

## THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS IN TURKEY

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### ABSTRACT

**Background** We evaluated the results of treatment in 158 consecutive patients with multidrug-resistant tuberculosis who were treated at our center in Istanbul, Turkey.

**Methods** A total of 21 female patients and 137 male patients (age range, 15 to 68 years) received treatment for multidrug-resistant tuberculosis between March 1992 and October 1999. The patients had previously received a mean of 5.7 antituberculosis drugs and were infected with organisms that were resistant to a mean of 4.4 drugs. All patients received at least three drugs thought to be active; the treatment was continued for at least 18 months after the conversion to a negative culture and for at least 24 months in the absence of first-line drugs.

**Results** The mean number of drugs given during the study was 5.5 (range, 3 to 9). Surgical resection was performed in 36 patients. Adverse effects led to discontinuation of one or more drugs in 62 patients (39 percent). Cultures became negative in 150 patients (95 percent) after a mean of 1.9 months (range, 1 to 9). The overall success rate of treatment was 77 percent, with cures in 78 patients (49 percent) and probable cures in 43 (27 percent). Treatment failed in 13 patients (8 percent). Seven patients died (4 percent). Seventeen patients (11 percent) did not complete the treatment regimen. Thirty-eight percent of the patients with unsuccessful outcomes were infected with organisms that were resistant to more than five drugs. In a step-down logistic-regression analysis, a successful outcome was independently associated with a younger age ( $P=0.013$ ) and the absence of previous treatment with ofloxacin ( $P=0.005$ ).

**Conclusions** Most patients with multidrug-resistant tuberculosis can be cured with the use of appropriate, intensive treatment regimens. (N Engl J Med 2001; 345:170-4.)

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**D**RUG resistance has become a major problem in the treatment of tuberculosis.<sup>1</sup> Resistance rates in Turkey are high because treatment approaches are often inappropriate, rates of treatment completion are low, and therapy is not directly observed. Despite a relatively stable number of new cases of tuberculosis each year, resistance to rifampin is growing, as is multidrug resistance.<sup>2</sup> We report our experience in treating patients with multidrug-resistant tuberculosis.

### METHODS

We conducted our study at the Sureyyapaşa Center for Chest Diseases and Thoracic Surgery, a referral center in Istanbul, Turkey, for workers and family members who receive state social and health services. The center has a comprehensive tuberculosis unit that was established eight years ago to supervise the treatment and follow-up of patients with multidrug-resistant tuberculosis. The unit offers long-term hospitalization (a stay of at least six months), with all needed drug therapy. After discharge, patients may be excused from work for long periods. All expenses during treatment (hospitalization, drugs, and surgery) are covered by the state organization; patients do not incur any expenses. Our tuberculosis unit has unlimited access to all services within the hospital, including the bacteriology, radiology, pathology, and biochemistry laboratories; lung-function testing and bronchoscopy; and the department of thoracic surgery, where resectional surgery is performed. Consultation with specialists is always available as needed.

Our study included 158 consecutive patients with multidrug-resistant tuberculosis who were negative for the human immunodeficiency virus and who received treatment between March 1992 and October 1999. There were 21 female and 137 male patients (age range, 15 to 68 years). Our retrospective evaluation included data on clinical, radiologic, and bacteriologic variables; the outcome of treatment; adverse drug effects; and the association between selected variables and the outcome.

### Diagnosis

On admission, the infection was classified as new or old on the basis of the medical history. Initially, *in vitro* susceptibility tests were performed for all patients with the use of Lowenstein-Jensen medium and the method of proportions. Susceptibility was determined on the basis of the following drugs and concentrations, with appropriate controls: isoniazid (paired samples), 0.5 and 1  $\mu\text{g}$  per milliliter; rifampin (paired samples), 20 and 40  $\mu\text{g}$  per milliliter; ethambutol, 2  $\mu\text{g}$  per milliliter; and streptomycin (paired samples), 5 and 10  $\mu\text{g}$  per milliliter. Resistance was defined as the growth of more than 1 percent as many colonies on drug-containing medium as on drug-free medium.

New cases of tuberculosis were treated according to the guidelines of the National Tuberculosis Control Programme — namely, with the use of isoniazid, rifampin, pyrazinamide, ethambutol, or streptomycin during the initial phase and with the use of isoniazid plus rifampin during the continuation phase. Patients remained hospitalized until smears were negative. Because of the delay in obtaining the results of susceptibility tests (a period of two to three months), we continued the treatment protocol in patients with new infections unless there was a positive smear in the fifth month after the start of treatment. Such a smear was considered to indicate treatment failure due to multidrug-resistant tuberculosis, and further treatment was individualized for all patients who met this criterion.

For patients with previous infections, medical records were reviewed. Documentation of treatment failure with protocols contain-

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ing isoniazid plus rifampin was regarded as evidence of multidrug-resistant tuberculosis.

