ISONIAZID-RESISTANT MYCOBACTERIUM TUBERCULOSIS: PREVALENCE, RESISTANCE SPECTRUM AND GENETIC DETERMINANTS OF RESISTANCE

Andreevskaya SN, Smirnova TG, Larionova EE, Andrievskaya IYu, Chernousova LN, Ergeshov A
Central Tuberculosis Research Institute, Moscow, Russia

The lack of simple, rapid diagnostic tests for isoniazid-resistant rifampicin-susceptible tuberculosis infection (Hr-TB) can result in low treatment efficacy and further amplification of drug resistance. Based on the clinical data, this study sought to estimate the prevalence of Hr-TB in the general population and characterize the phenotypic susceptibility and genetic determinants of isoniazid resistance in M. tuberculosis strains. Molecular-genetic and culture-based drug susceptibility tests were performed on M. tuberculosis isolates and M. tuberculosis DNA obtained from the patients with pulmonary TB undergoing treatment at the Central Tuberculosis Research Institute between 2011 and 2018. The tests revealed that Hr-TB accounted for 12% of all TB cases in the studied sample. Hr-TB strains were either resistant to isoniazid only (45%) or had multiple resistance to 2-6 anti-TB agents. Resistance to isoniazid was caused by mutations in the katG gene. Based on the literature analysis and our own observations, we emphasize the importance of developing simple molecular drug susceptibility tests capable of detecting simultaneous resistance to rifampicin and isoniazid and the necessity of their translation into clinical practice.

Keywords: M. tuberculosis, isoniazid resistance, drug susceptibility, molecular diagnostics, single nucleotide polymorphism, tuberculosis

Funding: this study was supported by the Ministry of Science and Higher Education of the Russian Federation and carried out under the Federal Targeted Program for Research and Development in Priority Areas of Development of the Russian Scientific and Technological Complex for 2014-2020, Project № 05.586.21.0065 (Project ID RFMEFI58619X0065).

Author contribution: Ergeshov A, Chernousova LN — study design; Larionova EE, Andrievskaya IYu — data acquisition; Smirnova TG — data analysis; Andreevskaya SN — manuscript preparation, literature analysis. All authors have equally contributed to the discussion of the obtained results.

Compliance with ethical standards: we retrospectively analyzed the results of routine laboratory tests performed on the patients undergoing treatment for tuberculosis at the Central Tuberculosis Research Institute. All patients gave informed consent.

Correspondence should be addressed: Sofya N. Andreevskaya
Yauzskaya alley, 2, Moscow, 107564; andsofia@mail.ru

Received: 11.12.2019 Accepted: 07.01.2020 Published online: 12.01.2020

DOI: 10.24075/brsmu.2020.001

ISONIAZID-RESISTENT MYCOBACTERIUM TUBERCULOSIS: ЧАСТОТА ВЫЯВЛЕНИЯ, СПЕКТРЫ РЕЗИСТЕНТНОСТИ И ГЕНЕТИЧЕСКИЕ ДЕТЕРМИНАНТЫ УСТОЙЧИВОСТИ

С. Н. Андреевская, Т. Г. Смиркова, Е. Е. Ларионова, И. Ю. Андривская, Л. Н. Черноусова, А. Эргешов
Центральный научно-исследовательский институт туберкулеза, Москва, Россия

