Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas

J-Y Wang, P-R Hsueh, I-S Jan, L-N Lee, Y-S Liaw, P-C Yang, K-T Luh

Background: A study was conducted to evaluate the effect of the empirical use of fluoroquinolones on the timing of antituberculous treatment and the outcome of patients with tuberculosis in an endemic area.

Methods: All patients with culture-confirmed tuberculosis aged ≥14 years diagnosed between July 2002 and December 2003 were included and their medical records were reviewed.

Results: Seventy-nine (14.4%) of the 548 tuberculosis patients identified received a fluoroquinolone (FQ) group, 218 received a non-fluoroquinolone antibiotic (AB group), and 251 received no antibiotics before antituberculous treatment. In the FQ group, the median interval from the initial visit to starting antituberculous treatment was longer than in the AB group and in those who received no antibiotics (41 ± 6.8 ± 7 days), and the prognosis was worse (hazard ratio 6.88 [95% CI 1.84 to 25.72]). More patients in the FQ and AB groups were aged >65 years (53.2% and 61.0% ± 31.5%), had underlying disease (53.2% and 46.8% ± 34.3%), and were hypoalbuminaemic (67.2% and 64.9% ± 35.1%). Of the nine mycobacterial isolates obtained after fluoroquinolone use from nine patients whose initial isolates were susceptible to ofloxacin, one (11.1%) was resistant to ofloxacin (after fluoroquinolone use for 7 days). Independent factors for a poor prognosis included empirical fluoroquinolone use, age >65, underlying disease, hypoalbuminaemia, and lack of early antituberculous treatment.

Conclusions: 14.4% of our patients with tuberculosis received a fluoroquinolone before the diagnosis. With a 34-day delay in antituberculous treatment and more frequent coexistence of underlying disease and hypoalbuminaemia, empirical fluoroquinolone treatment was associated with a poor outcome. Mycobacterium tuberculosis isolates could obtain ofloxacin resistance within 1 week.

T he fluoroquinolones (FQs) were introduced into clinical practice in the 1980s. With broad spectrum antimicrobial activity, they are recommended and widely used for the treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted diseases and chronic osteomyelitis.1–4 In contrast to many intestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as sexually transmitted treatment of bacteri...
14 days of the initial visit and was judged as completed if fulfilling the definition of the World Health Organization (WHO). All patients were followed until they completed treatment or until 30 June 2005.

Analysis of data
Differences between groups were analysed using either an independent sample $t$ test or the Mann-Whitney U test for continuous variables and the $\chi^2$ test for categorical variables. Survival curves for each variable were generated using the Kaplan-Meier method and were compared using the log rank test. If a significant difference ($p<0.05$) was found, the variables were entered into a multivariate survival analysis using Cox regression to identify factors independently associated with mortality.

RESULTS
Between July 2002 and December 2003 a total of 548 patients with newly diagnosed culture confirmed TB were identified. Pulmonary TB was diagnosed in 451 of them (82.3%), including 38 (6.9%) who had concomitant pulmonary and extrapulmonary TB. The remaining 97 patients (17.7%) had only extrapulmonary involvement. Serological tests for HIV were performed in 296 patients and were positive in 17. Of the 252 patients with unknown HIV serostatus, all were free of other AIDS defined illnesses during follow up.

Seventy nine of the 548 patients (14.4%) received a fluoroquinolone (FQ group) and 218 (39.8%) received non-FQ antibiotics (AB group) before the diagnosis of TB. Antibiotics including FQs were prescribed more than once in 65 patients. The FQ prescribed was ciprofloxacin in 42 patients.

