Drug Resistant Tuberculosis: Risk Factors and Resources- Utilization at a Chest Disease Clinic, Alexandria, Egypt

السل المقاوم للدواء : عوامل الخطورة و استخدام الموارد في عيادة الأمراض الصدرية، الاسكندرية ، مصر

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Abstract: Background: Drug-resistant TB is a relatively new phenomenon that now occurs throughout the world. Drug resistance arises due to the improper use of antibiotics in chemotherapy of drug susceptible TB patients such as administration of improper treatment regimens by health care workers and failure to ensure that patients complete the whole course of treatment. Essentially, resistance arises in areas with poor TB control programs. **Objective:** To determine risk factors of M/XDR-TB among TB patients attending a chest diseases clinic in Alexandria- Egypt for the period from December 2008 till June 2011 to improve case management and control of drug resistant TB. Also, it aimed to determine effect of M/XDR-TB on utilization of resources. **Design:** Case- control study. **Method:** Medical records of TB patients who were receiving treatment at the chest diseases clinic for the period from December 2008 till June 2011. Cases were patients underwent drug susceptibility tests and results confirmed M/XDR – TB. However, controls were TB patients without drug resistance based on results of drug susceptibility tests. Cases were 59 patients, and controls were 122 patients (ratio was 1:2). **Results:** almost the half of both cases (MDR/XDR patients) and controls were from the middle age group (25-45 years). Male gender, employment, history of TB contacts and having a positive smear to AFB on admission carry higher risks for developing MDR-TB (OR: 2.28, 3.46, 2.31, and 25.3 respectively). In logistic regression, the duration of treatment was the only significant factor (protective). All resources utilized were significantly higher for MDR-TB cases than for controls. **Conclusion and Recommendations**: treatment of M/XDR-TB is a cost effective intervention that necessitates urgent mobilization of resources.

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Key Words: M/XDR-TB- Risk factors- Resources Utilization.

Introduction:

Tuberculosis (TB) is contagious and airborne. It is a disease of poverty affecting mostly young adults in their most productive years. The vast majority of TB deaths are in the developing world. [1].The discovery of anti-tuberculosis drugs in the 1940's was hailed as a medical milestone. Tragically, in the last 25 years, the misuse of these "miracle"drugs has resulted in a new public health problem: drug resistant TB. [2] Drug resistance arises due to the improper use of antibiotics in chemotherapy of drug susceptible TB patients such as administration of improper treatment regimens by health care workers and failure to ensure that patients complete the whole course of treatment. Essentially, resistance arises in areas with poor TB control programs. [3]

Multidrug-resistant TB (MDR-TB) results from either primary infection with resistant bacteria or may develop in the course of a patient's treatment where the bacteria become resistant to at least Isoniazid and Rifampicin, the most effective anti-TB drugs. Moreover, extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to Isoniazid and Rifampicin (i.e. MDR-TB) as well as any Fluoroquinolone and any of the second-line anti-TB injectable drugs (Amikacin, Kanamycin or Capreomycin).[4]

In the new WHO's Multidrug and Extensively Drug-Resistant Tuberculosis: 2010 Global Report on Surveillance and Response, it is estimated that 440 000 people had MDR-TB worldwide in 2008 and that a third of them died.[1,4-5]Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India. In Africa, estimates show 69 000 cases emerged, the vast majority of which went undiagnosed.[5] In KwaZulu Natal in South Africa, an outbreak of XDR-TB killed 52 out of 53 people within three weeks, most of whom were HIV positive.[5]

The resistant forms of TB do not respond to the standard six month treatment with first-line anti-TB drugs and can take up to two years or more to treat with drugs that are less potent, more toxic and much more expensive from 50 to 200 times higher. While a course of standard TB drugs cost approximately US$ 20,

MDR-TB drugs can cost up to US$ 5 000, and XDR-TB treatment is far more expensive. [4-5]

Funding needed for MDR-TB control in 2015 will be 16 times higher than what is currently available in 2010.[5]. This high cost of management of MDR- TB is mostly the result of the cost of second- line drugs, the use of hospitalization (up to 50% of the total cost of treatment in middle- income countries) and the workforce necessary to ensure proper care. In spite these high cost, treatment of MDR- TB has been shown to be a cost- effective intervention. The recent experience in two regions of the Russian Federation has shown that even in settings gravely affected by drug resistance, it is possible to control MDR-TB.