Отсутствие ускоренной диагностики туберкулеза с участием возбудителя к изониазиду с сохраненной чувствительностью к рифампикину (ИР-ТБ) может быть причиной низкой эффективности терапии и приводить к амплifikации лекарственной резистентности, в том числе к формированию множественной лекарственной устойчивости. Целью работы было определить частоту встречаемости ИР-ТБ в современной популяции, охарактеризовать фенотипическую чувствительность и генетические детерминанты устойчивости к изониазиду представителей этой группы M. tuberculosis на реагентном материале. Анализировали результаты определения лекарственной чувствительности, полученные при исследовании молекулярно-генетическими и/или культуральными методами изолятов M. tuberculosis / ДНК M. tuberculosis, выделенных от больных туберкулезом лёгких из клинических отделений Центрального научно-исследовательского института туберкулеза за период 2011–2018 гг. Частота ИР-ТБ составила 12% от всех выявленных случаев туберкулеза. M. tuberculosis с ИР как монорезистентными к изониазиду (45%), так и полирезистентными (устойчивыми к 2–6 противотуберкулезным препаратам), а устойчивость к изониазиду была обусловлена мутациями в гене katG, приводящими к высокому уровню резистентности. На основании анализа литературных данных и собственных наблюдений подчеркивается важность разработки и внедрения новых простых молекулярных тестов для определения устойчивости одновременно к рифампикину и изониазиду.

Ключевые слова: M. tuberculosis, изониазид-резистентность, лекарственная чувствительность, молекулярная диагностика, однуклеотидный полиморфизм, туберкулез

Финансирование: работа выполнена при финансовой поддержке Министерства науки и высшего образования Российской Федерации в рамках Федеральной целевой программы «Исследования и разработки по приоритетным направлениям развития научно-технологического комплекса России на 2014–2020 годы», соглашение № 05.586.21.0065 (уникальный идентификатор соглашения RFMEFI58619X0065).

Вклад авторов: А. Эргешев, Л. Н. Черноусова — разработка дизайн исследования; Е. Е. Ларионова, И. Ю. Андривская — получение данных для анализа; Т. Г. Смиркова — анализ полученных данных; С. Н. Андреевская — написание текста руководства, обзор публикаций по теме статьи; все авторы участвовали в обсуждении результатов.

Соблюдение этических стандартов: был проведен ретроспективный анализ результатов, полученных при выполнении рутинных лабораторных исследований для проходящих лечение в Центральном НИИ туберкулеза; все пациенты подписали добровольное информированное согласие на проведение исследования.

Для корреспонденции: Софья Николаевна Андреевская
Яузская аллея, 2, г. Москва, 107564; andsofia@mail.ru

Статья получена: 11.12.2019 Статья принята к печати: 07.01.2020 Опубликована онлайн: 12.01.2020

DOI: 10.24075/vrsmu.2020.001

Drug-resistant tuberculosis (TB) is a serious public health concern. At present, the major focus is on fighting multidrug-resistant TB (MDR-TB), i.e. caused by strains resistant to at least 2 most effective anti-TB drugs: isoniazid and rifampicin. Russia has the third-highest burden of MDR-TB [2]. In 2018, the incidence and prevalence of MDR-TB in Russia stabilized at 5.6 and 23.6 cases per 100,000 population, respectively. However, the share of patients with MDR-TB among individuals...
DNA was performed using M. tuberculosis rpoB. DNA/cultures isolated in culture were amplified in a thermocycler equipped with a CFX96 optical quantification of mycobacterial DNA by real-time PCR (Syntol; Russia) following the manufacturer’s protocol. DNA fragments were quantified by real-time PCR (Syntol; Russia). All procedures were carried out in compliance with the manufacturers’ guidelines.

Statistical analysis

Descriptive statistics were used to analyze the results of the study, including the number of observations, frequencies, percentages, and 95% CI. The analysis was conducted in MS Excel (Microsoft; USA).

RESULTS

Clinical specimens collected from 4056 patients with pulmonary TB were subjected to culture-based and molecular testing. In 71 cases, neither M. tuberculosis DNA nor tubercle bacilli were detected; so those cases were excluded from the analysis. Phenotypic/genotypic drug susceptibility determination was determined for M. tuberculosis DNA/cultures isolated from the remaining 3985 samples. If the results of culture tests contradicted those of molecular tests, priority was given to culture-based data (Table 1). For example, 38 strains that demonstrated resistance to both isoniazid and rifampicin in culture tests but had no mutations in the rpoB gene implicated in rifampicin resistance were put into the MDR category because molecular rifampicin susceptibility tests used in our study could only detect a limited number of mutations, meaning that genetic determinants of rifampicin resistance might have been overlooked in the analysis. And, vice versa, 29 strains that tested positive for mutations in the rpoB gene and did not have the rifampicin-resistant phenotype were categorized as isoniazid-resistant.

