Mortality of Patients Hospitalized for Active Tuberculosis in Israel

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Abstract

Background: Pulmonary tuberculosis continues to be a major cause of mortality, particularly in developing countries. Despite modern anti-TB treatment, the elderly and immigrants from TB-endemic countries are at risk. Multidrug resistance has yet to be resolved..

Objectives: To determine the mortality rate and predictors of mortality among patients hospitalized with TB in Israel.

Methods: We evaluated the medical records of 461 patients with active pulmonary TB who were hospitalized in the respiratory care department during the 5 year period 2000–2004. Data included demographic, clinical, laboratory and radiological findings, drug resistance as well as adverse reactions to anti-TB treatment.

Results: Three main ethno-geographic groups were observed: 253 patients from the former USSR, 130 from Ethiopia, and 54 of Israeli origin (as well as 24 residents of other countries). Of the 461 patients 65 (13%) died in hospital. The factors that were best predictors of mortality were older age, ischemic heart disease, cachexia, prior corticosteroid treatment, hypoalbuminemia and pleural effusion ($P < 0.005$ for all). The ethno-geographic factor and the presence of multidrug-resistant bacteria had no significant effect on mortality in our study group.

Conclusions: The mortality rate in our study was relatively low, and there was no significant difference between the three ethno-geographic groups.

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Pulmonary tuberculosis is one of the oldest known diseases. Across the world, TB remains an important cause of mortality accounting for almost 2 million deaths yearly, most of them in developing countries [1-7]. Before the appearance of modern anti-tuberculosis treatment, about 50% of TB patients died. Nowadays, mortality from TB is lower, reflecting the quality of local health services [8,9]. Additional aspects contributing to the incidence and morbidity of TB are psychosocial and demographic factors, such as poverty, homelessness, and alcohol or drug addiction. Even in developed countries where the overall incidence of TB is low, it remains common among the elderly population due to prolonged life expectancy, use of drugs that suppress cellular immunity, and delay of the diagnosis of TB in the aged [10]. Human immunodeficiency virus infection is an important factor related to the increased morbidity and mortality of TB [3].

In Israel, an immigrant country, the population is unique in its provenance from different world regions, some of them endemic areas for TB [11]. Immigrants, numbering over 1 million, from the former Soviet Union and Ethiopia have been absorbed among the veteran population (constituting almost 20%). The annual number of newly diagnosed TB cases is about 500, with no significant change during recent years [12]. About 20% of the cases are hospitalized, most of them in the Department of Chronic Respiratory Care at Shmuel Harofe Hospital, which concentrates the treatment of severe cases from all over the country. The present study evaluates the mortality data among these hospitalized TB patients and relates it to their ethno-geographic origin.

Patients and Methods

We studied the medical records of patients with active pulmonary tuberculosis, hospitalized in the pulmonary diseases department of Shmuel Harofe Hospital during the 5 year period 2000–2004. This facility concentrates the treatment of most TB patients around the country who require hospitalization for active tuberculosis. In general, about 20% of newly diagnosed TB cases are hospitalized in Israel. The hospital is a public, governmental medical center affiliated to the medical school of Tel Aviv University.

The data gathered included ethno-geographic and demographic characteristics, clinical and laboratory findings, radiological features, adverse reactions to anti-TB drugs, and drug resistance. Multidrug resistances are those with M*ycobacterium tuberculosis* resistant to isoniazid and rifampicin. Extensive drug resistance cases are those resistant to isoniazid, rifampicin, one of the quinolones and one of the injectable drugs (streptomycin or amikacin) [13]. We also defined those with any other drug resistance, whether one or multiple drugs but not those in the category of MDR.

Statistical analysis was performed using the SPSS version. Differences in demographic and clinical features between the deceased and discharged cases as well as between the older (> 65 years old) and younger (< 65 years old) patients were studied using *t*-test, chi-square test, univariate correlations and multivariate logistic regressions for all epidemiological, clinical (related diseases and laboratory parameters) and other factors related to the TB disease that could be relevant to mortality. *P* value was determined by the two-tailed method.

