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Tuberculosis evolution and treatment outcome in drug addicted patients

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Abstract

Background: Drug injection is considered an important issue for the public health of the Republic of Moldova. In the RM the intravenous drug users (IVDU) are the key population for HIV infection, B and C hepatitis, TB and sexual transmitted diseases. The aim of the study was to assess the tuberculosis evolution and treatment outcome in intravenous drug addicted patients.
Material and methods: A retrospective selective, descriptive study targeting socioeconomic, demographic, economic and epidemiological peculiarities, case-management, diagnosis of radiological aspects and microbiological characteristics of 233 patients with pulmonary tuberculosis registered in Chisinau city from 2012 to 2016 among them 48 IVDU was performed. The results were compared with a sample of 34 IVDU.
Results: Men were predisposed for drug addiction and the age is younger in addicts with tuberculosis. Socioeconomic vulnerability is extended in the selected groups; however, the poverty deepness was more important in addicted patients with tuberculosis. Close contact with a sick patient predominated in addicts with tuberculosis, but nobody assessed the contact in addicts without tuberculosis. Associated diseases predominated in addicts with or without tuberculosis, more frequently were: HIV infected individuals, viral hepatitis and neurological disorders.
Conclusions: Risk factors for tuberculosis in drug addicts were: unemployment and associated lack of health insurance, patient's homeless state, middle adulthood and the immune suppressive condition – HIV infection. Major disease-related characteristic in IVDU patients was the presence of severe destructive forms of tuberculosis and "loss to follow-up" as outcome.

Key words: tuberculosis, drug use, addiction, risk factors.

Introduction

Drug use has important criminal and social implication in the Republic of Moldova (RM) [14, 17, 21, 23, 30, 31]. According to the national epidemiological data in 2009 on the left side of the territory of the RM were diagnosed 1333 new cases of drug users, among them 6.5% were women. The RM is an agrarian country and the production of the vegetable drugs from poppy and hemp raw material is affordable [31]. Despite this, the prices for opium, marijuana, heroin, cocaine and other drug extracts is continuously increasing. The total number of drug-related crimes during the period 2008-2010 decreased (2008-2103 crimes, 2009-1865 crimes, 2015-745 crimes), but the number of crimes related to the narcotics trade constituted only 15% [12]. So, it can be deducted that most of the trials are related against drug users and not against the drug trafficking. [31] The development of new narcotic and new generation psychotropic substances has serious health consequences. The prevalence of HIV infection among Moldovan intravenous drug users (IVDU) reached 21.0% in 2008 [3]. The globalization of the illicit drug use determined the development and improvement of the legislative basis for preventing consumption, combating illicit drug trafficking, also counseling and treatment of the drug addiction [27, 28, 35]. An important step in the prevention of the consumption and combating drug trafficking was the approval of the National Anti-drug Strategy for 2011-2018 [12]. The strategy was developed according to the European Anti-drug Strategy, Convention on Narcotic Drugs, Convention against Illicit Traffic of Narco-

tic Drugs and Psychotropic Substances, Declaration about the Principles on the Drug Demand Reduction [27, 28]. The implementation of the Strategy among young IVDU diminished the rate of died people due to the overdoses from 131 in 2002, to 8 in 2008 and 12 in 2009. However, the rate of IVDU with HIV infection reached 8.5%, with viral hepatitis – 9.1%, with TB 1.24% and sexual transmitted infection 12.7% in 2013 [17]. The IVDU have various barriers in the accessing health care and getting an effective treatment for their addictive conditions and associated diseases [9]. High degree of stigma and social marginalization contribute to the lack of the short-term residential treatment, therapeutic communities and rehabilitation services [34]. Due to highly repressive policies the IVDU are frequently incarcerated [31]. Prisons represent an extensive infectious reservoir [8, 29]. Specific needs of the key population IVDU are underestimated contributing to gaps in management of the diagnosis and treatment of tuberculosis [5, 35]. In several high tuberculosis countries the systematic screening of drug users through the chest X-ray and interferon-gamma assay is an important action in the control of the disease at the national level [7, 10, 13, 18].

Tuberculosis represents one of the 10 leading causes of death globally, according to the WHO Global Tuberculosis Report [40]. After the Millennium Summit, that was held in 2000, the 191 member states of the United Nations Organization adopted the 8 Millennium Development Goals (MDGs), which targeted the main directions of global efforts [32]. A major influence obtained the activities for

