



Modern approaches to pharmacotherapy of tuberculosis infection in children

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Abstract

Anti-TB drugs for children: Aetiotropic therapy is used for the treatment of tuberculosis (TB) in children, as well as in adult patients. Anti-tuberculosis drugs (anti-TB drugs) are divided into 3 lines, taking into account drug sensitivity in *Mycobacterium tuberculosis* (MBT). First-line anti-TB drugs (basic) are used to treat TB caused by drug-susceptible MBT. Second- and third-line (reserve) drugs are recommended for the treatment of MBT-induced multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, respectively.

Stages and regimens to treat tuberculosis: Chemotherapy of tuberculosis in children is carried out in 2 stages (intensive treatment and continuation of treatment) and includes 5 regimens. Each regimen assumes a certain combination of anti-TB drugs, indicating the duration and frequency of their administration. The final chemotherapy regimen is chosen only according to the results of determining the drug sensitivity. To improve the TB epidemic among children, it is important to improve the regimens for the use of anti-TB drugs. The effectiveness of anti-tuberculosis pharmacotherapy is largely determined by the MBT sensitivity and the rational choice of the chemotherapy regimen. The wrong choice of a chemotherapy regimen or its violation threatens to reduce the effectiveness of pharmacotherapy and expand the spectrum of resistance of the pathogen. The development of fixed-dose combination anti-TB drugs and special dosage forms for children will improve the quality of chemotherapy and adherence to treatment. Pharmacoeconomic studies are needed to increase the effectiveness of drug pharmacotherapy for tuberculosis infection in children and to optimize the costs of its implementation.

Keywords

drug resistance of mycobacterium tuberculosis, anti-tuberculosis drugs, tuberculosis chemotherapy regimens, tuberculosis infection in children.

Introduction

An estimated 10 million people (12% of them were children) worldwide fell ill with tuberculosis in 2019, according to The World Health Organization. The Russian Federation is one of the countries with the greatest burden of tuberculosis. The indicator of the total incidence of

tuberculosis in the country in 2019 was 41.2 per 100 000 population. The cases of multidrug resistance tuberculosis increased to 5.4 per 100 000 population in 2019. The epidemic of a new coronavirus infection caused by SARS-COV-2, which began in 2019, has affected the tuberculosis control. The number of people newly diagnosed with TB fell from 7.1 million in 2019 to 5.8 million in 2020.

Reduced access to prevention, diagnostics and treatment of TB has resulted in an increase in TB deaths – by 1.3 million TB deaths among HIV-negative people and by an additional 214 000 deaths among HIV-positive people. Still, we should not forget that tuberculosis is curable and preventable. The most effective method of treating tuberculosis patients is the use of aetiotropic chemotherapy with anti-TB drugs (World Health Organization 2021).

Anti-TB drugs for children

In the Russian Federation, the epidemic situation with regard to tuberculosis infection, including among the child population, remains difficult. The incidence of tuberculosis among children decreased from 12.4 per 100 000 population (2015) to 7.7 per 100 000 population (2019). Child mortality in 2019 was 0.3 per 100 000 population. The same indicator in 2015 was 0.6 per 100 000 population.

The difficult situation is largely due to the development of drug resistance of *Mycobacterium tuberculosis* (MBT) to the main anti-TB drugs (Nechaeva 2020). Russia, along with India and China, is included in the list of countries with a wide prevalence of drug resistance of MBT to anti-TB drugs (Vasilyeva et al. 2017). The proportion of patients with MBT resistant to **Isoniazid** and **Rifampicin** (multidrug resistance, MDR) among patients with respiratory tuberculosis in 2019 increased to 30.1% (Federal Research Institute for Health Organization and Informatics of the Ministry of Health of the Russian Federation 2019).

