Contributing Factors in Anti-Tuberculosis Treatment Failure

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ABSTRACT

Background: Tuberculosis is one of the most ancient recognised diseases of human being which remains as an important obstacle for public health, despite numerous scientific advances made in the recent decades.

Delay in treatment of tuberculosis due to socieoeconomic factors in addition to HIV epidemic increases the number of undiagnosed smear positive patients in communities. The patient's delay and physician's delay in diagnosis and treatment, inadequate therapy, errors in prescribing accurate regimens, financial problems of patients in taking drugs, lack of patient's knowledge about the regular use of drugs and interruption of treatment all result in the emergence of drug resistant tuberculosis which adds to the difficulties in the management of this obstacle. Regarding the difficulties faced in treatment of tuberculosis, determining factors responsible for treatment failure and the consequently developing resistance is essential.

Materials and Methods: This is a case control and sequential study which consists of hospitalised and out patient TB cases who have remained smear positive despite full course of anti-TB treatment. Eighty patients with this characteristic were compared with 80 controls who have responded to treatment.

Results: Eighty cases (44 females, 36 males) with median age of 28 yr. (15-73) were compared with eighty controls (41 females, 39 males) with median age of 29 yr. (16-70). There were no differences between two groups regarding nationality (Iranian vs. Afghan) (p>0.05) and economic status (p>0.05). There was significance difference regarding educational level of two groups, as it was significantly higher in control group (p<0.05). There was no significant statistical difference between two groups when living place was considered (urban, suburb, village) (p>0.05). The final interesting findings were high usage rate of four drug regimen and DOTS strategy in control group in comparison with the patients with treatment failure. (p<0.05, p<0.05, respectively).

If the time from the onset of patients symptoms to the initiation of proper treatment (total delay) was more than 8 weeks, no significant difference was noted. However, if this time period was less than 8 weeks, significant difference was detected (p<0.05). This study shows that an important factor in preventing from treatment failure and emergence of resistant forms is the immediate referral of the patient to physician (less than 8 weeks) resulting in prompt diagnosis and treatment.

Conclusion: Finally, DOTS strategy, early diagnosis, correct treatment of tuberculosis, patient's knowledge about tuberculosis, how to use and side effects of anti-TB drugs and duration of treatment all should be considered as effective factors for prevention of anti tuberculosis treatment failure and emergence of drug resistant bacilli. **(Tanaffos 2003; 2 (7): 61-68)**

Key Words: Tuberculosis, Treatment, Failure

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INTRODUCTION

Tuberculosis is one of the most ancient human diseases which has remained as an obstacle for public health despite significant scientific advances during recent century. It is estimated by WHO that in 2001 about 8.4 million people acquired new infection and this rate is expected to increase to 10.2 million in 2005.

Socioeconomic difficulties were associated with delay and errors in treating tuberculosis and HIV epidemic, all have resulted in numerous undiagnosed smear positive pulmonary tuberculosis which in combination with inaccurate use and control of anti-tuberculosis treatment have induced emergence of drug resistant bacilli contributing to more and more problems in tuberculosis control programs (1-3). Emergence of drug resistant bacilli is essentially the product of insufficient treatment. This inaccurate treatment consists of: delay in initiation of therapy, incorrect or inadequate combinations, financial problems of the patient regarding the purchase of medicine, lack of patient's knowledge about the importance of the disease, role of regular and correct treatment with unacceptable interruptions, and finally physician's delay (4-8).

Treatment of resistant tuberculosis particularly caused by MDR bacilli is very difficult, expensive, and often intolerable for the patients because the second line drugs used for this purpose are very toxic. Thus, prevention of resistance is preferred over its treatment (9-16). It must be mentioned that you cannot treat MDR-tuberculosis as easy as you can create it.

In this study, we have attempted to find the effective factors contributing to failure in treatment and we hope to find solutions to avoid these factors to reach a reasonable result in tuberculosis treatment.

MATERIALS AND METHODS

This case-control study was conducted on TB patients that were admitted in the TB wards and TB referrals of the TB clinic of Masih Daneshvari hospital. The case group consisted of all those smear positive TB patients whom had referred because of treatment failure.

This included:- 1- TB patients that remained smear positive despite five months of treatment, 2- TB patients that became smear negative during the initial stages of treatment, but changed to smear positive after 2 months of treatment (treatment failure). Meanwhile, based on the follow –ups of the TB/ pulmonary clinic (culture and smear), all the cured patients were considered as control group.

Both the case and control groups were examined by the pulmonologists of the hospital. A special questionnaire which was designed for this research was filled-out by the physicians for each individual; both in the wards and clinic.

In this study each of the case and control groups consisted of 80 individuals that were matched for age and sex. Sampling was that of a sequential form. The points that were considered in the questionnaire were as follow:- nationality; immigration; economical status (accommodation and income); residing in city, suburbs or village; level of education; onset time of symptoms; diagnosis and treatment; different therapeutic regimens and its duration; out patient treatment; complete or incomplete treatment; being admitted and receiving treatment while being under observation; the patient's knowledge of TB disease; anti-TB medication and duration of treatment. Later on, the results were analyzed by SPSS method.