Table 1 Characteristics of the 548 patients with culture confirmed tuberculosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FQ (n = 79)</th>
<th>Others (n = 218)</th>
<th>No antibiotic (n = 251)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>42 (53.2%)</td>
<td>133 (60.0%)</td>
<td>79 (31.5%)</td>
</tr>
<tr>
<td>Male sex</td>
<td>49 (62.0%)</td>
<td>150 (68.8%)</td>
<td>163 (64.9%)</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>42 (53.2%)</td>
<td>102 (46.8%)</td>
<td>86 (34.3%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (25.3%)</td>
<td>51 (23.4%)</td>
<td>50 (19.9%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>13 (16.5%)</td>
<td>29 (13.3%)</td>
<td>24 (9.6%)</td>
</tr>
<tr>
<td>Chronic renal insufficiency*</td>
<td>8 (10.1%)</td>
<td>30 (13.8%)</td>
<td>7 (28.8%)</td>
</tr>
<tr>
<td>Receiving steroid</td>
<td>5 (6.3%)</td>
<td>6 (2.8%)</td>
<td>11 (4.4%)</td>
</tr>
<tr>
<td>AIDS</td>
<td>5 (6.3%)</td>
<td>10 (4.6%)</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2 (2.5%)</td>
<td>5 (2.3%)</td>
<td>6 (2.4%)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>0</td>
<td>1 (0.5%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>17 (21.5%)</td>
<td>62 (28.4%)</td>
<td>72 (28.3%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>14 (17.7%)</td>
<td>27 (12.4%)</td>
<td>25 (10.0%)</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>20 (25.3%)</td>
<td>72 (33.0%)</td>
<td>43 (17.1%)</td>
</tr>
<tr>
<td>TB pleurisy or peritonitis</td>
<td>11 (13.9%)</td>
<td>43 (19.7%)</td>
<td>22 (8.8%)</td>
</tr>
<tr>
<td>Musculoskeletal TB</td>
<td>4 (5.1%)</td>
<td>9 (4.1%)</td>
<td>7 (2.8%)</td>
</tr>
<tr>
<td>TB lymphadenopathy</td>
<td>0 (0%)</td>
<td>6 (2.8%)</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>Urogenital TB</td>
<td>1 (1.3%)</td>
<td>10 (4.6%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>1 (1.3%)</td>
<td>1 (0.5%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Disseminated TB</td>
<td>3 (3.8%)</td>
<td>3 (1.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Symptom at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>52 (65.8%)</td>
<td>127 (58.3%)</td>
<td>177 (70.5%)</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>41 (51.9%)</td>
<td>103 (47.2%)</td>
<td>60 (23.9%)</td>
</tr>
<tr>
<td>CNS symptoms</td>
<td>4 (5.1%)</td>
<td>14 (6.4%)</td>
<td>7 (2.8%)</td>
</tr>
<tr>
<td>Neck mass</td>
<td>0</td>
<td>5 (2.3%)</td>
<td>6 (2.4%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>0</td>
<td>3 (1.4%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>2 (2.5%)</td>
<td>5 (2.3%)</td>
<td>6 (2.4%)</td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>2 (2.5%)</td>
<td>10 (4.6%)</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>None (incidental finding)</td>
<td>4 (5.1%)</td>
<td>17 (7.8%)</td>
<td>29 (11.6%)</td>
</tr>
<tr>
<td>Symptom &gt;14 days</td>
<td>46 (58.2%)</td>
<td>122 (55.0%)</td>
<td>172 (76.9%)</td>
</tr>
<tr>
<td>Ordering CXR at initial visit in PTB</td>
<td>69 (87.3%)</td>
<td>174 (79.8%)</td>
<td>194 (77.3%)</td>
</tr>
<tr>
<td>CXR finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibronodular infiltrates</td>
<td>25 (31.4%)</td>
<td>66 (30.3%)</td>
<td>84 (33.5%)</td>
</tr>
<tr>
<td>Alveolar consolidation</td>
<td>33 (41.8%)</td>
<td>86 (39.4%)</td>
<td>77 (30.7%)</td>
</tr>
<tr>
<td>Multiple nodules or mass</td>
<td>9 (11.4%)</td>
<td>20 (9.2%)</td>
<td>44 (17.5%)</td>
</tr>
<tr>
<td>Fibrocavitary</td>
<td>5 (6.3%)</td>
<td>15 (6.9%)</td>
<td>12 (4.8%)</td>
</tr>
<tr>
<td>Miliary shadowing</td>
<td>1 (1.3%)</td>
<td>8 (3.7%)</td>
<td>10 (4.0%)</td>
</tr>
<tr>
<td>No parenchymal lesion</td>
<td>6 (7.6%)</td>
<td>23 (10.6%)</td>
<td>24 (9.6%)</td>
</tr>
<tr>
<td>Lower lung field TB</td>
<td>18 (22.8%)</td>
<td>47 (21.6%)</td>
<td>36 (14.3%)</td>
</tr>
<tr>
<td>Cavity</td>
<td>9 (11.4%)</td>
<td>21 (9.6%)</td>
<td>43 (17.1%)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>&lt;35/35+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.7 (6.2)</td>
<td>32.2 (6.1)</td>
<td>37.4 (6.4)</td>
</tr>
<tr>
<td>Sputum AFS+ in PTB</td>
<td>8 (12.1%)</td>
<td>53 (24.3%)</td>
<td>65 (25.9%)</td>
</tr>
<tr>
<td>Single drug resistance</td>
<td>20 (25.3%)</td>
<td>48 (22.0%)</td>
<td>73 (29.1%)</td>
</tr>
<tr>
<td>Multidrug resistance</td>
<td>10 (12.7%)</td>
<td>17 (7.8%)</td>
<td>29 (11.6%)</td>
</tr>
</tbody>
</table>

