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ORIGINAL ARTICLE

Prognostic factors of treatment among patients with multidrug-resistant tuberculosis in Egypt

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Background/purpose: Multidrug-resistant tuberculosis (MDR-TB) represents 5% of TB cases globally. In Egypt, it represents 11.4% of TB cases (2.2% of new and 38.2% of previously treated). Our objectives were to evaluate the treatment outcomes and determine the associated prognostic factors among the first national treatment cohort of MDR-TB from 2006 to 2010.
Methods: All patients diagnosed with MDR-TB from July 2006 to December 2010 who were admitted to Abbassia Chest Hospital, the first Egyptian national center established for MDR-TB treatment, were included. They were followed up clinically, radiologically, and bacteriologically by sputum smear, culture, and drug-susceptibility testing at regular intervals. Individualized treatment regimens were prescribed according to each patient's drug-susceptibility testing and the drug treatment history. Patients received at least five effective drugs. Outcome rates, and crude and adjusted odds ratios of unsuccessful outcomes were calculated.
Results: The number of bacteriologically proven MDR-TB patients was 228, of which 225 were pulmonary cases. Half of the cases showed moderate or extensive lung lesions, and 15.8% were diabetics. A total of 158 (119 cured and 39 completed treatment) patients achieved successful outcome (69.3%), 16 (7.1%) failed treatment, 27 (11.8%) were lost to follow up, and 27 (11.8%) died. Predictors of unsuccessful outcome were delay in sputum culture conversion to 2 months or more, moderate or extensive lung lesions, and a history of diabetes.
Conclusion: A treatment success rate of approximately 69% was achieved with the first national treatment cohort of MDR-TB under the Egyptian program. Predictors of unsuccessful

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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treatment were delayed culture conversion, moderate or extensive lung affection, and diabetes.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least the two key first-line drugs: isoniazid and rifampicin. Resistance mainly arises through the selection of mutated strains by improper or inadequate treatment.[1] Globally, MDR-TB is estimated to account for 5% of TB cases, being higher among patients previously treated for TB (20.5%), than among new cases (3.5%).[2] The more resistant form of TB, extensively drug-resistant TB, was reported from 92 countries in the year 2012, and it is estimated to account for 9.6% of MDR-TB cases.[3] Treatment of MDR-TB is a lengthy regimen using mainly bacteriostatic, less effective, and more toxic drugs, and thus is poorly tolerated. Consequently, adherence is extremely difficult, and a disappointingly low average global success rate of 48%, with high rates of both mortality and loss to follow up, was reported. Proper operational and clinical case management is essential for treatment success.[1,3]

The Egyptian National Tuberculosis Control Program adopted the World Health Organization's strategy of Directly Observed Treatment with Short Course (DOTS) in 1996, and a nationwide coverage was reached by the year 2000. In 2002, a drug resistance survey was conducted with the detection of MDR-TB in 11.4% of the total TB cases (97 out of 849), of which 2.2% were among new cases (14 out of 632) and 38.2% among previously treated cases (83 out of 217).[4] The magnitude of MDR-TB cases was noticeable, especially among previously treated cases. Therefore, in 2003, Egypt applied to the Green Light Committee to establish a project for their management, planning to include four centers covering the whole country. The first center was in Abbassia Chest Hospital in July 2006, and three other centers are now established. The objectives of the current study were to evaluate the treatment outcomes and determine the associated prognostic factors among the first national treatment cohort of MDR-TB patients in Abbassia Chest Hospital from 2006 to 2010.

Methods

Setting and study design

Abbassia Chest Hospital was chosen as the first center for starting the national program of treatment of MDR-TB patients in Egypt. It is one of the biggest Egyptian chest hospitals, located in Cairo, with a capacity of 450 beds. A prospective cohort study was carried out including all the patients admitted during the study period (from June 2006 to December 2010). Patients were retrieved from all over the country to constitute the first national treatment cohort of MDR-TB.