E. Lesnic et al. Moldovan Medical Journal. October 2018; 61(3):15-23

RESEARCH STUDIES

reduction of extreme poverty (Objective 1), fighting HIV/AIDS, malaria and tuberculosis (objective 6). Despite of important progress in obtaining the results, on 15 September 2015 there were adopted new 16 objectives: Sustainable Development Goals (SDGs), oriented to the poverty alleviation, reducing inequalities, good health, well-being, and other objectives to be realized in the next 15 years [33]. The comprehensive approach to tuberculosis was identified in several objectives: to put an end to poverty and hunger, fight HIV/SIDA, malaria and tuberculosis, to provide sustainable development of communities (target – treatment support of patients with HIV/AIDS, tuberculosis, etc.). It demonstrated the importance of activities implemented to combat the poverty-related diseases and contributing conditions, one of them – the drug use [38]. As an immediate feedback to SDGs World Health Organization adopted the End TB Strategy in 2014 that targets the decrease with 90% of death cases due to tuberculosis and decrease with 80% incidence till 2030, comparing with 2015 [37]. The last WHO report estimated the RM remains one of the highest burdened countries by drug resistant tuberculosis with an estimated rate of 26% among new cases and 56% among previously treated cases [43]. The social determinants of tuberculosis were well recognized [39, 40, 41]. It was identified a strong relationship between social vulnerability and psychotropic substance abuse: tobacco smoking, alcohol abuse and drug use. [39] Addiction is a compulsive need for use of a habit-forming substance (nicotine, alcohol, or heroine) characterized by tolerance and well-defined symptoms upon withdrawal [9, 21, 39]. From the physiopathology point of view, addiction affects neurotransmission and interactions within reward structures of the brain, including the *nucleus accumbens, anterior cingulate cortex*, basal forebrain and *amygdale*. It affects neurotransmission and interactions between cortical and *hippocampus* circuits and brain reward structures, such as the memory of previous exposures to rewards (ex. alcohol, drugs, nicotine, food, sex). It leads to a biological and behavioral response to external triggers which engage the person in addictive behaviors. The frontal cortex of the brain and underlying white matter connections are fundamental in the manifestations of altered impulse control, judgment, and the dysfunctional pursuit of rewards. The frontal lobes are important in inhibiting impulsivity and in assisting individuals to appropriately delay gratification. Frontal lobe morphology, connectivity and functioning are still in the process of maturation during adolescence and young adulthood. The early exposure to substance use of a young person is a significant factor in the development of addiction. Addiction is characterized by: 1. inability to consistently abstain; 2. impairment in behavioral control; 3. craving or increased "hunger" for nicotine, alcohol, drugs or rewarding experiences; 4. diminished recognition of significant problems and interpersonal relationships; 5. dysfunctional emotional response. During addiction there is a significant impairment in executive functioning [35]. It manifests in problems with perception, learning, impulse control, compulsivity, and judgment. People with addiction

often manifest a lower readiness to change their behaviors. The developing of frontal lobes of adolescents and young adults may contribute to disturbance of executive functioning and predispose young people to engage in "high risk" behaviors, including engaging in smoking, alcohol or other drug use. Addiction is more than a behavioral disorder. Features of addiction include aspects of a person's cognitions, emotions, and interactions with others. It consists in period of relapse and remission. Clinical interventions are difficult to perform and are quite ineffective. Close monitoring of the behaviors of the individual and contingency management can contribute to positive clinical outcomes. The engagement in health promotion activities which underline personal responsibility and accountability, connection with others, and personal growth also contribute to the patient's recovery. It is important to note that addiction can cause disability or premature death, especially when is left untreated or is treated inadequately. Self-management with mutual support and professional care provided by trained staff is very important in the person's recovery from addiction [19, 21, 35]. Drug addiction is a chronic brain disease that causes the compulsive behavior to seek and use the substances. The addiction changes the decision-making capacity of the person and it should be treated like any other illness. Withdrawal syndrome is a pathological condition directly related to addiction, which occurs when the addicted consumer drops the doses. If dependence is strong, the withdrawal can manifest violent: hypertension, palpitations, deep sweating, muscle pain, joint pain, headache, vertigo, vomiting, psychomotor excitation, convulsions, anxiety, insomnia, psychological and physical discomfort. Methadone is a synthetic opioid with pharmacological effects similar to morphine products. Methadone is bioavailable consumed by oral or injected way. The main effect of methadone is expressed by receptors and is similar to that produced by endogenous opiates such as encephaline and endorphin. Methadone increases the elimination of neuromediators: acetylcholine, noradrenaline and dopamine. Methadone decreases the desire to use heroin and other opiates, eliminates the symptoms of the withdrawal and blocks the euphoric effects of other drugs or substances [21].

Genetic factors account one half of the likelihood that an individual will develop drug addiction. However the interaction of the environmental factors increases the predisposition for addiction. Culture also plays an important role for increasing the possibility that the persons with biological vulnerabilities develop addictions. Other factors that contribute to the appearance of addiction, leading to its characteristic bio-psycho-socio-spiritual manifestations are: 1. Biological failure in the function of reward circuits; 2. Repeated engagement in drug use or other addictive behaviors (alcohol, tobacco smoking), causing neuro-adaptation and engagement in addictive behaviors; 3 Cognitive and affective distortions, which impair perceptions and fail the ability to deal with feelings, resulting in significant self-deception; 4. Disruption from the healthy social supports; 5. Appearance of the problems in interpersonal relationships

which impact the development of addictive behavior; 6. Exposure to trauma or stress that determines an individual's coping abilities; 6. Distortion in meaning, purpose and values that establish attitudes, thinking and behavior; 7. distortions in the connection with person's self and community; 8. Co-morbid psychiatric disorders in persons who engage in substance use or other addictive behaviors [5, 36].