AFS, acid fast smear; AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; CXR, chest radiograph; PTB, pulmonary tuberculosis; TB, tuberculosis. *Chronic renal insufficiency was defined as a serum creatinine level >20 mg/l. 
†p<0.05 FQ group v no antibiotic group. 
‡p<0.05 other antibiotic group v no antibiotic group. 
§p<0.05 FQ group v other antibiotic group.
Table 2  Management and outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Empirical antibiotic use</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FQ (n = 79)</td>
<td>FQ, no underlying disease (n = 37)</td>
<td>Others (n = 218)</td>
</tr>
<tr>
<td>Initial visit to ordering TB studies (days)</td>
<td>6 (0–173)†‡</td>
<td>6 (1–173)</td>
<td>5 (0–163)</td>
</tr>
<tr>
<td>AFS — (n = 126)</td>
<td>9 (1–173)</td>
<td>4 (1–173)</td>
<td>3 (0–78)</td>
</tr>
<tr>
<td>AFS — (n = 422)</td>
<td>6 (0–159)</td>
<td>6 (1–61)</td>
<td>5 (0–163)</td>
</tr>
<tr>
<td>TB study to anti-TB treatment (days)</td>
<td>25 (3–231)†‡</td>
<td>31 (3–73)</td>
<td>7 (35–143)‡</td>
</tr>
<tr>
<td>AFS — (n = 123)</td>
<td>5 (1–21)†</td>
<td>4 (2–9)</td>
<td>21 (16–98)‡</td>
</tr>
<tr>
<td>AFS — (n = 363)</td>
<td>31 (3–231)†‡</td>
<td>33 (3–73)</td>
<td>16 (25–143)‡</td>
</tr>
<tr>
<td>Initial visit to anti-TB treatment (days)</td>
<td>41 (6–233)‡*</td>
<td>38 (6–175)</td>
<td>16 (0–198)‡</td>
</tr>
<tr>
<td>AFS — (n = 123)</td>
<td>15 (8–175)‡*</td>
<td>10 (8–175)</td>
<td>6 (0–105)‡</td>
</tr>
<tr>
<td>AFS — (n = 363)</td>
<td>42 (6–233)‡*</td>
<td>39 (6–96)</td>
<td>27 (0–198)‡</td>
</tr>
<tr>
<td>Ordering TB study at initial visit (days)</td>
<td>53 (67–111)</td>
<td>28 (70–131)</td>
<td>163 (74–81)</td>
</tr>
<tr>
<td>AFS — (n = 37–85)</td>
<td>64 (55–82)</td>
<td>62 (34–92)</td>
<td>62 (35–121)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed treatment</td>
<td>41 (51.9%)</td>
<td>23 (62.2%)</td>
<td>133 (61.0%)</td>
</tr>
<tr>
<td>Ongoing treatment</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Not treated</td>
<td>2 (2.5%)</td>
<td>2 (5.4%)</td>
<td>5 (2.3%)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>13 (16.5%)</td>
<td>7 (16.9%)</td>
<td>34 (15.6%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>23 (29.1%)</td>
<td>5 (13.5%)</td>
<td>45 (20.6%)</td>
</tr>
<tr>
<td>Died of TB</td>
<td>12 (15.3%)</td>
<td>3 (0–123)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>Died with TB</td>
<td>11 (14.5%)</td>
<td>2 (33)</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Length of survival (days)</td>
<td>85.5 (18–448)†</td>
<td>59 (26–448)</td>
<td>55 (1–708)‡</td>
</tr>
</tbody>
</table>

AFS, acid-fast smear; TB, tuberculosis.
*Data presented as median (range).
†p<0.05 FQ group v no antibiotic group.
‡p<0.05 other antibiotic group v no antibiotic group.
*0.05 FQ group v other antibiotic group.

levofloxacin in 21, and moxifloxacin in the remaining 16, and the mean (SD) duration of use was 9.5 (6.0) days. The initial diagnosis was community acquired pneumonia in 69 patients (87.3%), septic arthritis in four (5.1%), bacterial peritonitis in three (3.8%), and one (1.3%) each for urinary tract infection, meningitis, and fever of unknown origin.

