THE DYNAMICS OF LETHALITY BY THE PROGRESSION OF THE PULMONARY TUBERCULOSIS PROCESS OF THE NEW CASES PATIENTS

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Introduction. *Mortality among tuberculosis patients, both nationally and globally, has decreased significantly in the last 10 years, but the current epidemiological situation in tuberculosis allows to predict a new rise in the endemic state of the disease due to the increase of TB/HIV coinfection and the resistant tuberculosis.* **Material and methods.** *The patient's reports were analyzed – new cases, deaths due to the progression of tuberculosis registered in the Municipal Clinical Hospital of Phthisiopneumology, Chisinau, in 2 periods: the 1st period – 2001-2003 and the 2nd period – 2018-2020. During both periods, 64 new cases died in the hospital due to the progression of tuberculosis. Statistical data processing was performed with the application of the Student (t) test, the data were considered statistically true when p<0.05.* **Results.** *In the first period, the age between 25-54 years (81.3%) predominated, in the second period between 45-65+ (73.5%) years of the deceased patients. In both periods, a high share of unemployed patients was found. In the 2nd period compared to the 1st period a severe form of disseminated tuberculosis was established – generalized tuberculosis that was not registered in the first period, the number of deaths with TB/HIV increased 6 times, 4.5 times – with stomach resection in anamnesis, 2 times – with diabetes, 1.5 times with chronic alcoholism. Primary multidrug-resistant tuberculosis was confirmed at 21.9%, extensively resistant tuberculosis – at 4.7% of deceased patients.* **Conclusions.** *In the second period, the majotiry of the patients new cases due to the progression of tuberculosis died of severe forms of tuberculosis – generalized, increased number of comorbidities (mainly HIV infection), the presence of a large number of cases with primary resistant tuberculosis.*

Cuvinte cheie: letalitate, mortalitate, tuberculoză, cazuri noi, comorbidități, factori de risc.

DINAMICA LETALITĂȚII CAZURILOR NOI PRIN PROGRESAREA PROCESULUI DE TUBERCULOZĂ PULMONARĂ

Introducere. *Mortalitatea în rândul bolnavilor de tuberculoză, atât în țară, cît și la nivel global a scăzut semnificativ în ultimii 10 ani, însă situația epidemiologică actuală în tuberculoză permite prognozarea unei noi ascensiuni a endemiei bolii, din cauza extinderii cazurilor de coinfecție TB/HIV și a creșterii ponderii tuberculozei, determinate de rezistența germenilor la tratament.* **Material și metode.** *Au fost analizate fișele de observație a pacienților – cazuri noi, decedați din cauza progresării tuberculozei, înregistrate în Spitalul Clinic Municipal de Ftiziopneumologie din Chișinău, în 2 perioade: prima perioadă relevă anii 2001-2003 și a II-a -2018-2020. În ambele perioade, în staționar, au decedat cîte 64 de pacienți, dintre cazurile noi cauzate de progresarea tuberculozei. Prelucrarea statistică a datelor a fost efectuată cu aplicarea testului Student (t), datele fiind considerate statistic veridice pentru un p<0.05.* **Rezultate.** *În eșantionul de pacienți decedați, în prima perioadă a predominat vârsta cuprinsă între 25-54 ani (81,3%), iar în a II-a perioadă – 45-65+ (73,5%) ani. În ambele decade s-a constatat o pondere înaltă a pacienților neangajați în câmpul muncii. În perioada a II-a, comparativ cu perioada I, s-a stabilit o formă gravă a tuberculozei diseminate – tuberculoza generalizată, care nu a fost înregistrată în prima perioadă, a crescut de 6 ori numărul deceselor cu TB/HIV, de 4,5 ori – cu rezecția gastrică în anamneză, de 2 ori – cu diabet zaharat și de 1,5 ori – cu alcoolism cronic. Tuberculoza primară multidrogrezistentă a fost confirmată la 21,9 % dintre cazuri, tuberculoza rezistentă extinsă – la 4,7% dintre bolnavii decedați.* **Concluzii.** *În perioada a II-a au decedat mai mulți bolnavi, dintre cazurile noi cauzate de progresarea tuberculozei, ca formă gravă– generalizată, majorarea numărului de comorbidități (preponderent HIV infecția), prezența unui număr mare cazuri cu tuberculoză rezistentă primară.*