TB = tuberculosis

MDR = multidrug resistance

Results

During the study period, 461 pulmonary TB patients were hospitalized in the Department of Chronic Respiratory Care in our center. Most of them, 396 (86%), were successfully treated and discharged to ambulatory treatment in the community after a mean stay of 2.4 months. Sixty-five patients (14%) died in hospital [Table 1]. Clinical causes of death that may be directly or partially related to tuberculosis were respiratory failure in 12 patients (19%), general deterioration in 9 patients (15%), and a clinical picture of other infections: pulmonary, urinary and others in 23 patients (38%). In one-third of patients, the causes of death were not related to tuberculosis but were described by the attending physicians as related to the aging process (e.g., cardiovascular diseases).

Three main ethno-geographic groups were observed: 253 from the former USSR, 130 from Ethiopia (both groups arrived in Israel after 1990, when the massive immigration from the USSR began), and 54 were born in Israel or were citizens from an earlier immigration and have lived for about 30–40 years in Israel. A small group of patients (n=24) were residents of other countries.

The relevant data are presented in Table 1. The mean age of the deceased was significantly higher than those discharged from hospital: 67 ± 22 vs. 47 ± 20 years ($P < 0.001$). The group of elderly patients (> 65 years old) was relatively small, 28% of the total number of patients; however, the mortality in this group reached 31% while in those under age 65 years it was 6% ($P < 0.001$) [Table 2]. It is not surprising that non TB-dependent risk factors for mortality are more common in the older group – namely, ischemic heart disease, diabetes, and chronic obstructive pulmonary disease ($P < 0.001$ for all).

The deceased had more underlying diseases, in particular higher frequencies of IHD (41% vs. 8.6%, $P < 0.001$), COPD, diabetes and renal failure. These patients also had a higher incidence of cachexia at admission (30% vs. 6.8%, $P < 0.001$)

Table 1. Demographic data of hospitalized TB patients

	Deceased No (%)	Discharged No (%)	*P*
No.	65	396	
Age (yrs)	67 ± 22	47 ± 20	< 0.001
Gender: male/female	45/20 (69/31)	266/129 (67/37)	NS
Years in Israel	14.6 ± 16	7.6 ± 7.4	0.003
Length of stay in hospital(m)	1.3 ± 1.7	2.4 ± 2.6	< 0.001
Recurrent. admission	23 (36)	115 (29)	NS
Relevant diseases			
Ischemic heart disease	26 (40)	36 (9)	< 0.001
Congestive heart failure	5 (8)	8 (2)	NS
Renal failure*	11 (17)	16 (4)	0.001
Diabetes mellitus	10 (16)	36 (9)	0.08
Chronic lung disease	22 (34)	67 (17)	0.005
Cachexia **	30 (20)	28 (7)	< 0.001
HIV	5 (8)	44 (11)	NS
Hepatitis B	3 (5)	24 (6)	NS
Hepatitis C	5 (8)	40 (10)	NS
Alcoholism ***	5 (8)	44 (11)	NS
Drug addiction	8 (12)	48 (12)	NS
Smoking	24 (37)	158 (40)	NS
Corticosteroids ****	16 (24)	20 (5)	< 0.001

* Creatinine > 1.5 mg/dl

** Cachexia as a subjective clinical impression.

*** Alcoholism considered more than 6 alcoholic drinks daily.

**** Use of oral corticosteroids (≥ 5 mg/day prednisone) for more than 6 months.

Table 2. Effect of age on medical and laboratory data in the cohort of TB patients

	< 65 yrs old (n=332)	> 65 yrs old (n=128)	*P*
Mortality	20 (6)	40 (31)	< 0.001
Hemoglobin (g/dl)	12.3 ± 2.1	11.5 ± 1.9	< 0.001
Albumin (g\L)	3.5 ± 0.7	3.1 ± 0.7	< 0.001
COPD	48 (14.5)	41 (32)	< 0.001
IHD	14 (4)	37 (28.6)	< 0.001
Diabetes	17 (5)	30 (24)	< 0.001
Hepatitis C	39 (12)	5 (4)	0.02
Alcohol	47 (14)	1 (1)	< 0.001
Smoking	157 (47.4)	24 (19)	< 0.001
Cachexia	25 (7.6)	19 (15)	0.02

Data presented are the number and percentage for the age group, exept for the levels of hemoglobin and albumin.

