Risk factors for treatment failure in multidrug resistant tuberculosis in Tunisia: An analytic study

Facteurs de risque d'échec thérapeutique de la Tuberculose multirésistante en Tunisie: Etude analytique

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Abstract

Introduction-Aim: The emergence of multidrug resistant tuberculosis (MDR-TB) is a threat to global public health. The aim of our study was to determine risk factors for treatment failure in MDR-TB.

Methods: Retrospective study conducted between January 2000 and March 2019 including patients with MDR-TB. Characteristics of patients with therapeutic failure were compared to cured ones. Logistic regression analysis was used to identify risk factors for treatment failure.

Results: Our study included 140 patients aged of 42±13 years (18-80). Fifty-seven percent of patients had treatment success and 12% had treatment failure. In multivariate logistic regression analysis, treatment failure was associated with age over 45 years (OR=1.05; 95%CI, 1.024-7.736;p=0.014), primary education level and illiteracy (OR=5.022; 95%CI, 1.316-19.161;p=0,018), history of incarceration (OR=3.291; 95%CI, 1.291-21.083;p=0.016), undernutrition (OR=4.544; 95%CI, 2.304-54.231;p=0,027), extensive TB (OR=6.406; 95%CI, 1.761-23.922; p=0.038), initial high grade positive smears (OR=1.210; 95%CI, 1.187-32.657; p=0.045), positive smear culture at 90 days of treatment (OR=6.871, 95%CI, 3.824-23.541; p=0.003), poor adherence (OR=6.110; 95%CI, 2.740-12.450; p=0.021) and occurrence of psychiatric adverse events (OR=3.644 95%CI, 2.560- 27.268; p=0.041).

Conclusion: Therapeutic education, nutritional and psychological support and close follow-up are strongly recommended to optimize the prognosis of MDR-TB.

Key words: mycobacterium tuberculosis, susceptibility test, second-line drug, Prognosis, epidemiology, Tunisia, North Africa

Résumé

Introduction-Objectif: L'émergence de la tuberculose multirésistante (MDR-TB) est une menace pour la santé publique mondiale. Le but de notre étude était de déterminer les facteurs de risque d'échec du traitement de la TB-MR.

Méthodes: Étude rétrospective menée entre janvier 2000 et mars 2019 incluant des patients atteints de TB-MR. Les caractéristiques des patients en échec thérapeutique ont été comparées à celles des patients guéris. Une analyse de régression logistique a été utilisée pour identifier les facteurs de risque d'échec du traitement.

Résultats: Notre étude a inclus 140 patients âgés de 42±13 ans (18-80). Cinquante-sept pour cent des patients ont eu un succès thérapeutique et 12 % ont eu un échec thérapeutique. En analyse de régression logistique multivariée, l'échec du traitement était associé à l'âge supérieur à 45 ans (OR=1,05 ;IC95%[1,024-7,736];p=0,014), au niveau d'éducation primaire et à l'analphabétisme (OR=5,022 ;IC95%[1,316-19,161];p=0,018), antécédents d'incarcération (OR=3,291 ; IC95%[1,291-21,083];p=0,016), dénutrition (OR=4,544 ;IC95%[2,304-54,231];p=0,027), TB étendue (OR=6,406 ; IC95%[1,761-23,922]; p=0,038) , frottis initiaux positifs de haut grade (OR=1,210 ;IC95%[1,187-32,657]; p=0,045), culture de frottis positive à 90 jours de traitement (OR=6,871 ; IC95%[3,824-23,541]; p=0,003), mauvaise observance (OR=6,110 ; IC95%[2,740-12,450]; p=0,021) et la survenue d'événements indésirables psychiatriques (OR=3,644 ; IC95%[2,560-27,268]; p=0,041).

Conclusion: Une éducation thérapeutique, un soutien nutritionnel et psychologique et un suivi rapproché sont fortement recommandés pour optimiser le pronostic de la TB-MR.

Mots clés: mycobacterium tuberculosis, antibiogramme, médicament de deuxième intention, pronostic, épidémiologie, Tunisie, Afrique du nord

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Introduction

In Tunisia, TB continues to be a worrying reality faced by all healthcare establishments. Despite a well-established national TB control program (PNLT) since 1959, which has integrated the fight against MDR-TB into its priority activities since 2004, we have observed a resurgence of this infectious disease in recent years [1,2]. The incidence rate of MDR-TB is estimated at 0.46/100,000 inhabitants, including 1% among new cases and 27% among previously treated cases [1,2]. The risk of treatment failure is higher in MDR-TB than in drug-susceptible TB. Despite the severity of MDR-TB and the high risk of treatment failure, data concerning this subject is rare in the Maghreb region and particularly in Tunisia. Only a few teams were interested in the outcome of this infection. Thus, the aim of this study was to identify predictive factors of treatment failure of MDR-TB in Tunisia.

