Situation of multidrug-resistant pulmonary tuberculosis in Alexandria governorate from July 2008 to December 2012

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Aim The aim of this study was to estimate the prevalence, possible risk factors, patterns of resistance, and fate of multidrug-resistant pulmonary tuberculosis (MDR-TB) in Alexandria governorate as a representative part of Egypt during the period between July 2008 and December 2012.

Patients and methods This retrospective study included all patients with pulmonary TB that was recorded in Alexandria governorate during the period between July 2008 (the time that MDR ward was held in Alexandria) and December 2012. They were divided into two groups: group I included patients with pulmonary TB that was recorded in Alexandria governorate (1893 cases), and group II included patients with pulmonary TB who were admitted in El-Maamoura Chest Hospital (509 cases). They were subdivided into two subgroups: group IIa included patients with MDR pulmonary TB (82 cases), and group IIb included patients with pulmonary TB not categorized as MDR-TB (427 cases).

Results All patients with MDR-TB had acquired resistance. MDR-TB was more common in the male population, diabetic patients, and those with chronic chest disease. The effect of treatment of MDR-TB cases was as follows: cured patients, 49 (59.8%); patients under treatment, 10 (12.2%); treatment failure, four cases (4.9%); deceased patients, 10 (12.2%); and defaulters, nine (10.9%). The overall total prevalence rate of MDR-TB in Alexandria governorate from 2008 to 2012 was 4.3%.

Conclusion There was a decreasing trend of MDR-TB cases. History of anti-TB treatment is the strongest independent predictor of MDR-TB. The highest figures of resistance in the MDR group besides isoniazide and rifampicin were for streptomycin, whereas the lowest resistance was for ethambutol. *Egypt J Broncho* 2016 10:64–68

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Introduction

Strains of *Mycobacterium tuberculosis* that are resistant to both isoniazid and rifampicin with or without resistance to other drugs have been termed multidrug-resistant (MDR) strains. Isoniazid and rifampicin are keystone drugs in the management of tuberculosis (TB). However, resistance to either isoniazid or rifampicin may be managed with other first-line drugs [1].

Multidrug-resistant tuberculosis (MDR-TB) is caused by the transmission of MDR *M. tuberculosis* strains in new cases, or by the selection of single-drug-resistant strains induced by previous treatments [2].

The incidence of drug resistance has increased since the first drug treatment for TB was introduced in 1943. The emergence of MDR-TB followed the widespread use of rifampicin since the 1970s [3]. The spectrum of this form of TB now ranges from 'basic' MDR-TB, with resistance only to rifampicin and isoniazid, to XDR-TB, which has additional extensive drug resistance to at least three of the six main classes of second-line anti-TB drugs [4]. Alexandria governorate is one of the governorates of Egypt. It is located in the northern part of the country, directly on the Mediterranean Sea, making it one of the most important harbors in Egypt. It has a population of more than four millions and an area of 2900 km^2 [5].

Patients and methods

This retrospective study included all patients with pulmonary TB that was recorded in Alexandria governorate during the period between July 2008 (the time that MDR ward was held in Alexandria) and December 2012 and included patients admitted in El-Maamoura Chest Hospital in the MDR ward with culture-positive pulmonary TB during the same period of time. A total of 1893 cases were collected from El-Maamoura Chest Hospital, Kom El-Shogafa Chest Hospital, Moharam Bek Chest Clinic, El-Maamoura Chest Clinic, Bakoose Chest Clinic, Karmooze Chest Clinic, El-Amria Chest Clinic, Gabbary Chest Clinic, and El-Gomrok Chest Clinic. The inclusion criteria included patients suffering from pulmonary TB that was recorded in Alexandria

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governorate. The exclusion criteria included patients with extrapulmonary TB.

The patients were divided into two groups:

Group I included patients with pulmonary TB that was recorded in Alexandria governorate (1893 cases).

Group II included patients with pulmonary TB who were admitted in El-Maamoura Chest Hospital (509 cases).

