



DETECTION, DIAGNOSIS AND CLINICAL TUBERCULOSIS IN CHILDREN WITH HIV INFECTION

© E.B. Vasilieva¹, M.E. Lozovskaya¹, L.V. Klochkova¹, Yu.A. Yarovaya¹, O.M. Noskova²

¹St Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Russia;

²St Petersburg City Children's Infectious Diseases Hospital No 3, Saint Petersburg, Russia

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The problem of combination of tuberculosis (TB) and HIV remains relevant. Majority of HIV patients are young adults, 90% of which are women of childbearing age, thereby increasing the perinatal HIV transmission rate. In 2014 in Saint Petersburg, >5,000 children with perinatal contact HIV were reported and >300 children were confirmed with HIV infection. We present a comparative analysis of the case histories of 20 children with TB-HIV and 30 with tuberculosis without HIV infection. The analysis identified several cases of delayed diagnosis. In >50% of the cases, the diagnosis of HIV infection was confirmed after 1 year. Four children with HIV infection were diagnosed at school age and connected to suspected cases of tuberculosis. The clinical detection of TB occurs more commonly in children with HIV infection than in those without HIV infection (25% and 5%, respectively). In both groups, tuberculosis of the intrathoracic lymph nodes was predominantly observed; however, generalized forms of TB were also diagnosed in the group with co-infection (25% of the cases). HIV patients often have decreased body mass, low-grade fever, lymphadenopathy, and anemia. Hepatosplenomegaly was equally observed in both groups. More than one third (35%) of patients with co-infection had negative sensitivity to tuberculin, and Diaskintest was positive in 50% of the cases. The prevalence and severity of TB in children with HIV infection correlates with the severity of immunosuppression.

Keywords: tuberculosis; HIV infection; perinatal contact; children; diagnostics.

ВЫЯВЛЕНИЕ, ДИАГНОСТИКА И КЛИНИЧЕСКОЕ ТЕЧЕНИЕ ТУБЕРКУЛЕЗА У ДЕТЕЙ С ВИЧ-ИНФЕКЦИЕЙ

© Е.Б. Васильева¹, М.Э. Лозовская¹, Л.В. Клочкова¹, Ю.А. Яровая¹, О.М. Носкова²

¹ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России;

²ФБГУ СПб ГБУЗ «ДИБ № 3» Минздрава России, Санкт-Петербург

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Проблема сочетания туберкулеза и ВИЧ остается актуальной. Большинство больных – лица молодого возраста, 90 % женщин с ВИЧ-инфекцией детородного возраста, что ведет к повышению числа детей с перинатальным контактом по ВИЧ. В Санкт-Петербурге на 2014 год рождено более 5000 детей с перинатальным контактом по ВИЧ-инфекции, более 300 детей имеют подтвержденный диагноз ВИЧ-инфекции. Проведен сравнительный анализ историй болезни 20 детей с сочетанием ТВ-ВИЧ и 30 детей с туберкулезом без ВИЧ-инфекции. Анализ результатов исследования показал, что появляются случаи поздней диагностики. Так, более чем в половине случаев диагноз ВИЧ-инфекции подтвержден после 1 года. У четырех детей ВИЧ-инфекция диагностирована в школьном возрасте при обследовании в связи с подозрением на туберкулез. Выявление туберкулеза у детей с ВИЧ-инфекцией чаще, чем у детей без ВИЧ-инфекции, происходит клиническим методом (в 25 и 5 % соответственно). В структуре клинических форм туберкулеза в обеих группах преобладал туберкулез внутригрудных лимфатических узлов, но

в группе детей с КО-инфекцией чаще регистрируются генерализованные формы (25 % случаев). В клинической картине у пациентов с ТБ-ВИЧ чаще регистрируется снижение массы тела, субфебрилитет, полиаденопатия, анемия; гепатоспленомегалия выявлялась в обеих группах с одинаковой частотой. Более чем у трети (35 %) пациентов с КО-инфекцией определялась отрицательная чувствительность к туберкулину, по диаскин-тесту в 50 % случаев. Распространенность и тяжесть течения туберкулеза у детей с ВИЧ-инфекцией коррелирует со степенью иммуносупрессии.

Ключевые слова: туберкулез; ВИЧ-инфекция; перинатальный контакт; дети; диагностика.