Methods

Setting and study design

A multicenter retrospective study was conducted including all patients treated in both departments for MDR-TB between 2000 and 2019. Patients were divided into 2 groups: G1: patients with treatment failure, and G2: patients with treatment success.

Definitions

The definitions of cure and treatment failure were mentioned in the practical guide for management of the resistant tuberculosis published by international union against tuberculosis and respiratory infections in 2018 [3]. Cure was considered when complete treatment as recommended by the national program with no evidence of failure and three or more consecutive cultures taken at least 30 days apart which are negative after the intensive phase. If only one culture is reported as positive during this period and there is no concomitant evidence of clinical deterioration, the patient may still be considered cured, provided that this positive culture is followed by three consecutive negative cultures at minimum, carried out on samples taken at intervals of at least 30 days.
Treatment failure was considered when stopped treatment or need to change the permanent regimen of at least two anti-tuberculosis drugs due to:

*Absence of bacteriological conversion (negativation) at the end of the intensive phase.
*Bacteriological inversion (repositivation) in the continuation phase after bacteriological conversion (negativation).
*Absence of clinical improvement with at least 2 consecutive high grade positive smears (≥++) after more than 6 months of treatment
*Additional evidence of acquired resistance to fluoroquinolones or second-line injectable drugs.
*Adverse drug effects.

Malnutrition was defined by a body mass index (BMI) less than 18.5 Kg/m2 for a person aged between 18 and 69 years old and a BMI less than 21 for a person aged 70 years old and more.
Extensive radiological abnormalities due to TB on chest X-ray was defined as an extension greater than two thirds of the pulmonary field.

Statistical analysis

Data analysis was carried out using SPSS (version 21). Categorical variables were compared using Chi-square or Fisher's exact. Multivariate model was applied in order to specify the independent predictive factors of treatment failure. The level of significance of p was ≤0.05.

Ethical approval

Ethics committee's agreement was obtained.

Results

Our study allowed collecting 140 cases of MDR-TB. The sex ratio was 3.8. Ninety patients (64%) had poor socioeconomic conditions. Thirty-seven patients (26.4%) were unemployed. Smoking, the most common risk factor for TB, was noted in 106 patients (76 %) (Table 1). Malnutrition was found in 34.3% of patients.

Table 1. Demographics, clinical, radiological and bacteriological characteristics

Characteristics	Patients N=140 (%)
Habits	
Tobacco habit (cigarette)	106(76)
Tobacco habit (hookah)	31(22)
Alcoholism	56 (40)
Substance addiction	34 (24)
Foreign trip	23(16)
Incarceration	22(16)
Unprotected sex	22(16)
Comorbidities	
Diabetes	24 (17)
Hepatitis	7 (5)
Digestive pathology	7(5)
Psychiatric pathology	4 (3)
Cancer	4 (3)
Hypertension	3(2)
Rheumatic pathology	3 (2)
Chronic obstructive pulmonary disease	2 (1)
Psoriasis	1 (1)
Symptoms	
Cough	(83)
Weight lost	(90)
Anorexia	(69)
Hemoptysis	75(53)
Radiological finding	
Cavitations	110 (78%)
Nodules	101 (71%)
Pleural opacities	20(14.2)
Extensive lesions	70(50)
Bacteriological finding	
Initial high grade positive smears (≥ +++)	44(33.1)

Multi-resistance was secondary in 75% of cases (n=105). The circumstances of discovery of secondary multi-resistance were retreatment (27%), treatment failure (24%) and relapse of TB (17%). Weight loss was the most common symptom found in 126 cases (90%). The excavation was the most frequently encountered radiological anomaly. More than half of the patients (53%) had lesions extending to at least one lung. The radiological lesions were bilateral in almost 86 cases (61%) (Table 1).

The standard treatment regimen (injectable anti-TB drug (Amikacin, Kanamycin, Capreomycin), quinolone (Lefofloxacin, Ofloxacin) and group 1, 4 and 5 drugs (pyrazimanid, Ethambutol, Etionamide, clofazimine) was used in 121 patients (86%) p-Aminosalicylic acid was added to the standard regimen in 14 cases of resistance to pyrazinamide. Five patients were treated with a short therapeutic regimen. The mean duration of anti-tuberculosis treatment was 21.27 ± 5.72 months. The mean duration of the injection drug prescription was 6.96±1.25 months.

Side effects due to anti-tuberculosis treatments were observed in 111 patients (79.2%) (Table 2).

