyma, including the pleura and pleural fluid. The date of onset of tuberculosis was defined as the date of presentation to the hospital system (as an inpatient or an outpatient). Standard tuberculosis treatment included isoniazid, rifampin, pyrazinamide, and ethambutol. The time between presentation to the hospital system and initiation of standard tuberculosis treatment was assessed.

Laboratory techniques. Mycobacterial cultures were performed with BACTEC (Becton-Dickinson) 12B liquid culture medium and Löwenstein-Jensen agar medium. For RFLP analysis, M. tuberculosis isolates were cultivated on Löwenstein-Jensen medium, harvested, and heat killed. Genomic DNA was isolated, and RFLP analysis was performed according to a standardized method [12], with use of a 245-bp, right-sided probe (IS6110) and BioImage Whole Band Analyzer software, version 3.0 (Genomic Solutions).

Statistical analysis. Continuous variables were compared with use of Student’s t test for normally distributed data and the Mann-Whitney U test for nonparametric distributions. Categorical variables were compared with use of the χ² and Fisher’s exact tests. The statistical package Stata, version 6 (Stata), was used for all analyses. All P values were 2 sided; P < .05 was considered significant.

RESULTS

During the study, we assessed 54 adults with newly diagnosed, culture-confirmed tuberculosis. Of these, 16 did not have respiratory symptoms on presentation, and 5 did not have information available regarding antibiotic use before diagnosis. Thus, 33 patients were included in the study. The demographic characteristics of these patients are summarized in table 1.

Of the 33 patients, 16 (48%) received fluoroquinolones for presumed bacterial pneumonia before the diagnosis and treatment of tuberculosis; fluoroquinolone therapy was initiated within the first 2 days of presentation for all patients. Of the 16 patients who received fluoroquinolones, 11 were treated with levofloxacin, 1 with gatifloxacin, 2 with trovafloxacin, 1 with ciprofloxacin, and 1 with ciprofloxacin followed by trovafloxacin. Of the 17 patients who did not receive fluoroquinolones, 3 were treated with cephalosporins, 2 with a macrolide (clarithromycin or azithromycin), 1 with a cephalosporin and a macrolide, 1 with trimethoprim-sulfamethoxazole, and 7 with antituberculosis therapy; 3 patients received no antibiotics.

Specimens were obtained and sent for performance of an acid-fast bacilli (AFB) smear and culture a median of 2 days after presentation for the 16 patients who received fluoroquinolones, compared with 1 day after presentation for the 17 who did not. The result of the initial AFB smear was positive for 5 (31%) of 16 patients who received fluoroquinolones, compared with 8 (47%) of 17 patients who did not (P = .36). Of the 16 patients treated with empiric fluoroquinolones, 10 (63%) were discharged from the hospital before a diagnosis of tuberculosis was made. Of the 17 patients who did not receive fluoroquinolones, 5 (29%) were discharged before the diagnosis of tuberculosis was established (P = .06).

Of the 16 patients who received empiric fluoroquinolone therapy, 12 received fluoroquinolone monotherapy, and 10 (83%) of those 12 experienced improvement of symptoms; improvement occurred, on average, in 3 days. One of these 12 patients had concomitant Streptococcus pneumoniae bacteremia;

Table 1. Demographic characteristics of 33 patients with tuberculosis, according to whether they received empiric fluoroquinolone therapy for presumed bacterial pneumonia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoroquinolone therapy received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 16)</td>
</tr>
<tr>
<td>Age, median</td>
<td>50 (16)</td>
</tr>
<tr>
<td>Male sex</td>
<td>69 (16)</td>
</tr>
<tr>
<td>Black race</td>
<td>63 (16)</td>
</tr>
<tr>
<td>HIV seropositive</td>
<td>42 (12)</td>
</tr>
</tbody>
</table>

NOTE. Data are % of patients (no. with data available) or years (no. of patients with data available).
none of the other patients had cultures that grew pathogenic organisms other than \(M.\) \(tuberculosis\).

