Drug resistance pulmonary tuberculosis in the Eastern Province of Saudi Arabia

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ABSTRACT

Objectives: To evaluate the prevalence and pattern of antituberculous drug resistance and patients with pulmonary tuberculosis in the Eastern Province and its impact on the tuberculosis control program.

Methods: Patients with pulmonary tuberculosis, proven by culture, admitted to Dammam Chest Hospital from November 1993 through May 1996 were reviewed. Patients who had at least one documented isolate of mycobacterium tuberculosis resistant to at least one standard anti-tuberculosis drug were identified. Medical records were reviewed and information was retrieved regarding age, sex, nationality, history of previous tuberculosis, human immune deficiency status, and results of direct smear and chest radiograph abnormalities.

Results: A total of 411 cases of culture positive pulmonary tuberculosis with drug susceptibility testing, were identified during the period mentioned, of these 123 (30%) were Saudi nationals and 228 (70%) were non-Saudis. Drug resistance to at least one drug was observed in 43 (10.5%) patients, resistance to isoniazid alone was observed in 25 (6%) patients, whereas resistance to rifampicin was noted in only one (0.2%) patient, and to streptomycin in 3 (1%) patients, multidrug resistance was observed in 11 (3%) patients.

Conclusion: The study has shown that the overall drug resistance rate of 10.5% in the Eastern Province of Saudi Arabia is the lowest reported in the Kingdom, compared with Riyadh (13%), Taif (23%) and Gizan (44%). However, it appears to be similar to that reported in neighboring countries. In light of the study findings, and as per the recommendation of the World Health Organization, we suggest that a 4-drug regimen, as an initial treatment for pulmonary tuberculosis should be maintained, as resistance to isoniazid is still higher than the cut off value of 4%, and susceptibility testing for first line antituberculosis drugs should be carried out whenever possible. We also recommend applying stricter medical criteria for tuberculosis screening in newcomers, and for Saudi nationals, application of directly observed therapy should be a priority.

Keywords: Pulmonary tuberculosis, resistance, sputum positive.

Tuberculosis is a major cause of morbidity and mortality. It is estimated that one third of the world population is infected with mycobacterium tuberculosis and 8 to 10 million cases of active tuberculosis and 3 million deaths occur each year.[1] The fundamental goal of all tuberculosis control programs should be the early diagnosis and prompt initiation of an optimal, and where resources allow, supervised treatment.[2] In Saudi Arabia, tuberculosis remains an important public health problem. The incidence of active cases in 1991 based on official notifications was 14.8 per 100,000 while the estimated incidence was 30 per 100,000.[3] In addition, the rate of drug resistant tuberculosis is markedly high in certain regions.[4-6] Mycobacterium tuberculosis becomes drug resistant through random spontaneous genetic mutation. The proportion of naturally occurring resistance has been established for first line anti-tuberculous drugs. Isoniazid (INH) and Streptomycin (STR) $1/10^6$, Rifampicin (RIF) 1/

10^8, Ethambutol (EMB) $1/10^4$, and Pyrazinamide $1/10^3$.[7-8] Modern chemotherapy based on multi-drug regimens can prevent emergence of resistance to single agents.[9-11] Reliable information about the global incidence of drug resistant tuberculosis is difficult to obtain, as sputum culture and drug susceptibility testing are not routinely performed in certain areas where the disease is particularly common. Despite these limitations, large surveys of worldwide drug resistant tuberculosis have indicated that drug resistant tuberculosis is an alarming problem.[12] The prevalence of drug resistant tuberculosis in the Kingdom is largely unknown, except for a few studies in the large centers.[4-6] However, it varies from 44% to 9%, this variability may reflect differences in the patient population studied and in microbiology practice. The objective of our study was to evaluate the prevalence and patterns of drug resistance in the Eastern Province of Saudi Arabia and its impact on policies of the tuberculosis control program.

