MAJOR ARTICLE

# Extensively Drug-Resistant Tuberculosis in South Korea: Risk Factors and Treatment Outcomes among Patients at a Tertiary Referral Hospital

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***Background.*** Extensively drug-resistant (XDR) tuberculosis (TB) is a major public health threat in South Korea.

***Methods.*** We analyzed baseline epidemiological data for 250 patients enrolled in an ongoing prospective observational study of TB at a large tertiary referral hospital in South Korea.

***Results.*** Twenty-six subjects with XDR TB were identified; all were patients who had previously received TB therapy. Cumulative previous treatment duration (range, 18–34 months; odds ratio [OR], 5.6; 95% confidence interval [CI], 1.0–59), number of previously received second-line anti-TB drugs (OR, 1.3; 95% CI, 1.1–1.5), and female sex (OR, 3.2; 95% CI, 1.1–8.3) were significantly associated with XDR TB in crude analyses. After controlling for other factors in a multivariable model, cumulative previous treatment duration remained significantly associated with XDR TB (OR, 5.8; 95% CI, 1.0–61). Subjects with XDR TB were more likely to produce culture-positive sputum at 6 months, compared with patients with non–multidrug resistant TB (risk ratio, 13; 95% CI, 5.1–53). Kanamycin resistance was found to be predictive of 6-month culture positivity after adjustment for ofloxacin and streptomycin resistance (risk ratio, 3.9; 95% CI, 1.9–11).

***Conclusions.*** XDR TB was found to be associated with the cumulative duration of previous treatment with second-line TB drugs among subjects in a tertiary care TB hospital. Patients with XDR TB were more likely to not respond to therapy, and successful conversion of sputum culture results to negative was correlated with initial susceptibility to both fluoroquinolones and kanamycin but not to streptomycin.

Extensively drug-resistant (XDR) tuberculosis (TB) has recently emerged as a global health problem, threatening the success of TB-control programs worldwide [1–4]. A global survey of supranational reference laboratories for TB isolates collected during 2000–2004 identified XDR TB in 17 countries and estimated that 10% of the sampled multidrug-resistant (MDR) TB strains were XDR [1]. All TB isolates received by the South Korean National Reference Laboratory (Korean Institute of Tuberculosis, Seoul) during this period were included in this survey and among these MDR TB isolates 15% were further classified as XDR TB.

South Korea has a relatively high burden of TB for an industrialized country (73 cases per 100,000 persons in 2005) [5]. However, this is a substantial decrease from 1965, when the incidence was 668 cases per 100,000 persons, and the change reflects the success of South Korea's national TB program, which has focused mainly on treating new cases of TB [6]. Health care centers in South Korea do not use directly observed therapy; nonetheless, health professionals make an effort to ensure compliance with treatment by contacting

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patients who default. With this system, cure rates for new cases had reached 80% by 1994—higher than the 75% average for national TB programs that employed the directly observed therapy strategy in 2006 [7, 8]. With the introduction of standardized therapy in the 1980s, South Korea has seen a decrease in the prevalence of drug-resistant TB (from 23.8% in 1980 to 5.8% in 1995) among persons with new cases and a decrease in the rate of MDR TB (from 27.5% in 1994 to 7.1% in 1998) among persons with previously treated cases [6, 9]. Although the reported decreases in the incidence of TB and in the prevalence of drug-resistant TB are impressive, the battle against TB in South Korea is hardly over. For instance, it is not known whether similar success was seen in the private sector, which treats a greater number of recurrent and drug-resistant cases of TB, which have a higher default rate [9]. More recently, the rate of MDR TB among newly diagnosed cases has increased slightly, from 1.6% in 1994 to 2.4% in 2003 [10].

In 2005, a prospective cohort study of MDR TB was initiated at the National Masan Tuberculosis Hospital (Masan, South Korea). The objectives of this study were to characterize host and bacterial strain characteristics related to the development and progression of MDR TB and to collect baseline laboratory data for clinical trials in this patient population.

