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Susceptibility of First-Line Antituberculosis Drugs in Southeastern Turkey

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Abstract: ***Introduction: Tuberculosis (TB) continues to be one of the world's most mortal infectious disease even in the 21st century. Multiple Drug Resistant TB (MDRTB) is still a serious health care problem, especially in developing countries. It was aimed to evaluate the susceptibility rates of Mycobacterium tuberculosis complex (MTC) strains to first-line antituberculosis drugs.***
Methodology: MTC isolates obtained from clinical specimens sent to Dicle University Hospital Mycobacteriology laboratory from January 2012 to December 2015 were evaluated retrospectively. First culture-positive samples of the same patients were evaluated. BACTEC MGIT 960 TB (Becton Dickinson, USA) system was used for sensitivity testing of first-line anti-TB drugs; streptomycin (S), isoniazid (INH), rifampicin (RIF) and ethambutol (ETM).
Results: Overall 10993 clinical specimens were evaluated over a period of four years. A total of 415 MTC strains were isolated and susceptibility testing was carried out. Samples consisted of 341 (82,2%) pulmonary and 74 (17,8%) extra-pulmonary materials. Among 341 pulmonary isolates, 204 (59,8%) were Ziehl-Neelsen (Z-N) positive. Of 74 extra-pulmonary isolates, 31(41,9%) were Z-N positive. A total of 130 (31,3%) isolates were resistant to at least one anti TB drug. Single drug resistance was detected in 82 isolates (19,8%). Twenty one isolates (5,1%) were determined as multi-drug resistant (MDR). Ten (2,4%) isolates were resistant to all four drugs.
Conclusion: Our study indicated that drug resistance rates of our hospital are consistent with the average rates of Turkey. Evaluation of regional antituberculosis drug resistance along with rapid and accurate diagnosis would contribute to tuberculosis control programs.

Key words: Mycobacterium tuberculosis complex, MGIT 960 TB, isoniazid, rifampicin, ethambutol, streptomycin

I. INTRODUCTION

Tuberculosis (TB) is a mortal infectious disease caused by Mycobacterium tuberculosis complex(MTC). About 9,6 million cases were estimated to have had TB in 2014; 63% of them were notified to national TB programmes, while approximately 3 million cases were not reported to national TB programmes. Among TB cases, 1,1 million (13%) were estimated to be co-infected with Human Immun Deficiency Virus (HIV). In 2014, 1,5 million deaths from TB were reported; 0,4 million of them were HIV-positive. From 2000 to 2014, 43 million lives were saved by effective diagnosis and treatment. Laboratory diagnosis of TB and detection of drug resistance lead to accurate treatment protocols. Drug resistance not only leads to treatment difficulties but also increases risk of spreading drug resistant isolates in the community. Approximately 480 000 people were estimated to have had multi-drug resistant

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tuberculosis (MDR-TB); 3,5% of them were new and 20,5% were previously treated cases (1).

Effective TB control is related with rapid and accurate laboratory diagnosis. Sputum smear microscopy is the most frequent method for diagnosing TB due to its rapidness, cost-effectiveness and ease of application. Although increasing usage of rapid molecular tests in last decades, culture remains as the gold standard method.

BACTEC MGIT 960 is a broth-based, automated cultivation and detection method based on a fluorescent oxygen sensor. It provides an efficient and rapid procedure for detecting bacterial growth and for testing drug susceptibility (2),(3).

In the present study we aimed to evaluate drug susceptibilities of MTC strains in culture positive samples sent to our mycobacteriology laboratory, over a period of four years.

II. METHODOLOGY

Patients and setting

Clinical samples sent to Mycobacteriology Laboratory of Dicle University Hospital from January 2012 to December 2015 were evaluated retrospectively. First culture-positive samples of the same patients were evaluated. Clinical materials consisted of 341 (82.2%) pulmonary (297 sputum, 36 bronchoalveolar lavage, 8 post bronchoscopic sputum) and 74 (17.8%) extra-pulmonary samples (23 pus, 14 gastric fluid, 11 urine, 10 tissue, 9 pleural fluid, 5 peritoneal fluid and 2 cerebrospinal fluid). Procedures of the clinical specimens were conducted in a class II biological safety cabinet of Biosafety Level 3 Laboratory(4).

Ziehl-Neelsen staining

Each non-sterile material such as sputum was processed by the standard 4% NaOH and N-acetyl-L-cysteine method before staining(5). Sterile biological specimens such as cerebrospinal fluid were directly stained by Ziehl-Neelsen (ZN) without any process. Smears were examined under a light microscope for acid-fast bacilli(AFB) and were reported according to Forbes et al(6).