Methods. All pulmonary tuberculosis patients proven by culture and admitted to Dammam Chest Hospital, Eastern Province from November 1993 through May 1996 were reviewed. This is a referral hospital for tuberculosis patients in the region, according to the Ministry of Health regulation. As a result, the sample studied, represents the majority of tuberculosis patients in the region. Patients who had at least one documented isolate of mycobacterium tuberculosis resistant to at least one standard anti-tuberculosis drug were identified, medical records were reviewed and information was retrieved regarding age, sex, nationality, history of previous treatment for tuberculosis, human immune deficiency

(HIV) status, and results of direct smear and chest radiograph abnormalities. Cultures were performed at the Regional Laboratory of the Eastern Province using the Bactec radiometric system and mycobacterium tuberculosis was identified. Susceptibility testing was carried out using Bactec 12B medium, and bacterial suspensions were prepared from representative colonies. This is a retrospective study and by virtue of its nature, quality control cannot be ascertained. The concentration of the drugs after reconstituting with 5 ml of sterile water are as follows: INH 0.1 μg/ml, RIF 2.0 μg/ml, STR 6.0, 2.0 μg/ml, EMB 7.5, 2.5 μg/ml. The strain was declared resistance when the number of colonies in the drug-containing medium was 1% or more of the control growth. Multi-drug resistance (MDR) was considered when bacilli were resistant to at least RIF and INH. Initial resistance was considered when prior treatment was not reported, were as secondary resistance was considered in the presence of previous exposure to anti-tuberculous drugs. Chest radiographic abnormalities were classified as cavitary or non-cavitary. Cavitation was defined by the presence of either a classical cavitary shadow (gas-containing space within the lung parenchyma surrounded by a wall thicker than 1 mm) or translucency within the airspace pattern.

Results. A total of 411 cases of culture positive pulmonary tuberculosis with drug susceptibility testing, were identified between November 1993 through May 1996, of these 123 (30%) were Saudi nationals and 288 (70%) were non-Saudi. Indian patients constituted the highest proportion of non-Saudis 106 (26%) and the rest were from other Asian and African countries. As shown in Table 1, drug

Table 1 - Pattern of drug resistant tuberculosis in the Eastern Province, Kingdom of Saudi Arabia.

Nationality	Number of patients (%)	INH	STR	RIF	INH +STR	MDR	TOTAL (%)
Saudi	123 (30)	2	0	0	0	6	8 (6.5)
Non-Saudi	288 (70)	23	3	1	3	5	35 (12)
Indian	106 (26)	7	0	0	0	1	8 (8)
Filipino	59 (14)	10	1	0	1	0	12 (20)
Pakistani	21 (5)	3	0	0	0	0	3 (14)
Indonesian	26 (6)	0	1	0	0	1	2 (8)
Egyptian	18 (4)	2	0	0	1	1	4 (22)
Others	59 (14)	1	1	1	1	2	6 (10)
TOTAL	**41**	**25 (6%)**	**3 (1%)**	**1 (0.2%)**	**3 (1%)**	**11 (3%)**	**43 (10.5%)**

INH - Isoniazid; STR - Streptomycin; RIF - Rifampicin; MDR - Multi drug resistant

Table 2 - Comparison between MDR and non-MDR cases.

Parameter	MDR (%) N = 11	non-MDR (%) N = 32	P-value
Age	41 (13 - 75)	32 (17 - 58)	
Nationality			
Saudis	6 (5)	2 (2)	0.0001
Non Saudis	5 (2)	30 (10)	0.09
Resistance			
Initial	7 (64)	30 (94)	0.047
Secondary	4 (36)	2 (6)	0.015
HIV			
Positive	0	1	0.55
Negative	11	31	
Direct Smear			
Positive	8 (73)	29 (91)	0.02
Negative	3 (27)	3 (9)	0.07
Radiograph			
Cavitary	5 (45)	22 (66)	0.17
Non-cavitary	6 (55)	10 (34)	

MDR - multi drug resistant; HIV - human immunodeficiency virus

resistance to at least one drug was observed in 43 (10.5%) patients, higher among non-Saudis (12%) than in Saudi nationals (6.5%). Single drug resistance was noted in 29 (67%) patients, resistance to INH alone was found in 25 (6%) patients, which was higher among non-Saudis (8%) than Saudis (2%), where as resistance to RIF alone was noted in only one patient (0.2%), and to STR in 3 patients (1%), there was a significant variation in drug resistance between different nationalities. Single drug resistance was the highest among Filipino patients (Table 1). Multi-drug resistance (MDR) was observed in 11 (3%) patients, higher in Saudis (5%) than in non-Saudis (2%) (p<0.05). Table 2 compares MDR patients with those who had non-MDR, it shows that median age was higher in the MDR group 41 years (range 13 to 75) than the non-MDR group 32 years (range 17 to 58). Secondary resistance was noted in 4 (36%) patients with MDR, the majority of which are Saudis. Among patients confirmed to have drug resistance only 6 (14%) patients reported a previous history of taking antituberculosis drugs. Two of these were initially sensitive, and they acquired resistance because of incomplete treatment as patients have moved to another region. Also secondary resistance is more common in MDR (37%) than non-MDR (6%) patients, and negative direct smear was more frequent in MDR (27%) than non-MDR (9%) patients. On chest x-ray, more cavitary lesions were seen in non-MDR (66%) than in MDR (45%) patients. Positive HIV serology was noted in one patient only.