RESULTS

From 80 patients who had anti TB treatment failure, 44 were female and 36 male with median age of 28 yr. (range 15-73). From 80 control cases with successful response to therapy, 41 female and 39 male with median age of 29 (range 16-70) existed. Table 1 demonstrates the smoking status of the two

groups. As it is seen no significant statistical difference exists between the two groups (p>0.05).

Table 1. Smoking status of case and control groups

Smoking status	Case		Control	
	Number	(%)	Number	(%)
Smoker	57	71.2	51	63.8
Non-smoker	23	28.8	29	36.2
Total	80	100	80	100

There was no statistical difference regarding the nationality of patients in both groups (table 2) (p> 0.05).

Table 2. Nationality of patients and control group

Nationality	Patients		Control	
	Number	(%)	Number	(%)
Iranian	44	55	53	66.2
Afghan (Immigrant)	36	45	27	33.8

There was no difference between the patients and control group regarding the accommodation status (p>0.05).

There was no difference between two groups when the economic status was compared (table 3) (p>0.05).

Table 3. Economical status of the patients and control group

Income	Patients		Control	
	Number	(%)	Number	(%)
Low	46	57.5	34	42.5
Intermediate	31	38.75	38	47.5
High	3	3.75	8	10
Total	80	100	80	100

There was significant statistical difference between two groups, regarding educational status, and the treatment failure group had higher level of uneducated persons (p<0.05). The total number of uneducated individuals and those with elementary school education was 82.6% (66 persons) among the failed group as compared to 42.6% (34 persons) in cured group. Thus, as it is observed, educational status effects the treatment outcome; that is, the lower the education level, the higher would be the risk of treatment failure and vice versa.

Table 4. Educational level in two studied groups.

Educational level	Case		Control	
	Number	Percent	Number	Percent
Uneducated	41	51.3	21	26.3
Elementary school	25	31.3	13	16.3
Intermediate school	4	5	17	21.2
High school	8	10	26	32.5
University	2	2.4	3	3.7
Total	80	100	80	100

Regarding the location of life in both groups, there was no significant difference: 54 and 66 persons from patients and control groups respectively lived in cities, the remaining in suburbs and village (p>0.05).

Figure 1 demonstrates the kind of treatment used in the two groups.

In patient group, 40 cases (50%) received 4 drug treatment, 9 cases (11.2%) 3 drug and 31 cases (38.8%) two drug regimen, while all cases of control group received 4 drug regimen (p<0.05). This proves that administration of four-drug regimen at the initial

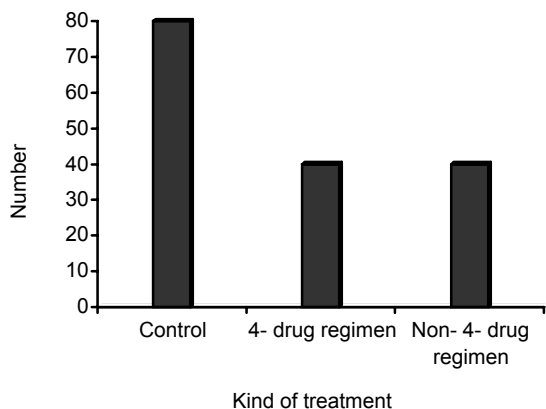stages of diagnosis would prevent from treatment failure.

Figure 1. The kind of treatment in two groups.

Figure 2 shows the frequency of patients that have received six months treatment course under direct observation. As observed, significant statistical difference exists between the two groups (p<0.05).
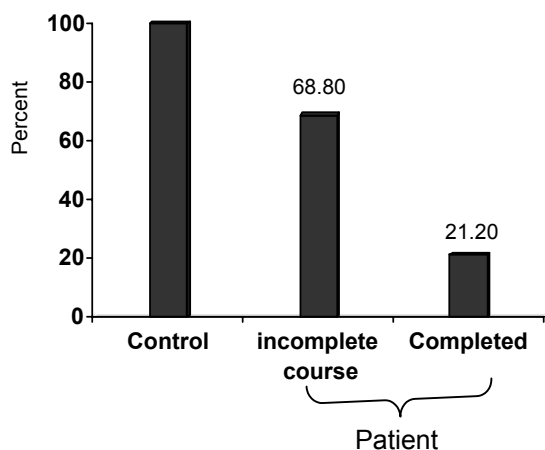

Figure 2. The duration of treatment in two groups.

The types of treatment given to the TB patients that had referred to TB center are demonstrated in table 5. As it is seen, out-patient treatment without any direct observation is responsible for the treatment failure. Meanwhile, giving treatment under direct observation to patients that are admitted in the hospital can prevent treatment failure (p<0.05).

Table 5. The type of treatment administered for the first time in both case and control groups.