## METHODS

***Study site and study population.*** Subjects included in this analysis were those enrolled in a prospective observational cohort study at a tertiary TB care center in South Korea. All new patients with TB who were admitted to the hospital were asked to participate in the study if they were at least 20 years of age, had clinical signs and symptoms suggestive of TB, had Ziehl-Neelsen acid-fast bacilli–positive sputum specimens, and were not pregnant. Patients who were subsequently found to be culture-negative for *Mycobacterium tuberculosis* or to be HIV positive were withdrawn from the study. Subjects who had received <30 days of previous TB treatment were assigned to cohort A, and those who had received ⩾30 days of treatment were enrolled in cohort B [11]. After the subject provided informed consent, an interview was conducted to collect demographic, epidemiologic, and clinical information. Patients' medical records were abstracted to collect detailed information about comorbidities and treatment history. Patients were observed monthly until the completion of the prescribed treatment regimen. Treatment outcome definitions for cure, failure, and default followed the guidelines of the World Health Organization [8].

Data collection and quality and protocol compliance, in-

**Table 1. Baseline characteristics of study subjects.**

| Characteristic | Patients with newly diagnosed tuberculosis ($n$ = 91) | Previously treated patients ($n$ = 159) |
|---|---|---|
| Male sex | 78 (86) | 131 (82) |
| Age, median years (range) | 45 (20–78) | 44 (21–74) |
| Education ($n$ = 247) | | |
| University or professional school | 5 (6) | 20 (13) |
| Middle, high, or night school | 57 (63) | 100 (64) |
| No formal education/elementary school | 28 (31) | 37 (24) |
| Occupation ($n$ = 218) | | |
| Construction or factory worker | 32 (41) | 44 (31) |
| Unemployed | 18 (23) | 28 (20) |
| Service sector | 12 (15) | 35 (25) |
| Professional/office work | 4 (5) | 17 (12) |
| Agriculture/aquaculture | 7 (9) | 9 (6) |
| Other | 5 (6) | 7 (5) |
| Contact with person with tuberculosis in the past year ($n$ = 217) | 11 (14) | 34 (24) |
| Purchased antibiotics in the previous 2 years ($n$ = 216) | | |
| Once per month | 8 (10) | 34 (24) |
| More than once per month | 9 (12) | 31 (22) |
| No | 60 (78) | 74 (53) |
| Diabetes mellitus | 16 (18) | 30 (19) |
| Hepatitis B | 3 (3) | 12 (8) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated.

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**Table 2. Treatment histories among 123 previously treated subjects with detailed previous treatment histories.**

| Characteristic | Value |
|---|---|
| Median no. of previous treatments (range) | 3 (1–15) |
| Median no. of second-line tuberculosis drugs reported to have ever been prescribed (range) | 3 (0–10) |
| History of at least 1 incomplete tuberculosis treatment regimen ($n$ = 141) | 117 (83) |
| Cumulative duration of previous treatments ($n$ = 123) | |
| ⩽8 months | 29 (24) |
| >8 months to ⩽18 months | 32 (26) |
| >18 months to ⩽34 months | 30 (24) |
| >34 months | 32 (26) |
| Treatment with the following drugs at least once in the past[a] | |
| HRZE exclusively | 49 (40) |
| HRZE; plus fluoroquinolones; plus streptomycin, kanamycin, or amikacin; plus a bacteriostatic agent | 41 (33) |
| HRZE plus any other combinations of drugs | 16 (13) |
| Patient was not prescribed any of HRZE agents | 17 (14) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. HRZE, isoniazid, rifampicin, pyrazinamide, and ethambutol.

[a] Indicates that treatment with the indicated drugs in the patient history, does not necessarily indicate that these were concurrently administered although in the case of the first-line agents HRZE, these would normally be concurrent.

cluding occurrence of adverse events, were monitored by an independent clinical research organization. Subjects included in this analysis were those enrolled starting in May 2005 for whom drug susceptibility test results were available as of 1 December 2006 ($n$ = 250). This study was reviewed and approved by the institutional review boards of the National Masan Tuberculosis Hospital and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (Bethesda, MD).

