Pro Index | Journal of Research in Innovative Teaching and Inclusive Learning
Volume: 1 Issue: 1 Year: 2023
ISSN: XXXX-XXXX | http://journals.proindex.uz

Cause-and-Effect Relationship of Immuno-Microbiological Parameters in Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

Dilnoza Tosheva Rakhmatovna

Assistant , Department of Microbiology, Virology and Immunology, Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan.

Abstract: The article presents a comprehensive description of tuberculous infection nidi, where children were exposed to this infection and developed multiple drug resistant tuberculosis It was found out that the risk to develop MDR TB in children was also related to exposure to a TB case with undetected resistance to rifampicin, which was to be taken into account when prescribing the chemotherapy regimen.

When prescribing preventive treatment to children exposed to MDR tuberculosis one should consider the potential risks and benefits.

Key words: multiple drug resistant tuberculosis, children, exposure to tuberculosis, preventive chemotherapy.

The incidence of tuberculosis in children is considered an important prognostic epidemiological indicator, reflecting the general epidemic situation of tuberculosis in the region This is due to the fact that tuberculosis in children most often occurs immediately after contact with a source of infection:

According to the results of studies by many authors, infection with Mycobacterium tuberculosis (MBT) and, as a consequence, the incidence of children and adolescents in outbreaks is tens of times higher than these indicators in the population as a whole, and more than half of the cases are identified from outbreaks with bacterial excretors. The highest risk of the disease is observed in “death centers” of tuberculosis patients, as well as during long-term contacts - for five years or more [2-4] Foci formed by persons who do not secrete MBT also pose a great danger to children, as well as foci unknown to the anti-tuberculosis service [2, 6, 7]. An urgent problem currently in the Russian Federation remains not only the high incidence of children from foci of tuberculosis infection, but also the fact that the proportion of children with tuberculosis is very high with multidrug resistance (MDR) of the pathogen to anti-tuberculosis drugs (ATDs) [2, 6] According to federal reporting forms on tuberculosis (forms No. 33 and 8), the proportion of children with bacterial excretion is consistently small and amounts to about 5.0-6.0% of the number of newly diagnosed persons with tuberculosis aged 0-14 years (in 2011 and 2012 – 4.6 and 4.3%, respectively , in 2015 – 4.6%, 2016 – 5.4%) However, the proportion of people isolating mycobacteria with MDR to PTP among them is quite high and tends to increase – from 22.5% of cases in 2010 to 34.6% in 2016, which almost reaches the level of MDR in adolescents - 38.4% in

2016. Undoubtedly, the priority direction of modern phthisiology is the prevention of the development of the disease, especially in childhood An integral part of the prevention of tuberculosis in children is considered to be the timely implementation of anti-epidemic and therapeutic measures in the focus of tuberculosis infection Thus, in the work of L. V. Lebedeva (1996) it was shown that the use of anti-TB drugs in children at risk for tuberculosis can reduce the risk of developing tuberculosis by 7-8 times.

Purpose of the study: to assess the epidemic danger of foci of tuberculosis infection in the development of tuberculosis in children with MDR pathogens and the effectiveness of preventive anti-tuberculosis treatment for children from foci with MDR MTB

Materials and methods: A retrospective analysis of various foci of tuberculosis infection as a source of development of tuberculosis with MDR MBT in children was carried out. The object of the study was medical documentation (medical history of an inpatient - form No. 003, extract from the medical history and outpatient card of a patient with tuberculosis - form No. 081) for children with tuberculosis aged 0-17 years, as well as data from the developed request questionnaire

(in agreement with the chief freelance specialist, pediatric phthisiatrist of the Ministry of Health of the Russian Federation), which was sent to anti-tuberculosis institutions of the constituent entities of the Russian Federation, receiving from them the necessary information on children with tuberculosis (without identification data) who were in contact with patients with tuberculosis Into the study included 101 children from 0 to 17 years old from foci of tuberculosis infection with established tuberculosis with MDR MBT at the source

To determine the degree of risk of developing tuberculosis culosis with MDR MBT in children from various foci of infection (contacts), two groups of foci were conditionally identified depending on the results of the drug susceptibility test (DST) of MBT at the suspected source 128 adult patients with tuberculosis were registered in 101 foci:

The first (1st) group of outbreaks (80 adult patients) – with established drug resistance of MBT at the source to at least isoniazid (H) and rifampicin (R) or rifampicin (MDR) This also included patients (5 people) with MBT resistance to isoniazid and rifampicin, fluoroquinolone (Fg) and one of the injection drugs (extensively drug resistant - XDR):

The second (2nd) group of lesions (48 adult patients) – without MDR MBT:

a) 25 people with established drug resistance of MBT at the source to isoniazid or several anti-tuberculosis drugs (but not MDR MBT);

b) 13 patients without bacterial excretion or data on drug sensitivity of MBT to PTPs;

c) 10 patients with preserved MBT sensitivity to PTP

Statistical analysis of the obtained data was performed using Microsoft Office 2010 program packages (Microsoft Excel version 14 0 7116 5000) To compare qualitative characteristics in independent samples, Fisher's tests were used The null hypothesis of no differences was rejected when the value criterion statistics $p < 0.05$

Research results: Foci of tuberculosis infection were represented by both newly diagnosed patients and patients with a chronic course of the tuberculosis process The distribution of adult patients by clinical forms of tuberculosis is presented in Table 1.As follows from Table 1, in patients representing foci of infection, fibrous-cavernous pulmonary tuberculosis was recorded in almost half of the cases (43.0%) Infiltrative pulmonary tuberculosis was diagnosed in a third of patients (32.8%) Disseminated pulmonary tuberculosis (12.5%) and caseous pneumonia (3.1%) were detected quite often Focal tuberculosis as a "minor" form of tuberculosis was found only in 6.3% of cases, and in 2.3% it was cirrhotic pulmonary tuberculosis has been regis

Fibrous-cavernous tuberculosis was somewhat more common in patients with MDR MTB (1st group of lesions) in comparison with patients without MDR pathogen (2nd group of lesions) - 48.8 and 33.3%, respectively, whereas disseminated processes were more often diagnosed in patients of the 2nd group of lesions (16.7% versus 10.0%) Infiltrative pulmonary tuberculosis was detected in approximately equal proportions in both groups of lesions: 33.7 and 31.2%, respectively ($p \geq 0.05$) Focal pulmonary tuberculosis was significantly more common in foci without MDR MBT - 8.3% versus 5.0% - in foci of MDR MBT:

Tuberculous processes in patients of both groups were predominantly widespread, affecting more than two segments of lung tissue or bilateral

Bacterial excretion was recorded in 82% of patients in both groups (105 out of 128 people) In the 1st group of lesions, all patients had bacterial excretion and MDR MBT to PTP In the 2nd group of foci with bacterial excretion there were 25 patients out of 48 (52 %) with varying resistance of the pathogen to anti-TB drugs, but not MDR MBT Massive bacterial excretion was characteristic of patients of the 1st group of lesions and was recorded 2.6 times more often than in patients of the 2nd group of lesions (62.50 ± 2.94 and $24.00 \pm 9.59\%$, respectively ; $p < 0.005$) Perhaps one of the putative signs of the risk of developing MDR tuberculosis in children from an outbreak without DST results at the source can be considered the presence of massive bacterial excretion

As a rule, MBT resistance was determined to several drugs simultaneously Thus, in the 1st group of lesions, MBT resistance to the combination of only isoniazid and rifampicin (HR) was observed in only 15% of patients; most often, resistance was determined to a combination of 4 drugs or more Resistance to only 1st line drugs was registered in more than half of the patients - 58.7% Resistance of the tuberculosis pathogen to 2nd line drugs in combination with HR occurred in 41.3% of cases - in 33 out of 80 patients , amounting to1-st group of lesions Of the 2nd line drugs, the combination of HR most often included kanamycin (Km) - in 38.8% of cases. Resistance to capreomycin (Cm) was noted in 7.5% of cases, to ofloxacin (Ofl) – in 8.8% of patients, and in all cases in combination with an injectable drug Since all sick children were diagnosed with tuberculosis with an MDR pathogen, foci with patients without MDR MTB and patients without bacterial excretion were of particular interest (2nd group of lesions) In more than half of the patients (52.1%) in this group, the sensitivity of MBT to PTPs was unknown, in almost a third of patients (27.1%) drug resistance of MBT to various drugs (except rifampicin) was determined, in 20.8 % of patients in this group of lesions, the sensitivity of the pathogen to PTP was preserved before the start of chemotherapy In patients from the 2nd group of lesions, drug resistance of MBT (in bacterial excretors) was more often observed to streptomycin and isoniazid - 92.3 and 76.9% of cases accordingly.