Group II was subdivided into two groups:

Group IIa included patients with MDR pulmonary TB (82 cases).

Group IIb included patients with pulmonary TB that was not categorized as MDR-TB (427 cases).

Files of group II were analyzed and the following data were collected:

(1) Medical history and physical examination.
(2) Laboratory investigations, including direct sputum smear examined using the Ziehl-Neelsen method for 3 successive days, sputum culture for *M. tuberculosis* with traditional culture on Lowenstein–Jensen medium, and drug susceptibility tests for first-line and some of the second-line anti-TB drugs (kanamycin and ofloxacin).

Data management and analysis

The collected data were revised, coded, tabulated, and introduced to a PC using Statistical Package for Social Science (SPSS 15.0.1 for Windows, 2001; SPSS Inc., Chicago, Illinois, USA).

Results

Tables 1–9. There was significant association between MDR-TB and male sex, age group 25–44 and unemployment (Table 1). There was statistically significant association between group IIa and group IIb as regards smoking, addiction, and alcoholism (Table 2). There was statistically significant association between group IIa and group IIb as regards DM, liver cirrhosis, and chronic chest disease (Table 3). There was statistically significant association between previous TB treatment and group IIa as all of them had acquired resistance (Table 4). Resistance to antituberculous drugs was as follows: 100% to INH, 100% to rifampicin, 93.9% to streptomycin, 30.1% to ethambutol, and no

Table 1 Description and comparison of the sociodemographic characteristics of MDR-TB cases (group IIa) and TB cases not categorized as MDR-TB in El-Maamoura Chest Hospital (group IIb)

Character	Group IIa (MDR cases) (n = 82) [N (%)]	Group IIb (TB cases) (n = 427) [N (%)]	χ^2	P	Significance
Sex					
Male	65 (79.3)	287 (67.2)	4.687	0.030	S
Female	17 (20.7)	140 (32.8)			
Age					
≤14	0 (0)	2 (0.5)			
15–24	10 (12.2)	37 (8.7)			
25–34	23 (28.1)	158 (37)			
35–44	21 (25.6)	145 (34)	14.935	0.02	S
45–54	16 (19.5)	45 (10.5)			
55–64	10 (12.2)	22 (5.1)			
≥65	2 (2.4)	18 (4.2)			
Occupation					
Unemployed	50 (61)	312 (73.1)	4.897	0.026	S
Employed	32 (39)	115 (26.9)			

MDR-TB, multidrug-resistant pulmonary tuberculosis; TB, tuberculosis.

Table 2 Description and comparison of habits of medical importance of MDR-TB cases (group IIa) and TB cases not categorized as MDR-TB in El-Maamoura Chest Hospital (group IIb)

Smoking	Group IIa (MDR cases) (n = 82) [N (%)]	Group IIb (TB cases) (n = 427) [N (%)]	χ^2	P	Significance
Nonsmoker	23 (28)	213 (49.9)	13.728	0.0002	HS
Smoker	59 (72)	214 (50.1)			
Addiction					
No	76 (92.7)	302 (70.7)	17.352	0.00003	HS
Yes	6 (7.3)	125 (29.3)			
Alcoholism					
No	77 (93.9)	289 (67.7)	23.412	0.000001	HS
Yes	5 (6.1)	138 (32.3)			

MDR-TB, multidrug-resistant pulmonary tuberculosis; TB, tuberculosis.

Table 3 Description and comparison of comorbidities associated with MDR-TB cases (group IIa) and TB cases not categorized as MDR-TB in El-Maamoura Chest Hospital (group IIb)

Comorbidity	Group IIa (MDR cases) (*n* = 82) [*N* (%)]	Group IIb (TB cases) (*n* = 427) [*N* (%)]	χ^2	*P*	Significance
IHD					
No	64 (78)	307 (72.9)	1.317	0.251	NS
Yes	18 (22)	120 (28.1)			
DM					
No	20 (24.4)	170 (39.8)	6.994	0.008	HS
Yes	62 (75.6)	257 (60.2)			
Liver cirrhosis					
No	79 (96.3)	307 (71.9)	22.43	0.000002	HS
Yes	3 (3.7)	120 (28.1)			
Chronic chest disease					
No	29 (35.4)	102 (23.9)	4.742	0.029	S
Yes	53 (64.6)	325 (76.1)			

DM, diabetes mellitus; MDR-TB, multidrug-resistant pulmonary tuberculosis; TB, tuberculosis; IHD, ischemic heart disease.