Discussion. Our study has shown that the overall drug resistance rate of 10.5% in the Eastern Province of Saudi Arabia is the lowest reported in the Kingdom, compared with Riyadh 13%, Taif 23% and Gizan 44%,[4-6] however it appears to be similar to that reported in neighboring Kuwait state.[11] An INH mono-resistance rate of 6% was noted, which is significantly higher in non-Saudis (8%) than in Saudis (2%). There is a large variation among non-Saudis between different nationalities, with a higher rate of resistance noted in Filipinos (17%) and the lowest in Indians (7%). Similar rates of resistance (10-20%) were also reported in patients coming from countries of high tuberculosis prevalence reflecting the pattern of resistance seen in their country of origin. Rifampicin is the most potent anti-tuberculous drug; it is essential for modern short course chemotherapy, resistance to Rifampicin alone is rare, in general less than 1%.[13-17] Emergence of resistance to RIF will weaken the success of modern short-course treatment of tuberculosis.[13] In our study, the striking very low RIF mono resistance rate 0.2%, compared to other parts of the country and in particular in Taif, where initial RIF resistance was found to be 15%.[4-6] This does not support the hypothesis postulated by others (namely, the prescription of RIF for treatment of non-tuberculous diseases) to explain the high rate of resistance in their regions, as this drug is also being used for the treatment of other diseases such as brucellosis in our region. Similar results of RIF resistance were reported elsewhere in the United States of America and Japan.[13,17] Another important finding in this study was the low rate of MDR (3%), although it is higher in Saudis (5%) than non-Saudis (2%); this might be explained by the young age of non-Saudis and the medical rules that exclude foreigners who have a significant medical problem or chest radiograph abnormalities suggestive of pulmonary tuberculosis.

The most important risk factors for MDR are non-compliance to the treatment and the infection with HIV.[18-22] None of our MDR cases were HIV positive. Expatriate workers are screened for pulmonary tuberculosis and other contagious diseases before entry, and only those who meet the medical clearance requirements are allowed. Two out of 6 Saudi patients who had MDR have resulted from incomplete treatment, because patients moved from our region to another, this cause of non-compliance was reported by others[19] and highlights the importance of ensuring complete treatment.

Drug resistance among patients without a previous history of tuberculous treatment was seen in 37 patients suggesting that patients who have an initial resistance constitute 86% of overall patients with resistance, and secondary resistance of 14%, higher in Saudis than non-Saudis. Probably indicating that patients under report their previous tuberculosis treatment.

Diagnosis of MDR pulmonary tuberculosis is frequently delayed because of negative direct smear and non-cavitary shadows,[23] this is also the case in our study where a substantial proportion of MDR cases (Table 2) had a negative direct smear and non-cavitary lesion. This emphasizes the importance of clinical suspicion of tuberculosis and the need for more sensitive and rapid diagnostic tests for early diagnosis and detection of resistance.

In light of the above mentioned findings and as per international guidelines for treatment of tuberculosis, we suggest that a 4-drug regimen, as the initial treatment for pulmonary tuberculosis, should be maintained as resistance to INH is still higher than the cut off value of 4%; recommended by the American Thoracic Society.[24] Susceptibility testing for first line anti-tuberculous drugs should be carried out, whenever possible, both for management and for epidemiological surveillance to follow the evolution of drug resistance. Foreigner manpower represents the vast majority of tuberculous cases and resistance; most are from countries with a high prevalence of tuberculosis. Given that the risk of developing active tuberculosis is markedly high in persons who have inactive pulmonary tuberculosis[25] thus; control of tuberculosis in Saudi Arabia cannot be achieved without collaboration between the Kingdom and countries providing the majority of manpower, in addition to the application of more strict medical criteria for screening of pulmonary tuberculosis in newcomers in such a way workers who have inactive tuberculosis are excluded. For Saudi nationals, improvement of infrastructures and rules to ensure completion of treatment by application of directly observed therapy should be a priority.

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