The disease was classified as extensive or limited on the basis of the radiologic findings. Extensive involvement was defined as the presence of cavities totaling at least 15 cm in diameter or moderately dense infiltrates involving at least 75 percent of the lung fields, or both.<sup>3</sup>

### Treatment

Drugs were classified according to their activity. Active drugs were those that had not been given previously or that had been administered for less than one month. All second-line drugs that had not been used previously were considered to be active. Drugs with uncertain activity were those that had been used previously but that were shown to be active on susceptibility testing. Drugs associated with treatment failure and those to which there was resistance on susceptibility testing were regarded as ineffective.

Regimens comprised at least three active first- or second-line drugs (or a combination of first- and second-line drugs), which were chosen, whenever possible, from the list of previously unused drugs. An appropriate aminoglycoside was always included if possible, in the following order of preference: amikacin (given to 120 patients), kanamycin (15), or streptomycin (8), depending on their cost and availability, and the pattern of resistance. For the 15 patients in whom none of these drugs were appropriate, capreomycin was selected. The preferred oral drugs were pyrazinamide (given to 50 patients), ethambutol (36), ofloxacin (126), protionamide (127), cycloserine (142), and aminosalicic acid (124) (Table 1).

Drugs with uncertain activity were always included in the treatment regimen. When the number of previously unused first- and second-line drugs was less than three, the following drugs with unproved activity were added to the regimen: rifabutin (in 15 patients), clarithromycin (27), clofazimine (11), and amoxicillin-clavulanate (44).

Treatment was continued for at least 18 months after the first negative culture had been obtained and for at least 24 months in the absence of first-line drugs. All patients were hospitalized at least for the duration of parenteral therapy.

The administration of all drugs was initiated at the same time and at full doses with dose intervals adjusted according to the patients' tolerance. Drugs that had life-threatening side effects (nephrotoxic or hepatotoxic effects) or that caused uncontrollable psychosis, visual disturbances, major ototoxicity or neurologic toxicity, or uncontrollable gastrointestinal disturbances were excluded. Patients in whom toxic effects were not documented received parenteral therapy five days a week for at least six months after a negative culture had been obtained.

Surgical resection was considered after two months of treatment for all patients who met the criteria recommended by Iseman et al.<sup>4</sup>: drug resistance with a high probability of failure or relapse, sufficiently localized disease, and the availability of drugs with adequate efficacy to cause rapid healing of the bronchial stump. Preoperative evaluation included computed tomographic scanning of the chest, lung-function tests, quantitative perfusion scintigraphy, and fiberoptic bronchoscopic biopsy.

Follow-up evaluations included a sputum smear, culture, and chest radiograph obtained every month during treatment, every other month during the first six-month period after the completion of therapy, and once during the subsequent six-month period.

A treatment response, a successful outcome (cure or probable cure), and a poor outcome were defined according to the recommendations of the World Health Organization (Table 2).<sup>5</sup> We analyzed the relation between the outcome of treatment and variables that might influence the outcome. Differences with regard to numerical values between the group of patients with successful outcomes and the group with poor outcomes were analyzed with the use of Student's *t*-test for variables with normal distributions and the Mann-Whitney *U* test for those without normal distributions. Nominal variables were assessed by the chi-square test. A step-down logistic-regression model was used to determine independent pre-

**TABLE 1. DRUGS AND DOSES USED IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS.**

DRUG	DOSE
Pyrazinamide	20–30 mg/kg of body weight daily
Ethambutol	15–25 mg/kg daily
Amikacin, kanamycin, streptomycin, or capreomycin	15 mg/kg (maximal dose, 1 g) 5 days a week
Aminosalicic acid	12 g daily
Clofazimine	300 mg daily
Amoxicillin-clavulanate	2–4 g daily
Clarithromycin	1000 mg daily
Protionamide	750–1000 mg daily
Cycloserine	750–1000 mg daily
Ofloxacin	400–800 mg daily
Rifabutin	300 mg daily

dictive factors for a successful outcome. A *P* value of less than 0.05 was considered to indicate statistical significance.