Table 4 Description and comparison between MDR-TB cases (group IIa) and TB cases not categorized as MDR-TB (group IIb) according to previous TB treatment

Previous TB treatment	Group IIa (MDR cases) (*n* = 82) [*N* (%)]	Group IIb (TB cases) (*n* = 427) [*N* (%)]	χ^2	*P*	Significance
No	0 (0)	275 (64.4)	114.874	0	HS
Yes	82 (100)	152 (35.6)			

MDR-TB, multidrug-resistant pulmonary tuberculosis; TB, tuberculosis.

Table 5 Pattern of resistance to antituberculous drugs used in MDR-TB patients (group IIa)

Drug resistance	*N* (%)
INH	82 (100)
Rifampicin	82 (100)
Streptomycin	77 (93.9)
Ethambutol	25 (30.1)
Ofloxacin	0 (0)
Kanamycin	0 (0)

MDR-TB, multidrug-resistant pulmonary tuberculosis.

Table 6 Regimen of the second-line antituberculous drugs used in the treatment of MDR-TB patients (group IIa)

Drug regimen	Type	*N* (%)
Drug regimen used	Regimen I	82 (100)

All patients in group IIa are treated by regimen I of second-line antituberculous drugs: (3 months: kanamycin daily + ofloxacin + cycloserine + ethionamide + PAS then: 6 months: kanamycin 5 times a week + previous drugs then: 12 months: ofloxacin + cycloserine + ethionamide + PAS); MDR-TB, multidrug-resistant pulmonary tuberculosis.

resistance to ofloxacin and kanamycin (Table 5). The cure rate was 59.8%, dead cases were 12.2% (two of the dead cases were diabetic, three cases were with IHD and one case had depression), under treatment was 12.2%, defaulter rate was 10.9%, and treatment failure was 4.9% (Table 8). A rising trend of MDR-TB cases from 2008 to 2009, and then a decreasing trend from 2009 to 2012 is shown. The overall total prevalence rate of MDR-TB in Alexandria governorate from 2008 to 2012 was 4.3% (Table 9).

Discussion

In this study, the mean age of group IIa was 37.1 ± 13.02 years. This mean age represents the period of physical, mental, and occupational stress. The current study coincides with the study by Abdel Fatah [6], which included patients admitted in Abassia Chest Hospital during the period between July 2006 and June 2008 in the MDR ward. There were 116 MDR-TB patients. He reported that the mean age was 36.7 years. In the current study, there were 65 male (79.3%) and 17 female cases (20.7%) in group IIa. The current study coincides with the study by Abdel-Aim (2003), who investigated the identification of gene mutation in *M. tuberculosis* isolated from patients resistant to rifampicin and isoniazid treatment. He reported that, of the MDR-TB patients, 82% were male and 18% were female [7]. Male predominance may be attributed to the greater exposure of the male population to infection in the community compared with the female population because of occupational and mental stress or other social factors, which prevent women from seeking medical advice early [8]. In group IIa in this study, there were 32 (39%) employed patients, whereas there were 50 (61%) unemployed patients. The current study is in agreement with the study by Safwat *et al.* (2011), who stated that the highest incidence of TB infection was found among unemployed patients, because they were mostly ignorant and illiterate and thus had an increased risk for TB [9]. The current study is not in agreement with the study by Hamdy and Wagdan (1991) [10], who studied the role of patient compliance during the treatment of TB and stated that the highest incidences of TB infection

Table 7 Description of total cases of MDR-TB (group IIa) according to adverse effects of treatment by second-line antituberculous drugs