The most effective method of treating tuberculosis patients is the use of aetiotropic chemotherapy with anti-TB drugs. According to scientists, tuberculosis infection can be successfully treated with adequate drug supply and rational use of drugs. With adequate pharmacotherapy, it is possible in most cases to complete effectively the main course of treatment of patients with tuberculosis (Zinchenko et al. 2018; Nechaeva 2020). Several chemotherapy regimens are used to treat children with TB infection. Constant monitoring of MBT resistance to anti-TB drugs and selecting the optimal modes of their use are necessary to increase the effectiveness of anti-tuberculosis pharmacotherapy.

This article presents an analysis of various regimens of chemotherapy for tuberculosis infection in children with the aim of optimizing them and increasing the effectiveness of the use of anti-tuberculosis drugs.

The basis for the management of patients of any age with tuberculosis infection is the appointment of aetiotropic pharmacotherapy – chemotherapy. In Russia, the treatment of patients with tuberculosis infection is based on guidelines approved by the Ministry of Healthcare of the Russian Federation (MH RF). Currently, the provisions of the Order of the Ministry of Health of the Russian Federation no. 951 of December 29, 2014 and no. 1246n of November 24, 2020 are in force (Ministry of Healthcare of the Russian Federation 2014, 2020). In accordance with the orders, the clinical guidelines have been developed and approved, specifying the provision

of anti-tuberculosis care to various categories of citizens, including for children and adolescents (Russian Society of TB Clinicians 2014, 2015, 2016).

Medicines for the treatment of respiratory tuberculosis are divided into 3 lines, taking into account the drug sensitivity. First-line anti-TB drugs are the mainstay of treatment for TB caused by drug-susceptible *Mycobacterium tuberculosis*. These include **Isoniazid**, **Pyrazinamide**, **Rifampicin**, **Rifabutin**, **Ethambutol**, and **Streptomycin**. If a patient has MBT with multidrug resistance (MBT resistance to **Isoniazid** and **Rifampicin**), they resort to prescribing drugs of the second-line (reserve) – **Kanamycin**, **Amikacin**, **Capreomycin**, **Levofloxacin**, **Moxifloxacin**, **Sparfloxacin**, **Bedaquiline**, **Protionamide**, **Ethionamide**, and **Aminosalicilylic acid**. The third-line, also a reserve one, includes antibacterial drugs: **Linezolid**, **Meropenem**, **Imipenem+Cilastatin**, and **Amoxicillin+Clavulanic acid**. They are recommended for the treatment of extensively drug-resistant tuberculosis (XDR) of the pathogen (MBT resistance to **Isoniazid**, **Rifampicin**, any drug from the group of fluoroquinolones and one of the injectable second-line anti-tuberculosis antibiotics: **Kanamycin** and/or **Amikacin** and/or **Capreomycin**) and pre-XDR (resistance of MBT to fluoroquinolone (**Ofloxacin** or **Levofloxacin**) or at least to one injectable second-line antibiotic (**Capreomycin**, **Kanamycin** or **Amikacin**), as well as in other cases when it is impossible to form a regimen of five effective drugs (Ministry of Healthcare of the Russian Federation 2014). The WHO recommends the use of **Delamanid** (registered in the Russian Federation in 2020) and **Clofazimine** as backup anti-TB drugs, but in Russia these drugs are not yet officially included in the therapy regimens.

Aetiotropic pharmacotherapy is prescribed to suppress the growth and reproduction of the MBT population in the body and to cure the patient (Ministry of Healthcare of the Russian Federation 2014; Russian Society of TB Clinicians 2014). At the same time, an integrated approach to the chemotherapy of tuberculosis infection is important, involving the combined use of anti-tuberculosis and antibacterial drugs to influence the causative agent of the infection and drugs for the prevention and correction of side effects that occur during the treatment period. According to the literature (Ivanova and Borisov 2017, 2018; Schegertsov et al. 2018; Athulnadh et al. 2020; Laghari et al. 2020; van der Walt et al. 2020), the most frequent side effects associated with the use of chemotherapy in patients with tuberculosis infection are toxic reactions (hepatotoxicity, gastrotoxicity, nephrotoxicity) and allergic reactions. The incidence of side effects from the liver is 44–60% of cases, which is confirmed by the results of studies by many researchers (Ivanova and Borisov 2018; Starshinova et al. 2018). It was found that hepatotoxicity is more often associated with taking first-line anti-TB drugs – **Rifampicin** (67%), **Pyrazinamide** (30%), and **Isoniazid** (7%) (Schaaf et al. 2016; Starshinova et al. 2018). To prevent the development of toxic reactions, at the same time with the start of anti-tuberculosis chemotherapy, it is recommended to prescribe corrective drugs