As in the 1st group of lesions, a fairly high proportion of patients had MBT resistance to ethambutol (38.4%), kanamycin (30%) In 7.6% of cases, drug resistance of MBT was noted to fluoroquinolones Children fell ill with approximately the same frequency that-berculosis with MDR MBT from a family focus of infection (father, mother) and periodically related focus (grandmother, grandfather, aunt, uncle) - 49.5 and 43.5%, respectively It is important to note that more than a third of children (40 out of 101 children - 39.6%), who fell ill with tuberculosis with MDR MBT, were from foci not related to foci with MDR MBT at the source.

It can be assumed that in adult patients with preserved MBT sensitivity before treatment, resistance to isoniazid and rifampicin could have developed during treatment, but DST was not performed It is possible that there was also an unknown source of infection of the child, which

could be a source of development of tuberculosis in the child with MDR pathogens, as well as patients with unknown sensitivity (in the absence of MBT detection)

In the vast majority of cases (74.1%), children and adolescents with MDR tuberculosis were in long-term contact with adult patients - from 3 years or more (46 children - 45.5% in the 1st group of foci and 29 children - 28 .7% in the 2nd group of outbreaks) Only a quarter of sick children (25.7%) were identified during the first two years of being in contact with a patient with tuberculosis Of these, 11 patients (5 from the MDR outbreak) were under the age of 3 years old, whose disease was accompanied by clinical symptoms and was identified by referral With a duration of contact of 3-4 years, 32.6% of children were identified (33 out of 101 contacts),

5 years or more - 41.5% (42 out of 101 children) In the outbreaks of group 1, tuberculosis was detected in 16.8% of children during the first two years, with a contact duration of 3 to 5 years - in 19.8% and more than 5 years – in 25.7% of children According to our data, before tuberculosis is detected in children, contact in foci with MDR MBT was longer than in foci without MDR MBT: for 3-4 years - 19.8 and 12.8%; for 5 years or more – 25.7 and 15.8% respectively. The most dangerous in terms of epidemics are considered to be the centers where patients with tuberculosis died In our study, 40 children and adolescents (39.6%) who became ill with MDR tuberculosis were from "death centers" The duration of the child's stay in the "death center" before detection The disease is presented in Fig. 1: in almost half of the cases (47.5%) the contact was long-term – 5 years or more Every third child (28.7%) from the "center of death"was in contact with a patient with MDR tuberculosis; 4.9% of children were in contact with patients who died from tuberculosis with mono- and polyresistant pathogens (not MDR), 5.0% of children were from"locus of death" with unknown drug sensitivity of MBT at the source In 30% of cases in the "locus of death" the source of infection was not one, but several (both parents, parents and close relatives, etc.) In some children, tuberculosis was not diagnosed in a timely manner, since the process was detected in the calcification phase .The most typical situation of prescribing chemotherapy to children according to the 4th regimen is a statement of the risk of developing MDR tuberculosis (contact with a patient with MDR MBT, progression of the process, relapse, etc.) In such cases, a combination of anti-TB drugs is usually compiled taking into account the drug resistance of mycobacteria at the suspected source of infection.

We studied and compared the drug resistance of MBT to anti-TB drugs in the suspected source and a child with tuberculosis with the drug resistance of MBT to drugs

The study found that drug resistance of MBT to first-line drugs in children from lesions of both groups (with MDR and without MDR MBT) was high to streptomycin - 82.5 and 84.2%, respectively; ethambutol – 49.2 and 50.0%, respectively Drug resistance of MBT to pyrazinamide was established in 11.1 and 7% of cases, respectively.

A comparison of the drug susceptibility test of MBT in children and adult patients with bacterial excretors with drug resistance to 1st line anti-TB drugs, which are the source of infection, showed complete coincidence in the spectrum of drug resistance in the case of a child with tuberculosis.