The median time between presentation to the hospital and initiation of antituberculosis treatment was 21 days (interquartile range, 5–32 days) among patients treated with empiric fluoroquinolones and 5 days (interquartile range, 1–16 days) among those who were not \((P = .04)\). We then evaluated the possible differences in clinical presentation that could account for why some patients received fluoroquinolones and others did not. There was no difference between the 2 groups in the proportion of patients who presented with cough, hemoptysis, fever, night sweats, or weight loss (table 2). There was also no difference in chest radiographic findings, median age, sex, and HIV infection status. However, shortness of breath was significantly more common among patients who received fluoroquinolones (present in 88% of such patients) than among those who did not (present in 47%; \(P = .02)\). Reliable data on duration of symptoms before presentation were not available for most patients. Because AFM smear status could influence whether empiric fluoroquinolone therapy was administered, we then performed a stratified analysis according to smear status. Among AFM smear-negative individuals, the median time between presentation to the hospital and initiation of antituberculosis treatment was 24 days for patients empirically treated with fluoroquinolones and 16 days for patients who were not \((P = .22)\); corresponding data for AFM smear-positive individuals were 9 days and 1 day, respectively \((P = .09)\).

To evaluate possible delays in the laboratory diagnosis of tuberculosis, we assessed the interval from the time a specimen was obtained to the time \(M.\) \(tuberculosis\) growth was observed in culture. The median time from sputum collection to observation of growth in culture was 15 days for persons who had received empiric fluoroquinolone therapy before a specimen was submitted for mycobacterial culture and 12 days for persons who had not \((P = .11)\).

The following cases demonstrate delays in the diagnosis and treatment of tuberculosis associated with treatment of presumed community-acquired pneumonia with fluoroquinolones, as well as the clinical consequences of such delays.

**Patient A.** A 22-year-old man with AIDS (CD4\(^+\) lymphocyte count, 22 cells/mL; HIV type 1–RNA level, 60,000 copies/mL) presented with a 17-day history of pleuritic chest pain and 3-day history of productive cough, fevers, chills, night sweats, and diarrhea. A chest radiograph revealed right paratracheal lymphadenopathy and right lower-lobe atelectasis with a small pleural effusion—all of which were new findings, as determined by comparison with a radiograph obtained 3 months earlier. An induced sputum sample was negative for bacteria and *Pneumocystis carinii*. Specimens for AFM smear and culture were ordered but not sent for performance of the tests. The patient was treated with a 7-day course of levofloxacin for presumed community-acquired pneumonia, and his symptoms resolved. A tuberculin skin test was performed, but the result was not read.

Three months later, the patient presented with a 6-week history of malaise and a 1-week history of fevers, nonproductive cough, shortness of breath, and delirium. He also reported a weight loss of 13.5 kg (30 pounds) during the previous 6 months. A chest radiograph demonstrated bilateral miliary infiltrates with right lower-lobe consolidation. Standard antituberculosis treatment was started. Cultures of sputum and CSF specimens subsequently grew *M. tuberculosis*. The patient’s neurologic status continued to decline, however, and he died 3 months later.

Two weeks after the patient’s death, his HIV-seronegative mother presented with new-onset ascites and a 3-week history of nonproductive cough, fevers, dyspnea on exertion, and night sweats. A chest radiograph and a CT scan revealed a large right pleural effusion without pulmonary parenchymal involvement. A CT scan of the abdomen demonstrated moderate ascites and enlarged, irregularly shaped ovaries. Laparotomy revealed diffuse miliary seeding of the peritoneal surfaces. Pathologic specimens of the right pelvic sidewall and fallopian tube revealed caseating granulomata that stained positive for AFM; cultures of these specimens grew *M. tuberculosis*. DNA fingerprinting of the *M. tuberculosis* isolates from both patients revealed an identical 11-band pattern.

**Patient B.** An 85-year-old man with a history of diabetes

### Table 2. Clinical characteristics of 33 patients with tuberculosis, according to whether they received empiric fluoroquinolone therapy for presumed bacterial pneumonia.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoroquinolone therapy received</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 16)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>88 (16)</td>
</tr>
<tr>
<td>Symptom at presentation</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>100 (15)</td>
</tr>
<tr>
<td>Fever</td>
<td>81 (16)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>44 (9)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>82 (11)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>88 (16)</td>
</tr>
<tr>
<td>Chest radiograph finding at presentation</td>
<td></td>
</tr>
<tr>
<td>Infiltrate</td>
<td>63 (16)</td>
</tr>
<tr>
<td>Cavity</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>38 (16)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are % of patients (no. with data available).
mellitus and dementia was admitted to the hospital after an episode of syncope associated with hypoglycemia. He also reported a 2-week history of fever and cough productive of brown sputum. Oxygen saturation level, as determined by pulse oximetry, was 94% with 2 L of oxygen. A chest radiograph revealed bilateral lower-lung infiltrates. A 10-day course of gatifloxacin was initiated for presumed community-acquired pneumonia. The patient’s hypoxia resolved within 24 h, and the productive cough improved soon thereafter. Sputum culture was negative for bacteria.