Definitions

Case definitions, definition of sputum conversion, and treatment outcome definitions were according to the recommendations of the World Health Organisation MDR-TB working group.[5] *Cured patients* were those who had completed treatment according to the protocol and had at least five consecutive negative cultures, 30 days apart in the final 12 months of treatment. Cure could still be considered in cases reporting only one positive culture during that time, followed by a minimum of three consecutive negative ones with no clinical deterioration. *Treatment completed* cases included patients who had completed treatment according to the protocol, but fewer than five cultures were performed during the final 12 months of treatment.[5] *Successful outcome* included both cured and completed patients.

Laboratory testing

Sputum smear microscopy and culture on Lowenstein—Jensen media were conducted in the laboratory of Abbassia Chest Hospital and according to the international standards. Drug-susceptibility testing (DST) was conducted in the national reference laboratory, which was chosen to be the supranational laboratory for the Eastern Mediterranean Region of the World Health Organization (WHO). DST was conducted for four first-line drugs (isoniazid, rifampicin, ethambutol, and streptomycin) and for three second-line drugs (capreomycin, amikacin, and ofloxacin). Testing was performed monthly until conversion and then every other month. DST was reassessed in cases with delayed conversion beyond the 3rd month of treatment, or in cases where cultures became positive after being negative previously.

Other scheduled investigations including assessment of serum glucose, creatinine, potassium, thyroid stimulating hormone (TSH), liver enzymes, and pregnancy test were performed. Human immunodeficiency virus status was assessed and all patients were negative.

Radiographic testing

Disease extension on the standard chest X-ray film (posterior—anterior) was categorized as follows: *mild*—included unilateral disease infiltration and unilateral cavity; *moderate*—included bilateral cavity or complete lobe destruction; and *extensive*—included any wider extension of the disease. Radiography was performed at patient enrollment and every 6 months thereafter.

Treatment regimens

The MDR-TB patients who were confirmed by drug-susceptibility tests (DST) were put on an individualized treatment regimen based on the resistance profile of the patients to the first-line anti-TB treatment and modified according to their treatment history. Treatment duration was 18 months after sputum culture conversion, as recommended by the WHO.[6]

All doses of drugs were directly observed during hospitalization and three times a week during the ambulatory period.

Statistical analysis

Data analysis was performed using SPSS version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. US). Categorical variables were compared using either Chi-square or Fisher's exact test. Crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CI_{95}) were calculated. A binary logistic multivariate model was applied to determine the independent predictors of the treatment outcome out of those factors that demonstrated significant association by bivariate analysis at a level of significance of $p \leq 0.05$.

Ethical approval

Research Ethics C at the Faculty of Medicine, Ain Shams University, approved this study protocol. A formal, informed written consent was obtained from every patient prior to starting the treatment.

Results

From 2006 until the end of 2010, 228 MDR-TB patients were admitted to Abbassia Chest Hospital. Their characteristics are reported in Table 1. The median age was 37 years, ranging from 7 years to 76 years. The number of female patients was 67 (29.4%). On hospital admission, 36.4% were smokers, 9.2% were alcohol users, and 11.4% were illicit drug users.

Extrapulmonary TB was diagnosed in three patients (1.3%). The number of new cases was six (2.6%); the majority of the patients were previously treated cases (222/228, 97.4%), among them 124 (55.9%) had previously received more than two treatment courses. The number of treatment courses ranged from one to seven, and the median was three. A history of TB illness for <5 years before starting treatment was most common (187/222, 84.2%). Twenty-six (26/228, 11.4%) patients had a positive history of receiving the second-line anti-TB drugs.