***Laboratory methods.*** Sputum specimens obtained from each participant were processed using sodium hydroxide and N-acetyl-L-cysteine, were screened for acid-fast bacilli with the Ziehl-Neelsen staining method, and were cultured in duplicate with a MB/BacT liquid culture system (bioMérieux) and Ogawa agar slants (egg-based medium; Shinyang Chemical). Drug susceptibility testing (DST) was performed on Löwenstein Jensen agar slants containing the relevant anti-TB drugs. Growth of >1% for isoniazid, rifampicin, and p-aminoslicylic acid (PAS) or of ⩾10% in the control in Löwenstein Jensen media for all other drugs [12] indicated resistance. Isolates were tested for resistance to critical concentrations of isoniazid (0.2 μg/mL), rifampicin (40 μg/mL), ethambutol (2.0 μg/mL), streptomycin (10 μg/mL), kanamycin (40 μg/mL), ofloxacin (2.0 μg/mL), ethionamide (40 μg/mL), cycloserine (30 μg/mL), and PAS (1 μg/mL). Resistance to pyrazinamide was determined by the pyrazinamidase assay [13]. MDR TB isolates were defined as TB isolates resistant to at least isoniazid and rifampicin [8]. XDR TB was defined as MDR TB with additional resistance to a fluoroquinolone and a second-line injectable anti-TB agent (i.e., kanamycin, capreomycin, or amikacin) [4].

***Data analysis.*** To assess the independent association of selected predictor variables with XDR TB, we constructed a multivariable logistic regression model that included variables that were significantly associated with XDR TB at a $P$ value ⩽.20 in the crude analysis. Cumulative treatment duration was calculated by summing the treatment duration for each TB episode that had treatment start and end dates specified; the resulting durations were categorized into quartiles. To determine significant risk factors for positive culture results at 6 months after enrollment, we constructed log-binomial regression models, using the likelihood ratio method to compute the 95% CIs for risk ratios. Statistical significance was set at $P$ < .05. When the number of subjects meeting specified model conditions was <5, exact methods were used to derive the ORs, their 95% CIs, and $P$ values. For variables with missing information, data analysis was conducted for patients with complete information. All statistical analyses were performed using SAS software for Windows, version 9.1 (SAS Institute).

## RESULTS

***Description of the study population.*** Of the 250 people included in our analysis, 159 (64%) had been previously treated for TB (cohort B). The median age of these subjects was 44 years, and 209 (84%) were male (table 1). This patient population had significant prior treatment history: the median number of previous treatment episodes was 3 (range, 1–15), with a mean cumulative duration of 28 months (range, 1–189 months). The median number of second-line anti-TB drugs previously prescribed was 3 (range, 0–10). Overall, 117 (83%) of the previously treated patients had not completed at least 1 prior treatment (table 2). Detailed records of prior treatment regimens were available for 123 patients (77%) in cohort B. Forty-nine (40%) of these patients had been pre-



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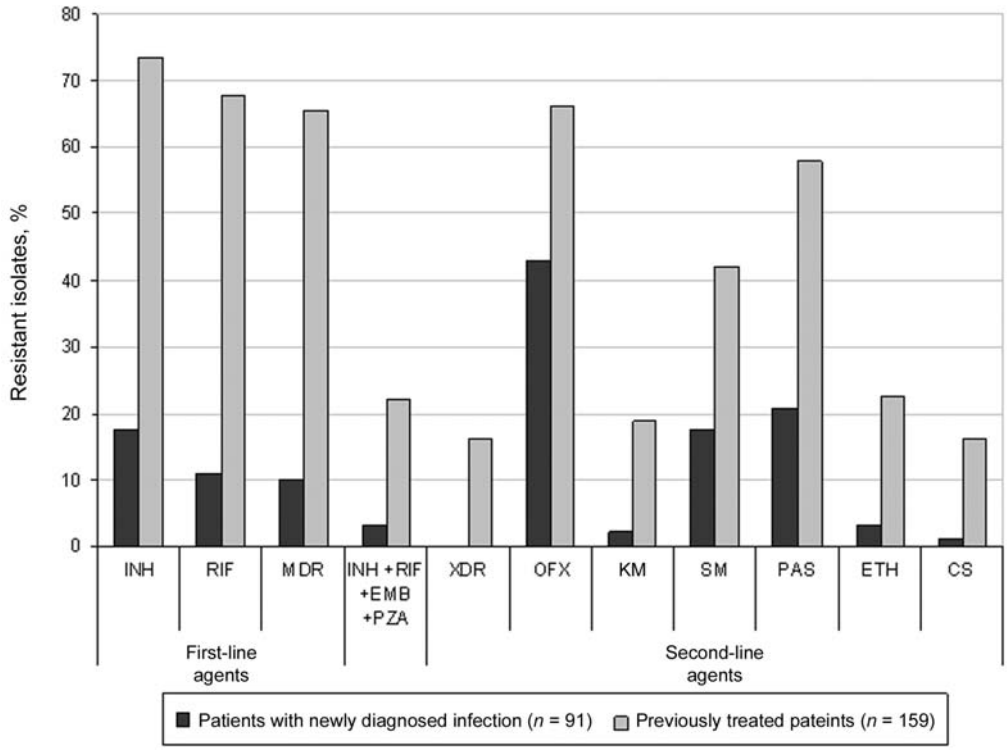


