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THE PECULIARITIES OF THE PATIENTS WITH MONO-RESISTANT AND POLY-RESISTANT TUBERCULOSIS

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Summary

Objective. Mono-resistant tuberculosis is the resistance to one of the first-line anti-tuberculosis drug, excluding the rifampicin, and poly-resistant tuberculosis means the resistance to more than one first-line anti-tuberculosis drug (izoniazid, rifampicine, streptomycine, ethambutol, with the exception of the combination of izoniazid and rifampicine. The study was conducted to assess the main peculiarities of the patients with mono-resistant and poly-resistant tuberculosis and their treatment outcome.

Material and methods. A cross-sectional, analytical, and retrospective study was performed, which included 124 new cases with mono-resistant and poly-resistant tuberculosis, diagnosed during 2014-2019. The patients were distributed into two groups: the 1st group included 85 (68.5%) cases with mono-resistant tuberculosis and the 2nd group – 39 (31.5%) cases with poly-resistant tuberculosis.

Results. Among 85 cases from the 1st group, 69 (81.2%) cases were resistant to streptomycine, 15 (17.5%) to izoniazid, and 1 (1.2%) to ethambutol. Among 39 cases of the 2nd group: 32 (82.0%) were resistant to izoniazid + streptomycine and 7 (18.0%) to isoniazid + ethambutol + streptomycine. The peculiarities of the patients did not show statistical differences in terms of the men/female rate and the affected age groups. Most of them had a socially-economical vulnerable state and high-risk factors. Patients were more frequently detected through the passive case-finding. No differences, according to the localization and extensibility, between the groups were established. The treatment success was registered in 66 (77.6%) cases of the 1st group and 31 (79.5%) cases of the 2nd group. The death occurred in 10 (11.8%) cases of the 1st group and 6 (15.4%) cases of the 2nd group.

Conclusions. Within the mono-resistance predominated resistance against the streptomycine and in poly-resistance was noted the resistance against the isoniazid + streptomycine. No differences in general characteristics, social-economical status, high-risk factors, localization, and extensibility of tuberculosis were found. The treatment outcome was suboptimal with a high rate of death in both groups. Individualized approach should be used in all patients for the improvement of the treatment outcome.

Keywords: tuberculosis, drug resistance, risk factors, outcome

Introduction

The extension of the drug resistance and the great number of *M. tuberculosis* strains resistant to anti-tuberculosis drugs (anti-TB) has currently become a major problem in the control of this infection in the majority of countries with a high incidence of tuberculosis (TB). This led to an increase in the number of treatment failure cases and the number of chronic patients. The main attention is attributed to TB cases with multi-drug resistance (MDR-TB) and resistance to Rifampicin (MDR/RR-TB) [1-5]. It is a dangerous phenomenon because it can lead to incurable forms of extensively drug-resistant tuberculosis (XDR-TB). This phenomenon can have serious repercussions so that the global incidence of TB in the 21st century can be worse. This way, WHO has claimed the phenomenon of drug resistance as of great global importance, and the researches on this topic have a major priority [6]. In 2019, the incidence of MDR/RR-TB cases was 34 per 100 thousand population in the Republic of Moldova. Among diagnosed with MDR/RR-TB cases, new cases were 33% and previously treated cases – 60% [7]. The Republic of Moldova ranks among the 30 countries of a global list of high-burden countries for MDR/RR-TB [7, 8]. A global total of 206.030 people with MDR/RR-TB were detected and notified in 2019, a 10% increase from 186.883 in 2018 [2, 7, 8]. The current policy of the World Health Organization (WHO) on tuberculosis control is based on the End TB Strategy (Strategy) [9]. The general goal of the Strategy is to end the global TB epidemic. The milestones of the Strategy for 2025 are: to reduce TB deaths by 75% compared with 2015, to reduce the global TB incidence (incidence < 55/100 000 population) by 50%, and zero families facing catastrophic costs due to TB [9].