In 18 patients M tuberculosis isolates before and after the use of FQs were preserved. Half of them had clinical specimens collected ≥7 days after the use of FQs (range 7–18 days). All of the 36 isolates were susceptible to ciprofloxacin, except one from a patient after using a FQ for 7 days. The patient presented with right knee arthralgia for 1 week and had not taken any medication before coming to our hospital. Among the 469 patients without empirical FQ use, 177 had previously been treated by local doctors and 76 of them had taken any medication before coming to our hospital. Among the 548 patients, 151 (27.5%) (69 FQ group, 82 non-FQ group, and 9 AB group) died within 3 months of the initial visit. At the terminal stage ciprofloxacin resistant bacteria were isolated from eight (61.5%), eight (26.7%), and one (50.0%) of the three groups, respectively (p = 0.090). Among these, multi-drug resistant Pseudomonas aeruginosa or Acinetobacter baumannii, defined as resistance to two or more classes of antipseudomonal agents,14 were isolated from four, two, and one, respectively (p = 0.052). One patient in the FQ group, two in the non-FQ antibiotic group, and five in the no antibiotic group died after completion of TB treatment.

Of the 12 patients in the FQ group who died of TB (table 2), the cause of death was septic shock without any evidence of concomitant bacterial infection other than M tuberculosis infection in eight, respiratory failure due to extensive pulmonary inflammation in three, and sputum impaction in one. No events of sudden death as a result of prolongation of the corrected QT interval (Qtc) were noted. In the other two groups, 15 patients died of septic shock without any evidence of concomitant bacterial infection other than M tuberculosis and eight died of respiratory failure (seven due to severe cæsious pneumonia and one to sputum impaction). A total of 45 patients (13 in the FQ group, 30 in the AB group, and two in the control group) died within 11 days of the initial visit. At the terminal stage ciprofloxacin resistant bacteria were isolated from eight (61.5%), eight (26.7%), and one (50.0%) of the three groups, respectively (p = 0.090). Among these, multi-drug resistant Pseudomonas aeruginosa or Acinetobacter baumannii, defined as resistance to two or more classes of antipseudomonal agents,14 were isolated from four, two, and one, respectively (p = 0.052). One patient in the FQ group, two in the non-FQ antibiotic group, and five in the no antibiotic group died after completion of TB treatment.

To identify the factors associated with the different prognosis in the three groups, survival analysis was performed on the 11 variables with significant inter-group
Other independent factors for a poor prognosis included age 

**DISCUSSION**

Our findings have confirmed that the empirical use of antibiotics, especially FQs, for presumed bacterial infection could delay the treatment for TB, especially in patients with smear negative specimens.7 15–18 Our results also show that patients who receive an FQ (but not non-FQ antibiotics) before standard anti-TB treatment have a poorer prognosis, most likely as a result of the emergence of drug resistant bacteria and the association with ageing, underlying disease, malnutrition, and delayed treatment. With empirical use of FQ for 1–3 weeks, 11.1% of the *M tuberculosis* isolates became ofloxacin resistant.

In a study conducted in Baltimore where the incidence of TB is relatively low, empirical FQ treatment was given to 16 patients with TB during a 40 month period and was associated with a significant delay in starting anti-TB treatment (21 v 5 days).7 Although the proportion of TB patients who received FQs in our study was less than that in Baltimore (14.4% v 48%), we found that the impact of widespread FQ use was greater in an endemic area of TB, with 79 patients during an 18 month period receiving empirical FQ treatment in whom anti-TB treatment was significantly delayed (table 2). Most of this delay occurred between the time that the bacteriological tests were ordered and the anti-TB treatment was started. However, the time required for the mycobacterial isolates to grow was similar for the three groups.

The proportion of patients who received TB tests at the initial visit was not significantly different, but the time from the initial visit to ordering TB tests was significantly longer in the FQ group. There are two possible reasons for these findings. Firstly, with the excellent in vivo activity of FQs against *M tuberculosis*,5 6 11–14 about two thirds of our patients with TB who had received an FQ showed clinical improvement so laboratory tests for TB were often not ordered until a later date (17.5 days v 11.4 days); this difference was not statistically significant. Even if the laboratory tests were performed with a partly improved clinical course and low index of suspicion, anti-TB treatment would not be started until the culture became positive and *M tuberculosis* was identified. Secondly, more patients who received an FQ were...
elderly and had hypoalbuminaemia and underlying co-

orbid conditions, implying a poor general condition. They
might therefore be too weak to expectorate adequate sputum
specimens for TB tests which could result in a low smear
positive rate and delayed treatment.