Isolates were resistant to a median of four drugs (range 2–6), and the vast majority were resistant to streptomycin (220/228, 96.5%) and ethambutol (183/228, 80.3%). Resistance to fluoroquinolones, except ofloxacin (3/228, 1.3%), was uncommon. Resistance to the second-line injectable drug kanamycin was detected in cases with extensively drug-resistant TB (2/228, 0.9%). Of the isolates, 180 (78.9%) were resistant to at least four drugs. Lung lesions were mild in 49.8% (112/225), moderate in 23.1% (52/225), and extensive in 27.1% (61/225) of the pulmonary cases. Diabetes was found among 15.8% (36/228) of patients.

Table 1 Demographics, clinical characteristics, and treatment outcome.

Characteristics	n = 228 (%)
Age < median value[a]	106 (46.5)
Age ≥ median value	122 (53.5)
Male sex	161 (70.6)
Smoking	83 (36.4)
Alcohol use	21 (09.2)
Illicit drug use	26 (11.4)
Pulmonary TB	225 (98.7)
Disease duration before treatment: ≥ 5 y[b]	35 (15.8)
History of diabetes	36 (15.8)
Previous use of any of second-line drugs[c]	26 (11.4)
Resistance to four or more drugs	180 (78.9)
Moderate and extensive lesions in X-ray[d]	113 (50.2)
Drug regimens	
I—Km, Ofx, Cs, Eto, PAS	209 (91.7)
II—Cm, Lfx, Cs, Eto, PAS, Clr, Amx/Clv	10 (4.4)
III—E, Km, Ofx, Cs, Eto, PAS	9 (3.9)
Sputum smear conversion before 2 mo[d]	114 (50.7)
Sputum culture conversion before 2 mo[d]	48 (21.3)
Successful[e]	158 (69.3)
Failure	16 (7.10)
Lost to follow up	27 (11.8)
Deaths	27 (11.8)

Amx/Clv = amoxicillin/clavulanate; Clr = clarithromycin; Cm = capreomycin; Cs = cycloserine; E = ethambutol; Eto = ethionamide; Km = kanamycin; Lfx = levofloxacin; Ofx = ofloxacin; PAS = *p*-aminosalicylic acid; TB = tuberculosis.

[a] Median age = 37 years.

[b] Percentage was taken from the 222 previously treated cases.

[c] Drugs either administered with Category IV regimen (7 cases) or sporadically used (19 cases).

[d] Percentage was taken from the 225 pulmonary TB cases.

[e] A total of 119 patients was cured and 39 completed the treatment period.

At least five effective drugs (range 5–7) were used for a median duration of 22 months (range 21–30 mo) for 174 (76.3%) patients (excluding deaths and those lost to follow up). Taking into consideration the patients' resistance profile and treatment history, three treatment regimens were used: Regimen I—kanamycin, ofloxacin, cycloserine, ethionamide, and *p*-aminosalicylic acid (209/228, 91.7%); Regimen II—capreomycin, levofloxacin, cycloserine, ethionamide, *p*-aminosalicylic acid, amoxicillin/clavulanate, and clarithromycin (10/228, 4.4%); and Regimen III—ethambutol, kanamycin, ofloxacin, cycloserine, ethionamide, and *p*-aminosalicylic acid (9/228, 3.9%).

The median time of sputum smear conversion to negative was 30 days (ranging from 27 d to 183 d). Conversion occurred in 114 (50.7%) patients before 2 months of treatment had elapsed, and they most probably became noninfectious. No conversion occurred in 16 (7.1%) patients.

The median time of sputum culture conversion was 60 days (interquartile range 58–121 d). Conversion before 2

months of treatment occurred in 48 (21.3%) patients, between 2–3 months in 93 (41.3%) patients, and after 3 months in 56 (24.9%) patients, with a maximum of 10 months. No conversion occurred in 28 (12.4%) patients.

As shown in Table 1, about half of the patients were cured (n = 119, 52.2%) and 39 (17.1%) completed the treatment, giving a successful outcome (cured and completed) in 158 (69.3%) patients. Treatment failure was declared in 16 (7.1%) patients, 27 (11.8%) were lost to follow up, and 27 (11.8%) died. The three extrapulmonary cases either completed treatment (2 patients) or were lost to follow up (1 patient).