MBT resistance to kanamycin was quite common - in 31.7% of sick children from the lesions of the 1st group and 39.5% from the 2nd group of lesions About 19% in both groups of lesions were children with MBT resistance to prothionamide, about 12% - to capreomycin and about 8% - to ofloxacin and PAS

Drug resistance of MBT to isoniazid and rifampicin in combination with other first-line drugs was registered in 47.6%, and in combination with reserve-line drugs - in 52.3%, and resistance to 5 drugs or more was observed in 35% of cases In general, MBT resistance to at least

rifampicin or rifampicin and isoniazid (MDR) in children from foci of tuberculosis infection was slightly higher than in patients with MDR MBT representing the foci.

Thus, the risk of developing tuberculosis with MDR MBT in children is high not only upon contact with a patient with MDR tuberculosis. In our opinion, lesions presented by patients with unknown MBT sensitivity to rifampicin may be a risk factor for the development.

MDR tuberculosis in children Especially, as our studies have shown, with chronic destructive processes and massive bacterial excretion in adult patients "Focuses of death" can be fully included in this category of foci .

In this regard, the question naturally arises: how to prevent tuberculosis in children from foci with MDR MTB in adult patients? In addition to anti-epidemic measures in the source of infection, the determining factors for preventing the disease are the isolation of the child from the site and adequate preventive anti-tuberculosis treatment Recommendations have now been developed for the preventive treatment of latent tuberculosis infection for children at high risk of developing tuberculosis (Guidelines for the management of patients with latent tuberculosis infection - WHO, 2015; Federal clinical recommendations for the diagnosis and treatment of latent tuberculosis infection (LTBI) in children - approved by the Russian Federation in 2015) Clinical recommendations for the preventive treatment of children in contact with tuberculosis patients with MDR pathogens have not been developed .Single publications on prescribing individually selected regimens taking into account MBT resistance at the source without evidence-based assessment of the effectiveness of preventive chemotherapy .

According to our data, of the number of children with tuberculosis (101 children) from the above-mentioned foci, preventive treatment with anti-tuberculosis drugs was carried out in slightly more than half of the cases (57.4%) (Table 2) With approximately the same frequency in the foci with MDR MBT and without MDR MBT - 58.8 and 55.3%, respectively (differences are not statistically significant; $p > 0.05$) Preventive treatment was not carried out in 42.6% of children, most often due to the lack of clinical follow-up at the TB doctor.

Almost all children received preventive treatment on an outpatient basis under the supervision of parents or relatives: 23 children out of 37 in group 1 (62.2%) and 16 out of 21 in group 2 (76.2%) Controlled preventive treatment (in hospital, sanatorium) was carried out only in 19 children out of 58 (32.7%) In most cases (53.5%) preventive treatment was traditionally carried out with one PTP isoniazid (H) in the average therapeutic dose – 10 mg/kg body weight for 3 months The proportion of children who were prescribed two PTPs (isoniazid and pyrazinamide – H + Z) was less than half – 46.5%, the drugs were prescribed mainly for 3 months

Repeated courses of preventive treatment based on contact were prescribed to 23.8% of children Two courses of preventive treatment before detection of the disease were prescribed to 17 out of 58 (29.3%) children (9 from group 1 and 8 patients from group 2 foci); three courses or more – 5 out of 58 (8.6%) children (two from the 1st group and three from the 2nd group of lesions) Repeated courses were prescribed, as a rule, with one PTP (isoniazid) for 3 months In the 1st group of lesions, there was a tendency towards more frequent prescription of two anti-TB drugs In the majority of sick children of both groups of lesions, more than 1 year passed from the moment of preventive anti-tuberculosis treatment to detection of the disease - 59.4% of cases (60 patients out of 101) In 37.6% of cases (38 children out of 101), the duration of CP was no more than 1-2 years before detection of the disease. Thus, despite the positive aspects associated with preventive treatment in general, preventive chemotherapy carried out by the traditional method turned out to be ineffective: all children from foci with drug-resistant MBT developed tuberculosis with drug-

resistant MBT, more than a third - in during the first two years from the date of prescription of preventive treatment.

Preventive treatment cannot be fully effective when children, being in the focus of infection, are constantly exposed to repeated infections with MTB.

Conclusion: It has been established that the primary role in the development of tuberculosis with MDR MBT in a child belongs to the focus where the patient lives, isolating strains of M. tuberculosis resistant to anti-TB drugs, since more than half of the children with drug-resistant MBT tuberculosis had a history of contact with patients with established MDR pathogen.

