

Drug-resistant tuberculosis in a tertiary referral teaching hospital of Korea

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Background : Resistance of *Mycobacterium tuberculosis* strains is an increasing problem worldwide. Our purpose was to determine the prevalence of drug resistance (DR) and risk factors of DR in patients with tuberculosis and to assess the clinical characteristics and socioeconomic status of patients with drug-resistant tuberculosis.

Methods : We retrospectively studied drug susceptibility tests and clinical and socioeconomic records for 308 cases of culture-positive *Mycobacterium tuberculosis* infection, diagnosed at Mokdong Hospital, Ewha Womans University from March, 1995 to February, 2000.

Results : DR to at least one drug was identified in 75 (24.4%); the rate of primary DR, 18.7% and acquired DR, 39.3%. Multi-drug resistance (MDR) was identified in 31 (10.1%); primary MDR, 7.0% and acquired MDR, 21.4%. The risk factors of DR were previous TB treatment, pulmonary involvement and associated medical illness. DR group showed lesser adherence to treatment than the drug-sensitive group. DR group showed more frequent self-interruption of medication, lower completion rate of treatment and higher failure rate of follow-up than the drug-sensitive group. In previously treated tuberculosis patients, higher rate of overall DR and MDR, larger number of resistant drugs and more frequent self-interruption of medication were observed than newly diagnosed patients. Among DR group, acquired DR (ADR) group was older, less educated and treated for longer duration and had more advanced disease than primary DR group.

Conclusion : Previously treated tuberculosis is a most important risk factor for DR. DR group, especially ADR, showed less compliance with treatment. More proper education and attention to prevent self-interruption should be given to a previously treated group. In TB prevalent areas, it should be considered to obtain initial drug susceptibility testing in high risk of DR.

Key Words : tuberculosis; drug resistance; Korea

INTRODUCTION

Tuberculosis (TB) is one of the major infectious diseases in severity and morbidity despite coverage of the National Tuberculosis Program and improved social and

economic conditions¹⁾. Recently, epidemic of acquired immune deficiency syndromes, poor isolation of drug-resistant subjects and increased numbers of poor and crowded residences have caused increased proportion of drug resistance (DR), especially multi-drug resistance (MDR)²⁻⁷⁾. In Korea, although the overall prevalence of tuberculosis is diminished to less than 1.0%, the rate of drug resistance, especially MDR in previously treated groups was still high^{8,9)}. It is important to define the risk factors,

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including the socioeconomic status of DR for the prompt isolation and proper management of drug-resistant tuberculosis. We examined current characteristics of DR in a university hospital setting and compared it to national studies.

MATERIALS AND METHODS

1. Study population

From March 1995 through February 2000, 308 patients with culture-positive *Mycobacterium tuberculosis* infection and their drug susceptibility testing were included. The medical records of these patients were reviewed and the following data were collected: age, sex, history of previous antituberculous treatment, familial history of TB, associated medical illness of diabetes mellitus, liver disease and malignancy, history of smoking and alcohol drinking, marital status, and employment status. Whether they graduated more than high school and had resided in their own houses were inquired of patients with drug resistant tuberculosis using interviews by letters or telephones.

2. Drug susceptibility test

The drug susceptibility testing against ten antituberculosis drugs was conducted by a laboratory certified under the Korean National Tuberculosis Association. The drug susceptibility of the *M. tuberculosis* isolates was determined by the absolute concentration method described in detail by Canetti et al⁽⁹⁾. The drugs and their critical concentrations for resistance are as follows: isoniazid 0.2 µg/mL; rifampin 40 µg/mL; ethambutol 2 µg/mL; streptomycin 10 µg/mL; kanamycin 40 µg/mL; prothionamide 20 µg/mL; cycloserine 30 µg/mL; paraaminosalicylic acid 1 µg/mL; ofloxacin 2 µg/mL. Pyrazinamide susceptibility was determined by pyrazinamidase test.