to patients. The main drugs for the prevention and elimination of emerging side effects are hepatoprotectors and B vitamins, in particular **Pyridoxine hydrochloride** (Russian Society of TB Clinicians 2016; Starshinova et al. 2018). Unfortunately, the rationality of using hepatoprotectors has not been fully proven due to the lack of sufficient scientific data obtained in accordance with the principles of evidence-based medicine (Novikov and Klimkina 2009).

In pediatrics, anti-tuberculosis and antibacterial drugs are prescribed in maximum therapeutic doses (Table 1), taking into account the child's age and body weight, with controlled continuous daily intake in accordance with the prescribed chemotherapy regimen (Ministry of Healthcare of the Russian Federation 2014; Russian Society of TB Clinicians 2016).

Table 1. Daily doses of anti-tuberculosis and antibacterial drugs for children and adolescents

Drug	Daily dose		Route of administration
	Daily, mg/kg	Max, mg/daily	
Isoniazid	5–10–15 mg/kg	600 mg	orally, intravenously, intramuscularly, intracavernously, inhalation
Rifampicin	10–15 mg/kg	600 mg	orally, intravenously
Pyrazinamide	15–20 mg/kg	1500 mg	orally
Ethambutol	15–25 mg/kg	1000 mg	orally
Streptomycin	15–20 mg/kg	1000 mg	intravenously, intramuscularly
Kanamycin	15 mg/kg	750 mg	intravenously, intramuscularly
Amikacin	15–25 mg/kg	1000 mg	intravenously, intramuscularly
Levofloxacin	10–20 mg/kg	750 mg	orally, intravenously
Moxifloxacin	10–15 mg/kg	400 mg	orally, intravenously
Protionamide	10–20 mg/kg	500 mg	orally
Ethionamide	10–20 mg/kg	500 mg	orally
Capreomycin	15–20 mg/kg	1000 mg	intravenously, intramuscularly
Cycloserine	10–20 mg/kg	750 mg	orally
Terizidone	10–20 mg/kg	750 mg	orally
Aminosalicilic acid	150–200 mg	10000 mg	orally, intravenously
Bedaquiline	Over 6 years old (15–30 kg) 200 mg daily for the first 2 weeks, then 100 mg 3 times a week (from the 3 rd week a break between taking the drug for at least 48 hours) Over 12 years old (more than 30 kg) – 400 mg daily for the first 2 weeks, then 200 mg 3 times a week (from the 3 rd week a break between taking the drug for at least 48 hours)		orally
Linezolid	10–12–15 mg/kg	600 mg	orally, intravenously
Amoxicillin+ Clavulanic acid	20–45 mg/kg (in terms of amoxicillin)	3000 mg	orally
Imipenem+ Cilastatin	15 mg/kg	2000 mg	intravenously
Meropenem	10–20 mg/kg	3000 mg	intravenously
Rifapentin	from 12 years old – 10 mg/kg	600 mg 2–3 times a week	orally

Stages and regimens to treat tuberculosis

Tuberculosis chemotherapy includes 2 stages. The first stage is an intensive phase of treatment, which is aimed at destroying the maximum amount of MBT. It is the first stage of treatment at which the acute manifestations of the disease are eliminated, bacterial excretion is stopped, the development of drug resistance is prevented, and infiltrative and destructive changes in tissues are reduced. The second stage is the continuation phase of treatment. This stage targets the remaining MBT and prevent its reproduction. Two-stage treatment promotes the consistent involution of the tuberculosis process, a stable clinical effect, and prevents the reactivation of tuberculosis (Ministry of Healthcare of the Russian Federation 2014).

