THE ROLE OF EXOGENOUS RISK FACTORS OF ANTITUBERCULOSIS TREATMENT FAILURE

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Abstract

Background and aim. The Republic of Moldova reports the highest incidence of tuberculosis and the lowest treatment success rate among European region countries. In most of the patients the antituberculosis treatment failure is correlated with social risk factors (low socio-economical state, epidemiological danger characteristics) and biological factors (young age, male sex, physiological conditions, associated diseases). Clinical factors (advanced forms of tuberculosis, chronic evolution, immune disturbances), therapeutic factors (treatment errors and interruptions, individualized regimens) and administrative factors (drug interruption in supply, suboptimal treatment quality) prevail in regions with defficient in health care delivery. The association of risk factors has a higher impact than the severity of one risk factor. The risk factor assessment is very important before initiation of the treatment, for establishing the plan of risk reduction measures for increasing the success rate. The aim of the study was to determine the impact of exogenous risk factors on antituberculosis treatment failure.

Methods. The study was conducted on 201 patients with pulmonary tuberculosis and treatment failure and 105 patients with pulmonary tuberculosis who successfully finished the antituberculosis treatment. Selected cases were investigated according national standards.

Results. The treatment failure occurred in patients belonging to socially disadvantaged groups, patients with harmful habits (alcohol abuse, drug use, active smoking), patients from infectious clusters. Migration, homelessness and detention releasing imperil the quality of treatment, thus predisposing to the treatment failure. Social, educational support and the substitutive therapy and withdrawal techniques (tobacco, alcohol, psycho-active substances) must be implemented in the high risk groups in order to diminish the risk of treatment failure and to increase the treatment success rate.

Conclusions. The study of exogenous risk factors in vulnerable groups will contribute to the precocious detection of patients predisposed to failing the tuberculosis treatment and will permit the initiation of measures centered on patient that will favor the increase of treatment quality and success rate.

Keywords: tuberculosis, treatment failure, risk factors

Background and aim

Tuberculosis represents a big challenge for public health [1]. According to the latest report of WHO for 2014, 9 million cases of TB were estimated, 1.5 milion deaths were registered, including 360.000 among HIV-positive persons [2]. In Republic of Moldova the epidemiological state started to worsen from the beginning of 1990, due to social economical crisis and abolishment of the annual radiological examination in the entire population [3,4]. In 2001 the National Tuberculosis Programme (NTP) was approved, starting with a pilot project in Chisinau city, which was extended to the whole country in 2005 [5]. The major principles of NTP were: detection of at least 70% of all new cases through smear microscopy and achievement of 85% of treatment success rate in new pulmonary cases [6]. Despite of all financial interventions, logistic and administrative international assistance, the highlighted objectives were not achieved. It was established a global incidence 99.7/100,000 population at the end of 2014 (WHO estimated incidence – 154/100,000 population), one half of patients (48.9%) were diagnosed with destructive pulmonary tuberculosis and 64.5% with very contagious pulmonary forms [4]. Due to this fact, the treatment success rate remains lower than in European Region Countries (the highest rate was established in 2006 – 62%, showing a stable state, without significant changes, 2007 – 57.8%, 2008 – 57.3%, 2009 – 52.3%, 2010 – 53.4%, 2011 – 67%) [6,7]. The most influencing index is the treatment failure rate. R. of Moldova registred constantly high rate of therapeutic failure 2001 - 18.5%, 2002 - 10.4%, 2003 - 12.1%, 2004 - 12.4%, 2005 - 10.9%, 2006 - 10.9%, 2007 - 9.2%, 2008 - 7.4%, 2009 - 6.2%, 2010 -19.6%, 2011 - 3.4%, 2012 – 3,2% [4,6].

Romania, neighbor country with similar social and economical conditions, registers a high rate of successfully treated cohort among new treated cases (85%). Death and the patients lost from follow-up constitute the significant proportion of those with unsuccessful treatment outcomes. Treatment outcomes among new pulmonary smear-positive patients included in drug-susceptible regimen did not change much during the last five years in Romania. Thus, the rate of patients who failed drug susceptible standard regimen remained stable: 2007 – 4.0%, 2008 – 3.9%, 2009 – 3.9%, 2010 – 4.0%. 2011 – 3.4% as well as the rate of MDR-TB treatment failed patients were much more higher and without significant changes during last period: 2007 – 33.7%, 2008 – 32.7%, 2009 – 36.7%, 2010 – 40.2%. A research study identifying the ethnographic distribution of treatment failure among patients from Romania, assessed that the main cause of failure of TB control actions are the lack of public awareness and low funding for medication regimens [8]. It was established that the highest rate of cases develop failure during the out-patient treatment phase as a lack of casework and follow-up [9]. Studying the factors associated with treatment failure in Bulgaria it was identified that the most prevalent risk factor is the advanced diseases [10]. Beside many different causes that are involved in the development of tuberculosis treatment failure: comorbidities, radiological extensibility of pulmonary TB, pharmacological peculiarities, the exogenous risk factors, also known as socio-epidemiological factors, are the most involved in the ensuring the highest treatment success rate [3,7].