Type of Anti TB treatment given for the first time after diagnosis		Patients		Control	
		Number	(%)	Number	(%)
Out patient	With control and observation (DOTS)	0	0	0	0
	Without control and observation	45	56.25	5	6.25
Admitted patient	With control and observation (DOTS)	13	16.25	53	66.25
	Without control and observation	22	27.5	22	27.5
	Total	80	100	80	100

There was no statistical difference, if the patient and physician delays are more than eight weeks from the onset of disease for diagnosis and treatment of tuberculosis.

In contrast, if the treatment is administered during 8 weeks, there is considerable success in the treatment (p<0.05).

Thus, the more rapid a patient refers to the physician, the more quickly a diagnosis is reached and hence treatment started.

The knowledge of patient about tuberculosis, duration of treatment, drug toxicities, and complications of drug interruption are very effective factors in preventing treatment failure as it is demonstrated in table 6 (p<0.05).

The type and duration of anti TB treatment in case group are shown in table 7. As seen in this table, a complete course of four-drug regimen is associated with more effective therapeutic response as

compared to other regimens (p<0.05). On the other hand, incomplete courses of 3-and 2-drug regimens are factors responsible for treatment failure.

Table 6. The effect of patient's knowledge about disease and treatment in two groups on the treatment outcome.

Knowledge about TB and its treatment	Patients		Control	
	Number	(%)	Number	(%)
Yes	21	26.25	74	92.5
No	59	73.75	6	7.5
Total	80	100	80	100

Table 7. Type and duration of treatment in case groups.

	Complete course	Incomplete course
Four drug regimen cat-I	21	19
Other therapeutic regimens besides 4 drug regimen	4	36
Total	25	55

DISCUSSION

As described in this study, there was no significant statistical difference in the treatment failure between native Iranian and Afghan immigrants. That is in accordance with high prevalence rate and drug resistance in both countries despite the lack of documented report of tuberculosis from Afghanistan. The rate of drug resistance seems to be high (5%) in comparison with other parts of the world (1%) (17). Financial status of the patients including monthly income and having accomodation had no significant statistical correlation with treatment failure. It seems that in Iranian community, the persons suffering from tuberculosis are supported by their family members either financially or psychologically. Also, a large portion of expenses for tuberculosis treatment are paid by insurance companies, and even a large number of tuberculosis

patients are treated free of charge by governmental health systems.

Thus, failure of treatment and drug resistance which may be the product of insufficient drug supply are not great problems in this community (8).

Educational level of patients was an important factor in prevention of treatment failure in this study. This is explained by the effect of delay in initiation of treatment, lack of compliance, treatment follow-up and interruption of drugs in uneducated or low educated persons (8,9).

In the present study, effective four-drug anti-TB regimen with DOTS strategy was a great index in prevention of treatment failure and emergence of insufficient drug regimens in creating drug resistance (18).

An American study in 1995 demonstrated that about 1/4 of new TB patients were treated with the regimens containing only 2 or 3 drugs that is in contrast to usual standard ATS/ CDC recommendation, and this may be one of the most important causes of drug resistance (19).

A study from national Jewish hospital in Denver demonstrated that the average cause of 3.93 treatment failure and drug resistance in each patient was the physician's error in prescribing two or three drugs with insufficient period of treatment (20).

In the present study, we observed significantly low rates of treatment failure in the group treated by DOTS strategy.

That is the same as Baltimore and Texas studies which mentioned that treatment by DOTS strategy resulted in a major reduction in the rate of treatment failure and drug resistance (21, 22).

A study, in New York also demonstrated considerable reduction in incidence of drug resistance following DOTS programs (23) which was confirmed by Dye et al., in another study (24).

A study in Hong Kong during 1986-99 emphasized the important role of DOTS in reduction of resistance rate (25). This is in contrast to countries like Latvia, South Korea, and Russia with high rate of resistance (54%, 28% and 27%, respectively). In these countries the major etiology of resistance is the lack of spohisticated tuberculosis control programs (26).

A considerable point in this study was the significant reduction in the rate of treatment failure in patients who had been treated for a period of less than 8 weeks for their complications.

It is well known that economical problems act as a barrier to early medical care and diagnosis of the patients, leading to continuous transmission of the bacilli in communities and, thus, more complications.

Early attempts in diagnosis and initiation of effective drug regimen preferably by DOTS is a major cause of reduction in morbidity and drug resistance (27).

In previous studies, a definite time for delay had not been defined. However, duration of 8 weeks observed in this study may be a good indicator for predicting the response to treatment or failure.

We conclude that insufficient treatment consisting of lack of compliance, interruption of treatment, incorrect drug prescription by physicians, outpatient therapy and most importantly patient's delay for seeking medical care, lack of patient's knowledge about the nature of disease and its treatment including complications and duration all can contribute to treatment failure and emergences of drug resistance (27).

Thus, high level of education in patients, appropriate time of diagnosis by physicians, creating a logic, intimate communication between patient and health workers caring for tuberculosis, good follow-up of treatment, and finally correct enforcement of DOTS strategy in our country will eventually lead to sophisticated management and prevention of treatment failure and drug resistance.

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