3. Definitions

The term 'previously treated TB patients' refers to patients with verified TB with treatment of more than one month in the past. The term 'drug resistance' means resistance to at least one antituberculosis drug, 'poly-drug resistance' means resistance to more than any two drugs and 'multi-drug resistance' means resistance to at least isoniazid and rifampin. The term 'primary DR' refers to resistance occurred in a patient who has never received antituberculosis therapy and 'acquired DR' refers to resistance developed during or following chemotherapy of subjects who had previously been regarded as drug-susceptible tuberculosis.

4. Data analysis

The data were analyzed using SPSS software. The ² test and independent T test were applied to compare variables between the two groups. Multiple logistic regression analysis was used to define the strength of major risk factors to develop DR.

RESULTS

1. Rate of drug resistance

Among 308 culture-positive patients, 187 had newly diagnosed TB and 84 had previously treated TB, except for 37 cases with no available record of previous TB history. Resistance to at least one drug was found in 75 (24.4%) out of 308 cases and MDR in 31 (10.1%). Among antituberculosis drugs, resistance to isoniazid was the most common (19.5%), followed by resistance to rifampin (12.3%), ethambutol (8.8%) and streptomycin (5.8%). Primary DR was found in 35 (18.7%) out of 187 cases and primary MDR in 13 (7.0%). Primary DR to isoniazid was 13.4%; rifampin, 9.1%; ethambutol, 7.0% and streptomycin, 4.8%. Acquired DR was found in 33 (39.3%) out of 84 cases and acquired MDR in 18 (21.4%). Acquired DR to isoniazid was 35.7%; rifampin, 22.6%; ethambutol, 15.5% and streptomycin, 8.3%. Each of acquired DR and acquired MDR was significantly higher than each of primary DR and primary MDR (39.3% vs. 18.7%; $p < 0.001$, 21.4% vs. 7.0%; $p < 0.01$) (Table 1).

Table 1. Resistance to antituberculosis drugs in culture-positive tuberculosis cases.

Type of drug resistance	All patients (n=308)		No previous treatment (n=187)		Previous treatment (n=84)	
	N	%	N	%	N	%
Any drug	75	24.4	35	18.7	33	39.3 [‡]
Single drug resistance	32	10.4	17	9.1	12	14.3
Poly-drug resistance	43	14.0	18	9.6	21	25.0 [‡]
Multi-drug resistance	31	10.1	13	7.0	18	21.4 [‡]
Isoniazid	60	19.5	25	13.4	30	35.7 [‡]
Rifampin	38	12.3	17	9.1	19	22.6 [†]
Ethambutol	27	8.8	13	7.0	13	15.5*
Streptomycin	18	5.8	9	4.8	7	8.3
Pyrazinamide	13	4.2	5	2.7	7	8.3*
Paraaminosalicylic acid	13	4.2	5	2.7	7	8.3*
Prothionamide	6	1.9	1	0.5	4	4.8*
Kanamycin	5	1.6	2	1.1	3	3.6
Ofloxacin	4	1.3	3	1.6	1	1.2
Cycloserine	0	0.0	0	0.0	0	0.0

* $p < 0.05$, [†] $p < 0.01$, [‡] $p < 0.001$ vs. no previous treatment

2. Comparison between drug-sensitive group and drug-resistant group

Drug-resistant group presented a history of previously treated TB (48.5% vs. 25.1%; $p<0.001$), pulmonary involvement of TB (92.6% vs. 80.1%; $p<0.05$) and associated medical illness more frequently than drug-sensitive group (29.4% vs. 19.5%; $p<0.05$). Drug-resistant group showed more frequent self-interruption of medication (38.8% vs. 13.4%; $p<0.001$), lower completion rate of treatment (39.7% vs. 58.4%; $p<0.01$) and higher failure rate of follow-up than drug-sensitive group (36.8% vs. 12.7%; $p<0.001$) (Table 2).