Objectives

The aim of the study was the assessment of exogenous risk factors for antituberculosis treatment failure, as well as clinical and radiological features of pulmonary tuberculosis in patients that failed the tuberculosis treatment.

Material and methods

An observational, selective, descriptive and retrospective case-control study on 306 new pulmonary tuberculosis cases was performed. The patients were investigated according to the National Tuberculosis Policy – 123. The diagnosis was established through the sputum examination at Ziehl-Neelson staining (2 collected and examined sputum samples) and standard culture on Lowenstein-Jensen medium and rapid MGIT 960 BACTEC (with drug sensibility testing), chest X-ray investigations. Patients were selected in the study according inclusion criteria: age >18 years old, diagnosis of drug-susceptible pulmonary tuberculosis new case established in the period 2009-2012, intensive phase of the tuberculosis treatment performed in the Chisinau Municipal Hospital of Pneumophthisiology, Republic of Moldova and after signing a consent form for enrolment. Patients were treated according to the standard regimen for drug-susceptible tuberculosis. The performed standard treatment was constituted of two phases: intensive phase during 2 months in hospital conditions (isoniazid, rifampicin, pirazinamid and ethambutol) and continuous phase - 4 months in out-patient setting (isoniazid and rifampicin). Treatment failure was appreciated as the microscopic smear positive patient after 5 and more months of tuberculosis treatment. The patients were divided in two groups: **the study group (SG)** included 201 new pulmonary tuberculosis cases that failed the antituberculosis treatment and a **control group (CG)** included 105 new pulmonary tuberculosis cases, that successfully finished the antituberculosis treatment. The statistical analysis was performed using EpiInfo software. 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 comparison between two groups of a continuous variable was performed using the independent sample t-test. The correlation between two variables was tested by using Pearson's correlation. Statistically significant difference was considered for a p value of <0.05. Univariate logistic regressions was used to appreciate the

power of each potential risk factor to determine treatment failure. Adjusted Odds ratio (OR) was calculated using two by two table. Low risk factor was confirmed at the value inteval between 1.2 and 1.6 expressed. medium risk factor at 1.7-2.5 and high risk factor for more than 2.5.

Results

The distribution by gender established the significant predominance of men in both groups: 143 (71.14%) vs 58 (28.96%) women of SG and 62 (64.7%) vs 39 (35.3%) women of CG (p<0.001), with men/women rate=2.46/1 in SG and men/women rate=1.59/1 in CG. Predictible value of male sex for treatment failure was established as a low risk factor with OR=1.457 with 95% confidence interval (CI): 0.884-2.402.

According to the distribution of patients into age groups it was established a similar repartition in both groups. Considering the totality of young age groups (till 45 years old) it was established the predominance of young adults in SG, and elders in CG. Simultaneously the total number of patients till 44 years was statistical higher in SG 130 (64.67±4.53%) than in CG (61 (58.09±3.28%) p<0.05), so it was found that young age represents a low risk factor for treatment failure with OR=1.457 (CI 95%: 0.884-2.402).

Patients were appreciated according to the educational level in such groups: primary 1 educational level, incomplete general studies, general studies (general secondary school), and 2 professional studies / superior studies. It was established that incomplete general studies 3 predominated in the SG (39 (19.4±2.78%) patients comparing with CG (6 (5.71±2.26%), p<0.001), and 4 professional studies predominated in CG (14 (13.4±3.31) patients comparing with CG SG 12 (5.9±1.67%) patients, p<0.001 degree of concludence).

The total number of patients with low educational level (primary school, incomplete general studies and general secondary school) prevailed in SG 66 (32.84±3.31%) than in CG (18 (17.14±3.67%) patients with degree of concludence p<0.05) and the patients with higher educational level (professional studies and superior studies) prevailed in CG (24 (22.86±4.09%) patients comparing with CG than in SG (24 (11.94±2.29%) patients with degree of concludence p<0.05). In accordance with exposed data. the low educational level was appreciated as medium risk factor for treatment failure with an OR=2.363. CI 95%: 1.314 – 4.249. We explain the fact, that low level of education and professional training, was associated to a lower intellectual status, thus diminished the patient's adherence to treatment and predisposed the treatment failure.