The most important step before initiation of the anti-tuberculosis treatment represents the early detection of the drug resistance [10]. Cultural methods remain the gold standard for TB diagnosis and phenotypic drug susceptibility testing, despite their low sensibility and long duration of the cultivation [11]. Modern developments in genetic diagnosis, especially rapid molecular tests, contribute to accurate and early detection of drug resistance [12, 13]. The resistance to izoniazid (INH) is determined by the mutations in *katG* and *inhA* genes, the resistance to rifampicine (RIF) by the *rpoB* mutation, the resistance to ethambutol (EMB) by the *embB* mutation, the pyrazinamide resistance by *pncA* mutation, and for streptomycin resistance by *rrs, rpsL, gidB* mutation [14-24]. Mono-resistant tuberculosis is defined as the

infection caused by *Mycobacterium tuberculosis* resistance to one first-line anti-TB drug, excluding the rifampicin and poly-resistant tuberculosis means resistance to two and more first-line anti-TB drugs (isoniazid (INH), rifampicin (RIF), streptomycin (STR), ethambutol (EMB)), with the exception the combination of INH+RIF. MDR-TB is the infection with the strains of Mycobacteria which are resistant to at least INH+RIF, the two most potents anti-TB drugs [10, 25]. International surveys on drug resistance demonstrated that mono-resistant TB and poly-resistant TB are more frequent than the MDR-TB, however, not in the high burden countries, such as the Republic of Moldova [4, 11]. Due to inadequate anti-tuberculous treatment, the mono- and poly-resistance can extend into MDR-TB and XDR-TB, showing a lower chance for healing. Standard therapy with first-line anti-TB drugs in mono- and poly-resistant tuberculosis is not always effective, in consequence, many cases will amplify their resistance till MDR-TB. That fact argued the strong necessity to perform a local survey targeting mono- and poly-resistant pulmonary TB patients to strengthen the treatment effectiveness.

The study was conducted to assess the main peculiarities of the patients with mono-resistant and poly-resistant tuberculosis in a cross-sectional study developed during the period 2017-2019, for establishing the measures for strengthening the treatment effectiveness.

Material and methods

The research was cross-sectional and retrospective. It included a series of 124 patients diagnosed with pulmonary TB during the period 01.01.2017 - 31.12.2019 in the Republic of Moldova.

The following inclusion criteria determined the selection of the patients in the research: a new case of pulmonary TB and signed informed consent. The patients were distributed into two groups: in the 1st group were included 85 (68.5%) patients in which the inclusion criteria were the mono-resistance, confirmed through the phenotypic drug susceptibility tests, and in the 2nd group were included 38 (31.5%) patients in which the inclusion criteria were the poli-resistance, confirmed through the same drug susceptibility tests. Among 85 cases from the 1st group, 69 (81.2%) cases were resistant to STR, 15 (17.5%) cases were resistant to INH, and 1 (1.2%) case was resistant to EMB. Among 39 cases of the 2nd group – 32 (82.0%) were resistant to INH + STR and 7 (18.0%) to INH + EMB + STR. In both groups were not included the patients showing the resistance against RIF, and the combination of the INH + RIF. The diagnosis of pulmonary TB was established according to the criteria provided by the national policy [25]. The sputum examination by Ziehl-Neelsen staining, culture on Lowenstein-Jensen and liquid BACTEC media, and chest X-ray investigations were performed in every patient from both groups.

The protocol schedule included the following data about the patients:

1. Biological and social characteristics: sex (male/female ratio), age (distribution in age groups according to the WHO recommendations), demographic characteristics (urban/rural).

2. Economic background: economic status (employed, unemployed, retired, disabled) and health insurance coverage (presence/lack of health insurance). Disability was defined as the condition which limited the working capacity, allowing the patient to be supported by the state policy providing financial support.

3. High-risk groups: homelessness, migration, history of detention, contact with TB patient.

4. Case-management: barriers to healthcare access, method of the TB detection, medical staff which detected the TB.

5. Tuberculosis-related characteristics: localization (pulmonary/extrapulmonary), microbiological results (smear microscopy, culture on the conventional media, molecular-genetic tests, and the drug susceptibility tests), comorbidities.

6. Anti-tuberculous treatment outcome.

The research was approved by the bioethics committee of the State University of Medicine and Pharmacy "Nicolae Testemițanu", on 21st November 2017 and registered with the number 14.