When prescribing anti-tuberculosis treatment and choosing a chemotherapy regimen, the epidemic danger of a patient, the severity of the course of the disease, the presence of concomitant diseases and conditions in the anamnesis must be taken into account. Often, phthisiatricians have to resort to prescribing individualized treatment, in the construction of which they pay attention to the pharmacokinetics of anti-TB drugs and their interaction with one another. Several chemotherapy regimens have been developed and approved for the treatment of patients with respiratory tuberculosis (Fig. 1).

The chemotherapy regimen is a combination of anti-tuberculosis and antibacterial drugs, indicating the duration and frequency of their administration, timing and content of control studies, and organizational forms of treatment. The final chemotherapy regimen is selected only according to the results of determining the drug sensitivity of MBT, and when the nature of the sensitivity to the drugs used changes, the chemotherapy regimen used is adjusted (Ministry of Healthcare of the Russian Federation 2014; Russian Society of TB Clinicians 2014, 2016).

The first and third regimes are used in the case of diagnosing drug-susceptible tuberculosis; the second, fourth and fifth – in drug-resistant tuberculosis (Russian Society of TB Clinicians 2016).

The first chemotherapy regimen is prescribed for children with bacterial excretion and with preserved drug sensitivity of the pathogen. The course of treatment takes at least 6 months with 4 first-line anti-TB drugs in the intensive care phase (at least 2 months, 60 doses) and two or three drugs in the continuation phase (at least 4 months, 120 doses). To achieve abacillation according to the first regimen in the intensive treatment phase, it is recommended to use a combination of **Isoniazid**, **Rifampicin**, **Pyrazinamide**, and **Ethambutol**. The use of **Ethambutol** can cause the development of optic neuritis. In this connection, the drug is prescribed to children only by the decision of the medical commission. **Ethambutol** can be replaced by **Streptomycin**, but only if the sensitivity of the secreted MBT is established. **Rifapentine** can be used in place of **Rifampicin**. The drug differs from **Rifampicin**