**Figure 1.** Drug resistance of isolates from patients in cohort A (i.e., patients with newly diagnosed tuberculosis) and cohort B (previously treated patients). The figure shows the percentage of isolates resistant to the individual agent (or combination of agents). CS, cylcoserine; EMB, ethambutol; ETH, ethionamide; INH, isoniazid; KM, kanamycin; MDR, multidrug resistance; OFX, ofloxacin; PAS, p-aminoslicylic acid; PZA, pyrazinamide; RIF, rifampicin; SM, streptomycin; XDR, extensive drug resistance.

viously treated only with isoniazid, rifampicin, pyrazinamide, and/or ethambutol. An additional 41 patients (33%) had also received treatment with a fluoroquinolone, an aminoglycoside, and a second-line bacteriostatic drug (not necessarily simultaneously) (table 2).

On the basis of DST data, 113 subjects (45%) were classified as having MDR TB, and 26 (10%) were further classified as having XDR TB. Among previously treated subjects, 65% had MDR TB, and 16% had XDR TB. Among patients who had received a new diagnosis, 10% had MDR TB, and none had XDR TB (figure 1).

***Risk factors for XDR TB.*** We examined sex, age, a diagnosis of diabetes, formal education level, the total number of second-line agents in the treatment history, the cumulative total duration of treatment, and a history of treatment interruption for association with XDR TB disease. Female sex, the number of second-line drugs taken in the past, and cumulative duration of treatment of 18–34 months were significantly associated with XDR TB in the univariate analysis. In a multivariate analysis, cumulative treatment duration of 18–34 months remained significant, and such subjects were 5.8 times (95% CI, 1.0–61 times) more likely to have XDR TB, compared with persons who were treated for ≤8 months (table 3). In addition, there was an increasing prevalence of drug resistance associated with longer treatment history ($P = .012$, by test for trend).

To investigate more thoroughly the association between previous treatment and drug resistance, we compared patients with new diagnoses, those who had received standard first-line therapy only, and those who had received first-line therapy, a fluoroquinolone, an aminoglycoside, and a bacteriostatic drug (figure 2*A*). In this analysis, a marked increase in the prevalence of MDR and XDR TB was apparent with increased prior exposure to antitubercular agents.

***The high prevalence of fluoroquinolone resistance in South Korean patients with TB.*** In both cohorts, we detected resistance to drugs that had not been prescribed for the treatment of their TB. This was most striking with respect to ofloxacin resistance. Although the prevalence of ofloxacin resistance was higher for patients who had been treated with a fluoroquinolone in the past (83%) than among subjects who had no record of having received a fluoroquinolone (54%), a high proportion of ofloxacin resistance could not be explained by reported fluoroquinolone use (figure 2*B*). The odds of ofloxacin resistance were increased 5.1-fold among persons who reported purchases of antibiotics unrelated to their TB treatment once per month, relative to those who reported none (table 4). There was an



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**Table 3. Association of demographic and clinical factors with extensively drug-resistant (XDR) tuberculosis (TB).**