Urgent investments in infrastructure, diagnostics, and provision of care are essential if the target established for 2015- the diagnosis and treatment of 80% of the estimated M/XDR-TB cases- is to be reached. [4] The target of halving the 1990 prevalence rate by 2015 could be achieved in three of six regions: Americas, Eastern Mediterranean, and Western Pacific regions. [1]

As the Egyptian MOH has been implementing treatment for drug resistant TB cases, it was important to obtain data on risk factors for M/XDR-TB among patients treated at one of the largest chest diseases clinics in Alexandria, Egypt. Due to the rising cost of M/XDR-TB worldwide, it was substantial to determine its effect on utilization of resources.

Objectives: The study aimed to determine risk factors of M/XDR-TB among TB patients attending a chest diseases clinic in Alexandria- Egypt for the period from December 2008 till June 2011 to improve case management and control of drug resistant TB. Also, it aimed to determine effect of M/XDR-TB on utilization of resources.

Material and Methods:

Study design: Case- control study where cases were patients with M/XDR - TB and controls were TB patients without M/XDR - TB.

Study setting: A chest diseases Clinic, Alexandria, Egypt.

Target Population and Sample Size: Medical records of TB patients who were receiving treatment at the chest diseases clinic for the period from December 2008 till June 2011. Cases were patients underwent drug susceptibility tests at the study clinic and results confirmed M/XDR – TB. However, controls were TB patients but had no drug resistance based on results of drug susceptibility tests that have been done in the study clinic. Cases amounted to 59 patients, while controls amounted to 122 patients (cases: controls ratio was 1:2). Medical records of the controls were randomly selected using stratified random sampling technique.

Inclusion Criteria: All confirmed M/XDR – TB cases were included in the study.

Exclusion Criteria: Transferred out cases were excluded from the study.

Data Collection Tool: A predesigned data collection sheet was designed. It included data on the demographic characteristics of patients (residence, age, gender, marital history, family size), education, social history (work status, monthly family income). The sheet also included data on smoking, alcohol abuse, drug abuse, HIV, imprisonment, psychological disorders, chronic lung disorders and history of previous contact with TB patients, and of concomitant diseases such as diabetes mellitus. Also, it included data on utilization of non- human resources (number of chest radiological investigations, smear examinations, culture tests performed during the whole course of treatment, anti- TB drugs prescribed during the whole course of treatment, non- specific drugs prescribed during the whole therapy, and complications experienced during the whole course of treatment, …..Etc).

Pilot Study: It was conducted on 15 medical records. Results revealed that there was no data about family income, education level, and marital status or history of HIV infection, psychological or chronic lung disorders. Also, there was no data about history of hospitalizations.

Definitions:

MDR- TB: is defined as resistance to at least both INH and RMP. [6]

XDR-TB: is defined as resistance to at least INH and RMP (MDR- TB), plus resistance to any one of the fluoroquinolone drugs and to at least one of the three injectable second- line drugs (ie amikacin, capreomycin, or kanamycin). [7]

Statistical Analysis: All data were statistically analyzed using SPSS program version 19.0. Continuous data were presented as mean, median and standard deviation, and categorical data were presented as number and percentages. Cases and controls were compared for risk factors associated with M/XDR- TB; test of significance at 5% p value was used. Odds ratio (OR) and 95% confidence interval were also calculated. Binary logistic regression analysis was used to model the predictors of M/XDR- TB. Univariate logistic regression of inference was applied, and this produced a list of candidate variables for entry into the

multivariate logistic regression model. A variable was considered a candidate predictor variable for the regression model if the univariate tests of inference were significant at less than .05 probability level.

Ethical Consideration: Formal approval from the Ministry of Health in Egypt was taken before conducting the research.

Results:

Regarding the profile of the patients' sample, nearly one in every 10 cases and one in every 4 controls were less than 25 years of age. The oldest age group (more than 65 years) represented a minority in both groups (1.7% of cases and 6.6% of controls). Males constituted 70% of cases, while male to female ratio was 1:1 for controls. Inversely, urban to rural residence ratio was 1:1 in cases and constituted 70% in controls. Speaking about the working status, nearly two thirds of cases and more than three quarters of controls were unemployed. Concerning the cases, more than the half of them were XDR cases.

Although alcohol intake and drug abuse were reported in small percentages, they were higher in cases than controls. Surprisingly, smoking was significantly higher in controls, and the same applies to imprisonment although not significant. Meanwhile, a bit higher number of cases reported a history of diabetes.

Of course all cases had a history of previous TB, while nearly one in every 10 controls did. Previous contact with a TB patient was reported by 4 in every 10 cases and 1 in every 4 controls. Nearly all cases and 70% of controls had positive smears for AFB on admission, while cavitations in X rays were reported in almost 40% of both groups.

