ORIGINAL ARTICLE

DIAGNOSTIC CHEMORESISTANT MYCOBACTERIUM TUBERCULOSIS IN THE TERNOPIL REGION OF UKRAINE

DOI: 10.36740/WLek202005122

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ABSTRACT

The aim: To analyze the changes in indicators of tuberculosis mycobacteria sensitivity to anti-mycobacterial drugs over the past nine years in Ternopol region (Ukraine) and to develop recommendations for the use of drug combinations in this region.

Materials and methods: The medical examinations were carried out in the Clinical and Diagnostic Laboratory of Ternopil Regional Tuberculosis Hospital during 2007-2017. Sensitivity analysis was carried out on a solid Löwenstein-Jensen medium and in liquid Meedlebrook medium using automatic bacteriological BACTEC 1443 tests with addition to the media of first line anti-TB drugs.

Results: The sensitivity of Mycobacterium tuberculosis to anti-TB drugs has decreased in 2017 comparing to 2007, both among new cases and relapses of the disease.During this period in newly diagnosed patients the number of M. tuberculosis sensitive to first-line anti-TB drugs has decreased by 6.1%.

Conclusions: Considering the increase in multi-resistant pathogens in newly diagnosed and relapsed of tuberculosis cases, it is necessary to use a modern express methods of diagnostics for the causative agents of tuberculosis and to study their sensitivity to antimycobacterial drugs, especially by using molecular genetics methods.

KEY WORDS: tuberculosis, Mycobacterium tuberculosis, chemoresistant anti-tuberculosis drugs

Wiad Lek. 2020;73(5):959-962

INTRODUCTION

The spread of pulmonary tuberculosis in Ukraine and other countries of the world remains a pressing concern. Spread of tuberculosis shows worrying trends, including more than 1.5 times increase in the frequency of tuberculosis cases during in the last decade of the past century.

The tuberculosis situation in Ukraine presents a complicated issue. It is not only a medical but also a social problem, reflecting the socio-economic conditions in the country, its educational and cultural level and the prosperity of is population, and finally the level of health care, including TB diagnostics and treatment services.

The main medical reasons for the deterioration of the tuberculosis epidemiological situation are: late detection of TB patients with widespread destructive process and massive bacterial excretion; and that until 2000 there was poor access to anti-mycobacterials drugs for treatment, prevention and anti-recidivism. Additionally, there are a number of fundamental problems affecting the situation with TB in the country: the decreased efficiency of treatment of TB patients; the problems of drug-resistant tuberculosis and extra-pulmonary tuberculosis; the problems of screening and microbiological diagnostics; tuberculosis incidence among health care workers, HIV-infected and AIDS patients, and in penitentiary system; the depreciation of clinical resources and decrease in the number human resources working in TB services[1, 2].

The increase in number of clinical cases with primary and secondary resistance to anti-tuberculosis drugs significantly complicates effective treatment of the disease. This is why tuberculosis is a leading reason of mortality in working age population [3, 4].

If resistant strains of M. tuberculosis are found in the patient, this decreases the clinical and bacteriological efficiency of tuberculosis treatment, significantly increases period of hospital stay and significantly increases financial cost of the treatment. Among drug-resistant strains now up to 60% poly-resistant, a significant increase. These strains are resistant to any two or more dugs of first line. Multi-resistance (multiple drug resistance) is a type of poly-resistance, meaning the resistance to isoniazid and rifampicin in the absence or presence the resistance to other anti-TB drugs [5].

According to the WHO, if left untreated, about 50% of such patients die within 5 years, 25% of them recover, and in 25% of the patients the process becomes chronic, therefore, they become a source of infection to others [5, 6].

Incidence of resistance to anti-TB drugs in Ukraine is very high and growing. According to the results of the WHO national DRS survey, 1 in 4 new TB cases is multidrug resistant. Moreover, up to 6% of all new cases are extensively drug resistant.