P by *t*-test or chi-square test.

Table 3. Clinical and laboratory data related to tuberculosis

	Deceased No (%)	Discharged No (%)	*P*
Radiographic involvement at admission (%)			
Unilateral	21 (33)	198 (50)	NS
Bilateral	35 (54)	182 (46)	NS
Miliary	6)8.5)	16 (4)	NS
Extra pulmonary	13 (20)	59 (15)	NS
Pleural effusion	22 (34)	46 (11.5)	< 0.001
Laboratory data			
Positive sputum smear (%)	40 (62)	325 (82)	< 0.001
Positive sputum culture (%)	44 (67)	337 (85)	< 0.001
Hemoglobin (basal)	11.2 ± 1.6	12.2 ± 2.1	< 0.001
Anemia (<12 g Hb)	45 (70)	186 (47%)	0.005
Change in Hb	-1.2 ± 1.8	0.5 ± 1.6	< 0.001
WBC (basal)	9.7 ± 4.6	7.8 ± 3	< 0.001
Change of WBC	3.3 ± 9.5	-1.2 ± 2.7	< 0.001
Albumin, g/L (basal)	2.76 ± 0.7	3.48 ± 0.6	< 0.001
Hypoalbuminemia (< 3 g/dl)	41 (63%)	91 (23 %)	< 0.001
Change of albumin	-0.44 ± 0.6	0.24 ± 0.6	< 0.001
Na, mEq/L (basal)	135 ± 7	137 ± 4	0.04
Change in Na	3.4 ± 8	1.7 ± 3.5	NS

P by *t*-test or chi-square test.

Changes are at discharge or time of death

IHD = ischemic heart disease

COPD = chronic obstructive pulmonary disease

Table 4. Consequences of anti-tuberculosis treatment

	Deceased No (%)	Discharged No (%)	*P*
Drug resistance (%)			
MDR	9 (14)	48 (12)	NS
XDR	2 (3)	12 (3)	NS
Any drug	3 (5)	59 (15)	0.03
Drug toxicity (%)			
Hepatotoxicity *	23 (35)	123 (31)	NS
Leukopenia	4 (6.3)	46 (11.6)	NS
Initial weight (kg)	52 ± 12	59 ± 14	0.002
Change in weight (kg)	-2 ± 8	3 ± 5	0.004

* Increased liver enzymes more than twice the upper limit.

MDR = multidrug resistance, XDR = extensive drug resistance.

Any drug resistance = 1 or multiple drugs but not those in the categories of MDR.

[Table 1]. Long-term corticosteroid treatment, mainly used by those with COPD, was more frequent among the deceased (25% vs. 5%, $P < 0.001$).

Data regarding radiographic findings and laboratory analyses are presented in Table 3. There were no major differences in radiological features, beside incidence of pleural effusion, 34% vs. 12% ($P < 0.001$). There were significant differences in the levels of albumin and hemoglobin between the two groups.

The consequences of anti-TB treatment are shown in Table 4. There were no differences in the frequency of drug resistance – multidrug resistance or extensive drug resistance – between the deceased and those discharged from hospital. Interestingly, among those discharged, there was a higher incidence of patients with any drug resistance. The incidence of adverse drug reactions (hepatitis or leukopenia) was similar in the two groups.