The total sample of drug-resistant M. tuberculosis strains was dominated by MDR isolates (Table 1). However, isoniazid-resistant strains that were susceptible to rifampicin were also well represented in the sample (502/3985; 12.60%).

The analysis of clinical data over the period from 2011 to 2018 revealed that Hr-TB amounted to about 14% of all TB cases per year reported in 2011–2012 and 2017–2018. In 2013–2016, the rate of detection for this TB form was lower (10–11%). We were unable to describe this linear trend with a sufficient degree of reliability (Table 2).

Because culture-based tests are less sensitive than molecular methods, the growth of M. tuberculosis in culture media was not detected for some specimens. Therefore, phenotypic sensitivity to anti-TB drugs was only determined for 260 isoniazid-resistant isolates of M. tuberculosis (Table 3). The following definitions were applied to identify the type of drug resistance of M. tuberculosis isolates [1]: monoresistance, i.e. resistance of the mycobacterium to only one anti-TB drug, and polyresistance, i.e. resistance of the mycobacterium to 2 or more anti-TB drugs but not to the combination of isoniazid and rifampicin.

Monoresistant isolates amounted to 117/260 (45%) cases. The rest 143 (55%) isolates were polyresistant (to 2–6 drugs). Polyresistant isolates were equally represented by M. tuberculosis strains resistant to both isoniazid and first-line drugs (42/143; 29.37%) and by the strains resistant to both isoniazid and second-line drugs (38/143; 26.57%); resistance to second-line drugs almost always included resistance to ethionamide (31/38; 81.58%). Co-resistance to first- and second-line drugs was the most common among the polyresistant isolates (63/143; 44.06%). Of them, co-resistance to isoniazid, ethambutol and ethionamide (HEEto), including...
their combinations with other second-line medications, was detected in 20/63 (31.75%) cases; polyresistance to isoniazid, pyrazinamide and ethionamide (HEZEto), including their combinations with other second-line drugs, was not so common (9/63 cases or 14.29%). Polyresistance to HEZETO was observed in 15/63 (23.81%) isolates. In 19/63 (30.16%) isolates, resistance spectra included other combinations of drugs (a total of 12 resistance spectra with 3 to 5 drugs).

Data on mutations in the genes associated with resistance to isoniazid were acquired for 451 M. tuberculosis isolates resistant to isoniazid (Table 4). In most cases (386/451 isolates or 85.59%), single nucleotide polymorphisms (SNPs) were detected in one of the genes associated with resistance to isoniazid. The presence of SNPs in 2 genes associated with isoniazid resistance was not so common (65/451 cases or 14.41%). The most prevalent were mutations at codon 315 of the katG gene (413/451 cases or 91.57%). In 348/413 (84.26%) cases, mutations were detected only in katG; in 62/413 (15.01%) isolates, mutations in katG co-occurred with SNPs in the inhA gene. In single cases, katG mutations co-occurred with SNPs in the ahpC gene.

The inhA15_C->T substitution was quite common (94/451; 20.84%); in 33/94 (35.11%) cases it was the only mutation detected. In other samples, this mutation co-occurred with SNPs at codon 315 of the katG gene.

For 209 isolates of M. tuberculosis with phenotypically confirmed resistance to isoniazid, the following distribution of mutant variants was observed: 152/209 (72.73%) carried a mutation in the katG gene only (315_Ser->Thr(1)); 32/209 (15.31%) carried a combination of katG315_Ser->Thr(1) and inhA15_C->T; 17/209 (8.13%) only inhA15_C->T was detected. The remaining 8 (3.83%) isolates with phenotypically confirmed resistance to isoniazid had mutations in other regions of the genes associated with isoniazid resistance (inhA10_C->T in the absence of other mutations, katG315_Ser->Asn; co-occurring katG315_Ser->Gly + inhA15_C->T, katG315_Ser->Thr(1) + inhA8_T->G, katG315_Ser->Thr(1) + ahpC10_C->T).