Statistical Analysis

The statistical analysis was performed using EpiInfo software. The data were appreciated as nominal or quantitative. The frequency and percentage were reported for nominal data, and the mean and standard deviation were reported for continuous data. The statistical analysis of the differences between normally distributed continuous variables was tested with the Student T-test. A p-value of <0.05 was considered statistically significant.

Results and discussion

Distribution of the patients according to the microbiological results established that smear microscopy identified a higher rate of microscopic positive for acid-fast-bacilli patients in the 1st group compared with the 2nd group. Culture positive were all patients due to the inclusion criteria of the established drug resistance on the phenotypic drug susceptibility tests. The results on the conventional phenotype drug sensitivity tests on Lowenstein-Jensen medium and BACTEC were available for all patients from both groups. A higher rate of patients from the 2nd group was tested for the drug sensitivity on the 2nd line anti-TB drugs on Lowenstein-Jensen and BACTEC media. Positive and sensible to RIF result at the molecular genetic test GeneXpert MTB/Rifampicin was more frequently identified in patients from the 2nd group. The combination of the positive and sensible to RIF results on GeneXpert MTB and positive on AFB were identified more frequently in the 1st group (table 1).

Distributing patients according to gender identified a male/female ratio of 5,5/1 in the 1st group, with 72 (84.7%) men and 13 (15,3%) women compared with the 2nd group where the male/female ratio was 3,34/1 – with 30 (76,9%) men and 9 (23,1%) women. No difference was identified regarding the distribution of the patients in age groups. It was identified the predominance of the patients with the

Table 1

Distribution of drug-resistant patients by microbiological features

Characteristics		1st group (MonoR-TB)	2nd group (PR-TB)	P-value
		N= 85 *(P%)*	N=39 *(P %)*	
Microbio-logical test results	Microscopic positive	56 (65,8)	18 (46,1%)	<0,05
	Culture positive	85 (100)	39 (100)	>0,05
	DST for 1st-line anti-TB drugs available	85 (100)	39 (100)	>0,05
	DST for 2nd-line anti-TB drugs available	16 (16,8)	12 (30,8)	<0,01
Molecular genetic test results	GeneXpert MTB/ Rifampicin is positive and sensible	71 (83,5)	39 (100)	<0,001
	Microscopic positive and GeneXpert MTB/ Rifampicin is positive and sensible	54 (63,5)	16 (41,6)	<0,001

Note: *Applied statistical test: paired simple T – test, P – probability; DST – drug sensitivity testing, N/A – non available;*

age between 35 and 54 years old in both groups, followed by those with the age between 45 and 54 years old. Distribution of the patients according to the demographic characteristics identified that a similar rate of the patients had an urban and rural residence. Also, no residence card and the homeless state were established at a similar rate, in each fifth patient from both groups. So, according to the distribution of the patients, considering the biological characteristics, it was established that men and young age individuals have the same probability to have any drug resistance, mono- and polyresistance to first-line anti-TB drugs. Demographic distribution identified that patients from urban and rural areas have the same probability to develop any drug resistance (Table 2).

Table 2

Distribution of drug-resistant patients by sex, age and demographic data

Indices	Gender Age Residence	1st group (MonoR-TB)	2nd group (PR-TB)	P-value
		N= 85 *(P%)*	N=39 *(P %)*	
Gender	Men	72 (84.7)	30 (76.9)	>0,05
	Women	13 (15.3)	9 (23.1)	>0,05
Age groups	18-24 years	4 (4.7)	3 (7.6)	>0,05
	25-34 years	15 (17.6)	6 (15.4)	>0,05
	35-44 years	29 (34.2)	12 (30.7)	>0,05
	45-54 years	20 (23.5)	9 (23.1)	>0,05
	55-64 years	13 (15.3)	7 (17.9)	>0,05
	65 and more	4 (4.7)	2 (5,2)	>0,05
Residence	urban	42 (49.4)	18 (46.1)	>0,05
	rural	43 (50.6)	21 (53.8)	>0,05
Other categories	Lack of residence card	12 (14.2)	6 (15.3)	>0,05
	Homeless	5 (6.8)	2 (5.2)	>0,05

Note: *Applied statistical test: paired simple T – test, P – probability;*

Distributing patients according to the economic status, it was established that almost one-half of both groups were constituted by employed persons and unemployed patients were one-third of both groups. In employed, disabled and retired people the health and social insurance was established. So, patients with the health and social insurance statistically predominated compared with those without, in both groups: 55 (64,8%) in the 1st group *vs* 26 (66,7%) in the 2nd group (table 3).