| Variable | No. of patients with XDR TB/total no. of patients ($n$ = 250) | OR (95% CI) | Adjusted OR (95% CI)[a] | $P$[b] |
|---|---|---|---|---|
| Sex | | | | |
| Male | 17/209 | 1.0 | 1.0 | |
| Female | 9/41 | 3.2 (1.1–8.3) | 2.3 (0.67–7.3) | |
| Age | | | | |
| >44 years | 13/123 | 1.0 | … | |
| ⩽44 years | 13/127 | 1.0 (0.40–2.4) | … | |
| Diabetes | | | | |
| No | 18/204 | 1.0 | 1.0 | |
| Yes | 8/46 | 2.2 (0.76–5.7) | 2.1 (0.64–6.9) | |
| Education | | | | |
| High school or less | 21/222 | 1.0 | … | |
| University or professional school | 5/25 | 2.4 (0.63–7.5) | … | |
| Previously treated patients | | | | |
| No. of agents previously prescribed | … | 1.3 (1.1–1.5) | … | |
| Cumulative duration of past treatment | | | | |
| ⩽8 months | 2/29 | 1.0 | 1.0 | |
| >8 months to ⩽18 months | 4/32 | 1.9 (0.25–23) | 2.1 (0.26–26) | |
| >18 months to ⩽34 months | 9/30 | 5.6 (1.0–59) | 5.8 (1.0–61) | |
| >34 months | 10/32 | 6.0 (1.1–62) | 5.4 (0.96–58) | .012[c] |
| History of at least 1 incomplete TB treatment regimen | | | | |
| No | 2/24 | 1.0 | … | |
| Yes | 23/117 | 2.7 (0.59–25) | … | |

[a] Adjusted for sex, diabetes, and cumulative duration of treatment; not adjusted for second-line anti-TB treatment because of collinearity with cumulative duration.
[b] Determined by test for trend.
[c] Cumulative treatment duration categories were treated as an ordinal variable.

apparent increase in odds of ofloxacin resistance associated with more frequent purchases of antibiotics, but the overall trend was only marginally significant ($P$ = .07).

***Clinical consequences of XDR TB.*** Patients who are referred to National Masan TB Hospital are usually referred while already receiving a drug regimen prescribed by their primary physician. Typically, this regimen is not changed for the first 6 months after admission to the hospital. After 6 months, both DST results and clinical response are reviewed before a recommendation is made regarding whether to continue or change the regimen for those patients whose sputum culture results remain positive. As of 1 December 2006, results for 6-month cultures were available for 104 patients. Three (6%) of the 49 patients whose isolates were not MDR at baseline had positive culture results at 6 months, whereas 8 (21%) of the 39 patients with MDR TB and 13 (81%) of the 16 patients with XDR TB had positive culture results at 6 months. Patients with XDR TB were 13 times (95% CI, 5.1–53 times) more likely to produce culture-positive sputum specimens at 6 months than were those who did not have MDR TB at baseline.

We used the 6-month sputum culture positivity data to compare outcomes among 55 patients with MDR TB who were receiving various second-line regimens to which their isolate was either resistant or susceptible (table 5). Patients with kanamycin-resistant TB at baseline were 3.9 times (95% CI, 1.9–11 times) more likely to have positive sputum culture results than were those with kanamycin-susceptible TB (95% CI, 1.6–27 times). On the other hand, patients with ofloxacin- and streptomycin-resistant TB were only marginally more likely to have positive sputum culture results at 6 months (OR for ofloxacin, 1.9 [95% CI, 0.43–12]; OR for streptomycin, 1.4 [95% CI, 0.25–7.2]) than were patients with strains susceptible to those agents (table 5).

## DISCUSSION

All of the XDR TB cases identified in this study were among non-HIV infected patients previously treated for TB, with no evidence of geographic clustering. The strongest predictors of having XDR TB were cumulative duration of prior treatment episodes and the number of second-line TB drugs previously prescribed. The subjects with XDR TB in a recent South African