Thus, our sample of isoniazid-resistant M. tuberculosis was dominated by the katG315_Ser->Thr(1) mutation corresponding to the substitution AGC->ACC (333/451; 73.84%), followed by the co-occurring katG315_Ser->Thr(1) + inhA15_C->T (60/451; 13.30%), and single inhA15_C->T (33/451; 7.32%). On the whole, these 3 mutant variants amounted to 426/451 (94.46%) isoniazid-resistant M. tuberculosis isolates.

DISCUSSION

We attempted to estimate the prevalence of isoniazid-resistant, rifampicin-susceptible M. tuberculosis strains isolated from the patients with pulmonary TB, who had presented at clinical departments of Central Tuberculosis Research Institute in 2011–2018.

The prevalence of this TB form and the rate of its spread vary across the world’s regions. For example, the analysis of data on drug susceptibility collected by WHO from 131 specialized healthcare institutions in 1994–2009 reveals that Eastern Europe had the highest burden of Hr-TB (15%), followed by Western and Central Europe (11%); in other WHO regions, Hr-TB prevalence did not exceed 8% [11]. In some regions, the prevalence of Hr-TB tended to decrease, whereas in others, it was increasing. No clear linear dynamics were established for the majority of WHO regions. In our study, the prevalence of isoniazid-resistant M. tuberculosis (12%) was similar to that in Eastern Europe and its dynamics were non-linear, just like in the majority of the world’s regions.

The systematic review of the link between primary resistance to isoniazid and the acquisition of secondary resistance to other anti-TB drugs [12] concludes that monoresistant strains acquire

| Year | Total isolates studied (abs.) | Number of M. tuberculosis isolates | Hr isolates | % (95% CI) |
|------|-------------------------------|----------------------------------|------------|----------|
|      |                               |                                  | abs.       |          |
| 2011 | 458                           | 67                               | 14.63 (11.69–18.16) |
| 2012 | 355                           | 52                               | 14.65 (11.35–18.70) |
| 2013 | 530                           | 54                               | 10.19 (7.89–13.06)  |
| 2014 | 554                           | 65                               | 11.73 (9.31–14.68)  |
| 2015 | 569                           | 65                               | 11.42 (9.06–14.30)  |
| 2016 | 502                           | 56                               | 11.16 (8.69–14.21)  |
| 2017 | 557                           | 76                               | 13.64 (11.04–16.75) |
| 2018 | 460                           | 67                               | 14.57 (11.64–18.08) |

Note: 1 — including cases for which no mutations were detected in the genes associated with resistance to isoniazid, rifampicin and fluoroquinolones; 2 — including 38 M. tuberculosis isolates for which no mutations in the rpoB gene (see the article) were detected; 3 — including 29 M. tuberculosis isolates carrying mutant rpoB but having no resistance phenotype; 4 — mono- or polyresistance to antituberculous drugs, excluding isoniazid.
additional resistance (no necessarily MDR) to other anti-TB drugs 5.1 times more often than drug-susceptible strains. High occurrence rates of polyresistant strains demonstrated in our study (65% of all Hr-TB isolates) insensitive to 1–5 drugs apart from isoniazid corroborate the possibility of drug resistance amplification in isoniazid-resistant M. tuberculosis.

Because first-line antituberculous drugs ethambutol and pyrazinamide are included in the standard chemotherapy regimen often prescribed empirically to newly diagnosed patients, it would be reasonable to expect high prevalence rates of Hr M. tuberculosis strains additionally resistant to these 2 drugs. Indeed, resistance to ethambutol was detected in almost 50% of all polyresistant M. tuberculosis isolates analyzed in our study (70/143, 48.95%; 95% CI: 40.89–57.06%); pyrazinamide-resistant isolates were slightly rarer (57/143, 39.86%; 95% CI: 32.20–48.05%).