Assessing the educational status, it was established that most of the patients from both groups graduated general school or lyceum. Professional studies or college predominated in the 1st group. Other educational levels were similarly distributed among groups (table 4).

Table 3

Socio-economic status of drug-resistant patients

Economic indices	State	1st group (MonoR-TB)	2nd group (PR-TB)	P-value
		N= 85 (P%)	N=39 (P %)	
Stable	Employed	46 (54.2)	17 (43,5)	>0,05
	Disable	4 (4.7)	5 (12.8)	>0,05
	Retired	5 (5.9)	4 (10.3)	>0,05
Vulnerable	Unemployed	30 (35.2)	13 (33.3)	>0,05
	Lack of insurance	30 (35.2)	13 (33.3)	>0,05

Note: *Applied statistical test: paired simple T – test, P – probability;*

Table 4

Distribution of drug-resistant patients according to the last graduated level

Educational level	Educational status	1st group (MonoR-TB)	2nd group (PR-TB)	P-value
		N= 85 (P%)	N=39 (P %)	
Primary level	Primary & general incomplete school	27 (31.7)	11 (28.2)	>0,05
Secondary level	Completed general school	37 (43.5)	21 (53.8)	>0,05
	Professional school	19 (22.4)	4 (10.2)	<0,05
	Absent	2 (2.3)	3 (7.7)	>0,05

Note: *Applied statistical test: paired simple T – test, P – probability;*

Distributing patients in high-risk groups established that one-third of the patients were residing in poor living conditions and a low number were homeless. History of migration in the last 12 months predominated in the 1st group. The history of detention was established in a few cases from both groups. Alcohol abuse before the tuberculosis diagnosis was established in a minor number of cases. The close contact with an infectious source slightly predominated in the 2nd group. Co-morbidities have an important impact on the acquiring and expansion of poly-resistance to multidrug-resistance. Patients with co-morbidities predominated in the 2nd group, among which HIV co-infected were more frequently (Table 5).

Studying case management, it was identified that general practitioners detected 42 (49,4%), symptomatic patients in the 1st group, compared with 16 (41.2%) patients in the 2nd group. High-risk group screening performed by the primary healthcare workers was used in a similar proportion to detect patients from both groups 13 (15.2%) in the 1st group and 7 (17.9%) in the 2nd group. Specialists detected 16 (41.2%), symptomatic patients of the 1st group, compared with 8 (20.5%) patients of the 2nd group. High-risk group screening performed by the specialists detected 8 (9.4%) patients from the 1st group and 5 (12.8%) in the 2nd group. Direct addressing to the specialized clinical services was used in a similar proportion in both groups (Table 6).

Table 5

Distribution of drug-resistant patients in high-risk groups

Risk groups	1st group (MonoR-TB)	2nd group (PR-TB)	P-value
	N= 85 *(P%)*	N=39 *(P %)*	
Poor living conditions	21 (24.7)	14 (35.9)	>0,05
Homelessness	5 (5.9)	3 (7.6)	>0,05
Migration	19 (22.3)	5 (12,9)	<0,05
History of detention	2 (2.3)	1 (2.5)	>0,05
Alcohol abuse	4 (5.7)	2 (5.2)	>0,05
From TB cluster	12 (14.2)	8 (20.5)	>0,05
Associated diseases	31 (36.5)	18 (46.2)	>0,05
HIV-infection	6 (7.1)	3 (7.6)	>0,05
Psychiatric diseases	2 (2.3)	1 (2.5)	>0,05
Illicit drug use	1 (1.1)	1 (2.5)	>0,05

Note: *Applied statistical test: paired simple T – test, P – probability; SG – social group, EG – epidemiological group, MBG – medico-biological group.*

