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Tuberculosis treatment outcome in a tertiary care setting

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BACKGROUND: The outcome of chemotherapy for pulmonary, extrapulmonary, and disseminated tuberculosis is not well documented, especially in developing countries. This study assessed tuberculosis treatment outcome, cure-to-treatment ratio and mortality among all types of tuberculosis patients in a tertiary care setting in Saudi Arabia.

METHODS: All cases diagnosed and treated for active *Mycobacterium tuberculosis* infection between 1991 and 2000 were included retrospectively. Data collected included type of tuberculosis involvement, treatment outcome, relapse, and co-morbidities.

RESULTS: Over a ten-year period, 535 cases of tuberculosis were diagnosed and treated. Isolated pulmonary tuberculosis was identified in 141 cases (26.4%), extrapulmonary tuberculosis in 339 cases (63.3%), and combined pulmonary and extrapulmonary disseminated involvements in 55 cases (10.3%). Co-morbidities were noted in 277 (52%) patients. Immunosuppression was found in 181 (34%) patients. The cure rate was 82%. The cure-to-treatment ratio was 86% in extrapulmonary tuberculosis and 78% in pulmonary tuberculosis, and 65% in disseminated tuberculosis. Overall mortality was 18%. Disseminated tuberculosis had the highest mortality (34.9%), followed by pulmonary (21.8%), then extrapulmonary tuberculosis (13.6%). Forty-seven percent of all mortalities were directly related to tuberculosis. Relapse was documented in 14 out of 349 patients (4%) who had 24 months of follow up.

CONCLUSION: Despite tertiary care support, complicated tuberculosis carries a high mortality. Earlier diagnosis and complete appropriate chemotherapy are essential for improved outcome.

Treatment outcome serves as a tool to control the quality of tuberculosis treatment provided by the health care system.[1] The global epidemiology of tuberculosis has been shaped in recent decades by HIV/AIDS, urbanization and poverty.[2] In the year 2002, the estimated tuberculosis incidence in the Eastern Mediterranean region was 7%. The death rate from tuberculosis, including death in people infected with the human immunodeficiency virus type 1 (HIV-1) was 28 per 100 000 population, the second highest mortality rate after that of Africa.[3] *Mycobacterium tuberculosis* infection in its various forms remains a major cause of high morbidity and mortality among infectious diseases worldwide. Tuberculosis is one of the top ten causes of global mortality.[4] Treatment completion for tuberculosis has been associated with improved patient survival.[5] A successful outcome in active tuberculosis is influenced by establishing an early diagnosis, initiating appropriate therapy, and adhering to and completing a treatment regimen. Relapse was frequent among patients with pulmonary tuberculosis who had received incomplete treatment.[6] As relapse did not occur among patients who have had a full course of modern chemotherapy, abolishing routine follow up was recommended. The rate of tuberculosis relapse is low for those who complete the treatment irrespective of the site of involvement.[7] Data on tuberculosis outcome, mortality, and relapse are limited in immunocompromised patients or patients with co-morbid conditions from developing countries. In this study, we report treatment outcome and mortality and compare the cure, relapse, and tuberculosis-related mortality for all pulmonary, extrapulmonary, and disseminated involvements at a tertiary care center.

METHODS

All cases of *M. tuberculosis* infection between 1991 and 2000 were identified from the databases of the Section of Infectious Diseases, Infection Control, and the Microbiology Laboratory. The outcome of all tuberculosis cases diagnosed and treated at King Faisal Specialist Hospital and Research Center was assessed retrospectively. This 700-bed facility is the main national tertiary care referral center for cancer, cardiac, organ and bone marrow transplantation, and HIV-infected patients. Demographic, clinical, and outcome data were abstracted from medical records using a uniform data collection form. Mortality data were assigned as tuberculosis-related (patients died on treatment due to tuberculosis or its complications) or unrelated (patients died due to medical conditions other than tuberculosis during or after treatment) by a single reviewing investigator. Cases were classified into extrapulmonary tuberculosis where organs other than the lungs were involved by *M. tuberculosis.* If the lungs were also actively involved as evidenced clinically, radiologically, or microbiologically, the condition was considered disseminated tuberculosis. Isolated pulmonary tuberculosis was considered if patients had evidence of tuberculosis involving the lungs only. All treatment courses were based on the guidelines of the National Tuberculosis Program, using four drugs. For pulmonary tuberculosis in immunocompetent patients, duration was for six months. For extrapulmonary tuberculosis in immunocompromised hosts, duration was extended to one year.