Polyresistant M. tuberculosis strains resistant to ethionamide (the second-line medication) were much more prevalent (80/143, 55.94%; 95% CI: 47.76–63.82%). This can be explained by the fact that ethionamide is a structural analogue of isoniazid; it inhibits synthesis of mycolic acids, thereby disrupting the structure of the bacterial cell wall. Therefore, these two drugs may have common targets and genetic determinants of resistance [5, 13].

In general, the use of first-line drugs in the therapy of Hr-TB leads to poor outcomes, including the lack of therapeutic effect, relapses, acquired MDR. Besides, standard empiric treatment of Hr-TB can promote MDR-TB epidemics, especially in the regions where such TB forms are not rare [7]. At the same time, timely adjustments to the regimen based on results of isoniazid susceptibility testing and the use of modified regimens reinforce therapeutic success and reduce the risk of relapses [14–16]. In this light, all clinical studies should be mentioned that aimed to establish an association between mutations in M. tuberculosis and the efficacy of treatment of Hr-TB with high doses of isoniazid [17, 18]. It is known that mutations in the katG gene, which dominated our sample, result in a high level of resistance to isoniazid whereas mutations in inhA, in a low level of resistance [5]. The studies revealed that therapy with isoniazid was effective when mycobacteria carried mutations in the inhA gene; katG mutations were associated with poor treatment outcomes [17, 18].

This emphasizes the need for effective regimens for the therapy of Hr-TB [8, 19]. Rapid drug susceptibility testing is critical. Molecular diagnostic methods are highly sensitive and rapid (1–2 days in comparison with weeks required for culture); they also provide valuable information about mutations carried by the strain and the level of isoniazid resistance [1]. Therefore, the demand for molecular methods in the diagnosis of TB and drug susceptibility testing is high. However, although tests based on allele specific PCR, bioarray technologies or DNA strips used in large TB healthcare centers expedite diagnosis, they impose strict requirements on staff qualifications and laboratory infrastructure.

Today, the only molecular test that can be deployed in any laboratory is Xpert MTB/RIF that utilizes the GeneXpert platform [20]. Unfortunately, this test can detect only genotypic resistance to rifampicin because these days all diagnostic procedures are largely focused on detecting MDR strains, which are resistant to rifampicin. Therefore, Xpert MTB/RIF cannot detect resistance to isoniazid in the strains that are sensitive to rifampicin (12% of our isolates). In the absence of additional diagnostic tools, isoniazid resistance of such strains will never be revealed, leading to inadequate chemotherapy regimens and amplification of MDR. This indicates the need for a simple molecular test that is as convenient as Xpert MTB/RIF and can be used in any laboratory.

CONCLUSIONS

Isoniazid-resistant tuberculosis can be regarded as a potential predecessor of MDR disease. It is important to control the spread of primary resistance to isoniazid and prevent acquisition of further resistance. Our analysis revealed high prevalence of M. tuberculosis