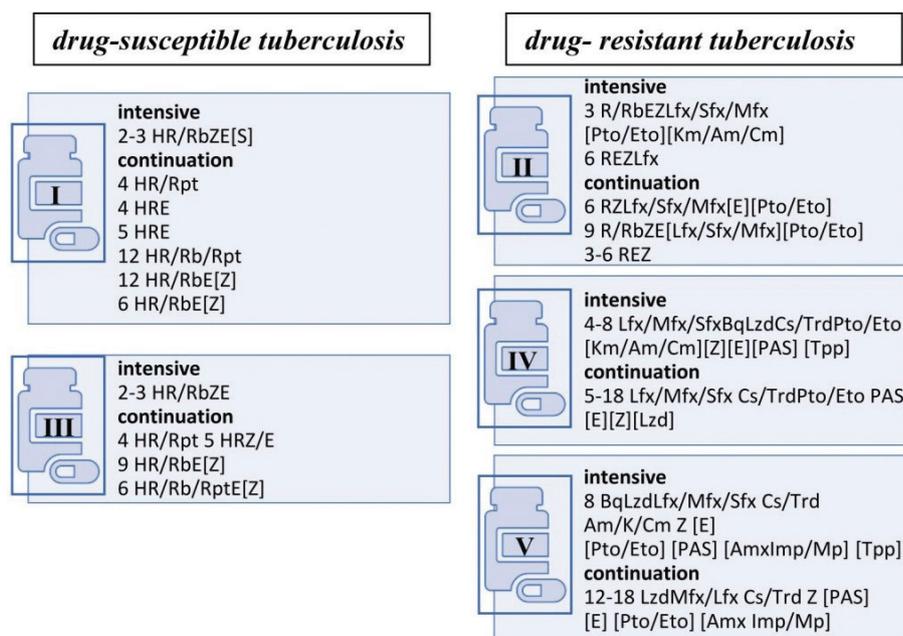


Figure 1. Chemotherapy regimens (I–V) for respiratory tuberculosis (Russian Society of TB Clinicians 2016). **Note.** The numbers in front of the drug abbreviation indicate the duration of treatment (months); a slash (/) indicates “or”; an alternative drug is indicated in square brackets; drug abbreviations: H – Isoniazid, R – Rifampicin, Rb – Rifabutin, Rpt – Rifapentine, Z – Pyrazinamide, E – Ethambutol, S – Streptomycin, Km – Kanamycin, Am – Amikacin, Pto – Protionamide, Eto – Ethionamide, Cm – Capreomycin, Lfx – Levofloxacin, Mfx – Moxifloxacin, Sfx – Sparfloxacin, Cs – Cycloserine, Trd – Terizidone, PAS – Aminosalicilic acid, Bq – Bedaquiline, Lzd – Linezolid, Amx – Amoxicillin + Clavulanic acid; Imp – Imipenem+Cilastatin, Mp – Meropenem; Trp – Thioureidoiminomethylpyridinium perchlorate.

by prolonged action and a lower risk of side effects from the liver (Samoylova et al. 2018). It should be born in mind that the prescription of Rifapentin is possible only for children who have reached the age of 12 (State Register of Medicines 2020). They proceed to the continuation phase in the absence of bacterial excretion, confirmed by the results of microscopic examinations, and the establishment of positive clinical and radiological dynamics. By the decision of the medical commission, the intensive care phase can be extended. In the continuation phase, Isoniazid with Rifampicin or Isoniazid with Rifampicin and Ethambutol are used. If there are contraindications for Ethambutol, it can be substituted for Pyrazinamide. Rifapentine may be given instead of Rifampicin. Rifabutin is recommended in place of Rifampicin for children with HIV infection receiving antiretroviral therapy.

Children with tuberculosis with established drug resistance of MBT to Isoniazid and sensitivity to Rifampicin, or from a contact with this type of sensitivity are treated according to the second regimen. The duration of the regimen should be at least 9 months (intensive phase – at least 3 months, 90 doses; continuation phase – at least 6 months, 180 doses). In the intensive phase, 4 anti-TB drugs of both the first- and second-line are combined, taking into account the results of determining the drug sensitivity of the pathogen. The recommended regimen is the following: Rifampicin, Pyrazinamide and Ethambutol with Levofloxacin for 6 months – intensive phase; Rifampicin, Pyrazinamide and Ethambutol up to 9–12 months in the continuation phase. The prescription of

Levofloxacin and other fluoroquinolones is allowed after the decision of the medical commission. Previously, the group of fluoroquinolones was not recommended for use in children. However, recent studies have confirmed the safety and the possibility of using Levofloxacin in the treatment of respiratory tuberculosis in children under 15 years of age (Russian Society of TB Clinicians 2016; Aksenova et al. 2019).

The prescription of the third chemotherapy regimen is indicated for children with tuberculosis without bacterial excretion and the risk of developing MDR. The duration of the intensive phase should be at least 2 months (60 doses), and the continuation phase should be at least 4 months (120 doses). For treatment in the intensive phase, 4 anti-TB drugs are used – Isoniazid, Pyrazinamide, Rifampicin, and Ethambutol. The continuation phase includes Isoniazid with Pyrazinamide or Isoniazid with Rifampicin and Pyrazinamide. Ethambutol may be used instead of Pyrazinamide in the three-way regimen.