The spectrum of drug resistance of MBT in children who contracted tuberculosis in the outbreak coincides with the spectrum of drug resistance of MBT at the source of infection, which must be taken into account when prescribing a chemotherapy regimen, defining the category of the patient as a risk of tuberculosis with MDR MBT.

However, tuberculosis with MDR MBT in children also develops in the case when MDR MBT is not established at the intended source, but the focus is represented by patients with chronic destructive tuberculosis and (or) with massive bacterial excretion, including from the “focus death" (39.6% of children fell ill not due to contact with MDR MTB) These facts must be taken into account when establishing a diagnosis of tuberculosis in children with a possible risk of MDR pathogen that caused tuberculosis, and, as a consequence, when prescribing an appropriate chemotherapy regimen All of the above indicates the need for a more thorough and broader epidemic investigation of the source of infection, timely separation of contact and implementation of high-quality preventive anti-tuberculosis measures for children to prevent the disease, taking into account all risk factors for the development of tuberculosis with MDR pathogen Preventive chemotherapy regimens for children from contact with MDR MBT require optimization: it is necessary to study the possibility of using reserve drugs, a combination regimen of more than two drugs, taking into account the sensitivity of MBT at the source of infection, the duration of prophylactic treatment In any case, when prescribing preventive chemotherapy, children in contact with a patient with tuberculosis with MDR pathogens need to weigh the risk-benefit ratio.

REFERENCES

1. Tosheva Dilnoza Rakhmatovna, Enterobiosis in Children Current Diagnostic Problems , EUROPEAN MULTIDISCIPLINARY JOURNAL OF MODERN SCIENCE https://emjms.academicjournal.io/index.php/ Volume: 7
2. Tosheva Dilnoza Rakhmatovna, Clinical and epidemiological aspects of the course of enterobiosis in school-age children,Journal of Advanced Research and Stability, Volume: 01 Issue: 03 | 2022
3. Tosheva Dilnoza Rakhmatovna, Helicobacter pylori in children with gastric dyspepsia syndrome ,Journal of Advanced Research and Stability, Volume: 02 Issue: 03 | 2022
4. Tosheva Dilnoza Rakhmatovna, Helicobacter Pylori and the Risk of Coronary Heart Disease (Literature Review),International Journal of Innovative Analyses and Emerging Technology, Vol. 1 No. 4 (2021)
5. Tosheva Dilnoza Rakhmatovna, Enterobiosis in Children Current Diagnostic Problems , EUROPEAN MULTIDISCIPLINARY JOURNAL OF MODERN SCIENCE https://emjms.academicjournal.io/index.php/ Volume: 7
6. Mansurova M.Kh., Sagdullaeva G.U., Atoeva M.A., Khodieva S.S. and other Dependence of the luminescence of the causative agent of listeriosis on the ages of the culture and the growing environment // Bulletin of the doctor. - Samarkand, 2015. - No. 2. - S. 85-87.

7. Султонова С. Х. Русский язык в Узбекистане: вчера и сегодня //Гуманитарный трактат. – 2018. – №. 25. – С. 8-10.
8. Султонова С. Х. ОБУЧЕНИЕ НАУЧНЫМ ТЕРМИНАМ НА ЗАНЯТИЯХ ПО РУССКОМУ ЯЗЫКУ КАК ИНОСТРАННОМУ //Finland International Scientific Journal of Education, Social Science & Humanities. – 2023. – Т. 11. – №. 1. – С. 777-784.
9. Султонова С. Х. СИНТАКСИЧЕСКИЕ КОНСТРУКЦИИ НА УРОКАХ РУССКОГО ЯЗЫКА КАК ИНОСТРАННОГО //O'ZBEKISTONDA FANLARARO INNOVATSIYALAR VA ILMIY TADQIQOTLAR JURNALI. – 2023. – Т. 2. – №. 15. – С. 769-775.
10. Розмахов М. Ю. Основные черты современного корейского языка в свете теории вариантности //Вестник Адыгейского государственного университета. Серия 2: Филология и искусствоведение. – 2016. – №. 2 (177). – С. 106-110.
11. Ханазарова С., Султонова С. Х. МОТИВАЦИЯ НА УРОКАХ РУССКОГО ЯЗЫКА //SUSTAINABILITY OF EDUCATION, SOCIO-ECONOMIC SCIENCE THEORY. – 2023. – Т. 1. – №. 10. – С. 8-12.