The socioeconomic and political crisis through which passes the RM determines the increasing of the social vulnerable population, among which the addictive habits are very frequent [3, 23, 30, 31]. The health-related risks in addicts are highly expressed. It was established a 55 times higher risk to develop tuberculosis among persons with alcohol use disorders, 10 times higher risk to develop tuberculosis among tobacco smokers and non-estimated high risk in IVDU population. The susceptibility for tuberculosis is determined by: 1. The social mixing patterns of addicts; 2. Weak immune system due to associated conditions (malnutrition, HIV-infection, gastro-intestinal disorders, etc.) leading to reactivation of the latent TB infection; 3. Toxic effects of drugs on different organs; 4. Micro- and macronutrient deficiency.

So, the aim of the study was to assess the tuberculosis features and treatment outcome in the intravenous drug addicted patients.

Objectives were: 1. Assessment of the tuberculosis extension among the population of the IVDU from the Republic of Moldova and its epidemiological evolution; 2. Assessment of general, socioeconomic and epidemiological risk factors of IVDU with tuberculosis and comparing with two control samples of IVDU and pulmonary tuberculosis; 3. Evaluation of the case-management, diagnosis, radiological aspects and microbiological characteristics of IVDU with tuberculosis comparing with a control sample of pulmonary tuberculosis; 4. Assessment of the specialized health care accessibility of the IVDU with tuberculosis comparing with the control sample of pulmonary tuberculosis.

Material and methods

It was performed a retrospective selective, descriptive study targeting social, demographic, economic and epidemiological peculiarities, case-management, diagnosis, radiological aspects and microbiological characteristics of 233 patients with pulmonary tuberculosis registered in Chisinau during the period 2012 to 2016. Among them, 48 were established being IVDU and 185 patients had no drug addiction. The results were compared with a sample of 34 IVDU without tuberculosis or a history of a previous treatment for tuberculosis. The electronic system for monitoring and follow-up of tuberculosis cases (SIME TB) was used for the selection. Data were extracted from the statistic templates F089/1-e "Declaration about patient's established diagnosis of new case/relapse of active tuberculosis and restart of the treatment and its outcomes" and F090/e "Declaration and follow up of multidrug-resistant tuberculosis". Inclusion criteria in the study group (SG): age more than 18 years

old, tuberculosis and associated intravenous drug addiction, signed informed consent allowed the selection of 48 patients. In the 1st control group (1st CG) were selected 185 new diagnosed cases with pulmonary tuberculosis without associated drug addiction, also in the past. Assessing the type of the drug addiction it was established that 45 (93.7%) of the IVDU from the SG had mental illness and behavior disorders due to the opioid use and 3 (6.3%) had mental illness and behavior disorders due to multiple drug use of psychoactive substances. In the 2nd CG 14 (41.2%) patients had mental illness and behavior disorders due to the opioid drug use, 16 (47.1%) had mental illness and behavior disorders due to multiple drug use of psychoactive substances and 4 (11.7%) patients had mental illness and behavior disorders due to the non-opioid substances use. Most of patients, 21 (61.7%) cases, were previously treated. Each second patient had a relapse – 10 (47.7%), 3 (14.3%) were after loss to follow-up, 7 (33.3%) had methadone addiction and 1 (4.7%) required the preventive treatment. Each third patient from the 2nd CG, 12 (35.3%), was hospitalized for the first time for the treatment of the withdrawal syndrome. Each second patient of the 2nd SG (21 (61.7%) had more than 10 years of drug use and the rest of the group had a shorter life history of addiction. Most of them, 26 (76.5%) cases, directly addressed to the narcological specialized institution and 8 (23.5%) patients by the third parts (relatives, police). Assessing the drug types, most of them – 14 (41.2%) used heroin, 10 (29.4%) a combination of drug with heroin and 10 (29.4%) other types of drugs.

All patients with tuberculosis were investigated and treated according to the National Clinical Protocol 123 "Tuberculosis in Adults" [22]. The "new case" was considered the patient never treated for TB or has taken anti-TB drugs less than one month. Previously treated were considered patients with relapse, treatment failure and loss to follow-up. For assessing the socioeconomic barriers and health care accessibility of the IVDU the 2nd control group (2nd CG) was selected and was composed of 34 patients. The investigational schedule included demographic, social and epidemiological data: sex (male/female ratio), age (distribution in age groups), demographic characteristics (urban/rural residence), educational level, socio-economic status (employed, unemployed, retired, disabled, student), health insurance status (lack of insurance), migration and detention history, presence of high risk (close contact with an infectious source, comorbidities, health care seeking behavior, way of the patient's detection). Enrolled patients from the SG were selected in the period 01.01.2012-31.12.2016. Patients from the 1st CG were enrolled during the period 01.01.2015-31.12.2015. For patients from the 2nd CG the period of selection – during 01.01.2017-31.05.2018. The samples of patients with tuberculosis were managed in the frame of the clinical services of the Municipal Clinical Hospital of Pneumophtisiology of Chisinau and the samples of IVDU were managed in the Republican Narcological Dispensary of the Republic of Moldova. Statistic analysis was carried out using the quantitative and qualitative research

E. Lesnic et al. Moldovan Medical Journal. October 2018; 61(3):15-23

RESEARCH STUDIES

methods [24, 26]. Statistical survey was performed using Microsoft Excel XP soft.