MGIT 960 TB method

MGIT vials were supplemented with 0.8 ml of BBL MGIT PANTA antibiotic mixture (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, and azlocillin) and OADC enrichment (Becton Dickinson, U.S.A) before inoculation. Sterile biological specimens such as cerebrospinal and pleural fluid were inoculated directly into MGIT vial while sputum and other non-sterile materials were underwent for homogenisation and decontamination before inoculation. Phosphate buffer (pH 6.8) was added up to a volume of 50 ml for neutralisation and the mixture was centrifuged at 3,000 rcf for 15 minutes. After removal of supernatant, the sediment was resuspended in phosphate buffer and 0.5 ml of the mixture was inoculated into MGIT vial. Also 0.2 ml cell suspension was inoculated on Lowenstein- Jensen medium slant and was incubated at 37^{o}C for 6 weeks. MGIT cultures were incubated at 37^{o}C in a BACTEC MGIT-960 instrument (Becton Dickinson) for 42 days. MGIT tubes with growth units of more than 75 were collected from the station.

Mycobacterium identification by BD MGIT^{TM}TBc ID test

MPT64 antigen of MTC was detected by a rapid chromatographic immunoassay from AFB smear positive MGIT tubes. 100 µl suspension from MGIT tube was added into the sample well of the ID test device and waited for 15 minutes. The appearance of two lines at ‘C’ (control) and ‘T’ (test) positions indicated MTC (1).

Drug suscebtibility testing (DST) by MGIT960 system

DST was performed for tubes identified as MTC. Five BACTEC MGIT 960 vials were used for this process; one for growth control (GC) and others for streptomycin (S), isoniazid (INH), rifampicin (RIF) and ethambutol (ETM). Drug concentrations for S, INH, RIF, and ETM were 1.0 mg/ml,

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0.1 mg/ml, 1.0 mg/ml and 5.0 mg/ml, respectively. MGIT supplement of 0.8 ml was added to all five tubes. GC tube was drug-free. The growth ratios between drug-containing tubes and GC tube were determined and susceptibility results were reported by MGIT960 system, automatically. Resistance and susceptibilities were defined by guidelines of the International Union Against Tuberculosis and Lung Disease (IUATLD) and the World Health Organisation (WHO). Multi drug resistant Mycobacterium tuberculosis complex (MDR-MTC) was defined as resistance to both isoniazid and rifampicin with or without resistance to any other drugs(7) .

Quality controls and data analysis

The reference strain of H37Rv (ATCC 27294) was used as quality control of MGIT 960 system, every batch of drugs and ZN staining method.

Data analysis was performed with SPSS version 10.0 sofware package for Windows (SPSS Inc, USA). Pearson's chi-square test was used for proportions. P value of <0.05 was considered significant.

III. RESULTS

From January 2012 to December 2015 10993 clinical samples were evaluated. Among them, 1112 (10.1%) were detected as MTC and drug susceptibility testing (DST) was carried out. A total of 415 culture positive patients enrolled in the study. Among 415 patients, 231 (55,7 %) were male and 184(44,3 %) were female. Mean age of the MTC isolated patients was 37± 18.8 (range 0 – 89 years). A total of 14 patients (3,4 %) were aged between 0-14 years and 55 patients (13,3 %) were 65 and above.

No. (%) of single and total drug resistant isolates

		Isoniasid		Streptomycin		Ethambutol		Rifampicin	
Year	Isolate no	Single n(%)	Total n(%)	Single n(%)	Total n(%)	Single n(%)	Total n(%)	Single n(%)	Total n(%)
2012	55	8 (14,5)	14 (25,5)	4 (7,3)	9 (16,4)	3 (5,5)	7 (12,7)	1 (1,8)	4 (7,3)
2013	132	12 (9,1)	27 (20,5)	7 (5,3)	22 (16,7)	1 (0,8)	2 (1,5)	1 (0,8)	6 (4,5)
2014	112	12 (10,7)	26 (23,2)	7 (6,3)	18 (16,1)	4 (3,8)	12(10,7)	3 (2,7)	12(10,7)
2015	116	10 (8,6)	22 (19,0)	6 (5,2)	16 (13,8)	3 (2,6)	7 (6,0)	0 (0)	4 (3,4)
Total	415	42 (10,1)	89 (21,4)	24 (5,8)	65 (15,7)	11 (2,7)	28 (6,7)	5 (1,2)	26 (6,3)