In 2014 for the first time Ukraine ranked among the top 5 countries with the highest MDR-TB burden in the world. The TB epidemic in Ukraine is characterized by widespread MDR- and extensively drug resistant TB, relatively high mortality rate as a result of untreated or inappropriately treated TB, and increasing TB/HIV co-infection rates [3].

Ukraine is currently implementing the fifth year of its 5-year national TB programme 2012–2016. 2016 will be a transition year to the new 2017–2021 programme. Implementation of TB response in Ukraine has been made possible in large part due to the funding from the Global Fund.

THE AIM

The aim of this study was to analyze the changes in indicators of tuberculosis mycobacteria sensitivity to anti-mycobacterial drugs over the past nine years in Ternopol region (Ukraine) and to develop recommendations for the use of drug combinations in this region.

MATERIALS AND METHODS

This study was approved by the ethics committee of the I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. All procedures were carried out in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

The medical examinations were carried out in the Clinical and Diagnostic Laboratory of Ternopil Regional Tuberculosis Hospital during 2007-2017.

Sensitivity analysis was carried out on a solid Löwenstein-Jensen medium and in liquid Meedlebrook medium using automatic bacteriological BACTEC 1443 tests with addition to the media of first line anti-TB drugs.

Inoculum 1.0 MacFarland and 0.5 MacFarland were prepared respectively for the tests on solid and in liquid media. Bacterial suspension was inoculated onto these media with either added anti-TB drugs or in control tubes without the drugs.

Absence of mycobacteria growth or low growth (up to 1% compared to the control growth) on media with the drugs confirmed sensitivity of this strain to the corresponding anti-mycobacterial drug.

In 2015, the Hospital implemented molecular genetics testing using GeneXpert MTB/RIF.Mycobacterium tuberculosis was detected in 3787 patients, including 2466 (65.1%) of patients with the first-time diagnosed pulmonary TB, 615 (16.2%) of the patients with relapses of pulmonary tuberculosis and 706 (18.7%) of the patients with another cases of repeated pulmonary tuberculosis. This patients were examined concerning their anti-TB drugs susceptibility. The obtained data were worked out statistically using licensed program „Microsoft Excel".

RESULTS AND DISCUSSION

Results of the study of Mycobacterium tuberculosis susceptibility to the first line of anti-TB drugs in the period of 2007-2017 are shown in Table I.

MBT sensitivity in the group of first-time diagnosed patients shows reduced the sensitivity to anti-TB drugs. Thus, in 2007 sensitive mycobacteria was observed in 58.1%, and in 2016 in 63.6%, but in 2017 – 52.0. Overall, sensitivity to the first-line drugs for this period decreased by 6.1%.

In the group of patients for whom this was a repeat TB diagnosis, meaning relapsed TB, the sensitivity of MBT to anti-TB drugs decreased. In 2007 sensitive mycobacteria was observed in 43.9% and in 2016, in 42.1%, in 2017 – 31.9% of the patients, thus during this period sensitivity decreased by 10.0%.

We further analyzed changing sensitivity of MBT to one of the TB drugs of the first line, that is, mono-resistance. The results are presented in Table II.

In the groupof patients with first-time diagnosed tuberculosis there is a reduction in the percentage of mono-resistant MBT strains from 21.9% to 13.0% in 2016 , and 21.1% in 2017 according to 2007. Among the relapsed patients there is a similar decrease from 21.1% to 9.7 % in 2017. In the group of patients with recurrent

Table I. Changes of Mycobacterium tuberculosis susceptibility to anti-TB drugs of the first line.