Table 2. Characteristics of patients with culture-documented tuberculosis.

Variables	Drug-sensitive group (n=233)	Drug-resistant group (n=75)
Age (year)	43.0 ± 18.9	43.5 ± 16.8
Body mass index (kg/m ²)	19.6 ± 3.1	20.2 ± 2.0
Male sex	58.4%	53.3%
Previously treated tuberculosis	25.1%	48.5% [†]
Family history of tuberculosis	22.7%	21.8%
Site of disease		
Pulmonary only	80.1%	92.6%*
Pulmonary & extrapulmonary	15.8%	7.4%
Extrapulmonary only	4.1%	0.0%
Cavitary disease in chest X-ray	19.5%	29.4%
Associated medical illness	12.7%	25.4%*
Diabetes mellitus	8.1%	16.4%*
Liver disease	3.6%	6.0%
Malignancy	1.8%	3.0%
History of smoking	52.1%	51.7%
History of alcohol abuse	6.3%	7.1%
Single	37.3%	29.1%
Unemployed	31.7%	21.3%
Self-interruption of regular medication	13.4%	38.8% [‡]
Process of treatment		
Completion of treatment	58.4%	39.7% [†]
Failure to follow-up	12.7%	36.8% [‡]

Data are mean ± SD. * $p<0.05$, [†] $p<0.01$, [‡] $p<0.001$ vs. drug-sensitive group

3. Risk factors of drug resistance

Multiple logistic regression analysis was applied to factors associated with DR and MDR. Previous treatment of TB was the strongest risk factor of DR (odds ratio, 2.67; $p<0.01$) and MDR (odds ratio, 3.69; $p<0.01$).

Pulmonary involvement of TB (odds ratio, 3.27; $p<0.05$) and associated medical illness (odds ratio, 2.30; $p<0.05$) were also risk factors of DR, but not of MDR (Table 3).

Table 3. Factors associated with resistance to antituberculosis drugs

Factor	Drug resistance		Multi-drug resistance	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Previous treatment of TB	2.67 (1.48-4.31)	<0.01	3.69 (1.67-8.13)	<0.01
Pulmonary involvement of TB	3.27 (1.21-8.34)	<0.05	-	0.34
Associated medical illness	2.30 (1.12-4.75)	<0.05	-	0.16

CI, confidence interval

4. Comparison between primary DR and acquired DR

Acquired DR group was older (48.2 ± 16.5 years vs. 39.6 ± 16.3 years; $p<0.05$) and lesser educated than primary DR group (11.1% vs. 38.9%; $p<0.05$). Acquired DR group also had higher rate of family history of TB (28.0% vs. 16.7%) and more lived in rented houses than primary DR group (30.8% vs. 22.2%), but it is not statistically significant (Table 4). Acquired DR group showed more involved lobes in chest X-ray (2.0 ± 0.8 vs. 1.4 ± 0.7; $p<0.01$) and longer duration of treatment than PDR group (18.3 ± 7.2 months vs. 10.6 ± 6.3 months; $p<0.05$) (Table 5).

Table 4. Demographic and social status of drug-resistant tuberculosis

Variables	Primary drug resistance (n=35)	Acquired drug resistance (n=33)
Age (years)	39.6 ± 16.3	48.2 ± 16.5*
Body mass index (kg/m ²)	20.2 ± 2.2	20.1 ± 1.8
Male sex	46.2%	53.8%
Family history of tuberculosis	16.7%	28.0%
History of smoking in male	76.5%	72.2%
History of alcohol abuse	6.7%	7.7%
Single	26.7%	32.0%
Unemployed	20.0%	22.7%
Highly educated	38.9%	11.1%*
Living in a rented house	22.2%	30.8%