Results

According to the data obtained from the monitoring and follow-up of cases system during the period 2011-2018 it was established an important fluctuation of registered tuberculosis among Moldovan drug users. In 2011 were registered 56 cases, 2012 – 48 cases, 2013 – 71 cases, 2014 – 70 cases, 2015 – 43 cases, 2016 – 47 cases and in 2017 – 55 cases [2]. Distributing selected patients, according to the sex it was established the statistical predominance of men in all three groups, with the highest rate in the 2nd CG. So, men were 33 (97.1%) in the 2nd CG, 42 (87.5%) in the SG and 138 (74.6%) in the 1st CG. The male/female ratio was 7/1 in the SG, 2.9/1 in the 2nd CG and 33/1 in the 1st CG. Men predominated statistically in the 2nd CG compared with the SG and the 1st CG. Repartition of the patients into age groups, according to the WHO recommendation identified that the largest subgroup in the SG was 35-44 years, followed by the 25-34 years in the SG. In the 1st CG predominated the 35-44 years group, followed in the same proportion of those with 45-54 years and 25-34 years old. In the 2nd CG the majority of patients were between 25-34 years old and every third patient was between 35-44 years old. Comparing the groups was identified statistical predominance of the young group of 25-34 years old in the 2nd CG compared with the SG and the 1st CG, as well in the SG compared with the 1st CG. The middle adulthood group of 35-44 years old predominated in the SG compared with the 1st CG and the 2nd CG. Patients aged between 45-55 years old predominated in the 1st CG compared with the 2nd CG and the SG. Obtained data demonstrated that the age for acquiring tuberculosis is younger in addicted patients than in those without drug addiction. The patients with tuberculosis had urban residence in two thirds of the groups (SG and 1st CG). The majority of the 2nd CG had urban residence. The statistical predominance

Table 1

Distribution of patients by sex, age and demographic data

Indices	Sex Age Residence	Study group N=48 (P%)	1st control group N=185 (P%)	2nd control group N=34 (P %)
Sex	Men	42 (87.5) *	138 (74.59) ●●●	33 (97.1)
	Women	6 (12.5) *	47 (25.41)●●●	1 (2.9)
Age groups	18-24 years	0***	24 (12.97)	3 (8.8)
	25-34 years	20 (41.7) ** #	36 (19.46) ●●●	20 (58.8)
	35-44 years	27 (56.2)*** #	52 (28.11)	10 (29.4)
	45-55 years	1 (2.1) **	42 (22.73) ●●●	1 (2.9)
	>55 years	0***	31 (16.4) ●●●	0
Resi-dence	Urban	35 (72.9) #	139 (75.13) ●●●	31 (91.2)
	Rural	5 (10.2) **	46 (24.86)●●●	3 (8.8)
	Homeless	8 (16.7) #	29 (15.68) ●●●	0

Note: Applied statistical test: paired simple T-test, P – probability.

Statistically significant differences between: study group IVDU-TB compared to the 1st control group TB: * – p<0.05;** – p<0.01; *** – p<0.001; study group IVDU-TB compared to the 2nd control group TB: # p<0.05; ## – p<0.01; ### – p<0.001; the 1st control group TB compared to the 2nd control group: ● – p<0.05; ●● – p<0.01; ●●● – p<0.001;

of the urban residence was identified in the 2nd CG compared with the SG and the 1st CG. Homeless patients were in a similar proportion in both groups with tuberculosis (SG and the 1st CG) which statistically predominated compared with the 2nd CG (tab. 1). So, distributing patients according to the biological characteristics it was argued that young IVDU men, from urban areas had high probability to get tuberculosis.

Distributing patients according to the economic status, it was established that employed persons, who are contributing to the health budget by paying taxes, health insurance policy and social taxes predominated in the 2nd CG compared with the study group. As to health insurance and social security more frequently had them patients from the same group. Unemployed patients statistically predominated in the SG

Table 2

Distribution according to the socioeconomic data

Indices	Economic state	Study group N=48 (P%)	1st control group N=185 (P%)	2nd control group N=34 (P%)
Economicaly stable	Employed	2 (4.7) ##	25 (13.51) ●●	10 (29.4)
	Insured	8 (16.7) ***###	46 (24.8)	12 (35.3)
Economicaly vulnerable	Disease disabled	3 (6.3)	14 (7.57)	3 (11)
	Retired	0	15 (8.11)	1 (2.9)
	Students	0	7 (3.78)	0
	Unemployed	43 (89.6) ***###	124 (67.03)	20 (58.8)
	Lack of health insur-ance	40 (83.3) *** ###	139 (75.13*)	22 (64.7)