Year	susceptible strains in patients with new tuberculosis		Susceptible strains in the patients which were treated previously			
			in patients with relapses pulmonary tuberculosis		in patients with other cases of pulmonary tuberculosis	
	number	%	number	%	number	%
2007	186	58.1	25	43.9	85	23.0
2008	185	62.1	21	42.0	12	27.3
2009	164	60.1	16	27.1	26	34.7
2010	155	63.5	20	47.6	11	32.4
2011	166	65.4	17	45.9	10	27.0
2012	149	64.5	18	33.3	18	42.9
2013	167	67.6	42	39.6	16	39.0
2014	145	57.5	30	31.9	6	20.0
2015	112	48.5	36	38.7	5	33.3
2016	161	63.6	40	42.1	6	27.3
2017	116	52.0	23	31.9	10	62.5

Table II. Changes of Mycobacterium tuberculosis mono-resistance to anti-TB drugs of the first line

Year	Mono-resistant strains in patients with new tuberculosis	Monoresistant strains in previously treated patients					
		in patients with relapses pulmonary tuberculosis		in patients with other cases of relapses pulmonary tuberculosis			
	number	%	number	%	number	%	
2007	70	21.9	12	21.1	73	19.7	
2008	53	17.8	11	22.0	9	20.5	
2009	61	22.3	12	20.3	20	26.7	
2010	49	20.1	8	19.0	6	17.6	
2011	53	20.9	8	21.6	7	18.9	
2012	28	12.1	11	20.4	7	16.7	
2013	34	13.8	16	15.1	8	19.5	
2014	37	14.7	15	16.0	9	30.0	
2015	42	18.2	11	11.8	4	26.7	
2016	33	13.0	13	13.7	2	9.1	
2017	47	21.1	7	9.7	3	18.8	

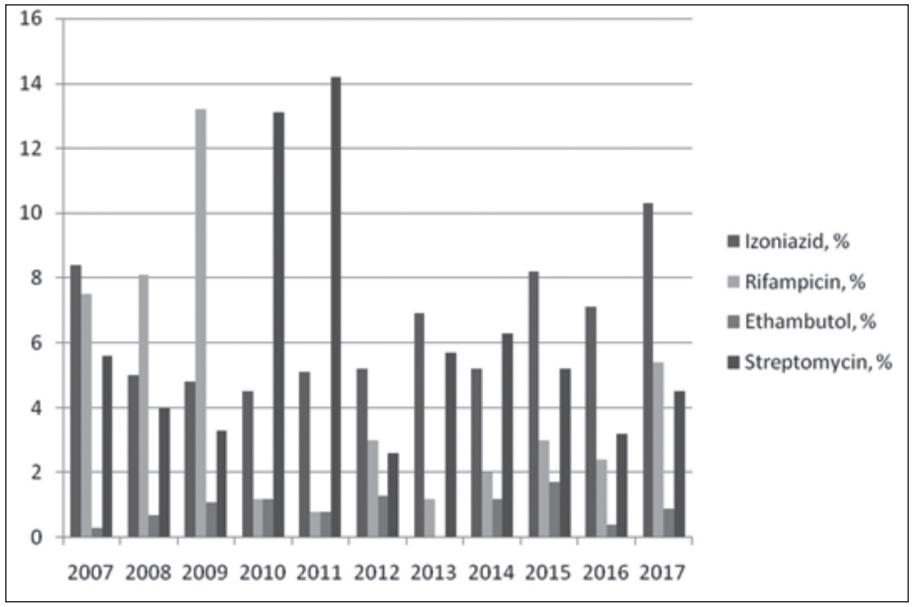

Figure 1. Changes in MBT mono-resistance in patients with newly diagnosed tuberculosis in 2007-2017.