Data are mean ± SD. * $p<0.05$ vs. primary drug resistance

Table 5. Clinical characteristics of drug-resistant tuberculosis

Variables	Primary drug resistance (n=35)	Acquired drug resistance (n=33)
Number of resistant drugs	2.3 ± 1.6	2.8 ± 1.9
Site of disease		
Pulmonary only	94.3%	90.9%
Pulmonary & extrapulmonary	5.7%	9.1%
Lesion of chest X-ray		
Cavitary disease	31.4%	27.3%
Number of involved lobes	1.4 ± 0.7	2.0 ± 0.8 [†]
Hospitalization	60.0%	48.5%
Associated medical illness	41.2%	58.8%
Diabetes mellitus	14.7%	18.2%
Liver disease	5.9%	6.1%
Malignancy	0.0%	3.0%
Self-interruption of regular medication	31.5%	46.9%
Process of treatment		
Completion of treatment	37.1%	42.4%
Failure to follow-up	34.3%	39.4%
Duration of treatment (months)	10.6 ± 6.3	18.3 ± 7.2*

Data are mean ± SD. * $p < 0.05$, [†] $p < 0.01$ vs. primary drug resistance

DISCUSSION

This study presented findings related to drug resistance in a TB endemic country not associated with HIV epidemic. The drug resistance in TB is one of the most important problems in the world and a major cause of morbidity and mortality²⁾. TB was one of the most common 10 causes of Korean adults' deaths until 1996⁸⁾. DR and severity of infection are important factors determining the mortality in TB patients. The national goal of TB control is closely related to control of DR. According to a national TB survey of Korea, the rate of DR was the highest in 1980 and then it tended to decline^{8, 9)}.

The rate of isoniazid-resistant TB was the highest among the antituberculous drugs throughout the world and the rate of rifampin-resistant TB was high in an endemic area^{5, 11-14)}. This study showed that nearly 20 percent of the patients with active TB could transmit isoniazid-resistant organisms. The use of rifampin with or without pyrazinamide in chemoprophylaxis for the case contact in a prevalent area of isoniazid-resistant TB is issued¹⁵⁾. The increasing resistance to rifampin is

particularly troubling, since rifampin is essential to short-course antituberculosis therapy¹⁶⁾. In this study, 10 percent of the total cases could transmit organisms resistant to both isoniazid and rifampin. Consensus on preventive therapy for MDR TB was not reached and the current recommendation was a regimen of pyrazinamide and fluoroquinolone for 4 months¹⁷⁾.

Because previous use of antituberculous medication was the most important risk factor of DR^{4, 6, 13, 14, 18, 19)} as shown in this study, and accompanied medical illness due to decreased immunity was high risk group of DR^{3, 20, 21)}, DR should be suspected in cases of delayed response to therapy or continued positive AFB smear despite treatment. The ability to complete antituberculosis therapy can be affected by housing status, employment status, level of literacy and psychological aspects²²⁻²⁵⁾. In this study, alcohol abuse, marital status or employment status did not influence the development of DR. Because patients with DR are usually treated with 2nd line antituberculosis drugs for a long duration, which are more toxic and costlier than first line drugs, they are apt to have poor adherence to medication compared with drug-sensitive patients. The other factors to develop DR are drug intolerance during therapy²⁵⁾, contact with DR TB²⁶⁾, birth and residence in an endemic area^{5, 6, 13, 14, 19)}, HIV infection^{6, 13)} and cavitary pulmonary tuberculosis^{18, 19)}.

The first large scale sample survey in Korea in 1994, cooperation with WHO and IUATLD^{7, 11)}, presented lower rates in overall DR and primary DR and higher rate in acquired DR compared with this study (Table 6). The discrepancies between this study and the nationwide study could originate from differences in the size and nature of the study population, study period and study area. The population of previous treated TB cases out of all cases in this study was higher than that in the national study (84 of 308 cases, 27.3% vs. 189 of 2675 cases, 7.1%). This could contribute to raise the overall rate of DR in this study. Although the rate of acquired DR was lower in this study than the national survey of 1994, the rate of MDR is about 3 times that of the national survey of 1994. The population of this study was derived mainly from residents in Seoul. Residents in other areas were only 52 (13.6%) out of 308 patients. Therefore, this study could represent drug resistance in Seoul as an urban area. Generally, an urban community is more crowded and has more chance to transmit an infectious disease than a rural community. As another reason to be considered, more advanced cases among newly diagnosed subjects might prefer to be treated in 3rd referral hospitals