Social determinants of tuberculosis are well recognized. Poverty represents a high risk for mycobacterial infection and active disease development, as well as, leads to big difficulty in successfully treatment ending. Assessing socio-economical level of investigated patients, was demonstrated the predominance of unemployed patients in SG (138 (68.66±3.27%) than in CG (59 (56.19±4.84%), (p<0.05). The rest of economical groups were distributed without statistical significance.

The total number of patients with disadvantaged socio-economic status (unemployed, retired, disabled, and student) was higher in SG 138 (68.66±3.27%) than in CG 59 (56.19±4.82%). (p<0.05). So thus, vulnerable socio-economical status was appreciated as low risk factor for treatment failure with OR=1.311 (CI 95%: 0.768–2.237). The obtained data showed that financial support provided during the tuberculosis treatment was required for maintaining the treatment adherence.

Distribution of patients according marital state assessed the cases as: married, single, divorced and widow persons. The comparative analysis of groups determined that married individuals were more frequently identified in CG (67 (63.80±4.69%)) patients than in SG (85 (42.28±3.48%) patients with high degree of concludence p<0.001) and single person's state predominated in SG (86 (42.79±3.49%) comparative with CG (23 (21.91±3.92%). p<0.001). So. Disadvantaged matrimonial state, including the groups of single persons, divorced, widows cases prevailed in SG (116 (57.71±3.48%) patients compared with the CG (38 (36.20±4.69%) patients, with degree of concludence p<0.001), being evaluated as a medium risk factor for treatment failure with OR = 2.174 (CI 95%: 1.011 - 3.089).

Thus, it may be additionally concluded that the family's and community's support has an important value during the tuberculosis treatment, diminishing the patient's stigma and degree of non-compliance.

Harmful habits showing a high risk for reducing the treatment quality are: tobacco smoking, chronic and abusive alcohol drinking and drug using. It was established the prevalence of tobacco smoking in SG 164 (81.59±2.73%) compared to CG 68 (64.35±4.67%), p<0.05. as well as the alcohol drinking 97 (48.25±3.52 %) vs 13 (12.38±3.21%) p<0.001. Drug using was detected only in several patients of SG (4 (1.99±0.98%). So, the active smoking was established as a medium risk factor. appreciated with OR=2.412 (CI 95%: 1.411-4.123). alcohol drinking was appreciated as a high risk factor with OR=6.601 (CI 95%: 3.469-12.559) and drug using was a low risk factor OR=1.49 (CI 95%: 0.331-3.660). So, the substitutive therapy and withdrawal technics (tobacco, alcohol, psycho-active substances) must be included in the standard treatment measures for reducing the risk of treatment failure and increasing the treatment success rate.

Evaluation of high risk characteristics was established the predominance of migrant patients in SG (78 (38.8±3.43%) patients compared to CG 31 (29.62±4.45%) patients, as well as the homelessness state were identified only in SG (9 (4.47±2.10%) patients.

Peculiarities conferring an epidemiological danger for the healthy population predominated in SG. So, contacts with contagious tuberculosis patients predominated in SG 79 (39.3±4.7%) compared with CG 24 (29.7±7.5%) and released from detention were 30 (14.9±3.6%) patients form SG. Considering obtained data, it can be concluded that continuous reinfection, maintained in tuberculosis cluster contributes to the treatment failure. Simultaneously, the patients released from detention were identified only in the failed treatment group, that demonstrated the absence of reintergation measures of ex-detainees in social and health care service of civic society. Homelessness state identified only in SG demonstrates the importance of tuberculosis treatment administration in all beneficial circumstances for patient. Patients living in extreme poverty (below the minimum wage) predominated in SG (123 (61.19±5.12%) cases compared to CG 37 (35.2±6.6%) cases, with high degree of concludence p<0.001). So, the poverty was appreciated as a medium risk factor for treatment failure with OR=2.406 (CI 95%: 1.479 - 3.914). All above exposed data demonstrated the need to strength the measures of social support targeting patients belonging to vulnerable groups for increasing the treatment quality and success rate.

Evaluating the case management it was established that the majority of all selected patients were detected by general practitioners. So, 193 (96.02±1.37%) cases of SG and 94 (89.52±2.99%) of CG were detected in the frame of primary health care assistance. Late detected patients with symptomatology evolving more than 3 months predominated in SG - 113 (56.21±3.49%) comparative with 34 (32.38±4.56%) cases of CG p<0.01. The patients with associated diseases predominated in SG - 143 (71.14±3.19%) cases compared to CG (51 (48.57±4.87%) cases. p<0.001.