Tuberculosis (TB) is one of the most common HIV-related diseases. TB–HIV coinfection still remains a significant problem in the Russian Federation, where the incidence of HIV is 43.9 per 100,000 population [1]. Majority of patients with TB–HIV coinfection are young; 90% of women currently infected with HIV are of childbearing age, which increases the risk of perinatal HIV infection [10]. Saint Petersburg is one of the areas most affected by HIV. In 2012, HIV prevalence in Saint Petersburg reached 988.5 per 100,000 population [1].

The combination of TB and HIV infection becomes increasingly threatening because of changes in women's reproductive behavior. Over the last 10 years, the number of women infected with HIV increased 15-fold, whose pregnancy resulted in delivery; approximately 14.6% of women do not visit a gynecologist during pregnancy and do not receive antiretroviral therapy (ART) [10]. According to the data from the Motherhood and Childhood Department of Saint Petersburg AIDS Center, as of 2014, over 5,000 children had perinatal HIV exposure; 300,000 children have confirmed HIV infection [2]. HIV-related conditions in children primarily include neurological disorders, TB (up to 65%), herpetic infection, and, less frequently, cancer [3]. The similarity between TB and HIV pathogenesis, vulnerability of the same population groups to these infections, and high prevalence of latent *Mycobacterium tuberculosis* infection underlie the TB–HIV epidemics and determine the difficulties associated with diagnosis [9]. TB–HIV coinfection in children aged 0–7 years is 10 times more prevalent than that in the other age groups. HIV infection is often revealed during examination of children with TB [4].

Aim: To analyze socioepidemiological risk factors, diagnostic methods, and clinical course of children with TB–HIV coinfection.

MATERIAL AND METHODS

We analyzed the medical records of 50 children aged 1–14 years with TB treated in the Saint Petersburg Children's Hospital for Infectious Diseases No. 3 between 2010 and 2014. The children were divided into two groups: group 1 included 30 children with TB but without HIV (TB group or control group) and group 2

included 20 children with both TB and HIV (case group or TB–HIV group). All children underwent comprehensive clinical and laboratory examinations, including tuberculin skin tests (TSTs), immunological testing, X-ray computed tomography, and multislice computed tomography. Data analysis was performed using Microsoft Excel 2007 in accordance with the rules of variation statistics. Pearson's chi-squared (χ^2) test was used to compare the results. Differences were considered significant for $p < 0.05$.

RESULTS

In 16 (52%) children without HIV infection and nine (45%) with HIV infection, the diagnosis of TB was established after routine screening using TSTs ($p = 0.1$). Seven (35%) children with TB–HIV coinfection and 13 (43%) without TB–HIV coinfection were suspected to have TB after their examination with TB contact investigation ($p = 0.1$). Children with HIV infection were more likely to be diagnosed with TB through clinical manifestations. In group 2, TB was clinically diagnosed in five children (25%), whereas only one (5%) in group 1 had pronounced clinical manifestations ($p = 0.04$).

Analysis of socioepidemiological factors (Fig. 1) demonstrated that 60% of children from group 1 had precarious living conditions, whereas all children from group 2 were from a disadvantaged social background. Children without TB–HIV coinfection were more likely to have a TB contact than those with HIV (71% vs. 50%). Maternal HIV infection was confirmed in 18% and 93% of children in groups 1 and 2, respectively ($p = 0.01$); therefore, by the time of delivery, the diagnosis of HIV was not established in two women. Parents of children with TB–HIV coinfection were more likely to abuse alcohol or recreational drugs than parents of children without TB–HIV coinfection (85% vs. 22%, $p = 0.02$; Fig. 2).

During the study, we also explored the circumstances in which HIV was detected. Among the 20 children with TB–HIV coinfection, 18 had confirmed perinatal exposure to HIV; in the remaining two children, the mothers' HIV status was not known. In eight children, the diagnosis of HIV was established during the first months of life; in the remaining 12 children, the diagnosis was confirmed later: at the age of 18 months