Table 6

Case-management of drug-resistant patients

Healthcare level	Detection ways	1st group (MonoR-TB)	2nd group (PR-TB)	P-value
		N= 85 *(P%)*	N=39 *(P %)*	
PHC	Detected by GPs-symptomatic	42 (49.4)	16 (41.2)	>0,05
	Detected by GPs -screening of HRG	13 (15.2)	7 (17.9)	>0,05
Ambulatory specialized level	Detected by SP-symptomatic	16 (18.9)	8 (20.5)	>0,05
	Detected by SP-screening of HRG	8 (9.4)	5 (12.8)	>0,05
Hospital	Direct addressing	6 (7.1)	3 (7.7)	>0,05

Note: *Applied statistical test: paired simple T – test, P – probability; PHC – public health care, GPs – general practitioners, HRG – high-risk group.*

Table 7

Radiological characteristics of patients

Parameters	Types	1st group (MonoR-TB)	2nd group (PR-TB)	P-value
		N= 85 *(P%)*	N=39 *(P %)*	
Pulmonary TB forms	PIT	71 (83,5)	33 (85.5)	>0,05
	PDT	12 (14.1)	4 (10.2)	>0,05
	FCVT	2 (2.3)	2 (5.2)	>0,05
Localization	Single lung	49 (57.8)	22 (56.4)	>0,05
	Both lungs	36 (42.3)	17 (43.6)	>0,05
Features	Infiltration	49 (83.6)	28 (71.8)	>0,05
	Lung destruction	14 (16.4)	11 (28.2)	>0,05
	Extensive forms	24 (28.2)	8 (20.5)	>0,05

Note: *Applied statistical test: paired simple T – test, P – probability; PIT – pulmonary infiltrative tuberculosis, PDT – pulmonary disseminated tuberculosis, FCVT – pulmonary fibro-cavernous tuberculosis.*

All patients from the 1st group were treated immediately after the detection till the availability of the results of the drug susceptibility testing with the standard regimen for established/presumed drug-susceptible TB, then was replaced with an individualized regimen according to the drug-resistance profile. Identifying the clinical radiological forms of pulmonary tuberculosis, it was established that pulmonary infiltrative tuberculosis was diagnosed in the most of patients from both groups. Other radiological forms, such as disseminated tuberculosis, slightly predominated in the 1st group and fibro-cavernous tuberculosis in the 2nd group. Distributing patients according to the number of the affected lungs it was established that one lung was involved in one-half of both groups, and both lungs were affected in 36 (42.3%) patients from the 1st group and 17 (43.6%) cases in the 2nd group. Destructive forms of pulmonary tuberculosis predominated in the 2nd group 11 (28.2%) compared with 14 (16.4%) in the 1st group, but extensive forms of pulmonary tuberculosis predominated in the 1st group. It can be explained by the fact the molecular genetic test GeneXpert MTB/Rif contributed to earlier detection of the patients from the 2nd group with more localized and less severe forms of pulmonary tuberculosis than those from the 1st group (table 7).

Distributing patients according to the outcome it was established a similar success rate in both groups. Patients died more frequently in the 2nd group. It is important to note that 2 (5.1%) from the 2nd group enhanced the poly-resistance to multidrug-resistance. Were lost to follow-up a limited number of patients from both groups. A higher number of patients from the 1st group failed the treatment, 6 (7.1) compared with only 1 (2.5) case in the 2nd group. Only 1 (1.1) patient in the 1st group was continuing the treatment.

Table 8

Treatment outcome of drug-resistant patients

Results	1st group (MonoR-TB)	2nd group (PR-TB)	P-value
	N= 85 *(P%)*	N=39 *(P %)*	
Total number of successfully treated including	66 (77.6)	31 (79.5)	>0,05
Cured	63 (74.2)	29 (74.4)	>0,05
Died	10 (11.8)	6 (15.4)	>0,05
Treatment failure	6 (7.1)	1 (2.5)	>0,05
Lost to follow-up	2 (2.3)	1 (2.5)	>0,05
Ongoing	1 (1.1)	0	>0,05