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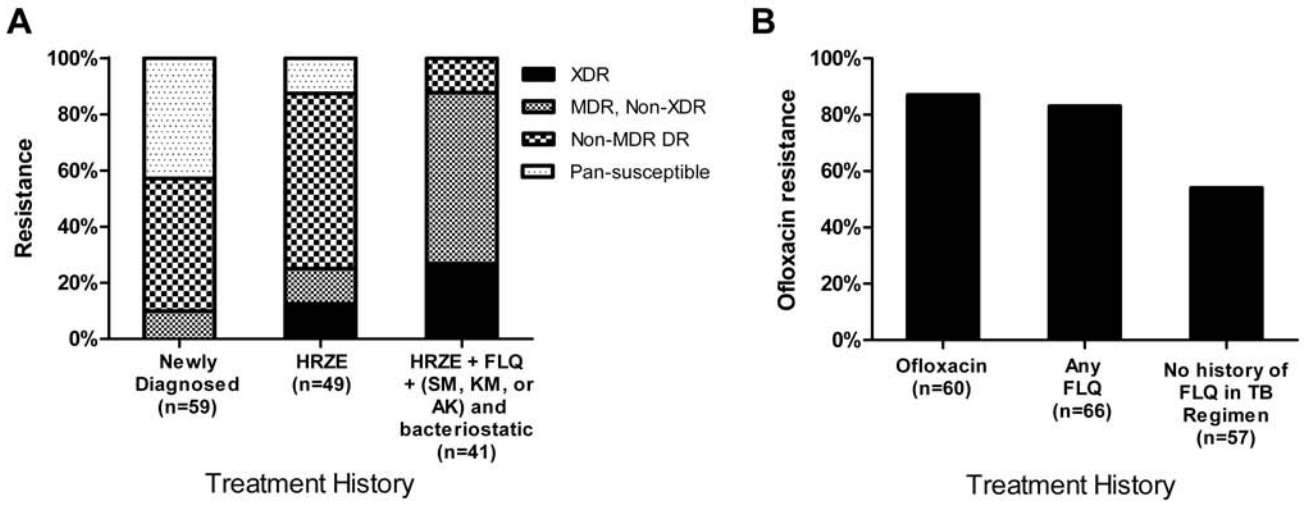


**Figure 2.** Drug resistance patterns according to treatment history. *A,* Drug resistance profile by treatment history (pan-susceptible, susceptible to all drugs tested; non-MDR DR, any drug resistance but not multidrug resistance; MDR, non-XDR, multidrug resistant but susceptible to either a fluoroquinolone [FLQ] of an injectable, according to the definition). *B,* Percentage of ofloxacin-resistant isolates recovered from patients with a history of receiving ofloxacin, a history of receiving any FLQ, or no history of previous treatment with a fluoroquinolone. AK, amikacin; HRZE, isoniazid, rifampicin, pyrazinamide, and ethambutol; KM, kanamycin; SM, streptomycin.

study consisted entirely of HIV-infected patients with low CD4 cell counts [3]. In that study, 55% of patients had not been previously treated, and nosocomial transmission was strongly suspected. In our study, the strong correlation with total duration of previous treatment suggests that XDR TB in South Korea may have involved more acquisition of resistance through lengthy and inappropriate treatment, although transmission is possible, as was observed in South Africa. More-detailed resistance history and molecular analysis of XDR TB cases in South Korea will be necessary to determine whether this phenomenon is affected by the nature of the patient population described here.

Women were significantly more likely than men to have XDR TB. TB diagnosis and DST may be delayed among female patients in South Korea, making treatment more difficult and inappropriate chemotherapeutic regimens more likely. Diagnostic delays among female patients have also been reported in other East Asian countries, such as Taiwan and Vietnam [14, 15]. It is also possible that the social standard for referring patients to the hospital may be different for male and female subjects; thus, providers may feel reluctant to refer female patients with less complicated infection to a tertiary care center.

In our study, ofloxacin-resistant TB was highly prevalent among patients who had no record of having been treated with a fluoroquinolone for TB and was associated with frequent purchases of antibiotics. Patients with newly diagnosed TB may have been exposed to a fluoroquinolone if the diagnosis of TB was delayed but treatment was given either via prescription or over-the-counter drugs. Although Korea put into effect a policy to ban nonprescription antibiotics in 2000 [16], over-the-counter antibiotics were still available during the ensuing years. Fluoroquinolone resistance and empirical use of fluoroquinolones have been associated with poor treatment outcome [17, 18] and delayed diagnosis [19] among patients with TB. Similarly high rates of fluoroquinolone resistance have been reported from other Asian countries [20], raising concerns about the utility of fluoroquinolones currently in clinical trials for TB treatment (i.e., moxifloxacin and gatifloxacin). These findings contrast with the situation in Latvia, the site of a retrospective cohort analysis of 204 patients with MDR TB, where fluoroquinolone resistance was found to be very low [21].