### RESULTS

The mean duration of disease before hospitalization was 80 months (range, 5 to 416). The mean number of drugs used previously was 5.7 (range, 3 to 10). Thirty-four patients (22 percent) had new infections and 124 (78 percent) had old infections. The mean number of drugs to which resistance was shown was 4.4 (range, 2 to 9). A total of 152 patients (96 percent) had at least one pulmonary cavity. The disease was extensive in 63 patients (40 percent) and was limited in 95 (60 percent). Concomitant diseases included di-

**TABLE 2. DEFINITIONS OF OUTCOMES.\***

OUTCOME	DEFINITION
Response to treatment	Conversion from positive to negative smears and cultures during treatment
Successful outcome	
Probable cure	Negative smears and cultures throughout treatment for at least 6 months
Cure	Negative smears and cultures throughout treatment for at least 18 months (or 24 months, in the absence of first-line drugs)
Poor outcome	
Treatment failure	Persistence of positive smears or cultures despite treatment for at least 18 or 24 months
Incomplete treatment	Failure to complete treatment because of adverse effects or for other reasons
Death	Death from tuberculosis or complications of treatment
Relapse	Recurrence of positive smear or culture after achievement of a cure

\*Definitions are based on the recommendations of the World Health Organization.<sup>5</sup>

abetes alone (in 23 patients), asthma (in 1), ischemic heart disease and diabetes (in 1), familial Mediterranean fever (in 1), and psoriasis (in 1).

There were 69 individualized treatment protocols. The three most common combinations of drugs were amikacin, ofloxacin, cycloserine, protionamide, and aminosalicic acid, a regimen given to 42 patients (27 percent); amikacin, ethambutol, pyrazinamide, ofloxacin, protionamide, and cycloserine, a regimen given to 9 patients (6 percent); and amikacin, ofloxacin, protionamide, cycloserine, pyrazinamide, and aminosalicic acid, a regimen also given to 9 patients (6 percent).

The mean length of hospitalization was 200 days (range, 60 to 450). During hospitalization, a mean of 5.5 drugs (range, 3 to 9) were administered, including a mean of 4.4 active drugs (range, 1 to 8). All patients received an aminoglycoside for a mean period of 6 months (range, 1 to 11). The mean follow-up period after the completion of treatment was 27 months (range, 6 to 85). Adverse effects resulted in the withdrawal of one or more drugs in 62 patients (39 percent). In two patients with drug-induced hepatitis, treatment was discontinued until the hepatitis had been controlled (Table 3).

In addition to chemotherapy, 36 patients (23 percent) underwent surgical resection, after 3 to 10 months of treatment (mean, 5.9). All but two of the patients had negative smears and cultures at the time of surgery. Cultures became negative in 150 patients (95 percent) after a mean of 1.9 months of treatment (range, 1 to 9). Treatment was successful in 121 patients (77 percent); 78 patients (49 percent) were classified as cured, and 43 (27 percent) had probable cures. The outcome was successful in 89 of the 122 patients treated without surgery (73 percent). Seventeen patients (11 percent) did not complete the treatment regimen. Treatment failed in 13 patients (8 percent). Seven patients died (4 percent). Of the 78 patients who were considered to be cured, 18 were subsequently lost to follow-up. For the other 60 patients, the duration of follow-up ranged from 20 to 85 months (mean, 39). Relapse was observed in 1 of the 78 patients 24 months after the completion of therapy, including surgery.

Of the 36 patients who underwent surgery, 21 (58 percent) had cures and 11 (31 percent) had probable cures, for an overall success rate of 89 percent. Two patients died, one did not have a response to treatment, and one did not complete the regimen.

There were no statistically significant differences between the group of patients with successful outcomes and the group with unsuccessful outcomes, with regard to sex, the number of drugs to which organisms were resistant or susceptible, the extent and duration of disease, or the number of drugs used in the study protocol. However, patients with unsuccessful outcomes had a higher mean age ( $42 \pm 11$  vs.  $36 \pm 12$

TABLE 3. ADVERSE EFFECTS OF DRUGS.

DRUG AND ADVERSE EFFECT	NO. OF PATIENTS TAKING DRUG	NO. WITH ADVERSE EFFECTS (%)
<b>Amikacin</b>	120	40 (33)
Hearing loss		38
Hearing loss and vertigo		1
Hearing loss and renal dysfunction		1
<b>Kanamycin</b>	15	2 (13)
Hearing loss		1
Vertigo		1
<b>Streptomycin</b>	8	2 (25)
Hearing loss		2
<b>Capreomycin</b>	15	3 (20)
Hearing loss		2
Renal dysfunction		1
<b>Cycloserine</b>	142	4 (3)
Psychosis		4
<b>Protionamide</b>	127	2 (2)
Hepatitis		2
<b>Aminosalicic acid</b>	124	2 (2)
Gastrointestinal disturbance		2
<b>Rifabutin</b>	15	7 (47)
Leukopenia		7
<b>Clarithromycin</b>	27	2 (7)
Rash		1
Gastrointestinal disturbance		1

years,  $P=0.008$ ), a larger median number of drugs used previously (six vs. five,  $P=0.048$ ), a higher incidence of antecedent ofloxacin use (57 percent vs. 30 percent,  $P=0.004$ ), and a lower frequency of ofloxacin use in the study protocol (65 percent vs. 84 percent,  $P=0.018$ ). The percentage of patients with organisms that were resistant to more than five drugs (in an analysis in which the number of drugs was classified as two or three, four or five, or six to nine) was significantly higher in the group with unsuccessful outcomes (38 percent vs. 12 percent,  $P=0.001$ ). Step-down logistic regression showed that age and previous use or non-use of ofloxacin had significant independent effects on the outcome of treatment ( $P=0.013$  and  $P=0.005$ , respectively) (Table 4).