| Resistance spectra | Number of M. tuberculosis strains |
|--------------------|----------------------------------|
| Monoresistance (H) | 117 | 45.00 (39.07–51.08) |
| Polyresistance (H + other anti-TB drugs except R): | 143 | 55.00 (48.95–61.05) |
| To 2 anti-TB drugs: | 71 | 27.31 (22.25–33.02) |
| HE | 17 | |
| HZ | 16 | |
| H Eto | 31 | |
| H Am | 3 | |
| H Cp | 1 | |
| H Lfx | 3 | |
| To 3 anti-TB drugs: | 36 | 13.85 (10.17–18.57) |
| HEZ | 9 | |
| HE Eto | 13 | |
| HE Lfx | 1 | |
| HZ Cp | 1 | |
| HZ Eto | 7 | |
| H Am Cp | 2 | |
| H Eto Am | 3 | |
| To 4 anti-TB drugs: | 21 | 8.08 (5.34–12.03) |
| HEZ Eto | 6 | |
| HEZ Am | 1 | |
| HEZ Lfx | 2 | |
| HE Am Cp | 2 | |
| HE Eto Am | 4 | |
| HE Eto Lfx | 2 | |
| HZ Eto Cp | 1 | |
| H Eto Am Cp | 1 | |
| H Am Cp Lfx | 1 | |
| To 5 anti-TB drugs: | 12 | 4.62 (2.66–7.89) |
| HEZ Eto Am | 2 | |
| HEZ Eto Lfx | 4 | |
| HEZ Am Cp | 2 | |
| HE Eto Am Lfx | 1 | |
| HZ Am Cp Lfx | 1 | |
| H Eto Am Cp Lfx | 1 | |
| To 6 anti-TB drugs: | 3 | 1.15 (0.39–3.34) |
| HEZ Eto Am Cp | 2 | |
| HEZ Eto Am Lfx | 1 | |
| Total | 260 | 100 |

Note: in the lists of resistance spectra, first-line drugs are separated from second-line medications by a space character.
of Hr-TB (over 12% of all analyzed cases) among isoniazid-resistant rifampicin-susceptible M. tuberculosis strains isolated from patients with pulmonary TB. The majority of such isolates carried mutations causing strong resistance to isoniazid. Our findings indicate the importance of rapid testing for sensitivity to both rifampicin and isoniazid based on molecular-genetic methods. There is a need for simple point-of-care tests that do not impose high requirements on laboratory infrastructure.

References

1. Order of the Ministry of Health of the Russian Federation of 9 December 2014 «Ob utverzhdenii metodicheskikh rekomendatsiy po sovershenstvovanju diagnostiki i lecheniya tuberkuleza organov dykhaniya». Russian.

2. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. (WHO/CDS/TB/2018.20).

3. Nechaeva OB. TB situation Russiania. Tuberculosis and Lung Diseases, 2018; 96 (8): 15–24. Russian.

4. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.33).

5. Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2009; 13(10): 1320–30.

6. Sandgren A, Strong M, Muthukrishnan P, Weiner BK, Church GM, Murray MB. Tuberculosis drug resistance mutation database. PLoS Med. 2009; 6 (2): e2;

7. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2017; 17 (2); 223–34.

8. World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis, Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.7).

9. Siddiqi SH, Rusch-Gerdes S. MGIT procedure manual for BACTEC MGIT 960 TB System. 2006.

10. Chernousova LN, Smirnova TG, Larionova EE, i dr. Standartnyye operationannyye protsedury. Opredelennye chvystvitetnosti mikobakternye tuberkuleza k protivotuberkuleznym preparatam vtorogo ryada s ispol'zovaniem sistemy BACTEC MGIT 960/320. Moscow, 2015. Russian.

11. Jenkins HE, Zignol M, Cohen T. Quantifying the Burden and Trends of Isoniazid Resistant Tuberculosis, 1994–2009. PLoS ONE. 2011; 6 (7); e22927.

12. Menzies D, Benedetti A, Paydar A, Martin L, Royce S, Pai M, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. J Infect. 2010; 60 (6): 452–7.

13. Cattamanchi A, Dantes RB, Metcalfe JZ, Jarlsberg LG, Grinsdale J, Magee MJ. Isoniazid monoresistance and rate of culture conversion among patients in the state of Georgia with confirmed tuberculosis, 2009–2014. Am J Public Health. 2015; 105 (3): 531–40.

14. Salindri AD, Sales RF, DiMocie L, Schechter MC, Kemper RR, Magee MJ. Isoniazid monoresistance and rate of culture conversion among patients in the state of Georgia with confirmed tuberculosis, 2009–2014. Am Ann Thorac Soc. 2018; 15 (3): 452–2.

15. Tolani MP, D’Souza DT, Misty NF. Drug resistance mutations and heteroresistance detected using the GenoType MTBDRplus assay and their implication for treatment outcomes in patients from Mumbai, India. BMC Infect Dis. 2012; (12): 9.