Our analysis showed that the empirical use of FQ was inde-

pendedently associated with a poor prognosis, most
probably owing to the emergence of ciprofloxacin resistant
isolates and multidrug resistant P aeruginosa or A bauman-
nii, which has been reported to increase infection related
mortality and a deterioration in the survival rate.13–19 In

addition, inappropriate use of FQs can result in the
development of FQ resistance in M tuberculosis.20–22

Although patients in the FQ and non-FQ antibiotic groups
improvement with the use of FQ treatment which masked
the bactericidal effect of the FQ on

Patients in the FQ group, on the other hand, could show
improvement because the progressively deteriorating disease
probably because the progressively deteriorating disease
contributed to the delay in anti-TB treatment. However, the

finding was consistent with the case reported by Ginsburg et

al who showed that FQ resistance can develop after only
13 days of exposure and suggested that mycobacterial
resistance to FQ could potentially occur during a short course
of treatment for a common bacterial infection. The delay in
anti-TB treatment resulting from empirical FQ use further
increased the morbidity and reduced the survival of TB
patients.23–25 In agreement with our previous study,18 the
survival analysis showed that death from TB was signifi-
cantly affected by the presence of conditions that would alter
the patients in the FQ group, those in the non-FQ antibiotic group were
older and more poorly nourished, more often had underlying
diseases, and presented acutely with constitutional symp-
toms and lower lobe infiltrates (table 1) than those who had
received no previous antibiotics. They therefore tended to
have an initial diagnosis of acute pneumonia which
contributed to the delay in anti-TB treatment. However, the
delay in this group was less than that in the FQ group,
probably because the progressively deteriorating disease
raised the suspicion of TB and prompted anti-TB treatment.

Patients in the FQ group, on the other hand, could show
improvement with the use of FQ treatment which masked
the presence of TB and markedly delayed the diagnosis.

Although patients in the FQ and non-FQ antibiotic groups
were similar in age, degree of malnourishment and under-
ylying disease, those in the non-FQ group who died tended to
die earlier than in the FQ group (table 2), probably because
the bactericidal effect of the FQ on M tuberculosis partially
alleviated the progression and prevented early mortality.

Our study was limited by the possible bias in patient
selection because it was conducted in a tertiary care referral
centre and only culture confirmed cases of TB were included.

Another major limitation was the unavailability of the
previous medication history, as many of the patients not
treated empirically with FQs could have received FQs before
coming to our hospital. However, our analysis showed that
the widespread use of FQs for the treatment of bacterial
infection resulted in a delay in the treatment of TB and a
worse outcome in an endemic area. Our data revealed that
14.4% of our TB patients received FQs before diagnosis of TB.

By causing the emergence of resistant bacteria, a significant
delay in the initiation of anti-TB treatment, and association
with conditions that compromise cellular immunity, the
empirical use of FQs in patients with TB was associated with
a poor outcome. In addition, the M tuberculosis isolates could
become resistant to ofloxacin within 1 week. We therefore
conclude that, in an endemic area of TB, a high index of
suspicion is required. M tuberculosis should be considered as
a possible causative pathogen in every infectious disease,
whether or not clinical improvement is noted after the use
of an FQ, and appropriate bacteriological and histopatho-
lolgical tests for TB should be performed as early as possible.

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REFERENCES
1 Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the
management of community-acquired pneumonia in adults. Infectious Diseases
3 Van Landuyt HW, Magerman K, Gordo B. The importance of the quinolones in
4 Huang ES, Stafford RS. National patterns in the treatment of urinary tract
infections in women by ambulatory care physicians. Arch Intern Med. 2002;
5 Yew WW, Piddock LJ, Li MS, et al. In-vitro activity of quinolones and
among Mycobacterium tuberculosis isolates from the United States and Canada.
pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis.
8 Center for Disease Control. Statistics of communicable diseases and
surveillance report in Taiwan area. 2003. Taipei, Taiwan: Center for Disease
assay (the RAPID BAP-MTB) and the BD ProbeTec ET system for detection of
4599–603.
10 Wang JY, Lee UN, Hsueh PR. Factors changing the manifestation of pulmonary