Terms used in this report are defined as follows:

Treatment completion: record of treatment course completion was noted.

Defaulters: record of loss of follow up, but no record of treatment completion elsewhere.

Transferred cases: transferred to another center but no treatment results available.

Cure: record of cure after treatment completion, based on clinical, radiological, and microbiological evidence.

Relapse: defined as re-treatment within 24 months after completing the initial first course of tuberculosis chemotherapy due to confirmed persistent disease clinically or microbiologically.

Epi Info Version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA and World Health Organization, Geneva, Switzerland) was used for data entry. Statistical analysis was performed using the Statistica Software Package Version 5.0 (StatSoft, Tulsa, OK). The Student's t test was used to calculate continuous variables, and the chi-square or Fisher's exact test was used for proportions. All reported *P* values are two-tailed and a value of 0.05 was considered significant.

RESULTS

Over the study period, 535 cases of tuberculosis were diagnosed and treated. Isolated pulmonary tuberculosis was identified in 141 cases (26.4%), extrapulmonary tuberculosis in 339 cases (63.3%), and both pulmonary and extrapulmonary disseminated involvements in 55 cases (10.3%). Table 1 summarizes the baseline data of all patients. All patients had microbiological and/or histopathological confirmation of tuberculosis except for 22 patients (4%) who were classified as having tuberculosis based on clinical judgment and a favorable response to tuberculosis chemotherapy. Diagnosis was significantly delayed in patients with extrapulmonary tuberculosis compared with patients with isolated pulmonary tuberculosis (7 weeks versus 4.3 weeks, P=0.003). Outcome data are summarized in Table 2. Follow-up, treatment, and outcome data were available for 401 patients (75%). Of the 535 patients, care was transferred to other health care facilities in 57 cases (10.6%) and 77 patients (14.4%) defaulted. Co-morbidities were noted in 277 patients (52%). The commonest was intentional immunosuppression therapy for organ transplantation, autoimmune diseases or neoplasia, which were noted in 181 (65.3%).

The overall cure rate for all tuberculosis cases that had follow-up data and completed treatment was 329/401 (82%). The cure-to-treatment ratio was 79/101 (78%), 222/257 (86%), and 28/43 (65%) in the pulmonary, extrapulmonary, and disseminated tuberculosis cases, respectively. Relapse was noted in 14 of 329 patients (4%) who had 24 months of follow up (pulmonary tuberculosis, 4.7%; extrapulmonary, 3.4%; and disseminated tuberculosis, 6.3%). Overall mortality was 72 of 401 (18%). The mortality rate in pulmonary tuberculosis was 22/101(21.8%), extrapulmonary, 35/257 (13.6%), and disseminated tuberculosis, 15/43 (34.9%). Mortality was directly related to tuberculosis in 34 patients (47%). The distribution of tuberculosis mortality for various forms of tuberculosis is presented in Table 3.

DISCUSSION

Although completion of treatment for active cases of tuberculosis is the most important priority for tuberculosis control programs, reporting treatment success rate, mortality, and relapse should also be highlighted. The National Tuberculosis Program (NTP) targets and sets a cure rate of more than 85% of detected

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Table 1. Baseline data on the study population.

	Pulmonary TB n=141	Extrapulmonary TB n=339	Disseminated TB n=55	Total n=535
Percentage female	59%	47%	58%	51%
Mean age, years (SD)*	51 (20)	45 (19)	44 (20)	46 (20)
Duration of symptoms in weeks (SD)†	4.3 (9.7)	7 (8.8)	5.7 (11)	6.2 (9)
Patients with co-morbidities	89 (63%)	156 (46%)	32 (58%)	277 (52%)

Data are number of patients and percentage unless otherwise noted. *Pulmonary TB patients significantly older (P=0.007) †Extrapulmonary cases significantly slower to diagnose (P=0.003)

Table 2. Tuberculosis outcome in a tertiary care hospital.

	Pulmonary n=141	Extrapulmonary n=339	Disseminated n=55	Total n=535
Transferred	18 (12.8)	36 (10.6)	3 (5.5)	57 (10.6)
Dead	22 (15.6)	35 (10)	15 (27)	72 (13.5)
Cured	79 (56)	222 (65.5)	28 (51)	329 (61.5)
Lost to Follow-up	22 (15.6)	46 (13.6)	9 (16.4)	77 (14.4)

Data are number of patients and percentage.