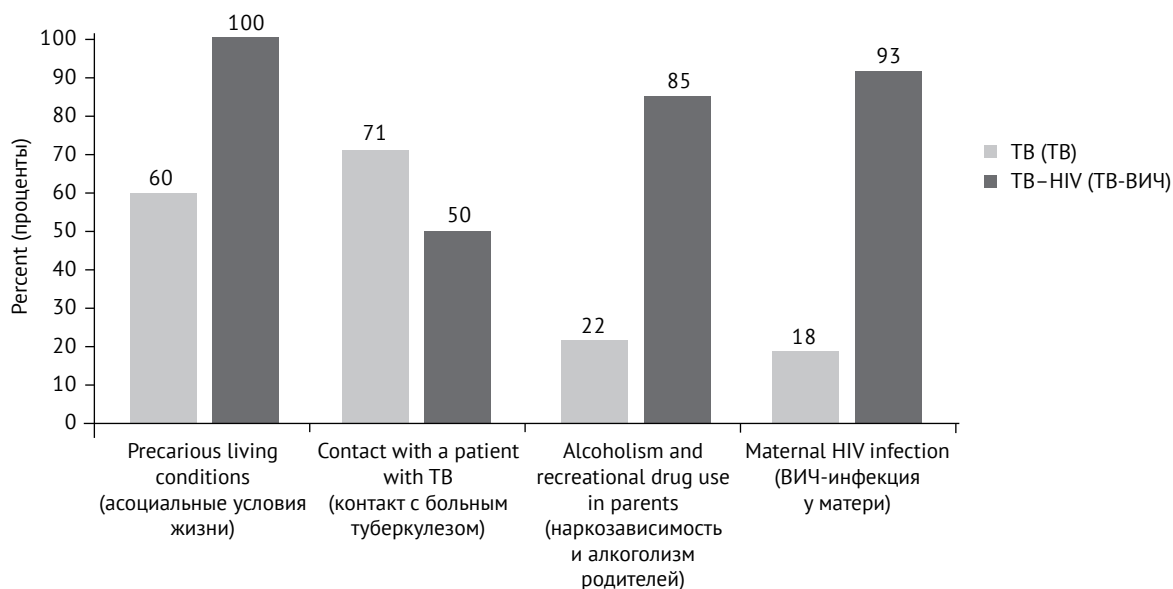


Fig. 1. Socioepidemiological characteristics of the children ($n_1 = 30, n_2 = 20$)

Рис. 1. Социально-эпидемиологическая характеристика групп пациентов. $n_1 = 30, n_2 = 20$

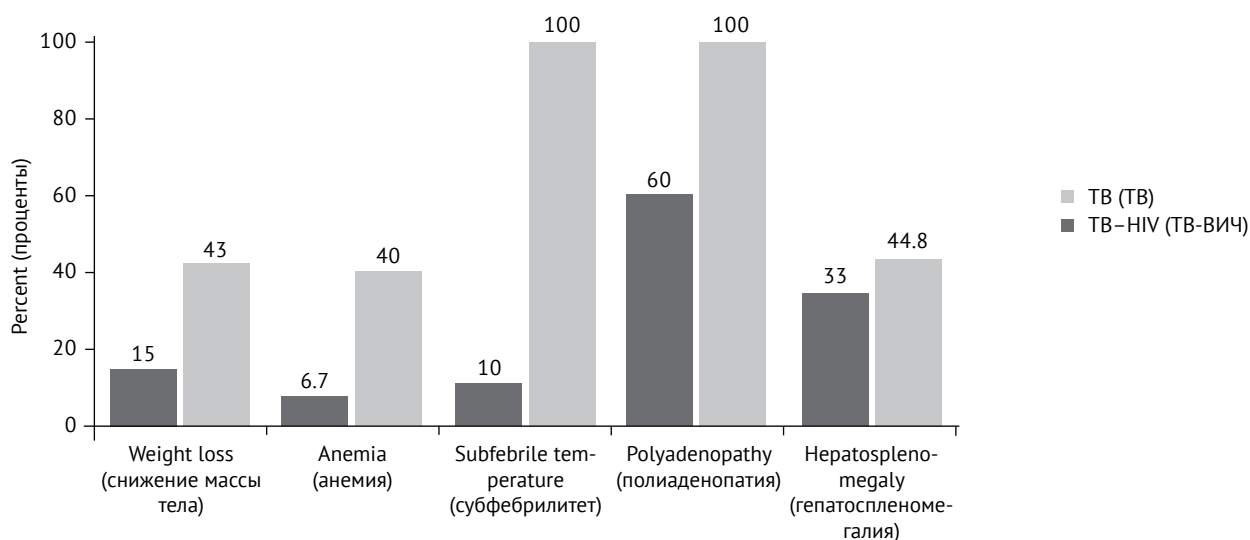


Fig. 2. Results of clinical and laboratory examinations ($n_1 = 30, n_2 = 20$)

Рис. 2. Результаты клинко-лабораторного обследования. $n_1 = 30, n_2 = 20$

($n = 4$), 2 years ($n = 2$), 3 years ($n = 2$), 7 years ($n = 1$), 8 years ($n = 1$), 9 years ($n = 1$), and 13 years ($n = 1$). Notably, four children (aged 7, 8, 9, and 13 years) were discovered to have HIV infection during their diagnostic examination for TB. Late diagnosis of HIV infection may be associated with insufficient testing of pregnant women and their antisocial lifestyle.