The factors that were predictors of death in univariate analysis included older age, congestive heart failure, IHD, COPD, renal failure, cachexia, prior corticosteroid treatment, hypoalbuminemia, anemia, hyponatremia, and pleural effusion on chest X-ray ($P < 0.005$ for all). Many other relevant factors such as diabetes, HIV, alcoholism, smoking, positive sputum smear or culture and extrapulmonary TB were not risk factors for death in this analysis.

In order to isolate the most important factors correlated to mortality of TB patients, logistic regression tests on all relevant parameters were performed and showed five main factors: IHD, older age, cachexia, corticosteroid use, and low albumin level – all of them with a very high significance ($P < 0.001$).

We found that the ethno-geographic factor had no significant effect on mortality in our study group. Mortality rates were 10.4%, 7.8% and 3.7% in the USSR, Ethiopian and Israeli born groups respectively (not significant). The small differences in mortality rates may be related to the age differences: USSR 51 ± 20, Ethiopians 44 ± 21, and Israelis 46 ± 19 ($P < 0.003$).

A significantly higher incidence of MDR was found in those born in the USSR, 16% vs. 8.5% among the Ethiopians and 5.6% of the Israelis ($P < 0.03$). In general, those with MDR-mycobacterium were those with recurrent admissions ($P < 0.05$ by chi-square).

Discussion

We had the opportunity to compare parameters linked to TB and in-hospital death in three ethno-geographic groups. Of the 461 patients, 65 patients (13%) died in hospital. In general, reported mortality from tuberculosis currently ranges from 11% to 40% and is related to geography [2]. The most recent report from Israel found TB mortality to be only 5%, however this number reflects all TB cases, including patients who are ambulatory [9,12].

The results of our study indicate that most patients died from causes directly related to TB disease – namely, respiratory failure, sepsis on a basis of immune suppression, and general deterioration. One-third of the patients died of causes not directly linked to tuberculosis but to age-related factors. This is at odds with the reported experience of 40–70% mortality directly linked to TB [14]. Since autopsies were not performed in any case of death due to religious and legal constraints in Israel [15], the final causes of death are based on clinical diagnosis only.

We found no significant difference in the incidence of mortality between the three ethno-geographic groups. All these patients were treated according to the standard accepted regimens. The local endemic factors in the country of origin, such as living conditions and the nature of the infective agent, do not seem to significantly influence the outcome of modern treatment. We found no reference in the literature to mortality rates in persons of different ethno-geographic origin in the same country. Thus, although the prevalence of TB in the United States is higher among the Asian and black populations as compared to Caucasians, the mortality rate is not different between these groups [2].

Age has a major impact on TB mortality [10,16,17]. In our study, a mortality rate of 31% was observed in older patients as compared to 6% in those under 65 years old. Co-morbidity and decreased immune function, mainly the cellular compartment that is responsible for the immune surveillance against mycobacterium, are important factors in the increasing TB mortality among the elderly. Not surprisingly, parameters linked to general deterioration such as cachexia, anemia and hypoalbumenia are related to mortality in TB.

What is surprising is that drug resistance was not correlated to mortality in our study. This has been reported by others too [18]. Multidrug resistance is a negative prognostic factor leading to long-term mortality. In hospitalized patients this factor may be less relevant [18-21].

The rate of adverse drug reactions to anti-TB treatment was not higher among the deceased. A higher incidence of adverse drug reactions correlated with mortality in elderly patients has been reported [14]. The atypical radiographic presentations of TB in the elderly, with greater involvement of the middle and lower lung fields [22,23], were not observed in our study group. Other studies support our findings [24,25].

In conclusion, our study group consists of hospitalized patients, which is a bias toward the most severe, advanced disease cases; the patients also included older patients with co-morbidi-

HIV = human immunodeficiency virus

ties and those with negative psycho-social factors leading to low compliance with treatment and therefore a tendency to multidrug resistance. Nevertheless, the mortality rate found in this study may be considered relatively low with no difference between the three ethno-geographic groups.

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