16. Huyen MN, Cobelens FG, Bluu TN, Lan NT, Dung NH, Keener K, et al. Epidemiology of isoniazid resistance mutations and their effect on tuberculosis treatment outcomes. Antimicrob Agents Chemother. 2013; 57 (8): 3620–7.
1. Приказ Министерства здравоохранения Российской Федерации от 29 декабря 2014 № 951 «Об утверждении методических рекомендаций по совершенствованию диагностики и лечения туберкулеза органов дыхания».
2. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. (WHO/CDS/TB/2018.33).
3. Нечаева О. Б. Эпидемическая ситуация по туберкулезу в России. Туберкулез и болезни легких. 2018; 96 (8): 15–24.
4. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.33).
5. Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2009; (13): 1320–30.
6. Sandgren A, Strong M, Muthukrishnan P, Weiner BK, Church GM, Murray MB. Tuberculosis drug resistance mutation database. PLoS Med. 2009; 6 (2): e2.
7. Geogia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2017; 17 (2): 223–34.
8. World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.7).
9. Siddiq SH, Rusch-Gerdes S. MGIT procedure manual for BACTEC MGIT 960 TB System. 2006.
10. Черноусова Л. Н., Смирнова Т. Г., Ларионова Е. Е., и др. Стандартные операционные процедуры. Определение чувствительности микобактерий туберкулеза к противотуберкулезным препаратам второго ряда с использованием системы BACTEC MGIT 960/320. Москва, 2015.
11. Jenkins HE, Zignol M, Cohen T. Quantifying the Burden and Trends of Isoniazid Resistant Tuberculosis, 1994–2009. PLoS ONE. 2011; 6 (7): e22927.
12. Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pat M, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med. 2009; 6 (9): e1000146.
13. Jeon CY, Hwang SH, Min JH, Prevots DR, Goldfeder LC, Lee H, et al. Extensively drug-resistant tuberculosis in South Korea: risk factors and treatment outcomes among patients at a tertiary referral hospital. Clin Infect Dis. 2008; (48): 42–9.
14. Bang D, Andersen PH, Andersen AB, Thomsen VØ. Isoniazid-resistant tuberculosis in Denmark: mutations, transmission and treatment outcome. J Infect. 2010; 60 (6): 452–7.
15. Salindri AD, Sales RF, D’Miceli L, Schechter MC, Kempker RR, Magee MJ. Isoniazid monoresistance and rate of culture conversion among patients in the state of Georgia with confirmed tuberculosis, 2009–2014. Ann Am Thorac Soc. 2018; 15 (3): 331–40.
16. Cattamanchi A, Dantes RB, Metcalfe JZ, Larsberg LG, Grinsdale J, Kawamura LM, et al. Clinical characteristics and treatment outcomes of patients with isoniazid-monoresistant tuberculosis. Clin Infect Dis. 2009; 48 (2): 179–85.
17. Tolani MP, D’Souza DT, Mistry NF. Drug resistance mutations and heteroresistance detected using the GenoType MTBDRplus assay and their implication for treatment outcomes in patients from Mumbai, India. BMC Infect Dis. 2012; (12): 9.
18. Huyen MN, Cobeles FG, Buu TN, Lan NT, Dung NH, Kremer K, et al. Epidemiology of isoniazid resistance mutations and their effect on tuberculosis treatment outcomes. Antimicrob Agents Chemother. 2013; 57 (8): 3620–7.
19. Stagg HR, Harris RJ, Hathrell HA, Obach D, Zhao H, Tsuchiya N, et al. What are the most efficacious treatment regimens for isoniazid-resistant tuberculosis? A systematic review and network meta-analysis. Thorax. 2016; 71 (10): 940–9.
20. World Health Organization. WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. Geneva: World Health Organization; 2017. WHO/HTM/TB/2017.04. Available from: https://www.who.int/tb/publications/2017/XpertUltra/en/. Accessed: 18 May 2019.