Majority of children in both groups had intrathoracic lymph node TB (76.6% and 75% of children in groups 1

and 2, respectively, $p = 1$) (Fig. 3). Generalized TB was more frequent in children with TB-HIV coinfection ($n = 5, 25\%$) than in children without TB-HIV coinfection ($n = 1, 3.5\%$; $p = 0.05$).

In addition, we analyzed vaccination data of children with TB-HIV coinfection. The principles of vaccination for children born to mothers positive for HIV are described in Annex No. 1 of the Order of the Ministry of Health of Russia No. 5 dated January 31, 2011 [6, 7].

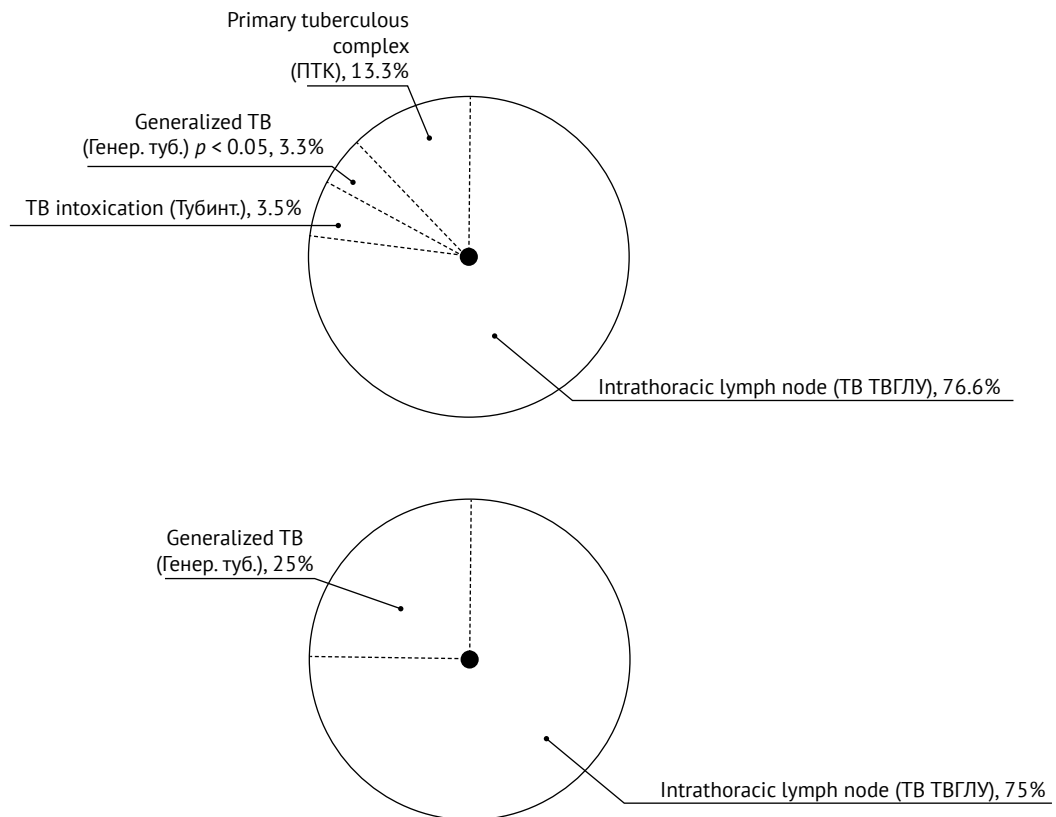


Fig. 3. Clinical forms of TB ($n_1 = 30, n_2 = 20$)

Рис. 3. Структура клинических форм туберкулеза. $n_1 = 30, n_2 = 20$

Children with perinatal exposure to HIV should undergo BCG vaccination only in the absence of clinical and laboratory signs of immunodeficiency and if a three-stage prevention of mother-to-child transmission of HIV was conducted. Otherwise, BCG vaccination should be deferred until the absence of HIV is confirmed [8]. Until 2010, maternal HIV infection was considered a contraindication for BCG vaccination; it was possible only after consultation with an infectiologist from the AIDS Center. We found that 11 of 20 children with TB–HIV coinfection were vaccinated with BCG at birth, and the remaining nine were not vaccinated. Importantly, all children who received BCG vaccination were born before 2011 and had perinatal exposure to HIV. All children positive for HIV with generalized TB underwent BCG vaccination at birth; one child had BCG revaccination at the age of 7 years.