Using the bivariate analysis (Table 2), the rate of unsuccessful outcome was found to be significantly higher among males (OR: 2.6, CI_{95}: 1.3–5.2, p = 0.007), smokers (OR: 2.3, CI_{95}: 1.3–4.1, p = 0.005), alcohol users (OR: 2.8, CI_{95}: 1.1–6.8, p = 0.024), drug users (OR: 2.5, CI_{95}: 1.1–5.8, p = 0.023), diabetics (OR: 2.3, CI_{95}: 1.1–4.9, p = 0.02), those with a positive history of intake of the second-line anti-TB drugs (OR: 3.6, CI_{95}: 1.6–8.4, p = 0.002), those with moderate or extensive lung lesions on X-ray (OR: 4.3, CI_{95}: 2.3–8.1, p = 0.000), and those whose culture conversion was delayed to 2 months or more (OR: 3.6, CI_{95}: 1.2–10.8, p = 0.001). Treatment outcome was not affected by age, patient's category (either previously treated or new case), number of drugs to which isolates were resistant, or the treatment regimen.

The median treatment durations were 22 months (range 21–30 mo) among successful and 23 months (range 21–26 mo) among unsuccessful treatment outcome groups. The difference in treatment duration was not statistically significant (t test = 0.964, p = 0.336). On multivariate analysis, significant predictors of an unsuccessful outcome were diabetes (OR: 2.7, CI_{95}: 1.02–6.99), moderate or extensive lung lesion (OR: 5.9, CI_{95}: 2.5–13.9), and delay in sputum culture conversion to 2 months or more (OR: 3.7, CI_{95}: 1.2–11.7).

Discussion

In this first national treatment cohort of MDR-TB patients, the achieved success rate was 69.3%. Rates of failure, loss to follow up, and death were 7.1%, 11.8%, and 11.8%, respectively. Application of individualized treatment regimens for at least 18 months after sputum culture conversion was performed, as well as application of DOTS strictly during the period of hospitalization and for two to three times weekly afterward.

Studies evaluating the performance of different country programs showed that the rates of treatment success ranged from 62% to 69%, failure from 6% to 8%, loss to follow up from 12% to 15%, and death from 9% to 13%.[7–9] Programs applying individualized treatment regimens for a duration of more than 18 months and DOTS strategy throughout this period achieved the highest success rate and reduced loss to follow up rate.[7–10] Their average rates of treatment success, failure, loss to follow-up, and death were 69%, 7%, 12%, and 9%, respectively.[7] Apart from the higher rate of death, our results showed comparability to other programs applying the same conditions.

The observed higher mortality might be due to the fact that most of the mortality cases (19 out of 27, 70.4%) showed moderate or severe lung lesion. These findings might be a result of the fact that a long time elapsed between their diagnoses as MDR-TB cases and the start of treatment; as the establishment of the MDR-TB management program began late in June 2006 in only one center (the study site); this delay might have negatively affected their outcome. Lower mortality and a lower rate of treatment failure can be observed in programs with a shorter delay in treatment commencement for MDR-TB patients, as well as in treatment cohorts with a higher percentage of those who had had no previous anti-TB therapy.[8,11,12] Treatment delay might not be a problem with the patient group that started treatment later, and the application of rapid diagnostic techniques might be an opportunity for improvement of the program performance.

Many predictors of treatment outcome among MDR-TB cases have been identified through various studies. The results herein documented the association of unsuccessful outcome, using bivariate analysis, with the male sex, smoking, alcohol use, illicit drug use, a history of diabetes, a history of previous use of a second-line anti-TB drugs, moderate or extensive lung lesions, and delay in sputum culture conversion to negative to 2 months or more. However, only three independent factors were identified by multivariate analysis, namely, a history of diabetes, moderate or extensive lung lesions, and delay in culture conversion to 2 months or more of treatment.