Table 3. Tuberculosis-related and -unrelated deaths among cases with 24 months of follow up.

	Pulmonary n=101	Extrapulmonary n=257	Disseminated n=43	Total n=401
TB-related	10 (9.9)	15 (5.8)	9 (20.9)	34 (8.5)
Not related	12 (11.9)	20 (7.8)	6 (14)	38 (9.5)
Total mortality	22 (21.8)	35 (13.6)	15 (34.9)	72 (18)

Data are number of patients and percentage.

new cases of sputum smear-positive tuberculosis. The NTP emphasizes curing as many patients as possible to reduce transmission of *M. tuberculosis* infection. A cure rate of at least 85% will decrease immediately the prevalence and the rate of transmission. The incidence will decrease gradually and there will be less acquired drug resistance. This in turn makes future treatment of tuberculosis easier and more affordable. Detecting the rate of defaulters will estimate roughly the threat of spreading resistant strains of mycobacteria.[8,9] In this study, 52 of 196 patients (27%) who were potentially infectious (with pulmonary and disseminated type) had no reportable outcome. The majority of them defaulted treatment. We are reporting rates of cure less than the 85% that is recommended by World Health Organization, even when transferred cases and defaulters were excluded. The cure-to-treatment ratio was 78% in the pulmonary and 65% in the disseminated type of infection.

The overall treatment success rate of all tuberculosis cases diagnosed between 1993 and 1999 from a tertiary care hospital in the western region of our country with a high prevalence of tuberculosis was 69.4% when patients who were lost to follow-up were excluded.[10] Such data are not only reflective of the tuberculosis treatment and control program, but also the competence of the health care system in identifying these cases, instituting appropriate treatment and successfully completing the course of chemotherapy.

The considerably high mortality rate among study cases may be related to the high population of patients with severe co-morbid illnesses in whom the diagnosis was delayed. It indicates the significant impact of the disease in severely ill patients, or those who are requiring corticosteroids. Such settings are associated with high mortality rates and low treatment success rates.[11-14] This hospital has been serving a large population of patients with immunocompromised conditions as a refer-

ral hospital, transplantation, hematology/oncology and HIV treatment center. In fact, the study institute has been managing more extrapulmonary tuberculosis since its early days.[12-14] Worldwide, the case-fatality rate of smear-positive pulmonary tuberculosis among persons on treatment is 3.8%.[15] There are limited data reporting treatment completion from the developing countries. The mortality among patients with pulmonary tuberculosis in a teaching hospital in Ghana was associated with increased age and more prolonged symptom duration prior to therapy.[16] In the year 2000, WHO surveillance of tuberculosis treatment in Europe recorded a successful outcome rate of 77%.[17] The tuberculosis treatment outcome in England in a district with high prevalence of disease was 88% for the cure-to-treatment completion ratio, 12% mortality, and a 1% relapse rate among 205 definite cases of pulmonary tuberculosis.[18] Multidrug-resistant tuberculosis (MDR-TB) was inversely associated with a successful outcome.[17] In a referral hospital from Turkey, the tuberculosis treatment success rate between 1997 to 1999 was 71.9%. Failure was encountered mainly among patients with rifampicin resistance and MDR-TB.[19] In our country outcome has never been reported on a large scale, including mortality and relapse. The future tracking of indicators of patient care such as delayed diagnosis and overall tuberculosis-related mortality rate may offer better efficiency in resource utilization, special care for high-risk patients and aid in the conduct of clinical trials.

At tuberculosis care facilities establishment of a management program is recommended as is evaluation of common predictors of outcome at presentation such as age, time from onset of symptoms to diagnosis, chest radiographic findings, culture and susceptibility results, smear status, HIV status, and the presence of associated co-morbid illnesses. Drug resistance proved the most important factor affecting treatment outcome. Success rates in re-treatment of patients with MDR-TB are low.[19] Physicians and other health care providers must devote a great deal of their time and effort to avoiding late diagnosis, start treatment as soon as the clinical suspicion is high, track adherence with medications, defaulters, patients transferred to other local units and make sure that patients with tuberculosis are adequately treated.

The limitation of this study is that it is from a single center and retrospective. The extrapulmonary tuberculosis may have been influenced by the high rate of tuberculous lymphadenitis, comprising around 40% of the cases. The early diagnosis, initiation and completion of appropriate treatment for tuberculosis have to be augmented by raising awareness among care providers.

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