Adverse effect	*N* (%)
Gastritis	
No	52 (63.4)
Yes	30 (36.6)
GIT disturbance	
No	59 (72)
Yes	23 (28)
Hypokalemia	
No	73 (89)
Yes	9 (11)
Hypothyroidism	
No	75 (91.5)
Yes	7 (8.5)
Hyponatremia	
No	76 (92.7)
Yes	6 (7.3)
Hyperuricemia	
No	77 (94)
Yes	5 (6)
Psychological disturbance	
No	79 (96.3)
Yes	3 (3.7)
Hepatotoxicity	
No	79 (96.3)
Yes	3 (3.7)
Renal toxicity	
No	81 (98.8)
Yes	1 (1.2)
Peripheral neuropathy	
No	81 (98.8)
Yes	1 (1.2)

GIT, gastrointestinal tract; MDR-TB, multidrug-resistant pulmonary tuberculosis.

Table 8 Description of total cases of MDR-TB (group IIa) according to final fate

Fate	*N* (%)
Cured	49 (59.8)
Death	10 (12.2)
Under treatment	10 (12.2)
Defaulter	9 (10.9)
Treatment failure	4 (4.9)

MDR-TB, multidrug-resistant pulmonary tuberculosis.

were found among employed patients, as employed patients had a greater exposure to the environment and patients as a source of infection. It was noticed that in group IIa the most frequent habit was tobacco smoking: 59 patients (72%) were smokers, and 23 patients (28%) were nonsmokers. The current study coincides with the study by Kamal (2006) [11], who revealed that the incidence of MDR-TB smokers was 61.53% and that of nonsmokers was 38.47%, and he stated that smoking represents a source of infection and a risk factor for TB. The current study is not in accordance with the study by Fawzy (2005), who evaluated the resistance

Table 9 Prevalence of MDR-TB cases (group IIa) among cases of TB in Alexandria governorate (group I) from 2008 to 2012

Year	Total TB cases in Alexandria (1893)	Total MDR cases in Alexandria (82)	Prevalence (%)
2008	390	20	5.1
2009	320	21	6.6
2010	387	13	3.4
2011	376	16	4.3
2012	420	12	2.9
Total cases	1893	82	4.3

MDR-TB, multidrug-resistant pulmonary tuberculosis; TB, tuberculosis.

to INH isoniazid and rifampicin in pulmonary TB patients in Abassia Chest Hospital as well as in Chest Clinics in Cairo in 2004. He reported that there was no statistically significant difference as regards smoking among TB patients [12]. This may be explained by the small number of MDR cases (21 cases) included in his study, which is nonrepresentative. In our study, the most common comorbidity associated with MDR-TB in group IIa was diabetes (62 cases; 75.6%), followed by chronic chest diseases (53 cases; 64.6%). No reported cases of MDR-TB were HIV positive. The current study coincides with the study by Safwat *et al.* (2011), who reported that the most common comorbidity associated with MDR-TB was diabetes (33 cases; 18.3%), followed by chronic chest diseases (16 cases; 8.9%). No reported cases of MDR-TB were HIV positive. He stated that diabetes mellitus leads to decreased immunity of the patients, which results in reactivation of the primary TB infection and the occurrence of the resistance to the anti-TB drugs [9]. In the current study, in group IIa, all patients had acquired resistance: acquired resistance, 82 cases (100%), and primary resistance, 0 cases (0%). The current study coincides with the surveillance carried out in Egypt in 2012, which showed that the incidence of acquired resistance was higher compared with the incidence of primary resistance [13]. The present study coincides with the study by Safwat *et al.* (2011), who reported that the incidence of acquired resistance was greater than that of primary resistance; the incidence of acquired resistance was 69.4% and that of primary resistance was 30.6% [9]. In the present study, the resistance of anti-TB drugs in group IIa was as follows: resistance to isoniazid was 100%, resistance to rifampicin was 100%, resistance to streptomycin was 93.9%, resistance to ethambutol was 30.1%, resistance to ofloxacin was 0%, and resistance to kanamycin was 0%. The results of the current study coincide with the study by Safwat *et al.* (2011), who revealed that the resistance to isoniazid was 100%, resistance to rifampicin was 100%, resistance to streptomycin was 81.1%, and resistance to ethambutol was 75.6% [9]. In group IIa in this study, the most common complications of second-line anti-TB drugs were gastritis and gastrointestinal