Assessment of clinical symptoms and laboratory parameters demonstrated that five children (15%) with TB alone and eight (43%) with TB–HIV coinfection experienced weight loss ($p = 0.04$). Three children (10%) from group 1 were found to have subfebrile temperature, whereas all 20 (100%) from group 2 had subfebrile temperature ($p = 0.007$). Polyadenopathy was diagnosed in 18 (60%) children without HIV and 20 (100%) with HIV

($p = 0.02$); moreover, children with TB–HIV coinfection had multiple palpable lymph nodes in 6–9 groups. Hepatosplenomegaly was diagnosed through palpation and abdominal ultrasound examination in case of liver and spleen enlargement of ≥ 1 cm. Liver and spleen enlargement was equally often detected in both groups: in 10 (33%) children with TB and nine (44%) children with TB–HIV coinfection ($p = 0.8$). Anemia was diagnosed in two (6.7%) children negative for HIV and seven (40%) positive for HIV ($p = 0.03$). Children with TB–HIV coinfection had more pronounced intoxication, slow weight gain, longer subfebrile condition, and symptoms persisting for more than 6–9 months, despite comprehensive therapy (including anti-TB, antiretroviral, and pathogenetic therapies).

We analyzed the frequency of various comorbidities in both groups. Chronic recurrent herpetic infection was observed in 10 (50%) children with HIV infection and three (10%) without HIV infection ($p = 0.03$). Eight (40%) children with TB–HIV coinfection and three (10%) without TB–HIV coinfection had allergic dermatitis ($p = 0.04$). Candidiasis was diagnosed in five (25%) children from group 1. One child positive for HIV (5%) had thrombocytopenic purpura. Hepatitis B was detected in two (10%) children from group 2 and

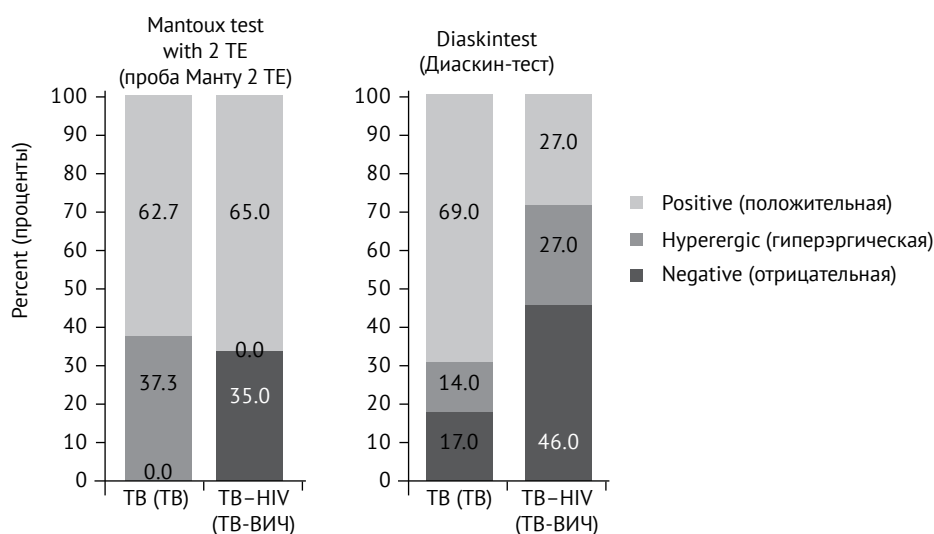


Fig. 4. Results of skin tests (Mantoux test with 2 TE and Diaskintest), $n_1 = 30$, $n_2 = 20$

Рис. 4. Результаты постановки кожных тестов (пробы Манту с 2 ТЕ и Диаскин-теста). $n_1 = 30$, $n_2 = 20$

one (3%) from group 1; hepatitis C was diagnosed in two (10%) children with HIV and one (3%) from group 1 ($p = 0.01$).