The diagnosis of infiltrative tuberculosis was confirmed through the radiological investigations in the most of patients: 179 (89.05±2.01%) cases in SG and 85 (80.95±3.83%) in CG. Fibrocavitary pulmonary tuberculosis (chronic form of tuberculosis) was diagnosed only in the SG (6 (2.99±1.2%) cases). Nodulary pulmonary tuberculosis (limited form of tuberculosis) was diagnosed only in CG (8 (7.61±2.59%) cases). Both lungs were involved in the infectious process more often in SG (163 (81.10±2.72%)) compared to CG (36 (34.29±4.63%) cases. p<0.001). Simultaneously, extended forms of pulmonary tuberculosis were prevailed in the SG: 187 (93.03±1.79%) cases in comparison with 58 (55.24±4.85%) cases in CG, p<0.001.

Table I. Case distribution by age groups.

Age (years)	Control Group (M±m%)	Study Group (M±m%)
18-24	14.3±3.41	15.92±2.58
25-34	20.9±3.97	23.38±2.96
35-44	22.9±4.09	25.37±3.07
45-54	20.9±3.97	21.89±2.91
55-64	19.05±3.83	10.95±2.20
>65	1.91±1.33	2.49±1.09

Table II. Case distribution in groups according to educational level.

Educational level	Control Group (M±m%)	Study Group (M±m%)
Primary	11.4±3.01	13.4±2.40
Incomplete general	5.71±2.26	19.4±2.78 •
General school	60.0±4.78	55.2±3.51
Professional school	13.3±3.31	5.9±1.67 •
Superior studies	9.52±2.87	5.9±1.67

Legend: • - statistical difference between control group and study group

Table III. Distribution according to professional status.

Professional state	Control Group (M±m%)	Study Group (M±m%)
Employed	28.57±4.41	23.38±2.98
Unemployed	56.19±4.84	68.66±3.27 •
Retired/disabled	10.47±9.89	4.47±1.45
Student	4.77±2.07	3.49±1.29

Legend: • - statistical difference between control group and study group

Table IV. Distribution according to matrimonial state.

Marital status	Control Group (M±m%)	Study Group (M±m%)
Married	63.80±4.03	42.28±3.48 •
Single person's status	21.91±3.92	42.79±3.49 •
Divorced/widow	14.29±3.41	14.93±2.51

Legend: • - statistical difference between control group and study group

Table V. The structure of groups with high risk characteristics.

High risk characteristics	Control Group (%)	Study Group (%)
Smoking	64.35±4.67	81.59±2.73 •
Chronic/abusive alcohol drinking	12.38±3.21	48.25±3.52 •
Drug using	0	1.99±0.98
TB cluster membership	29.7±7.5	39.3±4.7
Migration	29.62±4.45	38.8±3.43
Detention releasing	0	14.9±3.6 •
Homelesses	0	4.47±2.10
Extreme poverty	35.2±6.6	61.19±5.12 •

Legend: • - statistical difference between control group and study group

Discussion

Tuberculosis represents a big challenge for public health due to the fact of involving in the epidemiology of young adults - economically active group of population. Moreover, young men have a complex of associated risk factors that contribute to diminishing the treatment outcome. Distribution of patients by gender and age groups, established that young men are more predisposed to fail the tuberculosis treatment than older age groups and female sex. Statistical evaluation established that that young age (till 44 years old) and male sex constituted low risk factors for tuberculosis treatment failure. Social vulnerable characteristics as low educational level, unemployed economical groups and single marital state defined as middle risk factors. Harmful habits, largely identified among TB patients, contributed to development of treatment failure. Concomitantly pauper life conditions were appreciated as high risk factor. High risk peculiarities as contact with an infectious patient, the state of the person released from detention, homelesseness state were determined as epidemiological factors, which were associated with social ones. The most of studied cases were detected by general practitioner. Late diagnosed cases with severe and extended forms of pulmonary tuberculosis were more often confirmed in patients that developed tuberculosis treatment failure.

Conclusion

The study of exogenous risk factors in vulnerable groups, could contribute to increasing the awareness of risk reducing measures and lead to precocious initiation of an adequate tuberculosis treatment. Standard tuberculosis treatment must be associated with social, educational support, substitutive therapy and withdrawal techniques (tobacco, alcohol, psycho-active substances) in high risk groups for diminishing the risk of treatment failure and increasing treatment success rate.

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