11 Crump JA, Reller LB. Two decades of disseminated tuberculosis at a university
2003;37:1037–43.
12 Ousler KK, Moore RD, Bishai WR, et al. Survival of patients with pulmonary
35:752–9.
14 Hsu DF, Olkaita MP, Murphy FA, et al. Fluoroquinolone-resistant Pseudomonas
aeruginosa: risk factors for acquisition and impact on outcomes. J Antimicrob
15 Kiflouny D, Timponje J, Yeaman MR, et al. Can administration of a
2000;4:1092.
16 Abiose OA. Does the use of fluoroquinolones for the empiric treatment of
35:1572–3.
17 Agarwal A. TB should be diagnosed before using a fluoroquinolone. BMJ.
2003;327:164–5.
19 Murray CK, Hosenthal DR. Treatment of multidrug resistant Acinetobacter.
20 Sullivan EA, Kreiswirth BN, Palombo L, et al. Emergence of fluoroquinolone-
21 Ginsburg AS, Cooper N, Parrish N, et al. Fluoroquinolone resistance in
22 Ginsburg AS, Woolwine SC, Cooper N, et al. The rapid development of
23 Pablos-Mendez A, Sterling TR, Frieden TR. The relationship between delayed
or incomplete treatment and all-cause mortality in patients with tuberculosis.
24 Alwood K, Karuly J, Moore-Rice K, et al. Effectiveness of supervised,
impatient therapy for tuberculosis in HIV-infected patients. AIDS. 1999;8:
1103–8.
26 Hughes MJ, Sylfield SP, Darbyshire JH, et al. Deaths occurring in newly
notified patients with pulmonary tuberculosis in England and Wales. Br J Dis
Cyclophosphamide in scleroderma lung disease

A round 40% of patients with systemic sclerosis will develop significant interstitial lung disease. No agent has been proved in a randomised controlled trial to be effective in this condition. This multicentre, double blind, randomised, placebo controlled trial evaluated the effectiveness of oral cyclophosphamide in patients with scleroderma who had restrictive lung function, exertional dyspnoea, and evidence of active alveolitis.

One hundred and fifty eight patients were randomised to receive cyclophosphamide (up to 2 mg/kg/day) or placebo for 1 year. There was a small but significant difference in the primary outcome measure—change in forced vital capacity (FVC)—at 12 months, favouring cyclophosphamide (−1.0 (0.92)% predicted v −2.6 (0.9)% predicted, p<0.03). This benefit was maintained after a further 12 months off study medication. There was no improvement in gas transfer but small improvements were seen in the transitional dyspnoea index and some quality of life measures. Those with more severe fibrosis at baseline had the greatest benefit in FVC.

Adverse events were more common in the cyclophosphamide group, including a significantly greater incidence of leucopenia and neutropenia. The potential longer term associations with malignancy were not evaluated within this 2 year period.

This is the first placebo controlled study to demonstrate a benefit of treatment for scleroderma related interstitial lung disease. However, these benefits were small and need to be weighed against the risk of adverse side effects.

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No need to stay in hospital after antibiotic switch in pneumonia

This was a multicentre retrospective analysis during one of two 6 month periods in 1998–9 which assessed the benefit of in-hospital observation after the switch from intravenous to oral antibiotics in patients with community acquired pneumonia (CAP) aged at least 65 years. The US Medicare National Pneumonia Project database was used to create a sample population from 4341 hospitals in all 50 states of the US and the District of Columbia. 5248 patients fulfilled the eligibility criteria and were divided into two groups (2536 “not observed” and 2712 “observed for 1 day”).

There was no significant difference between the groups in 14 day hospital re-admission rate (7.8% in the “not observed” v 7.2% in the “observed for 1 day” group, p = 0.367) or 30 day mortality (5.1% in the “not observed” v 4.4% in the “observed for 1 day” group, p = 0.258). There were substantial economic implications of early discharge, with projected annual savings of up to $27.1 million. There were a few limitations to the study; the number of days of observation after the switch was based on calendar days and not hours, and those patients who were observed for 1 day to address active medical or social reasons were also included in the “observed for 1 day” group.

The authors conclude that low risk patients with CAP can be safely discharged soon after changing from intravenous to oral antibiotics, although there was a non-significant trend to lower 30 day mortality in those observed. The potential benefits of such an approach are shorter hospital stays and, perhaps, greater patient satisfaction. However, a randomised controlled trial is required to confirm the results of this study.

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Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas


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