Concerning the drug regimens, the greatest majority of controls (94%) were receiving rifadin, INH, ethambutol and pyrazinamide combination. Nearly 4 in every 5 MDR cases (78%) received kanamycin, ethonamide, cycloserine, PASA and ofloxacine combination. As regards the duration of treatment, one third of MDR-TB cases received treatment for one and half to two years, while 14% of them received treatment for more than two years. All controls' duration of treatment was less than 6 months. Only one third of MDR-TB cases completed the treatment course, while 70% of controls did. Nearly one fifth of controls interrupted their treatment course. Less than 2% of controls died during the course while one in every five MDR-TB cases died.

Table 1 reveals the results of the univariate analysis of risk factors of T.B patients to develop MDR-TB. It can be noticed that male gender, employment, history of TB contacts and having a positive smear to AFB on admission carry higher risks for developing MDR-TB (OR: 2.28, 3.46, 2.31, and 25.3 respectively)

As regards the outcome of treatment, patients with interrupted treatment were nearly 6 times exposed to develop MDR-TB (OR = 5.67). Similarly, patients who died were 26 times exposed to develop MDR-TB (OR = 25.5). All these results were statistically significant.

Table 2 demonstrates the results of binary logistic regression analysis of identified risk factors for MDR-TB. All factors identified to have a significant risk with developing MDR-TB were entered in a logistic regression; the factors remaining in the equation were gender and duration of treatment. The duration of treatment was the only significant factor (protective).

Table 3 shows that the median for all the items of resources utilized (anti TB drugs, non specific drugs, number of smears and cultures, as well as frequency of complications) was significantly higher for cases of MDR/TB than for controls (P <0.0001)

Table (1): Univariate Analysis of Risk Factors of TB Patients Attending a Chest Disease Clinic in Alexandria

Characteristics	Cases (n=59)		Controls (n=122)		P value	Odds Ratio (95% CI)
	No.	%	No.	%		
Age						
< 25	6	10.2	29	23.8	0.11	0.45 (0.2-1.3)
25-	27	45.8	59	48.4	---	1.0
45-	25	42.4	26	21.3	0.039*	2.1 (0.9-4.6)
65-	1	1.7	8	6.6	FE(0.274)	0.27 (0.01-2.4)
Gender						
Male	41	69.5	61	50.0	0.013*	2.28 (1.1-4.7)*
Female	18	30.5	61	50.0		1.0
Residence						
Urban	30	50.8	84	68.9	0.019*	0.47 (0.2-0.9)*
Rural	29	49.2	38	31.1		1.0
Work status						

Employed	23	39.0	19	15.6	0.0005*	3.46 (1.6-7.6)*
Unemployed	36	61.0	103	84.4		1.0
Alcohol intake						
Yes	3	5.1	0	0	FE(0.033)*	-NA-
No	56	94.9	122	100		
Drug abuse						
Yes	4	6.8	4	3.3	FE(0.441)	2.15 (0.4-10.7)
No	55	93.2	118	96.7		
Smoking						
Yes	15	25.4	53	43.4	0.019*	0.44 (0.2-0.9)*
No	44	74.6	69	56.6		
Imprisonment						
Yes	2	3.4	6	4.9	FE(1.0)	0.68 (0.1-3.9)
No	57	96.6	116	95.1		
History of diabetes mellitus						
Yes	15	25.4	26	21.3	0.536	1.26 (0.6-2.8)
No	44	74.6	96	78.7		
History of previous anti TB treatment						
Yes	59	100.0	14	11.5	0.0001*	-NA-
No	0	0	108	88.5		
History of previous TB contacts						
Yes	26	44.1	31	25.4	0.011*	2.31 (1.1-4.7)*
No	33	55.9	91	74.6		
AFB smear on admission						
Positive	58	98.3	85	69.7	0.0001*	25.3 (3.6-508.5)*
Negative	1	1.7	37	30.3		
Chest radiography on admission						
Presence of cavitation	24	40.7	46	37.7	0.7	1.13 (0.6-2.2)
No cavitation	35	59.3	76	62.3		
Patient under DOTS control						
Yes	59	100.0	121	99.2	0.486	-NA-
No	0	0	1	.8		
Drug regimen						
R, INH, Etb, P	0	0	115	94.3		
Etb, K, Etn, C, O	4	6.8	0	0		
K, Etn, C, PASA, O	46	78.0	5	4.1		
R, INH, Etb, S, P	0	0	2	1.6		
Etn, C, PASA, O, A	9	15.3	0	0		
Duration of treatment in months						
< 6	9	15.3	122	100.0	0.0001*	0.0 (0-0.01)
6-	16	27.1	0	0	---	-NA-
12-	6	10.2	0	0	----	-NA-
18-	20	33.9	0	0	----	-NA-
24-	8	13.6	0	0	----	1.0
Outcome of treatment						
Completeness	20	33.9	85	69.7		1
Failure	2	3.4	12	9.8		0.71(0.147-3.42)
Interrupted	8	13.6	23	18.9		5.67(1.77-18.7)*
Death	12	20.3	2	1.6		25.5(5.28-123.1)*
Still under treatment	17	28.8	0	0		

FE(P): Fisher's Exact test

R: rifadin, INH: isoniazide, Etb: ethambutol, S: streptomycin, K: kanamycin, Etn: ethonamide, C: cycloserine, PASA: para amino salicylic acid, O: ofloxacine, A: amikacin, P: pyrazinamide.