INTRODUCTION

Tuberculosis (TB) represents one of the priority public health problems, and its prevention and control are strategic objectives of national interest. Mortality due to tuberculosis is one of the main indicators used to assess the epidemiological situation and determine the "burden of tuberculosis". Tuberculosis is the 2nd leading infectious disease killer after COVID-19. According to the UN Sustainable Development Goals and the "The End TB" strategy, by 2035 the incidence is forecast to be reduced by 90% and mortality by 95%, but progress in achieving these goals is becoming slow (1, 2). The COVID-19 pandemic has significantly affected the successes achieved in the fight against this disease throughout the world, for the first time in the last 10 years the tuberculosis mortality rate has increased (3, 4, 5). According to WHO data, TB and HIV-infection are the main causes of population mortality in the world. Globally in 2019, 208,000 TB/HIV died out of 1.4 billion TB deaths, and in 2020 – 214,000 died and contributed to the increase in mortality to 1.5 billion (1).

The occurrence of new cases of tuberculosis are more frequently influenced by the following risk factors: malnutrition, HIV-infection, disorders dependent on alcohol consumption, smoking, diabetes, etc. Social factors such as worsening socio-economic conditions (no place to live, lack of employment, criminal history, drug addiction and alcoholism, migration processes) contribute to late access to medical services and this fact results in the development of extensive, serious processes of fatal tuberculosis. The majority of patients are hospitalized in somatic inpatient units, where they are diagnosed and transferred to specialized hospitals (6, 7).

At the global level in the years 2000-2017, a positive trend in the decrease in the incidence and mortality from tuberculosis is attested. Tuberculosis mortality fell by about 42%. From all WHO regions in the years 2013-2017 in the European Region the decrease in mortality was 11%. However, against the backdrop of the decrease in tuberculosis mortality, there is a radical change in the aspect of the share of tuberculosis patients associated with HIV infection (8). In 2001, the DOTS strategy was introduced in the Republic of Moldova, when tuberculosis mortality was 20.1 deaths per 100,000 inhabitants. The high morta

lity rate remained until 2013, after which it slowly decreased to 5.1 deaths per 100,000 inhabitants in 2020 (9, 10).

According to international sources, the current epidemiological situation in tuberculosis allows forecasting a new rise in the tuberculosis endemic due to the expansion of HIV co-infection cases and the increase in the share of resistant tuberculosis, which contributes to a high mortality of patients with this disease (11).

Unlike other characteristics, lethality is a precise indicator for assessing the effectiveness of medical-curative actions. Lethality is used to assess the dynamics of the process, its changes over time, sex, age groups.

Aim of study: Studying the dynamics of the lethality of new cases through the progression of pulmonary tuberculosis in 2 periods of organization of the tuberculosis service in the municipality of Chisinau.

Study objectives: We set out to address the particularities of age, sex, social status, comorbidities, forms of tuberculosis, the development of mycobacterial resistance to antituberculosis drugs at the current stage of patients who died in the hospital. These data will allow us to highlight the risk factors that will be used to form groups of people at risk to develop advanced forms of tuberculosis, which can evolve into death.

MATERIAL AND METHODS

Patient observation sheets were analyzed – new cases, deceased due to the evolution of tuberculosis registered in the Municipal Clinical Hospital of Pneumology, Chisinau, in 2 periods: 1st period 2001-2003 (the period of introduction of the DOTS strategy) and 2nd period 2018-2020 (the period of the "The End TB" strategy). In both periods, 64 new cases died in the hospital due to the evolution of tuberculosis. The anamnestic, clinical data, paraclinical results of patients who died of tuberculosis were studied. The statistical processing of the results was carried out in a computerized way.

The data analysis was carried out using the Microsoft Office 2003 Excel component and the Epi Info 7.1 program with the help of the functions and modules of these programs. To estimate

significant differences, the Student test was used (differences are significant in the case of p-values <0.05; P – characteristic rate, SE – standard error) in 2 periods: 1st period 2001-2003 (the period of introduction of the DOTS strategy) and 2nd period 2018-2020 (the period of "The End TB" strategy).