The fourth chemotherapy regimen is prescribed for children with tuberculosis with established resistance of the pathogen to Rifampicin and Isoniazid and sensitivity to drugs of the fluoroquinolone group, with unknown drug sensitivity to other anti-TB drugs, as well as for patients at risk of MDR of the pathogen. For the treatment of such children (with MDR MBT), anti-TB drugs are used, divided into three groups depending on their effectiveness. Group A consists of Levofloxacin or Moxifloxacin with Bedaquiline and Linezolid. Bedaquiline is a new diarylquinoline drug approved for use in children.

Clinical studies have confirmed its effectiveness and safety (Esposito et al. 2016; Pym et al. 2016; D'Ambrosio et al. 2017; Migliori et al. 2017; World Health Organization 2019). **Cycloserine** and **Terizidone** are in group B. Group C includes **Ethambutol**, **Pyrazinamide**, **Imipenem+Cilastatin**, **Meropenem**, **Amikacin (Streptomycin)**, **Ethionamide** or **Protionamide**, and **Aminosalicylic acid**. **Kanamycin** and **Capreomycin** are prescribed only for life-saving reasons due to their high toxicity. Treatment of patients with MDR according to the fourth regimen should be carried out for at least 18–20 months (long-term regimen) or at least 9–12 months (short regimen). The short regimen is indicated in the case of exclusion of resistance to drugs of the fluoroquinolone group and injectable antibiotics, and in cases of limited and minor forms of tuberculosis in children. The fourth treatment regimen consists of at least 5 drugs: **Levofloxacin** or **Moxifloxacin**, **Bedaquiline**, **Linezolid**, **Cycloserine** or **Terizidone**, and/or **Protionamide** or **Ethionamide** (Russian Society of TB Clinicians 2016). The fourth regimen can be standard or custom. An individualized regimen is indicated for patients with respiratory tuberculosis with established drug resistance of the pathogen to **Isoniazid** and **Rifampicin** and sensitivity to drugs of the fluoroquinolone group, with known results of sensitivity to anti-TB drugs of the second-line (reserve).

In 2019, WHO introduced a new approach to the formation of tuberculosis chemotherapy regimens, including combinations of new drugs with antimycobacterial activity. In particular, the groups of drugs were revised according to the order of inclusion in the chemotherapy regimen when MBT with MDR or **Rifampicin** resistance is detected. Group A includes **Levofloxacin** (or **Moxifloxacin**), **Bedaquiline**, and **Linezolid**; Group B – **Clofazimine** and **Cycloserine/Terizidone**; Group C (if it is impossible to use drugs of groups A and B) – **Ethambutol**, **Delamanid**, **Pyrazinamide**, **Imipenem+Cilastatin**, **Meropenem**, **Amikacin (Streptomycin)**, **Ethionamide/Protionamide**, **Aminosalicylic acid** (World Health Organization 2019).

The use of the standard fifth chemotherapy regimen is justified in patients with tuberculosis with suspected XDR pathogen without bacteriological confirmation, as well as from a proved close contact with a tuberculosis patient with XDR-MBT. An individualized regimen is necessary for children with respiratory tuberculosis, with established drug resistance of the pathogen to **Isoniazid** and **Rifampicin** in combination with established or suspected resistance to **Ofloxacin**. The duration of pharmacotherapy according to the fifth regimen is at least 18–24 months (intensive phase – at least 6–8 months; continuation phase – at least 12 months). The terms of treatment for patients with limited uncomplicated processes with good positive dynamics can be reduced to 15–17 months (Russian Society of TB Clinicians 2016). In the intensive phase of therapy, at least 6 drugs are used, to which sensitivity is preserved. It is recommended to include **Bedaquiline**, **Linezolid**, and **Levofloxacin** in the regimens. In the continuation phase, 4 drugs are prescribed with the addition

of **Moxifloxacin** or **Levofloxacin** and other drugs with preserved sensitivity.