Table 2. Side effects and treatment outcome

		N=140 (%)
Side effects of second-line drugs		
	Digestive disorders	108 (77)
	Auditory toxicity	56 (50)
	Osteo-articular disorders	54 (39)
	Neuropsychiatric disorder	42 (30)
	Cutaneous toxicity	37 (26)
	Buttock injection site infection	8 (6)
	Ophthalmological toxicity	8 (6)
	Hypersensitivity reaction	8 (6)
	Muscular disorders	8 (6)
	Renal disorders	7 (5)
	Endocrine disorders	3 (2)
	Liver disorders	2 (1)
	Hematological disorders	1 (1)
Outcome of TB		
	Cure	80 (57)
	Failure	17 (12)
	Death	16 (14)
	Under treatment	19 (14)
	Lost to follow up	16 (11)
	Transfer out	4 (3)

The outcome of TB was cure in of 80 cases (57%), treatment failure in of 17 cases (12%) (Table 2). Therapeutic failure was retained because of positive sputum cultures at 6 months of treatment in 12 patients (70.5%), sputum culture conversion in maintenance phase in 5 patients (29.4%), appearance of resistance to fluoroquinolone in 2 patients (11.7%), to fluoroquinolone and aminoglycosides in 2 patients (11.7%) and occurrence of an anaphylactic reaction to Ethionamide in one patient (5.8%).

Univariate study showed that multiple characteristics were significantly higher in G1 than in G2 (Table 3).

Table 3. Comparison between characteristics of patients in G1 and G2

Characteristics	G1 (n=17) N (%)	G2 (n=80) N (%)	p
Age category (> 45 years)	9(52)	21(26)	0,002
Men	15(88)	51(64)	0,03
Illiterate or primary school level	14 (82)	41(52)	0,001
Tobacco habits	15 (88)	32 (40)	0,003
Under nutrition	8(53)	12(15)	0,02
Median BMI (kg/m2)	18,2 ± 2,68	21,5± 4,06	0,02
Anemia	9(53)	12 (17)	0,04
Initial high grade positive smears (≥ 3+++)	14(82)	17(21)	0,03
Extensive lesions in X-ray	15(91)	37(47)	0,002
Side effects of second-line drugs	1 (6)	0	0,02
Diarrhea	1 (6)	0	0,02
Depression	5 (4)	0	0,04
Psychosis	3 (18)	0	0,01
Poor adherence to treatment	7(41)	16(20)	0,01
Positive sputum culture at 90 days of treatment	10(61)	10(13)	0,02

The multivariate study identified as independent predictive factors of treatment failure: older age, level of primary education and illiteracy, history of incarceration, malnutrition, extensive lung involvement, initial high grade positive smears, positive cultures at 90 days of treatment, poor treatment compliance and occurrence of adverse psychiatric effects (Table 4).

Table 4. Independent predictive factors of treatment failure of MDR-TB.

Predictive factors of treatment failure of MDR-TB	P	Ajusted Odds Ratio Ajusté	IC 95%	
			Inferior	Superior
Age category (> 45 years)	0,014	1,205	1,024	7,736
Illiterate or primary school level	0,018	5,022	1,316	19,161
Undernutrition	0,027	4,544	2,304	54,231
Extensive lesions in X-ray	0,038	6,406	1,761	23,922
Initial high grade positive smears (≥ +++)	0,045	1,210	1,187	32,657
Psychological side effects	0,041	3,644	2,560	27,268
Poor adherence to treatment	0,021	6,110	2,740	12,450
Positive sputum culture at 90 days of treatment	0,003	6,871	3,824	23,541

Discussion

The emergence of resistance to anti-tuberculosis drugs constitutes an obstacle to the effective control of tuberculosis. MDR-TB, which most often results from poor compliance with treatment, is a particularly serious form of tuberculosis because it is caused by bacilli resistant to at least isoniazid (H) and rifampicin (R) [4]. Despite the use of treatment, the prognosis of this condition remains reserved for several reasons related to both the patient and the treatment. Thus, we carried out this work in order to study the particularities of resistant TB and to identify the predictive factors of treatment failure.

Our study shows that: MDR-TB was primary in a quarter of cases (25%). More than half (51%) of our patients were under 42 years old. The majority of patients (56%) were male with a sex ratio of 3.82. Nearly 2/3 of the patients

(60%) had poor socio-economic conditions and more than a third (34%) of the patients were malnourished. The radiological lesions were extensive and bilateral in more than half of the cases (53%).The evolution after treatment was marked by recovery in 57.1%, death in 14% of cases and treatment failure in 12.1% of cases. Predictive factors of treatment failure are age more than 45 years, level of primary education and illiteracy, history of incarceration, malnutrition, extensive lung involvement, initial high grade positive smears, and positive cultures at 90 days of treatment, poor treatment compliance and occurrence of adverse psychiatric effects.