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

Statistically significant differences between: study group IVDU-TB compared to the 1st control group TB: * – p<0.05;** – p<0.01; *** – p<0.001; study group IVDU-TB compared to the 2nd control group TB: # p<0.05; ## – p<0.01; ### – p<0.001; the 1st control group TB compared to the 2nd control group: ● – p<0.05; ●● – p<0.01; ●●● – p<0.001;

compared with the 1st CG and the 2nd CG. The same rate was established regarding the patients who lacked the health and social insurance. Despite the predominance of the disabled patients, retired and students in the 1st SG compared with other groups, the statistical significance was not achieved. So, the socioeconomic vulnerability was identified in all selected patients, but its deepness was more evident in the IVDU patients with tuberculosis (tab. 2).

Assessing the educational level, it was established that most of the patients from the SG and the 1st CG graduated upper secondary level of the education. The rate of patients with upper secondary level statistically predominated in the SG and the 1st CG compared with the 2nd CG. Primary and low secondary education statically predominated in the 2nd CG compared with the SG and 1st CG. Secondary technical vocational education predominated in the 1st CG compared with the SG and the 2nd CG, but the statistical difference was not achieved. Bachelor studies predominated in the 2nd CG but the statistical difference was not achieved either. Exposed data are revealed in the table 3.

Hierarchy of risk groups, according to the widest rate of patients identified that the major social characteristics of patients from all three groups were the vulnerable economic state and living in poor conditions. Extreme poverty, expressed by homelessness was identified only in the study group and the 1st CG. History of migration during the last year statistically predominated in the 1st CG compared with the SG and the 2nd CG. History of imprisonment statistically predominated in the SG compared with the 1st CG. Close in-

Table 3

Distribution according to the last graduate level

Education	Study group	1st control group	2nd control group
	N=48 (P%)	N=185 (P%)	N=34 (P %)
Primary &low secondary education	10 (20.8) ###	46 (24.8)●●●	22 (64.7)
Upper secondary education	27 (56.2) ###	91 (49.2)●●●	1 (2.9)
Secondary technical vocational education	7 (14.6)	36 (19.5)	3 (8.8)
Bachelor studies	4 (8.3)	12 (6.5)	4 (11.7)

Note: Applied statistical test: paired simple T-test, P – probability; Statistically significant differences between: study group IVDU-TB compared to the 1st control group TB: * – p<0.05;** – p<0.01; *** – p<0.001; study group IVDU-TB compared to the 2nd control group TB: # p<0.05; ## – p<0.01; ### – p<0.001; the 1st control group TB compared to the 2nd control group: ● – p<0.05; ●● – p<0.01; ●●● – p<0.001;

fectious contact, established as being a member of a family TB clusters statistically predominated in the SG compared with the 1st CG. There were no available data for the 2nd CG.

The review of comorbidities in 3 substances users established a high prevalence of HIV infection, hepatitis C and sexual transmitted diseases in most of the researches [15, 16, 29].

Table 4

Distribution according to the risk groups

Category	Risks	Study group	1st control group	2nd control group
		N=48 (P%)	N=185 (P%)	N=34 (P %)
Socioeconomic	Poverty	29 (60.4)	106 (57.29) ●●●	14 (41.2)
	Homelessness	8 (16.7) ###	29 (15.68) ●●●	0
	Migration	2 (4.2)	24 (12.97) ●●●	0
	History of detention	16 (33.3) ***	2 (1.1)	7 (20.6)
Biological	Close contact	15 (31.2) ***	15 (8.11)	NA
	Associated diseases	48 (100) ***	50 (27.03) ●●●	31 (91.2)
	HIV-infection	21 (43.7) ***###	11 (5.94)	1 (2.9)
	Chronic alcoholism	3 (6.2) ***	13 (7.03) ●●●	12 (35.2)
	CRD	8 (16.7)	15 (8.2)	7 (20.6)
	GID	10 (20.8) ###	4 (2.1) ●●●	28 (82.3)
	Viral hepatitis	2 (4.6) #	2 (1.1) ●●●	8 (23.5)
	Mental disorders (excluding IVDU)	1 (2.1) ###	4 (2.16)	31 (91.2)
	Neoplasm	1 (2.1)	1 (0.5)	0
	Renal diseases			4 (11.7)
	Others	2 (4.6)		

Note: Applied statistical test: paired simple T-test, P – probability; NA-non available, CRD-chronic respiratory diseases, GID-gastrointestinal diseases.
Statistically significant differences between: study group IVDU-TB compared to the 1st control group TB: * – p<0.05; ** – p<0.01; *** – p<0.001; study group IVDU-TB compared to the 2nd control group TB: # p<0.05; ## – p<0.01; ### – p<0.001; the 1st control group TB compared to the 2nd control group: ● – p<0.05; ●● – p<0.01; ●●● – p<0.001;