Poor treatment outcome was reported, in a number of previous studies, to be associated with factors such as male sex, alcohol usage, illicit drugs usage, and smoking.[8,13–16] However, the role of sex was not documented in two studies conducted in India and Switzerland.[17,18] Our data could not provide sufficient evidence to document the role of any of these factors in prediction of treatment outcome.

Previous and inadequate TB treatment, and a previous use of second-line drugs have been documented as significant risk factors for poor treatment outcome due to the development of more drug resistance.[8,19,20] Despite the number of studies that documented this fact, the data herein did not prove any of these factors. The insufficient sample of new MDR cases (6 patients) limited our ability to evaluate the effect of previous TB treatment, since previous treatment was reported in 97.4% of our sample.

Neither the treatment regimen nor the initial resistance to a greater number of drugs was found to have an effect on the outcome. Some studies also reported that the outcome was not affected by the regimen used or the patients' resistance profile.[9,18] The small sample that received either the second (10 patients) or the third (9 patients) regimen, as well as the slight differences between them may explain the inability to demonstrate any effect of each regimen on the outcome. The risk of poor treatment outcome among diabetics was about three times that among nondiabetics. The role of diabetes in both the development of resistance and the risk of treatment failure and death among MDR-TB patients has been extensively studied. The relationship between diabetes mellitus and MDR-TB is a point of controversy. While some studies could not find such a relation,[21–23] others observed an increased risk of MDR-TB, ranging from 2.1 to 8.8 times,

Table 2 Factors affecting treatment success among MDR-TB patients ($n = 228$).

	Unsuccessful $n = 70$ (30.7%)	Successful $n = 158$ (69.3%)	p	Crude OR (CI_{95})	Adjusted OR (CI_{95})[a]
Sex					
Male	58 (36.0)	103 (64.0)	**0.007**	2.6 (1.3–5.2)	2.3 (0.9–5.9)
Female	12 (17.9)	55 (82.1)			
Age category (y)					
≥37	44 (36.1)	78 (63.9)	0.061	1.7 (0.9–3.1)	ND
<37	26 (24.5)	80 (75.5)			
Tobacco use					
Smokers	35 (42.2)	48 (57.8)	**0.005**	2.3 (1.3–4.1)	1.4 (0.5–3.5)
Nonsmokers	35 (24.1)	110 (75.9)			
Alcohol use					
Users	11 (52.4)	10 (47.6)	**0.024**	2.8 (1.1–6.8)	0.40 (0.1–3.5)
Nonusers	59 (28.5)	148 (71.5)			
Drug use					
Users	13 (50.0)	13 (50.0)	**0.023**	2.5 (1.1–5.8)	2.1 (0.3–14.8)
Nonusers	57 (28.2)	145 (71.8)			
DM history					
Diabetics	17 (47.2)	19 (52.8)	**0.02**	2.3 (1.1–4.9)	2.7 (1.02–6.99)
Nondiabetics	53 (27.6)	139 (72.4)			
Patient category					
Previously treated	69 (31.1)	153 (68.9)	0.79	2.3 (0.3–19.7)	ND
New cases	1 (16.7)	5 (83.3)			
Second-line drugs[b]					
Yes	15 (57.7)	11 (42.3)	**0.002**	3.6 (1.6–8.4)	1.8 (0.7–4.8)
No	55 (27.2)	147 (72.8)			
X-ray lesions[c]					
Moderate &extensive	51 (45.1)	62 (54.9)	**0.000**	4.3 (2.3–8.1)	5.9 (2.5–13.9)
Mild	18 (16.1)	94 (83.9)			
Drug resistance					
Four or more drugs	57 (31.7)	123 (68.3)	0.541	1.2 (0.6–2.5)	ND
Less than four drugs	13 (27.1)	35 (72.9)			
Drug regimens					
Km, Ofx, Cs, Eto, PAS	61 (29.2)	148 (70.8)	1.0	1.4 (0.3–7.1)	0.6 (0.09–4.4)
Cm, Lfx, Cs, Eto, PAS, Clr, Amx/Clv	7 (70.0)	3 (30.0)	0.07	8.2 (1.03–64.9)	0.7 (0.03–15.7)
Km, Ofx, Cs, Eto, PAS, E[d]	2 (22.2)	7 (77.8)			
Conversion time (mo)[e]					
≥2	37 (24.8)	112 (75.2)	**0.001**	3.6 (1.2–10.8)	3.7 (1.2–11.7)
<2	4 (8.3)	44 (91.7)			
History of TB[f]					
≥5 y	11 (31.4)	24 (68.6)	0.961	1.02 (0.5–2.2)	ND
<5 y	58 (31.0)	129 (69.0)			