The effectiveness and safety of antituberculosis pharmacotherapy in children depends on the duration and continuity of treatment. Short course or premature refusal from chemotherapy does not allow achieving the final clinical effect, which results in the aggravation and progression of the tuberculosis process. Long-term use of chemotherapy in children is dangerous due to the occurrence of side effects with the development of gross disorders of cellular metabolism and a gradual decrease in the sensitivity of MBT to drugs. Violation of the regime for taking anti-TB drugs threatens to expand the spectrum of resistance of the pathogen. One of the main reasons for early discontinuation of chemotherapy for tuberculosis (especially in children) is the inconvenience of taking a large number of drugs. Recent studies have been aimed at this aspect of pharmaceutical care in pediatric phthisiology. Fixed-dose combined anti-TB drugs have been developed. An increase in adherence to treatment has been proven in the case of the use of such drugs (Faust et al. 2019; Tsiligiannis et al. 2019; Wademan et al. 2019). In addition, the combination of anti-TB drugs makes it possible to sum up their therapeutic effect. The destruction of MBT occurs faster, and the likelihood of drug resistance formation decreases (Faust et al. 2019). A recent Russian multicenter observational study demonstrated that the use of fixed-dose combined anti-TB drugs in patients with newly diagnosed tuberculosis or its recurrence with preserved MBT sensitivity to **Isoniazid** and **Rifampicin** in chemotherapy regimens I and III was effective and was characterized by sufficient safety and tolerability (Tyulkova et al. 2020).

Another reason for the insufficient effectiveness of antituberculosis chemotherapy in children may be lack of special children's dosage forms of antituberculosis drugs on the Russian pharmaceutical market (Usacheva et al. 2020). A number of scientists point out the need to expand the range of anti-TB drugs used by developing and introducing oral liquid dosage forms, tablets for dispersion in the oral cavity (Kim et al. 2016; Purchase et al. 2019). Research is underway to develop innovative dosage forms for the treatment of tuberculosis by incorporating anti-TB drugs into nanoparticles, nanocapsules, and liposomes for further targeted transport to the site of infection (Zinchenko et al. 2018, Sanzhakov et al. 2013).

Conclusion

For the treatment of tuberculosis infection in children, as well as in adult patients, actiotropic chemotherapy is used. Antituberculosis drugs are divided into 3 lines, taking into account the drug sensitivity of *Mycobacterium tuberculosis*. First-line anti-TB drugs (basic) are used to treat TB caused by drug-susceptible MBT. Drugs of the second- and third-lines (reserve) are recommended for the treatment of tuberculosis caused by MBT with multi-drug

resistance and extensively drug resistance, respectively. Chemotherapy of tuberculosis in children is carried out in 2 stages (intensive treatment and continuation of treatment) and includes 5 regimens. Each chemotherapy regimen involves a certain combination of anti-TB drugs, indicating the duration and frequency of their administration, and organizational forms of treatment. The final chemotherapy regimen is selected only according to the results of determining the drug sensitivity of MBT, and when the nature of the sensitivity to the drugs used changes, the chemotherapy regimen used is adjusted.

To improve the TB epidemic among the child population, it is important to improve the regimens for the use of anti-TB drugs. The effectiveness of antituberculosis pharmacotherapy is largely determined by the MBT sensitivity and the rational choice of the chemotherapy regimen. The wrong choice of chemotherapy regimen does not allow achieving the desired clinical effect, is associated with the risk of side reactions and a decrease in

the sensitivity of MBT to drugs. Violation of the anti-TB drugs regimen, including the duration and continuity of treatment, threatens to decrease the effectiveness of pharmacotherapy and to expand a spectrum of resistance of the pathogen. The development of fixed-dose combined anti-TB drugs and special dosage forms for children will improve the quality of chemotherapy. Increase adherence to treatment has been proven with the use of such drugs. At the same time, the destruction of MBT happens faster, and the likelihood of the formation of drug resistance decreases. Pharmacoeconomic studies are needed to increase the effectiveness of drug pharmacotherapy for tuberculosis infection in children and to optimize the costs of its implementation.

Conflict of interest

The authors declare no conflict of interests.

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