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CHALLENGES, LESSONS LEARNED AND INTERNATIONAL COLLABORATION IN PROVIDING PREVENTIVE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS (DR TPT) IN CHILDREN IN SERBIA

IZAZOVI, NAUČENE LEKCIJE I MEĐUNARODNA SARADNJA U PREVENTIVNOM LEČENJU MULTIREZISTENTNE TUBERKULOZE (DR TPT) KOD DECE U SRBIJI

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Summary Drug-resistant forms of TB continue to be the global public health threats. Multidrug-resistant TB (MDR-TB) is defined as TB resistant to rifampicin and isoniazid, essential anti-TB drugs. Both MDR-TB and rifampicin-resistant TB (RR-TB) are treated with second line anti-TB drugs. Preventing the progression of a drug-resistant tuberculosis (DR-TB) infection to disease is an important pillar of the DR-TB elimination strategy. International guidelines have recently proposed fluoroquinolones for tuberculosis preventive therapy (TPT) in DR-TB contacts. Till 2019, no preventive therapy for MDR TB contacts has been performed in Serbia since it was not included in the national TB treatment and contact tracing guidelines. In 2019 and 2022 for the first time, several children and adolescents appeared as close contact with MDR TB cases. DR TB preventive treatment was performed at Hospital for Children's Lung Diseases and TB, "Dr Dragisa Misovic" Clinic in Belgrade, Serbia in two children aged 2 and 3, in line with latest WHO guidelines, due to international collaboration and national multidisciplinary expert support. During the implementation of TPT for child contacts of MDR TB, we have learned that our capacities for TB program coordination, international and in-country multidisciplinary expert collaboration, epidemiological investigation, contact tracing as well as DS and DR TB management in children are good. However, we faced a lot of legislation and systemic challenges that affected the implementation of DR TPT. The main challenges were lack of pediatric drug formulations, lack of indications for levofloxacin use for TB and use in this age group.

Keywords: preventive therapy, multidrug-resistant tuberculosis, adolescents, children

Sažetak Forme tuberkuloze otporne na lekove i dalje predstavljaju globalnu pretnju javnom zdravlju. Tuberkuloza otporna na više lekova (Multi drug resistant – tuberculosis MDR-TB) se definiše kao tuberkuloza (TB) otporna na rifampicin i izoniazid, esencijalne lekove u borbi protiv tuberkuloze. MDR-TB i TB rezistentna na rifampicin (RR-TB) leče se lekovima protiv TB druge linije. Sprečavanje progresije infekcije tuberkuloze otporne na lekove (DR-TB) u bolest je važan stub strategije eliminacije DR-TB. Međunarodne smernice su nedavno predložile fluorokinolone za preventivnu terapiju tuberkuloze (TPT) u kontaktima sa DR-TB. Do 2019. u Srbiji se nije sprovodila preventivna terapija za kontakte sa MDR TB , jer nije bilo uključeno u nacionalne smernice za lečenje TB i praćenje kontakata. Tokom 2019. i 2022. godine, se pojavilo nekoliko dece i adolescenata kao bliski kontakt sa slučajevima MDR TB. Preventivno lečenje tuberkuloze obavljeno je u Bolnici za dečije plućne bolesti i tuberkulozu, KBC-a „Dr Dragiša Mišović" u Beogradu, kod dvoje dece uzrasta 2 i 3 godine. U skladu sa najnovijim smernicama SZO, zahvaljujući međunarodnoj saradnji i nacionalnom multidisciplinarnom ekspertskom timu, primenjena je preventivna terapija za kontakte sa MDR-TB. Tokom implementacije TPT za kontakte dece sa MDR TB pokazalo se da su naši kapaciteti za koordinaciju programa TB, saradnja međunarodnih i multidisciplinarnih stručnjaka, epidemiološko ispitivanje, praćenje kontakata tuberkuloze osetljive na standardne lekove (engl. drug-susceptible - DS) i DR TB kod dece zadovoljavajuća. Međutim, suočili smo se sa mnogo zakonskih i sistemskih izazova. Glavni izazovi su bili nedostatak pedijatrijske formulacije lekova, nedostatak indikacija za primenu levofloksacina za tuberkulozu i upotrebu u ovoj uzrasnoj grupi.