RESULTS

The distribution of deceased patients by gender in both periods was similar: men – 51 (79.7%), and women 13 (20.3%); M/W ratio = 3.9/1.

Distribution of deceased patients according to age (tab. 1): up to 25 years in both periods the cases of death were similar (no statistical difference for p=0.3). In the 1st period, statistically significantly, young people between 25-44 (52.9%) years predominated (p<0.05). In the 2nd period, the level of lethality was higher in people aged between 55-64 years (p<0.05).

Table 1. Distribution of deceased patients according to age.

Age	1st period (64)		2nd period (64)		p<0.05
	N	(P±SE%)	N	(P±SE%)	
<25	1	1.6±1.6	3	4.7±2.6	0.3
25-34	15	23.4±5.2	7	10.9±3.9	0.05
35-44	17	26.6±5.5	7	10.9±3.9	0.02
45-54	20	31.3±5.8	21	32.8±5.9	0.85
55-64	7	10.9±3.9	17	26.6±5.5	0.02
65+	4	6.3±3.0	9	14.1±4.3	0.14

Table 2. Social status of deceased patients.

Social status	1st period (64)		2nd period (64)		p<0.05
	N	(P±SE%)	N	(P±SE%)	
Employed	3	4.7±2.6	11	17.2±4.7	0.02
Unemployed	53	82.8±4.7	36	56.2±6.2	0.0008
Disabled	3	4.7±2.6	3	6.3±3.0	0.69
Retirees	5	7.8±3.4	14	21.9±5.2	0.02

Most of the patients who died (tab. 2) in both periods were unemployed. In the 2nd period period compared to the 1st period, the number of employees and people of retirement age increased (p<0.05), and the number of people with special needs remained unchanged.

In the 1st period, 11 (17.2%) patients died without living conditions, and in the 2nd period – 15 (23.4%); in the 1st period – 12 (18.7%) and in the 2nd period – 11 (17.2%) were in prison.

36 people (56.2%) had contact with tuberculosis patients both inside and outside their homes in the 1st period: family – 8 (12.5%), relatives – 3 (4.7%), with friends – 12 (18.7%), at work – 1 (1.6%), in prison – 12 (18.7%). During the 2nd, 35 people (54.7%) had contact: family – 10 (15.6%), relatives – 2 (3.1%), with friends – 10 (15.6%), at work – 2 (3.1%), in prison – 11 (17.1%).

The majority (89.8%) of the deceased patients were transferred from municipal somatic hospitals, and 5.1% were hospitalized through emergency medical assistance and on the recommendation of the phthisiopneumologist.

The number of patients who died from infiltrative tuberculosis decreased significantly in the 2nd period compared to the 1st period (p<0.05) (tab. 3). Generalized tuberculosis was registered in approximately half of the patients who died in the 2nd period, and in the 1st period there was no case. Fibro-cavitary tuberculosis had a non-significant decreasing trend in the 2nd period (p>0.05).

Analyzing the interval at which death occurred compared to the time of hospitalization, it was found that 4.7% of patients died in the first 24 hours; 2-10 days – 42.2%; 11-20 days – 21.9%; 21-30 days – 10.9% of cases. Thus, it can be seen that 79.7% died in the first month.

Table 3. Distribution of deceased patients according to forms of tuberculosis.

TB form	1st period (64)		2nd period (64)		p<0.05
	N	(P±SE%)	N	(P±SE%)	
Infiltrative	12	18.7±4.9	3	4.7±2.6	0.01
Caseous pneumonia	33	51.6±6.2	22	34.3±5.9	0.04
Disseminated	11	17.1±4.7	5	7.8±3.3	0.1
Generalized	-	-	30	46.9±6.2	-
Fibro-cavitary	8	12.5±4.1	4	6.3±3.0	0.22

Table 4. Comorbidities of deceased patients.