tract (GIT) disturbance: 36.6% of patients had gastritis, 28% had GIT disturbance, 11% had hypokalemia, 8.5% had hypothyroidism, 7.3% had hyponatremia, 6% had hyperuricemia, 3.7% had psychological disturbance, 3.7% had hepatotoxicity, 1.2% had renal toxicity, and 1.2% had peripheral neuritis. These results coincide with those of Safwat *et al.*, who stated that gastritis was the most common complication (88.3%), followed by peripheral polyneuritis (76.7%), hypothyroidism (44.4%), hepatitis (8.3%), central nervous system complication (16.1%), hypokalemia (23.3%), and irritable bowel syndrome (46.7%) [9]. This coincides with the study by Abdel Fatah (2009) [6] as well, who stated that GIT disturbance was the most common complication (84%), followed by peripheral polyneuritis (58.4%), hypothyroidism (57.5%), skin manifestations, arthralagia, and psychosis (29.2%), depression (26.5%) and electrolyte disturbance (17.7%). In this study, effect of treatment of the MDR-TB cases was as follows: cured patients, 49 (59.8%); patients under treatment, 10 (12.2%); treatment failure, four cases (4.9%), deceased patients, 10 (12.2%); and defaulters, nine cases (10.9%). This study coincides with the study by Safwat *et al.* (2011), who stated that, of the 180 cases, 117 (65.0%) patients were cured, 38 (21.1%) were under treatment, three cases (1.7%) had treatment failure, 17 patients (9.4%) died, four cases (2.2%) were defaulters, and surgical interference was applied in one case (0.6%) [9]. This study coincides with the study by Abdel Fatah (2009) [6], who stated that, of the 113 cases, 72 patients (63.8%) were cured, 18 (15.9%) patients were under treatment, 10 cases (8.8%) had treatment failure, eight patients (7.1%) died, and five patients (4.4%) were defaulters. In the current study, the overall total prevalence rate of MDR-TB in Alexandria governorate from 2008 to 2012 was 4.3%. This result is in disagreement with the study by Safwat *et al.* (2011), who stated that the prevalence rate of MDR-TB in Egypt was 0.45% from 2006 to 2009 [9]. Abdel Fatah (2009) [6] stated that the prevalence rate of MDR-TB in Egypt was 0.37% from 2006 to 2008. Nada (2009) [14] stated that the prevalence rate of MDR-TB in Egypt was 0.45% from 2006 to 2009. This difference may be due to fact that the prevalence rate in these studies was for the total number of TB cases in Egypt and not for Alexandria governorate as shown in the current study, and this may be explained by the better case finding in Alexandria governorate due to the presence of MDR ward.

Conclusion

The overall total prevalence rate of MDR-TB in Alexandria governorate from 2008 to 2012 was 4.3%. There was a decreasing trend of MDR-TB cases. History of anti-TB treatment is the strongest independent predictor of MDR-TB. Other risk factors for MDR-TB were being middle aged, unemployment and illiteracy, presence of comorbidities such as diabetes mellitus and chronic chest disease, and smoking habit. The highest figures of resistance in the MDR group besides isoniazid and rifampicin were for streptomycin, whereas the lowest resistance was for ethambutol, the most common complications of the second-line anti-TB drugs were gastritis, followed by GIT disturbance. The effect of treatment of the MDR-TB cases was as follows: cured patients, 59.8%; patients under treatment, 12.2%; treatment failure, 4.9%; deceased patients, 12.2%; and defaulters, 10.9%.

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Conflicts of interest

There are no conflicts of interest.

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