The results of skin testing are shown in Figure 4. Positive Mantoux tests were equally frequent in the two groups: 19 (62.7%) in group 1 vs. 13 (65%) in group 2 ($p = 0.05$). Hyperergic reactions were observed only in children without HIV infection ($n = 11$, 37%). Seven (35%) children with TB-HIV coinfection had negative Mantoux tests. Children without HIV infection were more likely to have positive results of Diaskintest than children with TB-HIV coinfection [21 (69%) vs. 5 (25%), $p = 0.04$]. Hyperergic reactions were observed in five (25%) and four (14%) children from group 2 and 1, respectively ($p = 0.09$). The frequency of negative Diaskintest results was higher among children with HIV than among controls [10 (50%) vs. 5 (17%), $p = 0.04$].

Furthermore, we analyzed the correlation between immune status, viral load, and TB forms among children with TB-HIV coinfection. Severe generalized TB was primarily diagnosed in children with severe immunodeficiency (CD4 count of 2%–9%) and high viral load (675,000–1,000,000 copies/mL). Low viral load (65,000–480,000 copies/mL) and moderate immunosuppression (CD4 count of 15%–34%) were observed in children with intrathoracic lymph node TB in infiltration, thickening, or calcification phase.

All children with TB-HIV coinfection had their HIV diagnosis confirmed at the Center for Infectious Diseases. Only one child was diagnosed with 4A stage of HIV infection, whereas the rest of the children had 4B stage HIV infection. ART was prescribed by a physician from the Center for Infectious Diseases; TB treatment was then adjusted [11]. We observed positive dynamics in

response to treatment, including a decrease in viral load and an increase in CD4 count. Children with generalized TB demonstrated a slower improvement compared with patients with localized TB. In these children, CD4 counts did not return to normal values even after completion of the main course of TB treatment (12 months) along with constant administration of ART.

CONCLUSIONS

1. The number of children with TB-HIV coinfection is not declining; particular attention should be paid to late diagnosis of HIV infection in children with known perinatal exposure.
2. TB diagnosis in children with TB-HIV coinfection is largely based on clinical manifestations. Children positive for HIV are more likely to have generalized TB than those without HIV. The prevalence and severity of TB directly correlate with the level of immunosuppression.
3. More than 30% of children with TB-HIV coinfection have negative TST and Diaskintest results. Comprehensive examination is required to confirm the diagnosis of TB.
4. Severe generalized TB was primarily diagnosed in children with TB-HIV coinfection with severe immunodeficiency and high viral load.
5. Early diagnostics of TB in children with HIV requires close interaction of general practitioners and TB specialists to organize preventive examination of children with perinatal HIV exposure.

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◆ Information about the authors

Elena B. Vasileva – MD, PhD, Associate Professor, Department of TB. St Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: helenchern27@mail.ru.

Marina E. Lozovskaya – MD, PhD, Dr Med Sci, Professor, Head, Department of TB. St Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: lozovskaja-marina@rumbler.ru.

◆ Информация об авторах

Елена Борисовна Васильева – канд. мед. наук, доцент, кафедра фтизиатрии. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: helenchern27@mail.ru.

Марина Эдуардовна Лозовская – д-р мед. наук, профессор, заведующая, кафедра фтизиатрии. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: lozovskaja-marina@rumbler.ru.

◆ Information about the authors

Ludmila V. Klochkova – MD, PhD, Associate Professor, Department of TB. St Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: lklochkova@yahoo.com.

Iulia A. Yarovaya – MD, PhD, Associate Professor, Department of TB. St Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: julia_yarovaya@mail.ru.

Olga M. Noskova – Tuberculosis Department. Saint Petersburg State Healthcare Institution “Children’s City Infectious Diseases Hospital No. 3”, Saint Petersburg, Russia. E-mail: julia_yarovaya@mail.ru.

◆ Информация об авторах

Людмила Владимировна Клочкова – канд. мед. наук, доцент, кафедра фтизиатрии. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: lklochkova@yahoo.com.

Юлия Анатольевна Яровая – канд. мед. наук, доцент, кафедра фтизиатрии. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: julia_yarovaya@mail.ru.

Ольга Михайловна Носкова – туберкулезное отделение. Санкт-Петербургское государственное учреждение здравоохранения «Детская городская инфекционная больница № 3», Санкт-Петербург. E-mail: julia_yarovaya@mail.ru.