Comorbidities	1st period (64)		2nd period (64)		p<0.05
	N	(P±SE%)	N	(P±SE%)	
Chronic alcoholism	19	29.7±5.7	27	42.2±6.2	0.13
HIV infection	2	3.1±2.1	12	18.8±4.9	0.004
Hepatitis and liver cirrhosis	9	14.1±4.3	8	12.5±4.1	0.79
Stomach resection	2	3.1±2.1	9	14.0±4.3	0.02
Diabetes Mellitus	3	4.6±2.6	5	7.8±3.6	0.46
Other pathologies	9	14.1±4.3	3	4.7±2.6	0.067
No pathologies	20	31±2.3	-	-	0.006

The patients who died as a result of the progression of tuberculosis also had other pathologies (tab. 4). The number of deceased with chronic alcoholism in the 2nd period compared to the 1st period increased by 1.5 times, diabetes by 2 times, statistically insignificant (p>0.05), HIV infection increased the probability of death by 6 times, gastric resection in the antecedents of 4.5 times (the data were statistically significant for p<0.05); hepatitis and cirrhosis remained at the same level in both periods. All patients of the 2nd period had concurrent pathologies.

In the 1st period, sputum microscopy for acid-alcohol-resistant bacilli (AARB) was positive in 46 (71.1%), and in the 2nd period – in 29 (45.4%) deceased patients. In the 2nd period, the results of molecular-genetic analyzes and by sputum culture were negative – in 8 (12.5%), positive sensitive – in 27 (42.2%), positive multidrug-resistant (MDR) – in 17 (21.9 %) and extensively drug-resistant (XDR) – in 3 (4.7%), and 12 (18.7%) patients were not evaluated due to their serious condition at hospitalization.

DISCUSSIONS

The comparative study in different time periods of new cases and people who died due to the progression of the tuberculous process in hospital conditions highlighted some clinical and para-clinical peculiarities that occurred during the 20-year interval. The results of the research demonstrated a decrease in the mortality of new cases due to the progression of the tuberculous process in the 2nd period compared to the 1st period, but the number of in-hospital deaths in the 2nd period increased significantly. In the current conditions, concomitant diseases play an important role in the increase in tuberculosis mortality. Low-income countries with high disease prevalence, TB/HIV co-infection and drug-resistant TB will face great difficulties in achieving the mortality indicators proposed by "The End TB" strategy. TB/HIV co-infection is one of the main causes of lethality through the development of severe forms of tuberculosis. Alcohol abuse and chronic alcoholism is another cause, which contributes to the late detection of tuberculosis patients with severe and extensive forms (caseous pneumonia, fibrocavitary tuberculosis), to the development of multidrug resistance of mycobacteria to antituberculosis medication with the progression of lesions and unfavorable outcome. Diabetes mellitus is another concomitant disease, which, through its complications, causes difficulties in antituberculosis therapy and in the successful completion of treatment (1, 3, 8).

All patients in the 2nd period had associated di-

seases (the number of deaths with TB/HIV increased 6 times, 4.5 times – with previous gastric resection, 2 times – with diabetes, 1.5 times with chronic alcoholism. The unfavorable social status in both groups (unemployed, without suitable living conditions) contributes to late treatment and progression of the tuberculosis process. The Republic of Moldova is among the 30 countries in the world with a high burden of multidrug-resistant tuberculosis. Primary multidrug-resistant tuberculosis (MDR) was confirmed in 21.9%, extensively resistant tuberculosis (XDR) – in 4.7% of deceased patients. Tuberculosis pa-tients, who died in the hospital, presented unfavorable living conditions and were also confirmed with concomitant diseases, such as be HIV infection, chronic alcoholism and diabetes, which corresponds to the data of other authors.

In both periods, about ½ of the patients had contact with tuberculosis patients, the number of people previously in detention remaining constant, and in the 2nd period the number of people without adequate living conditions increased insignificantly. Patients who died in the 2nd period compared to the 1st period had an older age.

CONCLUSIONS

1. In the 2nd period, compared to the 1st period, there were more cases of death due to the progression of tuberculosis in advanced, generalized forms, with the presence of comorbidities (HIV infection, diabetes, chronic alcoholism, gastrointestinal tract pathology).

2. Sputum microscopy for AARB was established in over half of deceased patients from both periods. In the 2nd period, primary multidrug resistance to antituberculosis treatment was found in a ¼ of the death cases.

3. In both periods, the deceased patients had an unfavorable social status (unemployed, without appropriate living conditions or with criminal record).

CONFLICT OF INTERESTS

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ETHICAL APPROVAL

The article does not have ethical approval.

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