Table (2): Binary Logistic Regression Analysis of Identified Risk Factors for MDR-TB Patients in a Chest Disease Clinic in Alexandria

Risk factors	B	Wald test	P	Exp (B)
Gender	1.679	3.734	0.053	5.358
Duration of treatment	-1.157	16.84	<0.0001*	0.314
Constant	2.951	5.875	0.015*	19.122

Table (3): Distribution of TB Patients according to Utilization of Resources at a Chest Disease Clinic in Alexandria

Resources utilization	Cases (n=59)	Controls (n=122)	Test of sig
Number of Anti T.B drugs prescribed			
Min-Max	5-5	4-5	
Median	5	4	Z=12.32
Mean±SD	5.0±0.0	4.1±0.2	P<0.0001*
Number of non- specific drugs prescribed			
Min-Max	7-18	2-14	
Median	13	6	Z=10.08
Mean±SD	12.6±2.5	6.1±2.5	P<0.0001*
Number of smear examinations done			
Min-Max	1-25	1-8	
Median	11	4	Z=8.19
Mean±SD	12.4±6.5	4.2±1.5	P<0.0001*
Number of culture examinations			
Min-Max	0-21	0-2	
Median	9	0	Z=11.51
Mean±SD	9.4±5.3	0.2±0.4	P<0.0001*
Frequency of complications experienced			
Min-Max	1-11	0-5	
Median	3	1	Z=6.02
Mean±SD	3.6±2.3	1.5±1.1	P<0.0001*

Discussion:

Control of TB remains one of the most serious challenges to global health.[8] A new and devastating threat to TB control is the emergence of strains that cannot be cured by standard anti tuberculosis drug regimens[9]

The fact that high rates of TB were documented in middle aged adults is not unusual, and is a problem in many countries.[10-12] In the present study, almost the half of both cases and controls were between 25 – 45 years. Similar age distribution was frequently observed in hospitalized TB patients in Georgia in 2009. [13] The lowest prevalence of drug resistance in our study was reported in the elderly group more than65 years (1.7%). This might be explained by reduced exposure due to sedentary lifestyle of old people. Old people also showed the least prevalence in the WHO Global Project on Anti – Tuberculosis Drug Resistance Surveillance carried out in the late nineties.[14]

According to our results, male gender carried a higher risk of developing MDR-TB. This fact of male predominance has been supported by the WHO's Global Report on M/XDR-TB Surveillance and Response (2010), [4] where 95% of reporting countries mentioned that the majority of cases were males. This has been referred to the differences in access to health services or exposure to different levels of risk for developing drug resistance. However, further analysis suggested that the overall risk of harboring MDR-TB strains isn't influenced by sex.

Not surprisingly, all our MDR-TB patients had a history of previous TB, and received anti tuberculosis drugs. Particularly patients who interrupted treatment were significantly 6 times more exposed to develop MDR-TB. Reports on anti tuberculosis drug resistance surveillance indicate higher levels of drug resistance among previously treated cases.[15,16]. Although lower percentages of patients in two different Indian studies[17,18] reported previously receiving anti TB treatment (44% and 69% respectively), Kaul (1998) [19] referred this to reluctance of Indian patients to mention prior anti TB treatment arising from a fear of stigmatization, as well as fear from DOTS centers to refuse their treatment seeing them as problem cases. Default from therapy before completion was strongly associated with MDR-TB as mentioned by Kimerling

et al talking about their study conducted in Siberia 1999.[20]

Evidently, caring of MDR-TB patients has been proved to utilize significantly much more resources in our study. According to the National Tuberculosis Center, appropriate care of MDR-TB patients would cost more than the care of all drug susceptible cases combined.[2] Not only treatment, M/XDR-TB case finding is unlike routine case finding and requires advanced, costly and labor intensive laboratory technology.[21]

Conclusion and Recommendations:

Although expensive, treatment of M/XDR-TB has been shown to be a cost effective intervention. However, it necessitates mobilization of both national and international resources, urgent investments in infrastructure, diagnostics and provision of care, if target established for 2015 – the diagnosis and treatment of 80% of the estimated M/XDR-TB cases - is to be reached.

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