Bold indicates significant association at a p-value ≤0.05.
Amx/Clv = amoxicillin/clavulanate; CI_{95} = 95% confidence interval; Clr = clarithromycin; Cm = capreomycin; Cs = cycloserine; DM = diabetes mellitus; E = ethambutol; Eto = ethionamide; Km = kanamycin; Lfx = levofloxacin; MDR-TB = multidrug-resistant tuberculosis; ND = not included in the logistic model, insignificant by bivariate analysis; Ofx = ofloxacin; OR = odds ratio; PAS = p-aminosalicylic acid; TB = tuberculosis.
[a] Using stepwise logistic regression, excluding extrapulmonary and not converted cases.
[b] History of previous use of any of the second-line drugs.
[c] Three cases were extrapulmonary TB.
[d] The reference group.
[e] Thirty-one cases were excluded: 28 not converted and three extrapulmonary.
[f] Six new cases were excluded.

and a relapse with resistant strains among diabetics.[24–27] On the other hand, an increased risk of poor treatment outcome of MDR-TB was documented among diabetics.[5,28–30] In addition, diabetes may act as a potentiating factor of the adverse effects of anti-TB drugs, especially those related to renal dysfunction and peripheral neuropathy.[5] In light of the previous evidence, detection of diabetes comorbidity is strongly required. Active screening for diabetes among TB patients is suggested as a more cost-effective measure than screening for

TB among diabetics, especially in countries with a low TB burden, where the yield of the screening for TB will be low.[31] In Egypt, as a low TB-burden country,[3] screening for diabetes among TB cases may be a plausible option, to be incorporated within the TB control program.

Extension of lung tissue destruction was found to be an independent predictor of the treatment outcome with a sixfold increase in the risk of poor outcome with more destruction. This finding was previously documented in many studies in which the presence of cavity and extensive disease was associated with a poor bacteriologic response.[19,30,32]

Bacteriological improvement as well as the infectious status of patients was determined by the sputum culture conversion, and this factor was found to be a significant predictor for treatment outcome. Earlier conversion increases the likelihood of successful outcome, and it could be used as an interim indicator of the outcome. Similar results were observed in India and Latvia.[13,33] The median time to culture conversion in the current study was 60 days, similar to that reported from Latvia (60 d) and Georgia (68 d),[33,34] but shorter than that from Armenia (3.7 mo).[35] This relatively long conversion time among Armenians was due to the presence of a high level of ofloxacin resistance.[35] Delayed culture conversion was previously found to be associated with male sex, smoking, low body mass index, resistance to second-line drugs, and extensive lung affection with the presence of cavities.[33–35] Patients with such characteristics should be targeted with more aggressive management, not only for the sake of a better prognosis, but also to shorten the period of infectiousness.

In conclusion, about 69% treatment success was achieved with the first national treatment cohort of MDR-TB cases. The high mortality rate highlighted the importance of continuing the efforts for rapid diagnosis and treatment. Predictors of unsuccessful outcome included moderate or extensive lung affection, delay of sputum culture conversion to 2 months or more, and a history of diabetes.

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