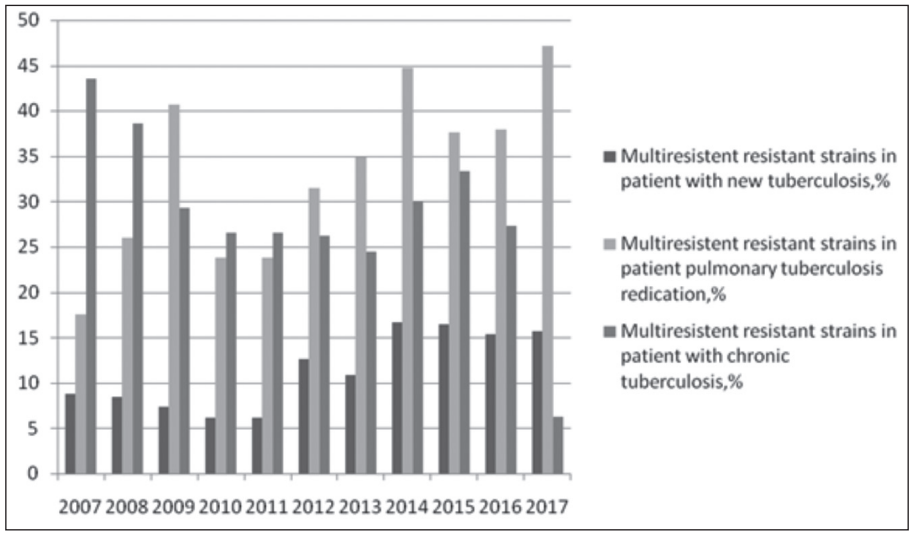

Figure 2. Changes in M. tuberculosis multi-resistance in 2007-2017.

TB there is a sharp decrease in absolute numbers, and thus percemtage ratio fluctuations from 17.6% to 30.0%. These results indicate marked decrease in mono-resistant MBT strains and thus increase in multi- and poly-resistant ones (Table II).

Figure 1 presents changes in the sensitivity of MBT to one of the first-line TB drugs among patients with newly diagnosed tuberculosis. Resistance to isoniazid has gradually decreased from 8.4 % (2007) to 5.1% (2011), however, since 2012 is began to increase again in 2017 reached 10.3%. Maximum resistance of MBT to rifampicin was recorded in 2009 at 13.2%, and then it decreased gradually to 5.4% in 2017. Resistance to ethambutol was minimal, but there has been its gradual increase during the study period, from 0.3% in 2007 to 0.9% in 2017. MBT resistance to streptomycin sulfate was growing very quickly, and in 2011 reached 14.2%. Because of this, the drug had been withdrawn from the schemes of intensive therapy, and currently is rarely used.

As the data presented in figure 2 demonstrate, particularly striking is the twofold increase in multidrug-resistant strains of Mycobacterium tuberculosis in patients with newly diagnosed tuberculosis in 2017 compared to 2007-2009.

In addition, from 2007 to 2016 we detected 2-fold increase in the of drug-resistant forms of Mycobacterium tuberculosis in patients with relapse of tuberculosis.

There was about 1.3 times decrease in the number of multidrug-resistant strains in patients with chronic pulmonary tuberculosis in 2016 compared to 2007 (Fig. 2).

In recent years there was a marked increase in the number of resistant strains of M. tuberculosis in the Ternopil region of Ukraine. This greatly complicates the treatment of patients and reduces the effectiveness of treatment, especially in patients with recurrent TB.

In the groups of patients with first-time TB diagnosis and relapsed tuberculosis there is a observed decrease in the percentage rate of mono-resistant strains of MBT. The frequency of detected multi-resistant strains Mycobacteria in patients with new tuberculosis and tuberculosis relapses has increased in about 2 times.

CONCLUSIONS

Considering the increase in multi-resistant pathogens in newly diagnosed and relapsed of tuberculosis cases, it is necessary to use a modern express methods of diagnostics for the causative agents of tuberculosis and to study their sensitivity to antimycobacterial drugs, especially by using molecular genetics methods.

This will allow to adjust antimycobacterial therapy for each individual patient, and to reduce the frequency of recurrence in newly diagnosed and relapsed tuberculosis patients with multidrug-resistant pathogens.

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The work is a fragment of the research project of the I. Horbachevsky Ternopil National Medical University «A comprehensive approach to symptoms control, immediate and long-term prognosis in the context of comorbid pathology in the internal diseases clinic and family physician practice» (State Registration No. 0118U000361).

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Conflict of interest:
The Authors declare no conflict of interest

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Received: 29.01.2020
Accepted: 02.04.2020

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article