E. Lesnic et al. Moldovan Medical Journal. October 2018; 61(3):15-23

RESEARCH STUDIES

Comorbid patients statistically predominated in the SG and the 2nd group compared with the 1st CG. Among associated diseases, HIV infection was established in every second patient of the SG, which statistically predominated compared with the 1st CG and the 2nd CG. Chronic alcoholism statistically predominated in the 2nd CG compared with the SG and the 1st CG. Chronic respiratory diseases predominated in the SG and the 2nd CG. Gastro-intestinal disorders predominated in the 2nd CG compared with SG and the 2nd CG. Viral hepatitis predominated in the 2nd CG compared with SG and the 1st CG. Mental disorders predominated in the 2nd CG compared with the SG and the 1st CG. In this subgroup were not included illnesses due to the drug addiction. No other statistical differences were established among groups regarding the associated diseases. Data were revealed in the table 4.

Studying case-management it was identified that general medical staff in terms of the general practitioners, was involved in the detection of one half of the 1st CG and one third of the SG. The rate of high risk groups investigated through active screening was low in both groups, but the value was lower in the SG. Despite that drug users are a high risk group target by the screening procedures their proportion detected by active screening was lower compared with the general population. Detected by the specialists as symptomatic cases were in a higher proportion in the SG compared with the control group, but the statistical difference was not achieved. Direct addressing to the specialized services for diagnosis and treatment of tuberculosis was higher in the SG and demonstrated multiple barriers for accessing the healthcare at the primary level. Other ways of detection predominated in the control group and were used for diagnosis of patients hospitalized in somatic clinical hospitals. Obtained data established a lower accessibility of the health care services by the IVDU, due to their social vulnerabi-

lity. The accessing of the tuberculosis specialized institutions was obtained by independent addressing avoiding the primary health care staff in a large proportion of cases. Information is exposed in the table 5.

Distributing patients according to the registered case type was identified that every second patient was a "new case" – 23 (47.9%) and every fourth was "relapse" – 12 (25%). In a similar rate were patients included in the treatment after a previous loss to follow-up and after a treatment failure – 6 (12.5%) patients for each category type. Diagnosed and transferred from abroad was 1 (2.1%) patient. Following the diagnosis only 46 (95.8%) patients started the treatment. One patient died and diagnosis was established after his death and one patient was transferred for treatment abroad (2.1% for each category type). The standard treatment for new drug-susceptible tuberculosis in the RM is used since 2000 and lasts 6 months, according to the WHO recommendation [22, 42]. It consists in a two phases regimen with four first-line drugs: isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) in the intensive phase and two first-line drugs: isoniazid and rifampicin in the continuation phase. For previously treated cases was used a two phase regimen which lasts 8 months: 3 months with H, R, E, Z and streptomycin and 5 months with H, R and E. Patients with rifampicin-resistant or MDR-TB were treated with second-line drugs for 18 months or more divided in two phases The regimen composition during the intensive phase lasts 6 months and included kanamycin (Km) or capreomycin (Cm), levofloxacin (Lfx), para-amino salicylic acid (PAS), ethionamide (Eto), cycloserine (Cs) and pyrazinamide (Z) and for continuation phases during 12-18 months of Lfx, PAS, Etho, Cs and Z.

Identifying the clinical radiological forms of pulmonary tuberculosis it was established that infiltrative opacities were identified in a similar proportion in both groups. Destructive forms of pulmonary tuberculosis were identified in a similar proportion in both groups, however the severest destructive form defined fibro-cavernous tuberculosis was diagnosed only in the study group. Appreciating clinical radiological forms it was established that the majority of cases had pulmonary infiltrative tuberculosis, however statistical predominance was identified in the control group. Other radiological forms: disseminated tuberculosis and fibro-cavernous tuberculosis prevailed in the study group, but the statistical difference was obtained only for the fibro-cavernous tuberculosis. Distributing patients according to the number of the affected lungs, it was established that both lungs were involved in the majority of both groups, but the predominantly in the study group. No differences were established regarding the rate of patients with parenchimal destruction in one or both lungs. Extensive forms, affecting 3 and more segments were diagnosed in a similar proportion in both groups (tab. 6).

When assessing the laboratory features of the enrolled pulmonary tuberculosis cases, it was identified that one half of patients were microscopic positive for acid-fast-bacilli in both groups. A similar proportion was identified to have

Table 5

Case-management characteristics of tuberculosis patients

Health level	Detection ways	Study group N=48 (P%)	1st control group N=185 (P%)
PHC	Detected by GPs-symptomatic	16 (33.3) ***	103 (55.67)
	Detected by GPs-screening of HRG	5 (10.4)	28 (15.13)
Ambulatory specialized level	Detected by SP-symptomatics	13 (27.1)	34 (18.38)
	Detected by SP-screening of HRG	4 (8.3)	7 (3.78)
Hospital level	Direct addressing	10 (20.8) **	10 (5.41)
Others	Other ways	0	3 (1.62)

Note: Applied statistical test: paired simple T-test, P – probability; GP-general practitioner, SP-specialist, HRG-high risk group. Statistically significant differences between: study group IVDU-TB compared to the 1st control group TB: * – p<0.05;** – p<0.01; *** – p<0.001.