As expected with the lack of effective drugs, subjects from whom XDR TB isolates were recovered at baseline were more likely to have positive culture results at 6 months than were those with MDR TB or non-MDR TB. We also found that kanamycin resistance was more predictive of positive 6-month

**Table 4. Association of self-reported antibiotic purchase 2 years before study enrollment and ofloxacin resistance at baseline among patients with newly diagnosed tuberculosis.**

| Antibiotic purchase in past 2 years | No. of fluoroquinolone recipients/total no. of patients | OR (95% CI) | $P^a$ |
|---|---|---|---|
| None | 22/60 | 1.0 | |
| <1 per month | 4/9 | 1.4 (0.25–55) | |
| ⩾1 per month | 6/8 | 5.1 (0.81–55) | .07 |

**NOTE.** Analysis is based on data for 77 patients with complete antibiotic purchase information.

[a] Determined by test for trend.



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**Table 5. The risk of positive 6-month culture results among patients with multidrug-resistant tuberculosis, by baseline drug susceptibility.**

| Variable | No. of patients with positive culture results/ total no. of patients ($n$ = 55) | RR (95% CI) | Adjusted RR (95% CI)[a] |
|---|---|---|---|
| Kanamycin susceptibility | | | |
| Susceptible | 6/37 | 1.0 | 1.0 |
| Resistant | 15/18 | 5.1 (2.6–13) | 3.9 (1.9–11) |
| Ofloxacin susceptibility | | | |
| Susceptible | 2/18 | 1.0 | 1.0 |
| Resistant | 19/37 | 4.6 (1.6–27) | 1.9 (0.43–12) |
| Streptomycin susceptibility | | | |
| Susceptible | 6/21 | 1.0 | 1.0 |
| Resistant | 15/34 | 1.5 (0.76–3.8) | 1.4 (0.88–2.9) |

**NOTE.** RR, risk ratio.

[a] Adjusted for the listed groups.

culture results than was ofloxacin or streptomycin resistance among patients with MDR TB. Kanamycin and streptomycin are both aminoglycosides and share a common mechanism of action, which is consistent with the nearly identical in vitro growth inhibitory and bactericidal effects of these 2 agents, which show identical killing kinetics of intracellular TB in human macrophages [22]. These 2 agents also have similar dosages, administrative schedules, routes of administration, maximum serum concentrations, and half-lives [23]. However, streptomycin and kanamycin differ markedly in 2 pharmacokinetic parameters: the degree of protein binding (streptomycin is 35%–57% protein bound, whereas kanamycin is effectively unbound) and the volume of distribution (76.4–115.4 L for streptomycin, compared with 13.2–28 L for kanamycin) [23, 24]. One possible reason is that streptomycin, being both protein bound and well distributed in tissue, simply has a lower effective concentration at the pulmonary surface where sputum is being sampled.

Our study had several limitations. First, the prevalence estimates of MDR TB and XDR TB cannot be extrapolated to the general population, because the study population came from a referral hospital that specializes in treating patients with severe TB. Also, drug susceptibility tests of injectible drugs, such as capreomycin and amikacin, and fluoroquinolones other than ofloxacin were not performed. Thus, it is likely that the prevalence of XDR TB was underestimated. Moreover, the cross-sectional nature of our study did not allow us to determine the drug resistance status of patients prior to the regimen that they had previously taken; thus, it is possible that drug resistance may have predated the lengthy regimen. Information on variables such as cumulative duration of treatment and previous treatment regimen were missing for a portion of patients. It is uncertain how this misclassification would affect the associations, but the bias would have to be substantial for the direction of the associations to change.

In summary, we have documented a significant burden of XDR TB associated with prior treatment with second-line drugs among previously treated patients, as well as a high proportion of fluoroquinolone resistance among patients with newly diagnosed cases. Fluoroquinolone resistance, at least in this population, has already significantly penetrated circulating MDR TB strains, limiting the utility of this class of compounds. The development of fluoroquinolone resistance in these TB strains may have been the consequence of widespread availability of these agents without prescription control for the treatment of non-TB disease. This prospective evaluation of treatment regimens used for MDR TB and XDR TB has also led us to the surprising finding that kanamycin susceptibility may be a more important predictor of outcome for patients with MDR TB than is fluoroquinolone susceptibility. These results underscore the urgent need for improved strategies for prevention, detection, and cure of MDR TB and XDR TB through development of new therapeutic agents, faster diagnostics, and greater awareness of drug-resistant TB in the medical community. In the context of South Korea, improving the follow-up of patients with TB in both the public and private sector will contribute to reduction in drug resistance and TB overall.

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