Our study has the advantage of collecting all the patients of the Tunisian reference centers of MDR-TB. Despite the small number of our population, the data of our study can be representative of all patients with MDR-TB in Tunisia because the only centers that have second-line anti-tuberculosis treatment are those included in our study. In North Africa and the Maghreb, data on MDR-TB are rare. To our knowledge, our study is the first in this region to identify the predictive factors of treatment failure in this population.

Our study has the limitation of being retrospective. However, we were able to find all parameters studied in patient records.

In our study, the average age of our patients was 38±13 years, comparable to that reported in other European, American and African studies [6-10]. The average age was less than 50 years. Indeed, it has been demonstrated in several studies that an age below 40 years is a risk factor for MDR-TB [10].

In our Tunisian population, age over 45 is a predictive factor for treatment failure. The same finding was found in patients with MDR-TB who failed treatment in Vietnam, Ethiopia, Ukraine, Russia, India and the Philippines [11-15]. This may be due to the frequency of comorbidities such as diabetes, which is known to be a risk factor for MDR-TB and increases risk of treatment failure and death [16].

Treatment failure was significantly more frequent among smoking men.

A systematic review of 35 studies conducted by Johnston showed that male sex is associated with other risk factors for MDR-TB (smoking, alcoholism, incarceration, drug addiction), which are risk factors for poor treatment compliance and therefore treatment failure [17]. Thus the direct role of the male sex in the occurrence of treatment failure was not demonstrated in our study. Smoking is thus implicated in treatment failure since it reduces the effectiveness of immune cells in the lungs.

In our population, patients who were illiterate or had a low level of education had a risk multiplied by 5 of treatment failure. Tang's study conducted in China including 1,662 patients found that 52% of patients who had failed treatment were educated up to primary level, ¾ of whom had poor socio-economic conditions, 64% had no access to care [18].

In our study, 34.3% of patients were malnourished. Several studies have shown that nutritional status is one of the most important determinants of therapeutic success in MDR-TB [8,9]. Similarly, in our series, 53% of patients who presented treatment failure were malnourished. Indeed, malnutrition can be the result of extensive forms of TB and poor socioeconomic conditions, which are predictive factors of treatment failure [14]. In addition, malnutrition decreases the cellular immune response against mycobacteria [11]. Thus, it appears that nutritional support is essential to compensate for therapeutic failure [11].

In our study, the presence of extensive pulmonary lesions is a predictive factor for treatment failure and increases this risk by 6. Gadallah's study carried out in Egypt on 228 cases of MDR-TB found the same result [16]. Several authors explain this finding by the frequency of diagnostic delay, poor therapeutic compliance and several immunosuppression factors such in patients with extensive lung disease, which increases their risk of treatment failure [19,20].

We noted in our study that Initial high grade positive smears was more observed in the group of patients with MDR-TB in treatment failure compared to that of cured tuberculosis patients. Our results agree with those of the literature [21]. This can be explained by the fact that the extension of the anatomo-radiological lesions are greater in this situation [22].

A delay in bacilloscopic negativation was more observed in G1. Smear cultures at 90 days of treatment were positive in 61% of patients of G1 vs 13% in G2. This could be explained by initial higher grade positive smears in this group. Indeed, the study of Djouma including 1286 tuberculosis patients with positive bacilloscopies, showed that the high grade positive smears (>++ or >+++) was an independent factor associated with a delay in negativation of smear culture [23].

The occurrence of MDR-TB causes psychological and social upheavals. Indeed, the diagnosis of MDR-TB can lead to loss of housing and employment due to stigma. This can affect access to health and social services. Added to this sensitive psychosocial context, multiple psychological side effects of second-line treatment may be encountered [11]. A psycho-social follow-up must be granted to these patients and their families. Poor treatment compliance represents the main obstacle to the management of MDR-TB.

Improving therapeutic compliance requires optimizing the DOTS strategy [24].

Reducing the rate of loss of follow-up remains dependent on the proximity and availability of appropriate healthcare structures, an improvement in the organization of the services responsible for tuberculosis control activities and an improvement of effectiveness and quality of information, education and communication with patients [13]. Regular health education sessions can be organized by group are strongly recommended. It is therefore necessary to increase the accessibility of patients to treatment as much as possible by organizing care structures allowing them to receive free treatment near their home with a regular supply.

Conclusion

Our study has identified the factors associated with

treatment failure whose management would help reduce treatment failure. Close follow-up with therapeutic education, nutritional and psychological care and ideally financial aid are strongly recommended in this category of patients.

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