RESEARCH STUDIES

E. Lesnic et al. Moldovan Medical Journal. October 2018; 61(3):15-23

Table 6

Clinical forms and radiological features of tuberculosis patients

Index	Radiological features	Study group N=48 (P%)	1st control group N=185 (P%)
Clinical forms of pulmonary TB	PIT	30 (62.5) ***	170 (91.89)
	PDT	7 (14.6)	15 (8.11)
	FCVT	7 (14.6) ***	0
Extrapulmonary TB	Bone and joints TB	3 (6.25)	NA
	Pleurisy	1 (2.1)	NA
Localization	One lung	9 (18.7) ***	80 (43.24)
	Both lungs	39 (81.2) ***	105 (56.75)
Extensiveness	Limited	20 (41.7)	79 (42.7)
	Extensive	28 (58.3)	106 (57.3)
Radiological features	Infiltration	20 (41.7)	79 (42.71)
	1 lung destruction	18 (37.5)	80 (43.24)
	2 lungs destruction	10 (20.8)	26 (14.05)

Note: Applied statistical test: paired simple T-test, P – probability; PIT-pulmonary infiltrative tuberculosis, PDT-pulmonary disseminated tuberculosis, FCVT-fibro-cavernous tuberculosis. NA-non-available; Statistically significant differences between: study group IVDU-TB compared to the 1st control group TB: * – p<0.05;** – p<0.01; *** – p<0.001.

Table 7

Microbiological features of tuberculosis patients

Microbiological characteristics N=48 (P%)		Study group N=185 (P%)	1st control group
Mo	Microscopic positive	20 (41.7)	101 (54.5)
	Culture positive	24 (50)	99 (53.51)
	GeneXpert performed	25 (52.1)	185 (100)
	GeneXpert MTB/Rif positive	13 (27.1)	185 (100)
	GeneXpert MTB/Rif positive susceptible	4 (8.3)	147 (79.46)
	GeneXpert MTB/Rif positive rezistent	9 (18.7)	38 (20.54)
M0, M2/3	Poliresistance by DST	1 (2.1)	14 (7.56)
	MDR-TB by DST	8 (16.7)	36 (19.46)
	Susceptible by DST	40 (83.3)	135 (72.97)
Other forms	XDR-TB	1 (2.1)	0

Note: N/A- non available; DST-Drug susceptibility testing, M0 beginning of the treatment, M2/3 the end of the intensive phase of the treatment; MDR-multidrug resistant tuberculosis, XDR-TB extensively drug-resistant tuberculosis; Statistical assessment was not performed due to including criteria in the control group.

positive bacteriological results (culture on solid Lowenstein-Jensen or liquid MGIT BACTEC). The molecular genetic assay was performed in one half of the study group and in the entire control group. The differences between groups were determined by the period of the selection. The molecular genetic test was implemented in 2014 in the RM. The sensibility to the rifampicin through GeneXpert MTB/Rif assay was established positive in two thirds of the control group. Drug sensitivity testing identified mono- and poliresistance in both groups in a similar proportion. In a similar proportion were identified patients resistant to rifampicin through GeneXpert MTB/Rif assay or conventional drug sensitivity test. The drug resistance was established in a similar proportion using the drug sensitivity testing and GeneXpert MTB/Rif assay in both groups. Every fifth patient from both groups had MDR-TB. Established data were exposed in the table 7.

All selected patients were treated according to the National Clinical Protocol "Tuberculosis in adults". The standard treatment for drug susceptible tuberculosis was used for treatment of a similar proportion of both groups: 35 (72.9%) and 149 (80.54%) patients respectively. Every fifth patient from the study group was treated as previously treated cases – 9 (18.7%) patients. Even the rate of MDR-TB was in average similar in both groups, only a minor proportion of patients from the SG started the treatment for drug resistant tuberculosis – 4 (8.33%) in the SG compared with 36 (19.46%) in the CG. It is important to emphasize that the standard treatment for MDR-TB could be started only if the therapeutic compliance of the patient is established and the clinical tolerance is acceptable. Assessing treatment outcome, it was established a high statistical difference in the treatment success, which predominated in the control group 158 (85.4%) compared with 21 (43.7%) in the study group. The rate of patients lost to follow-up statistically predominated in the study group 10 (20.8%) compared with 2 (1.08%) in the control group. The rate of died patients predominated in the study group 8 (16.7%) compared with 11 (5.95%) in the control group, but the statistical difference was not achieve (tab. 8).

Table 8

Treatment outcome of tuberculosis patients

Index	Radiological features	Study group N=48 (P%)	1st control group N=185 (P%)
Available final outcomes	Treatment success	21 (43.7) ***	158 (85.4)
	Treatment failure	1 (2.1)	2 (1.08)
	Loss to follow-up	10 (20.8) ***	2 (1.08)
	Death	8 (16.7)	11 (5.95)
Non available final outcomes	Still continuing	8 (16.7)	12 (6.48)

Note: Applied statistical test: paired simple T-test, P – probability.