Table 1:Single and total resistance of first-line drugs

Among 341 pulmonary samples, 204 (59,8%) were Z-N positive. Of 74 extra-pulmonary isolates, 31(41,9%) were Z-N positive. DST was performed for the first-line anti-TB drugs; S, INH, RIF and ETM. Overall, 285 (68,7 %) MTC isolates were susceptible to all four antibiotics tested. A total of 162 (70.1%) isolates of male patients and 123 (66,8%) isolates of female patients were susceptible to first line antituberculosis drugs. The difference in any drug resistance between males and females (p>0.05) was not significant. A total of 82 (19,8 %) isolates had single drug resistance while 21 (5,1 %) isolates were MDR-TB. There was no significant difference in multi drug resistance between males and females (p>0.05). Other than multi drug resistance, combined antibiotics resistance was shown in 27 (6,5 %) isolates(Table 1). The prevalence of resistance was most common to INH with 21,4 % (89 isolates), followed by S (15,7%, 65 isolates), ETM (6,7%, 28 isolates) and RIF (6,3%, 26 isolates). Single and total drug resistance rates were decreased for each drug from 2012 to 2015 (Table 2).

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	No. (%) of isolates per year				
	2012	**2013**	**2014**	**2015**	**Total n(%)**
Sensitive to all first line drugs	33 (60)	95 (72)	72 (64,3)	85 (73,3)	285 (68,7)
Total Single Drug Resistance	16 (29)	21 (15,9)	26 (23,2)	19 (16,4)	82 (19,7)
Multi Drug Resistance (MDR)	3 (5,5)	5 (3,8)	9 (8)	4 (3,4)	21 (5,1)
Other resistance combinations	3 (5,5)	11 (8,3)	5 (4,5)	8 (6,9)	27 (6,5)
Total	55 (100)	132(100)	112 (100)	116 (100)	415 (100)

Table 2: Drug resistance patterns for years

IV. DISCUSSION

Tuberculosis (TB) has been an important infectious disease especially in developing countries. It has been encountered more commonly in Asia and Africa, among immunosupressed patients and male population. High incidence of HIV, immigration and weakness of the tuberculosis control programmes are claimed to be the most important factors influencing high drug resistance rates (1). Turkey had received a considerable number of immigrants from Syria and other Asian countries especially in the last decades. The youngest TB patient in this study was a five-months old Syrian immigrant baby. According to the literature, immigrants and refugees are considered as high risk populations for TB(8; 9). Local population movements from rural areas to urban areas were also high in Turkey. The incidence of TB was reported as 24 per 100.000 in Turkey but incidence and prevalence might be higher due to under-reporting(10) . Our hospital is a tertiary hospital serving many cities in the southeast of Turkey and tuberculosis is a common infection diagnosed in our hospital.

In the present study we did not investigate the immune status and underlying diseases of the patients. On the other hand we observed that the number of male patients with tuberculosis was higher than females. As reported in some worldwide studies, men were exposed to high risk factors such as smoking, alcoholism and drug addiction compared to women to get tuberculosis.(11-13). According to Tuberculosis in Turkey 2013 Report, 58,6 % of TB patients were male and 41,4 % were female in 2011(10). In our study, 55,7 % of the patients were male and 44,3 % were female. Tuberculosis burdens women in a substantial level due to big families and poor living conditions.

Furthermore, Tuberculosis in Turkey 2013 Report indicated that 68,4 % of total TB cases were aged 15-54 years, 4,9 % were aged 0-14 years and 13,5 were elderly patients (>65 years) (10). In our study, the mean age of our cases was 37± 18.8. Fourteen patients (3,4 %) were aged between 0-14 years, while 55 patients (13,3 %) were 65 and above.

Antituberculosis drug resistance rates and prevalence of MDR-MTC strains varied among regions, worldwide. In Global TB report of 2014, World Health Organization (WHO) reported 136 000 diagnosed and around half a million estimated cases of MDR tuberculosis worldwide(1). According to a surveillance data including 80 countries and 8 territories between 2007–2010,

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MDR-TB cases were reported as highest in the Russian Federation (28.9%) and the Republic of Moldova (65.1%)(13). In a national survey study from Uganda, 1.4% of new cases and 12.1% of previously treated cases were reported as multi-drug resistant. Among new cases, the proportions of INH and RIF resistance were 5% and 1.9% respectively, they increased to 23.3% and 12.1% respectively among relapse cases(14). In a study conducted in Tanzania, multi drug resistance rate was reported as 6.3%, while 12.7% of MTC isolates were resistant to any antituberculosis drug(15). According to a survey study conducted in Jilin Province of China, MDR-TB proportions were reported as 8.6% for new and 23.2% for relapse patients. Among new patients, the proportions of isoniazid, rifampin, ethambutol, and streptomycin resistance were 17.3%, 10.6% , 4.4% and 26.4%,respectively. These first line drug resistance proportions were 36.4%, 28.9%, 11.9% 39.1% among re-treated patients, respectively(16). In a study conducted in Sudan, MDR TB was reported in 5% of new cases and 24% of relapse patients(17). A study in Nepal revealed multi-drug resistance as 22.22% in new cases and 37.20% in relapse cases. Drug susceptibility rates for ETM, RIF, S and INH was reported as 66.10%, 60.33%, 59.66% and 41.69%, respectively.(18)