## DISCUSSION

There have been many large, well-documented case-series analyses of the treatment of tuberculosis.<sup>6</sup> Despite many recommendations, however, no treatment regimens have proven efficacy against multidrug-resistant tuberculosis. Moreover, treatment usually involves potentially toxic drugs.<sup>7</sup> There is controversy over whether to consider multidrug-resistant tuberculosis treatable or untreatable, given the often limited resources available.<sup>8-10</sup>

**TABLE 4.** CHARACTERISTICS OF PATIENTS, TREATMENT REGIMENS, AND DISEASE IN RELATION TO THE OUTCOME.\*

VARIABLE	UNSUCCESSFUL OUTCOME (N=37)	SUCCESSFUL OUTCOME (N=121)	P VALUE	LOGISTIC REGRESSION	
				REGRESSION COEFFICIENT	P VALUE
Age (yr)	42±11	36±12	0.008	-0.042	0.013
Sex					
Male	35	102	>0.05	-1.178	0.168
Female	2	19			
Median no. of drugs previously used	6	5	0.048	0.258	0.385
Median no. of drugs to which isolate was resistant	5	4	>0.05	-0.047	0.856
Extensive disease (% of patients)	46	38	>0.05	-0.811	0.084
Median no. of active drugs	5	5	>0.05	0.213	0.503
Median no. of drugs used in study regimen	5	5	>0.05	0.077	0.837
Duration of disease (mo)	70±56	83±90	>0.05	0.006	0.082
Previous use of ofloxacin (% of patients)	57	30	0.004	-1.123	0.005
Inclusion of ofloxacin in study regimen (% of patients)	65	84	0.018	0.978	0.117

\*Plus-minus values are means ±SD.

Our study shows that multidrug-resistant tuberculosis is treatable and that a similar strategy for managing new and old infections is effective. In our case series, there was a bacteriologic response rate of 95 percent. The rates of cure, probable cure, and overall success were 49, 27, and 77 percent, respectively. With medical therapy alone, a successful outcome was achieved in 73 percent of cases.

In an early study of the treatment of multidrug-resistant tuberculosis, Goble et al. reported an overall response rate of 56 percent.<sup>3</sup> The response rates have been higher in more recent studies. In a study of patients in New York, the rate of successful treatment was 96 percent,<sup>11</sup> and a report from Korea cited a bacteriologic response rate of 83 percent<sup>12</sup>; in the latter study, a successful outcome was mainly associated with the use of quinolones.

Despite these encouraging results, the emergence and rapid growth of multidrug-resistant tuberculosis are still a matter of great concern. Our data also demonstrate how programs for the control of tuberculosis and multidrug-resistant tuberculosis should not be implemented. We often see patients in whom drug resistance has developed because of inappropriately or poorly implemented primary programs of tuberculosis control. For example, in Turkey case finding is mainly passive and follow-up is inconsistent; thus, estimates of the overall prevalence or cure rate throughout the country cannot be made. The problem is further complicated by the unrestricted sales of all first-line antituberculosis drugs.

Rifampin, for example, has been sold since the 1970s without any restrictions, and in recent years, second-line antituberculosis drugs have also become available without restrictions. Failure to control the use of these drugs will inevitably make multidrug-resistant tuberculosis even more common.

When a treatment fails despite hospitalization and the use of a regimen that includes isoniazid and rifampin, we individualize the therapy. In our series, we did not perform susceptibility tests for second-line drugs because the probability of primary resistance is relatively low as a result of the recent introduction of these drugs and because acquired resistance to these drugs can be suspected from the medical history.

The inclusion of ofloxacin in the study protocols and its absence in previous regimens were associated with a successful outcome. Moreover, ofloxacin was well tolerated, and no severe adverse events were associated with its use. In fact, among the second-line drugs, ofloxacin was the only one that did not have to be withdrawn in one or more cases because of adverse events.

In a step-down, logistic-regression analysis, older age and the inclusion of ofloxacin in previous regimens were significantly associated with a poor outcome. In addition, there was a significant relation between resistance to more than five drugs and an unsuccessful outcome.

In our study, 89 percent of the patients who underwent surgery had successful outcomes. However, the

role of surgical resection in the treatment of multidrug-resistant tuberculosis requires validation by comparative studies.

In conclusion, our data indicate that multidrug-resistant tuberculosis is a curable disease, provided that an appropriate approach to control is implemented and that appropriate treatment protocols are used.

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