Statistically significant differences between: study group IVDU-TB compared to the 1st control group TB: * – p<0.05;** – p<0.01; *** – p<0.001.

All the patients of the 2nd CG were managed and treated with the standard treatment of the drug addiction according to the National Clinical Protocol [21]. Most of them – 26 (76.4%) were hospitalised and treated being supported by the national insurance company and 8 (23.5%) – supported by private costs. The methadone was used to treat the

E. Lesnic et al. Moldovan Medical Journal. October 2018; 61(3):15-23

RESEARCH STUDIES

Table 9

Risk factors for tuberculosis among IVDU patients

Factors		Statistical indices			
		RR	OR	Pearson's	AR(%)
Age	35-44 years	1,56 (1,08-2,26)	3,08 (1,21-7,84)	0,01	48
Social economical features	Unemployment	2,59 (1,2-5,6)	6,02 (1,91-19,07)	0,0011	34
	Lack of insurance	0,0015	3,22 (1,15-9,02)	0,001	54
	Homelessness	1,6 (1,18-2,21)	5,67 (0,74-43,3)	0,05	100
	HIV infection	2,1 (1,58-2,84)	27,10 (3,24-203,31)	4,0E-5	93

Note: RR-relative risk, OR-odds ratio; AR-attributable risk.

Table 10

Risk factors for death due to the tuberculosis progression

Factors		Statistical indices			
		RR	OR	Pearson's	AR(%)
Radiological characteristics	Destructive forms of TB	1,57 (1,13-2,02)	5,63 (1,6-48,12)	0,05	100
	Both lungs involvement	2,67 (1,36-5,26)	3,32(1,51-7,21)	0,001	30
Treatment outcome	Loss to follow-up	4,84 (3,3-7,2)	24,08 (5,01-114,3)	0	95

Note: RR-relative risk, OR-odds ratio, AR-attributable risk, N/A-non available.

withdrawal syndrome 8 (23.5%) patients. Each third patient was treated with the standard regimen associated with other drugs due to disease complications. So, in 9 (26.5%) were associated neuroleptic drugs, in 8 (23.5%) antidepressant drugs and 7 (20.6%) antibiotics. Antibiotics were used for prevention of nosocomial infections due to subclavian venous catheter placement. The average duration of the treatment during the hospitalisation was 21 days. Most of the IVDU 31 (91.2%) patients were therapeutically compliant and 3 (8.8%) were lost to follow-up. The withdrawal syndrome was successfully treated in 31 (91.2%) patients. No deaths were registered. The working capacity and performances were restored in 29 (85.3%) cases and diminished in 5 (14.7%) patients. The drug use consequences were identified in 28 (82.3%) patients. It is important to emphasize that in one patient could be several consequences and sequellae. So, the diminished mnestic capacities were identified in 28 (82.3%), lack of peripheral venous access – in 20 (8.4%) and postinjectional signs – in 18 (52.9%) cases.

An important research outcome represents the relative risk (RR), odds ratio (OR) and the attributable risk (AR) indices for identifying the priority interventions in the frame of high risk groups [24,16]. In the table 8 were represented only risk factors and features which predominated and exposed statistical difference between the study group and the 2nd CG. It was established that major risk factors for tuberculosis in drug addicted were: unemployment and associated lack of health insurance, patient's homeless state and the immune suppressive condition – HIV infection and middle risk factors was the middle adulthood. Attributable risk established the hierarchy of risks: homelessness, HIV infection, lack of health insurance, middle adulthood and unemployment (tab. 9).

The next table reflects the assessment of the disease-related features which statistically predominated in the group of IVDU with tuberculosis compared with patients with tuberculosis without drug addiction. It was established that major disease-related characteristic in IVDU patients is the severe destructive forms of tuberculosis. The major treatment outcome was the "loss to follow-up". Both lung involvements were assessed as a disease-related characteristic with middle degree impact (tab. 10).

Conclusions

Men were predisposed for drug addiction; however, women frequently developed tuberculosis.

The age for acquiring tuberculosis is younger in addicted patients than in those without drug addiction.

Socioeconomic vulnerability is extended in the groups of patients with tuberculosis, with or without addiction, however the poverty deepness was more important in addicted patients.

Low level of education predominated in drug addicts.

Close contact with a sick patient predominated in addicted patients with tuberculosis, but nobody assessed the infectious contact in addicted patients without tuberculosis.

Associated diseases predominated in addicts with or without tuberculosis, more expressed were: HIV infected individuals, viral hepatitis and neurological disorders.

Risk factors for tuberculosis in drug addicted were: unemployment and associated lack of health insurance, patient's homeless state, middle adulthood and the immune suppressive condition – HIV infection.

Major disease-related characteristic in IVDU patients was the presence of severe destructive forms of tuberculosis and "loss to follow-up" as a final outcome.

RESEARCH STUDIES

E. Lesnic et al. Moldovan Medical Journal. October 2018; 61(3):15-23

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