A CT scan of the chest revealed a nodular left lower-lobe infiltrate. A sputum sample was then obtained and sent for mycobacterial culture; the specimen was smear-negative for AFB. The patient was discharged home to complete his course of gatifloxacin. Twelve days later, *M. tuberculosis* was isolated from the sputum AFB culture. Standard antituberculosis treatment was then initiated, 21 days after the patient had initially presented.

**Patient C.** A 69-year-old woman with long-term immunosuppression because of liver transplantation as well as a history of ulcerative colitis, primary sclerosing cholangitis, hepatitis C virus infection, and chronic renal insufficiency presented to her primary-care physician with a 1-month history of progressive shortness of breath and cough productive of yellow sputum. She had immigrated to the United States from Iran 12 years earlier and was PPD negative before liver transplantation, which had been performed 9 years before presentation. A physical examination revealed that she was afebrile. A chest radiograph revealed minimally increased lung markings but no infiltrate, nor did it show any changes compared with a chest radiograph obtained 10 months earlier. A 14-day course of levofoxacin was initiated, and the cough and shortness of breath improved.

Five weeks later, the patient returned to the clinic with recurrent shortness of breath, wheezing, low-grade fever, productive cough, and weight loss. A chest radiograph revealed a right middle-lobe infiltrate. The patient was treated with a 14-day course of levofoxacin, and her symptoms improved.

Six months later, the patient was admitted to the hospital with a several-week history of fever, chills, and shortness of breath. A chest radiograph revealed subtle, possibly nodular lung markings in the lower lobes bilaterally. The patients was treated with intravenous levofoxacin, and the fever resolved. She was discharged home receiving continued azithromycin therapy.

Four months later (i.e., 11 months after her initial presentation), the patient developed hemoptysis. A CT scan of the chest that revealed a right hilar mass with partial right middle-lobe collapse; reticulonodular infiltrates in the right upper, middle, and lower lobes; and nodular densities in the left lung base. The patient was admitted to the hospital for performance of diagnostic fiber-optic bronchoscopy and discharged shortly thereafter without initiation of any antibiotic therapy. Culture of a specimen of bronchoalveolar lavage fluid grew *M. tuberculosis* after 8 days. The patient could not be contacted, and she missed her follow-up clinic appointment. One week later, she presented to the emergency department, reporting decreased appetite, diarrhea, nausea, and fever. A chest radiograph revealed diffuse bilateral interstitial infiltrates consistent with miliary tuberculosis. Standard antituberculosis treatment was then initiated, 12 months after her initial presentation.

**DISCUSSION**

It is striking that almost one-half of the patients in this study—all of whom presented with respiratory symptoms and subsequently received a diagnosis of culture-confirmed tuberculosis—were treated with fluoroquinolones before the diagnosis of tuberculosis was established. Although this is consistent with national patterns of treatment for community-acquired pneumonia in the United States [3], such widespread use of fluoroquinolone monotherapy among persons subsequently found to have active tuberculosis is of concern. The incidence rate of tuberculosis in the United States is relatively low; the effect of widespread fluoroquinolone use could be much greater in areas where tuberculosis is endemic [13]. A recent study, although its findings were not specific to fluoroquinolones or tuberculosis, demonstrated that receipt of antibiotics can delay hospital admission and mask the correct diagnoses in patients with infectious diseases [14]. In one recent case report, treatment with a fluoroquinolone may have been associated with a delay in the diagnosis of tuberculosis [15]. However, this association has not been assessed in a cohort of tuberculosis patients.

Importantly, in our study, the receipt of empiric fluoroquinolone therapy was associated with a delay in the initiation of appropriate antituberculosis therapy, relative to the time to initiation of antituberculosis therapy among persons who did not receive fluoroquinolones. Even after stratifying by AFB smear status, fluoroquinolone use was associated with a delay in the initiation of antituberculosis therapy, although these differences were not statistically significant because of the small sample size. The clinical course of patient A demonstrates the clinical consequences that can be associated with delays in treatment initiation, such as morbidity, mortality, and secondary transmission of *M. tuberculosis*, with subsequent development of active disease. Fluoroquinolone use was also associated with a delay in the growth of *M. tuberculosis* in culture (i.e., a delay in the laboratory diagnosis of tuberculosis), but this difference was not statistically significant.