Ključne reči: preventivna terapija, multirezistentna tuberkuloza, adolescenti, deca

INTRODUCTION

Drug-resistant forms of TB continue to be the global public health threats. Resistance to rifampicin – the most effective first-line drug – makes the greatest importance as well as concern. Multidrug-resistant TB (MDR-TB) is defined as TB resistant to rifampicin and isoniazid. Both MDR-TB and rifampicin-resistant TB (RR-TB) are treated with second line anti-TB drugs. Globally, the estimated annual number of people who developed MDR-TB or RR-TB (MDR/RR-TB) was relatively flat between 2020 and 2023, after a slow downward trend between 2015 and 2020. The estimated number in 2023 was 400 000 (1,2). In 2023, the estimated proportion of people with TB who had MDR/RR-TB was 3.2% among new cases and 16% among those previously treated (1). Serbia started organized treatment for this severe disease in 2009, due to the support to the donation of the Global Fund to fight AIDS, tuberculosis and malaria (GFATM), aligned national treatment guidelines for drug-resistant TB with the latest World Health Organization (WHO) treatment guidelines and adjusted selection of drugs for treatment regiments with the profile of drug-resistance of the patients and procured all necessary second line anti-TB drugs for adult patients (3). After the end of GFATM support to Serbia, National Health Insur-

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ance Fund continued to procure all drugs through the STOP TB/Global Drug Facility Mechanism (4).

Based on national guidelines, first line drug susceptibility testing (DST) is performed to all culture positive samples for all drugs in four regional laboratories in Serbia, while so far there was no available DST for fluoroquinolones (5). Based on the data of Institute of Public health of Serbia "Dr Milan Jovanovic Batut", number of MDR TB cases in Serbia decreased in the last fifteen years and notified proportion of people with TB who had MDR/RR-TB decreased from 2,5% to1% among new cases and from 15% to ≤ 10% among those previously treated cases (6). So far, there were below 10 adolescent cases of MDR TB diagnosed and successfully treated in Serbia. Second line anti TB drugs for adults were applied. There are no available child formulations since there were no diagnosed MDR TB cases among children.

Effective TB treatment, including its drug-resistant forms, relies on the use of several medicines administered in combination for an adequate duration. Compared with treatments for drug-susceptible forms of TB, MDR TB regimens require a longer course of treatment, a higher pill burden and the use of medicines with a higher toxicity profile; in addition, patients may develop significant adverse events and have poorer treatment outcomes (3). Historically, patients with certain drug-resistance patterns were often treated for 20 months or longer. In 2016, a standardized shorter treatment regimen (9–12 months) was recommended for patients with MDR/RR-TB strains not resistant to fluoroquinolones or second line injectable agents, although longer regimens (18–20 months) continued to be an option for patients who were not eligible for the shorter option (7,8).

Preventing the progression of a drug-resistant tuberculosis (DR-TB) infection to disease is an important pillar of the DR-TB elimination strategy. International guidelines have recently proposed fluoroquinolones for tuberculosis preventive therapy (TPT) in DR-TB contacts, although the available evidence is low quality (9).

Household contacts of a patient with active pulmonary TB are at high risk for a TB infection and disease as they have prolonged exposure to index cases (10,11). A meta-analysis published by Shah and colleagues, showed that 47% (95% confidence interval 30–61%) of the DR-TB patients' household contacts are infected (12). The prevalence of TB infection and disease is particularly high among children who are in household contacts and exposed to RR-TB, reaching up to 57% in an observational study published by Kim and colleagues (13). These transmission rates are even higher between mother and children in the household.

Several regimens have been tested as DR-TB preventive therapy for adults and pediatric population using one, two or three drugs thought to be effective against the source case, including isoniazid, pyrazinamide, ethambutol, fluoroquinolones and/or ethionamide. The strong evidence-based policies for TPT of DR-TB contacts are lacking because the current published data primarily consists of small cohort studies. No randomized, controlled trial data is available to date. The fluroquinolone-based regimens, either fluoroquinolone monotherapy or fluoroquinolone with a companion drug, e.g., ethambutol or ethionamide, are the most evaluated (14).

Till 2019, no preventive therapy for MDR TB contacts has been performed in Serbia since it was not included in the latest national TB treatment and contact tracing guidelines (15,16). In 2019 and 2022 for the first time, several children and adolescents appeared as close contact with MDR TB cases. As there was no previous in country clinical experience related to the topic, upon request for help and guidance from the colleagues from Hospital for Children's Lung Diseases and TB in Belgrade, NTP Manager at the Institute of Public Health of Serbia initiated the communication with the WHO Collaborating Centre for TB and Lung Diseases, Maugeri Care and Research Institute, Tradate, Italy. They provided expert support to our country through e-platform ERS/WHO TB Consilium (17) by two independent opinions. The suggested regimens were presented to the national experts and after in country consultations among expert clinicians (pulmonologists and pediatricians' pulmonologists) and decision making, TPT was implemented (18).