rather than in a public TB care center as in rural areas. Actually, in this study, patients with primary DR showed a higher rate of hospitalization despite a younger age than those with acquired DR, and the rate of primary MDR in this study was far higher than that in the national survey of 1994. Our data had comparable results with the report from Chungnam University of Korea²⁷⁾.

In this study, patients with acquired DR showed chronic reluctant course, low education level and low economic status compared with those with primary DR. Traditionally, patients with DR TB are classified as having acquired DR or primary DR on the basis of a history of previous TB treatment^{28, 29)}. Only cases of primary DR are assumed to be due to transmission of DR strains. Recent studies based on restriction-fragment length polymorphisms, useful in distinguishing different strains of *M. tuberculosis*, revealed that recent transmission as well as true acquisition of DR during therapy was an important cause of DR, especially MDR, even in previously treated cases in certain urban populations^{30, 31)}. Therefore, traditional clinical classification based on a history of previous treatment may result in misinterpretation and the underestimation of transmission. Improper isolation and poor ventilation due to crowding are important reasons for spread of TB particularly in the low socioeconomic status of urban areas. The resistant cases, especially previously treated, remain sources of infection for prolonged periods

and they are likely to infect others³¹⁻³⁵⁾. Finally, the high rate of DR and MDR in acquired cases contribute to increasing rates of DR and MDR in primary cases.

When dealing with a patient who has resistant TB, it is very important that the physician evaluate the situation fully. When seeing a patient who has already been treated for TB, susceptibility tests should be ordered. The only way to ensure that patients take their medication properly is to give it to them, i.e. direct observed therapy (DOT)³⁴⁾. Although routine DOT can not be afforded in many countries with a high prevalence of MDR TB, application of DOT is requisite in drug resistant TB, especially for poor adherence to treatment, to prevent the development of further drug resistance³⁶⁾.

Previously treated tuberculosis is a most important risk factor for DR. DR group, especially ADR, showed less compliance with treatment. More proper education and attention to prevent self-interruption should be given to a previously treated group. This study showed a higher rate of primary DR and primary MDR compared to the national study, suggesting more severe cases among newly diagnosed patients treated in tertiary referral hospitals rather than public TB care centers. High rate of acquired DR contributes to increasing the rate of primary DR. Initial drug susceptibility testing is necessary to guide optimal treatment to a culture positive case with the high risk of DR, especially in TB prevalent areas.

Table 6. Drug resistance among Korean patients with tuberculosis in our study and other reports

Study group	Ewha Womans University Mokdong Hospital	Korea, Global Surveillance by WHO/ IUATLD ⁶	Chungnam National University Hospital ⁷
Period	1995.3- 1999.12	1994.7- 1994. 9	1995.1- 1996.6
Number of patients	n=308 P=187 R=84	n=2675 P=2486 R=189	n=92 P=66 R=26
Overall drug resistance (%)	24.4	14.4	26.0
Poly-drug resistance (%)	14.0	7.1	-
Primary drug resistance (%)	18.7	11.3	16.7
Acquired drug resistance (%)	39.3	54.0	50.0
Multi-drug resistance (%)	10.1	3.4	8.6
Primary MDR (%)	7.0	1.6	3.0
Acquired MDR (%)	21.4	27.5	23.0
Isoniazid (%)	19.5	10.4	19.5
Rifampin (%)	12.3	4.3	9.7
Ethambutol (%)	8.8	4.5	9.7
Streptomycin (%)	5.8	3.6	11.9
Pyrazinamide (%)	4.2	1.8	5.4

P, number of new cases; R, number of retreatment cases.

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