Discussion

Our study established that most of the patients with anti-tuberculosis drug resistance were confirmed with the resistance to one anti-TB drug. The mono-resistance to STR predominated, followed by the resistance to INH. The WHO guidelines in the treatment of tuberculosis recommended reducing the use of STR, as many studies reported a high rate of STR-resistant cases [26, 27, 28]. Our study confirmed that among the mono-resistant cases 81,2% of patients were resistant against STR and among poly-resistant cases predominated the combination of STR and INH in 82,0% cases. WHO reported that INH-resistant TB accounts for approximately 8% of all TB cases worldwide [26]. Our research identified that the resistance to INH accounted for 17,5% of cases. A lower rate of INH and EMB-resistant cases was also reported by international studies [5]. No mono-resistance against EMB was identified in our study, but a low number of patients (15%) with poly-resistance included the resistance to EMB cases. Similar data confirmed a lower rate of the cases with EMB resistance compared with the resistance to STR and INH cases [5]. The results of some clinical studies report that INH-resistant tuberculosis is associated with a higher successful treatment outcome (80-95%) compared with other mono-resistant cases [29, 30, 31]. Other clinical studies denoted suboptimal outcomes of INH-resistant tuberculosis with a high failure rate, between 18% and 44%, under the treatment with first-line anti-TB drugs [32, 33, 34]. Our research demonstrated a low rate of treatment success in mono-resistant TB, however, we should emphasize that most of our patients were resistant to STR. Some authors analyzed the obtained data from the patients with mono-resistance to INH and concluded that a better treatment success, a lower rate of therapeutic failure, relapse, and acquired drug resistance were associated with a longer duration of the treatment with rifampicin [33, 35, 36]. The patients from our study were treated individualized according to the drug susceptibility test with a duration from 9 to 12 months, which contributed to the successful outcome in 66 (77.6%) cases with mono-resistant TB and 31 (79.5%) cases with poly-resistant TB. As concluded by other authors, special attention should be granted to mono- and poly-resistant TB, because the treatment with the 1st line anti-TB drugs, especially with inadequate treatment regimens, can lead to treatment failure. Thus, standard therapy with first-line anti-TB drugs in mono- and poly-resistant tuberculosis is not always effective, in consequence, many cases will amplify their resistance to other anti-tuberculosis drugs into multidrug resistance [3, 35-38]. Thus, the standard treatment

with 1st line anti-TB drugs is a great challenge for obtaining a high rate of treatment success [3, 36-42]. The analysis of the peculiarities of the patients diagnosed with mono- and poly-resistant TB did not show statistical differences in terms of the men/female affected ratio and the most affected age group, which was between 35 and 54 years old. In most of the patients, the social and economic status was vulnerable, associated with low educational levels and increased rate of high-risk factors: close contact with TB patients, migration, and co-morbidities. Patients were more frequently detected through the passive case-finding. Data about the general characteristics of the patients selected in our study were similar to those published by other studies [4, 11]. International practical recommendations for strengthening the anti-TB program emphasized that access to the rapid drug susceptibility testing to 1st line and 2nd line anti-TB drugs and individualized treatment according to the results of the drug susceptibility test, would reduce mortality and improve treatment outcomes, which could be also applied in our study.

Conclusions

- Patients with mono-resistance to STR or INH predominated among patients with mono-resistant TB.
- Poly-resistance, which included the resistance to STR and INH was established in most of the patients with poly-resistant TB.
- Peculiarities of the patients diagnosed with mono- and poly-resistant TB did not show significant statistical differences in terms of the men/female affected rate, distribution in age groups, low social and economic, low educational levels, an increased rate of high-risk factors: close contact with TB patients, migration, and co-morbidities.
- Patients with both, mono- and poly-resistant TB were more frequently detected through the passive case-finding, which ensures the diagnosis of the symptomatic cases.
- The suboptimal treatment success rate was associated with a high rate of death in both, mono- and poly-resistant TB.
- Mono- and poly-resistant TB represent the background for treatment failure and represents one of the main causes for the development of MDR-TB. Early microbiological detection of resistant strains of Mycobacteria will contribute to the onset of an adequate treatment according to its susceptibility and will ensure an optimal treatment outcome.

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