Further in this report we present the case of two young children, aged 2 and 3 years, who were exposed to MDR-TB through their mother and were found to have latent TB infection (LTBI). Two siblings, a 2-year-old and a 3-year-old, were brought to our pediatric TB clinic for evaluation due to prolonged household exposure to their mother, who had been diagnosed with MDR-TB. The mother had pulmonary MDR-TB confirmed by culture and drug susceptibility testing (DST), since December 2021 she was treated at the Special Hospital for lung diseases and TB "Ozren"-Sokobanja. Both children were asymptomatic at presentation, with no history of fever, weight loss, or respiratory symptoms. They had normal physical examinations, and their growth parameters were appropriate for age.

Diagnostic workup was as follows: QuantiFERON-TB Gold test: Positive in both children; Chest X-ray: Normal in both children; Clinical evaluation: No signs of active TB disease; Gastric Aspirate for Acid-Fast Bacilli (AFB) and Culture: all three specimens came negative; HIV Testing: Negative.

Given their positive QuantiFERON-TB Gold results and lack of clinical or radiographic evidence of active TB, both children were diagnosed with latent TB infection (LTBI) secondary to MDR-TB exposure.

Preventive Treatment Plan: Since the children were exposed to MDR-TB, available guidelines and ERS/WHO TB Consilium suggested preventive therapy regimen: Levofloxacin (15mg/kg/day, once daily) and Pyridoxine (Vitamin B6) to prevent neurotoxicity. This regimen was chosen in relation to the mother's MDR-TB strain, which was resistant to isoniazid and rifampicin but susceptible to fluoroquinolones.

According to the protocol for the treatment of MDR-TB and the decision of the National TB Committee, with the consent of the pediatric Consilium, our patients were given chemoprophylaxis Levofloxacin 15mg/kg, daily. This formulation of the drug was the only one available at that time. Unfortunately, it could not be adapted to the age of the child. Another obstacle was the lack of an indication of the drug for TB treatment as well as lack of adequate indication for the use of this drug in children in our country (19,20).

After additional consultations, the National Expert Committee opinion was to use Ethambutol instead of Levofloxacin. Both children were discharged for further treatment at home to continue prophylaxis: Ethambutol 15mg/kg in one dose daily for six months. The children were monitored closely for potential drug-related side effects.

Follow-Up and Monitoring was performed during preventive treatment (0–6 months) by:

- Monthly clinical evaluations: Monitoring for symptoms of TB, medication side effects, and adherence.
- Monthly liver function tests
- Growth monitoring: Ensuring normal weight gain and development.
- Repeat Chest X-ray if symptoms develop.

Post-Treatment Follow-Up (6 months – 2 years)

- Every 3–6 months clinical follow-up until 24 months post-exposure.
- Chest X-ray at 12 months and 24 months post-exposure, even if asymptomatic.
- Immediate evaluation if any TB symptoms develop (fever, weight loss, persistent cough, night sweats).

Outcome:

At the two-year follow-up:

- Both children remained asymptomatic, with normal growth and development.
- No radiological evidence of TB disease.
- No side effects from preventive treatment were observed.
- No progression to active TB.

Preventing progression from LTBI to active MDR-TB is crucial in young children due to their high risk of severe disease. While there is no universally accepted regimen for MDR-TB LTBI, fluoroquinolone-based preventive therapy is increasingly recommended, particularly when the source case is fluoroquinolone-susceptible. Close monitoring during treatment and follow-up is essential to ensure safety and efficacy.

This case highlights the importance of early identification and preventive treatment of children exposed to MDR-TB. A six-month TB preventive treatment course successfully prevented TB disease in these children, reinforcing the need for proactive management in similar cases.

During the implementation of TPT for child contacts of MDR TB, we have learned that our capacities for NTP coordination, international collaboration and in-country multidisciplinary expert collaboration, epidemiological investigation, contact tracing as well as DS and DR TB management in children are good. However, we faced a lot of legislation and systemic challenges that affected the implementation of DR TPT. The main challenges were lack of pediatric drug formulations, lack of indications for levofloxacin use for TB and use in this age group. In addition, we faced with lack of second line DST anti TB drugs. Although Serbia is low DR TB burden country, having in mind increasing number of migrants from high DR TB burden countries working in Serbia in the areas and places with high frequencies of contacts (public transport, restaurant, factories), the need for intensified DR TB contact tracing and programmatic DR TST implementation will be increasing.

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