Unlike previous studies of delays in the diagnosis and treatment of tuberculosis [11, 16, 17], our study found no demo-
graphic or clinical characteristics at presentation (with the exception of shortness of breath) that were associated with receipt of empiric fluoroquinolone therapy. It is unclear why the presence of shortness of breath was associated with empiric fluoroquinolone treatment. Shortness of breath is a nonspecific symptom, and such clinical features cannot reliably distinguish the etiologic agent of pneumonia [2]. Information on the severity of symptoms and the presence of comorbid conditions was limited in this retrospective study.

Interestingly, of those patients who received fluoroquinolone monotherapy, 83% experienced improvement in the symptoms of tuberculosis, and clinical improvement occurred an average of 3 days after the initiation of therapy. The clinical course of patient B illustrates the rapid clinical response of tuberculosis to fluoroquinolone monotherapy. The conclusion that the clinical response in the other patients was due to treatment of tuberculosis and not another pathogen is supported by the fact that M. tuberculosis was the only pathogen isolated for all but 1 of the patients. This demonstrates that a clinical response to fluoroquinolones does not exclude the diagnosis of tuberculosis and, therefore, does not aid the clinician in distinguishing between tuberculosis and community-acquired pneumonia.

It is difficult to assess the true effect of fluoroquinolone therapy on delays in the initiation of antituberculosis therapy. The longest delays occur among patients for whom mycobacterial cultures are not performed at the initial presentation. However, in the absence of culture data, it is difficult to prove that a person indeed had tuberculosis. In this study, we assessed patients with culture-confirmed disease to ensure that patients did, indeed, have tuberculosis. However, this criterion requires that a culture was performed and, therefore, could have led to an underestimation of the delays in diagnosis attributable to fluoroquinolones. Once cultures grow M. tuberculosis, antituberculosis therapy is initiated, if it has not already been initiated empirically. It could be argued that some of the delay in initiating appropriate antituberculosis treatment that we found in this study was due to the fact that clinicians did not have mycobacterial cultures performed in a timely manner, rather than directly due to previous fluoroquinolone therapy. However, patients’ rapid clinical response to fluoroquinolone therapy may make clinicians less likely to consider the diagnosis of tuberculosis and may cause them to delay ordering appropriate diagnostic tests (as was the case, for example, for patient C).

For patients A and C, there were long delays between initial presentation and initiation of tuberculosis treatment. Although one cannot know with certainty whether these patients had tuberculosis at the initial presentation, their clinical presentations were consistent with tuberculosis. For patient A, the secondary transmission of M. tuberculosis to his mother also strongly supports the hypothesis that there was a delayed diagnosis of tuberculosis. The clinical courses of both patients underscore the importance of performing mycobacterial cultures for persons with symptoms and/or a history consistent with active tuberculosis. This is important, even though tuberculosis case rates are decreasing [18].

Although this study illustrates the problems associated with administration of empiric fluoroquinolone monotherapy among persons with tuberculosis, there may be a role for fluoroquinolones in tuberculosis treatment. Further studies of fluoroquinolones in combination with other antituberculosis agents for the treatment of active tuberculosis are warranted [19, 20].

There are at least 2 limitations to this study. First, all of the patients presented to the hospital for care. Thus, this study sample may not be representative of all patients with tuberculosis. However, most patients with tuberculosis present to a hospital or hospital-based clinic to receive medical attention and have therapy initiated there, even if the majority of antituberculosis therapy is subsequently received in the outpatient setting. Second, isolates of M. tuberculosis were not assessed for susceptibility to fluoroquinolones. Fluoroquinolone resistance can develop in M. tuberculosis, although, in one study, it developed after a median of 64 days of fluoroquinolone exposure, far greater than the 7–14-day treatment course for community-acquired pneumonia [21]. Although testing of M. tuberculosis for susceptibility to fluoroquinolones is not routinely performed, the high proportion of patients in this study who received fluoroquinolone monotherapy suggests that this issue should be assessed, particularly in areas with high levels of resistance to first-line antituberculosis agents.

Because the use of fluoroquinolones for the treatment of community-acquired pneumonia is widespread, the delay in the diagnosis and treatment of tuberculosis associated with fluoroquinolones is important. M. tuberculosis should be considered to be a possible causative pathogen in persons who present with community-acquired pneumonia, and an appropriate diagnostic work-up should be initiated for patients who have symptoms consistent with tuberculosis.

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References