In Turkey, different drug resistance rates were reported from several studies of various regions and hospitals. According to Tuberculosis in Turkey 2013 Report, a total 4828 patients were examined for TB in 2011. Overall 20.5% of TB patients had at least one drug resistance and 5.4% of them had multi drug resistance. The highest drug resistance was reported for isoniazid as 13.7%(10). In a study from western Turkey, MDR-TB rate was reported as 4.6 % while drug resistance rates for INH , RIF, S and ETM were 14.4 %, 7%, 2.1% ve 2.8%, respectively (19). Another study in western Turkey revealed the rate of any drug resistance, multi drug resistance and isoniazid resistance in MTC strains as 21.1%, 7.3%, and 16.9%, respectively.(20) A study carried out in the south region of Turkey reported MDR-TB rate as 2% and ETM, INH, S and RIF resistance rates as %3.2 , %2.9, %2.1, %0.5, respectively (21). In a five-years study with 189 MTC strains, Çelik C. et al. reported MDR-TB as 1.6%, and INH, RIF, S and ETM resistance rates as 3.7%, 3.7%, 1.1% and 0.5%, respectively (22). A study conducted in the north region of Turkey reported 157 (74.05%) of 212 isolates as susceptible to all four antituberculosis agents. Total resistance rates for isoniazid, streptomycin, rifampicin, and ethambutol were reported as 17.5%, 13.7%, 5.7% and 5.7 %, respectively(23). In central Turkey, a study showed that mono-drug resistance proportions were 18.7 % for INH and 15.6 % for S, while no resistance was shown to RIF and ETM (24). In another study, 16 MTC strains isolated from central nervous system clinical samples were identified and tested for drug susceptibility with BACTEC 460 TB method. Streptomycin resistance rate was shown as 12.5%, while 18.7% of isolates were reported as resistant to at least one or more of the drugs (25). A study in southeastern Turkey revealed 40.2% of MTC isolates as resistant to at least one drug and 19.7% as multi drug resistant(26).

Reports of antituberculosis drug resistance from our hospital varied by years. Özekinci et al. evaluated drug susceptibility testing of 100 MTC strains performed by BACTEC 460 TB system between 2001 and 2003. Overall 29% of MTC isolates were reported as resistant to at least one or more antituberculosis drug and resistance rate per drug was found as 24%, 13%, 11% and 10% for isoniazid, streptomycine, rifampine and ethambutol, respectively(27). In a cross-sectional survey study of 116 TB patients at our hospital, 27.5% of MTC isolates were reported as resistant to at least one or more drug and 11.3% were multi-drug resistant. Isoniazid resistance (21.5%) was the most frequently occuring resistance pattern (28). In a study conducted between May2011 and May

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2012, antituberculosis drug susceptibility testing of 150 MTC strain was performed by MGIT-960 TB system. Overall 59% of MTC strains were found susceptible to all first line antituberculosis drugs, while 41% of strains were reported as resistant to at least one anti TB agent. Isoniasid, streptomycin, rifampine and ethambutol resistance proportions were 27.9%, 12.79%, 9.3% and 8.13%, respectively(29).

In the current study, we evaluated 415 MTC strains over a period of four years. Overall, 285 (68,7 %) MTC isolates were susceptible to all first-line anti TB drugs, while 130 (31,3%) isolates were resistant to one or more drug. Single drug resistance was detected in 82 isolates (19,8%). Twenty one isolates (5,1%) were determined as multi-drug resistant (MDR). The prevalence of resistance was most common to INH with 21,4 % (89 isolates), followed by S (15,7 %, 65 isolates), ETM (6,7%, 28 isolates) and RIF (6,3 %, 26 isolates). Our study indicated that, over the years, no increase was found in mono and multi-drug resistant tuberculosis in our hospital and region.

Our study has some limitations. Since it was a retrospective study, we could not obtain the registries of all patients and differentiate drug resistance of new and re-treated cases. Also we could not get information about immune status and concomitant diseases of the patients.

V. CONCLUSION

Tuberculosis remains to be a life threatening disease especially with multi drug resistant isolates. Our study indicated that drug resistance rates of our hospital are consistent with the average rates of Turkey, stated by the Ministry of Health. Evaluation of regional antituberculosis drug resistance would contribute to tuberculosis control programs in Turkey. Rapid and accurate diagnosis as well as regional drug resistance determinations are crucial parts of the tuberculosis control activities.

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