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SYSTEMATIC REVIEW

Multiresistant tuberculosis: when should multi-resistant tuberculosis be suspected in children and adolescents?

Tuberculosis multirresistente: ¿cuándo se debe sospechar una Tuberculosis multirresistente en niños y adolescentes?

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ABSTRACT

Introduction: multidrug-resistant tuberculosis (MDR-TB) caused by Mycobacterium tuberculosis mainly affects the respiratory system but can spread to other organs. Its resistance arises from inappropriate use of antibiotics, complicating treatment. Its control depends on rapid diagnoses and solid health programs, especially in young people, where conditions such as HIV worsen the prognosis.
Method: a systematic review of bibliography published in scientific journals was carried out with the aim of compiling all the evidence available to date in order to answer the question posed. When to suspect MR TB in children and adolescents?
Results: multidrug-resistant tuberculosis in children presents significant diagnostic and clinical challenges. The studies reviewed highlight risk factors such as history of treatment and contact with resistant TB. Tools such as GeneXpert and MTBDRplus facilitate rapid diagnosis, and preventive therapy with isoniazid could reduce progression to active TB in close contacts.
Conclusion: taken together, the findings underscore the importance of combining advanced diagnostic methods, a comprehensive assessment of the epidemiological context, and additional support strategies to address the challenges of MDR-TB in children and adolescents. This combination of approaches can guide clinical decision making and strengthen capacity to effectively identify and treat youth at risk for MDR-TB.

Keywords: Tuberculosis; Multidrug-Resistant; Adolescent; Child; Antitubercular Agents; Tuberculosis/diagnosis.

RESUMEN

Introducción: la tuberculosis multirresistente (MDR-TB) causada por Mycobacterium tuberculosis afecta principalmente el sistema respiratorio, pero puede diseminarse a otros órganos. Su resistencia surge por un uso inadecuado de antibióticos, complicando el tratamiento. Su control depende de diagnósticos rápidos y programas de salud sólidos, especialmente en jóvenes, donde condiciones como el VIH agravan el pronóstico.
Método: se realizó una revisión sistemática de bibliografía publicadas en revistas científicas con el objetivo de recopilar toda la evidencia disponible hasta el momento para poder responder a la pregunta planteada. ¿Cuándo sospechar de TBC MR en niños y adolescentes?
Resultados: la tuberculosis multirresistente en niños presenta desafíos diagnósticos y clínicos significativos. Los estudios revisados destacan factores de riesgo como antecedentes de tratamiento y contacto con TB resistente. Herramientas como GeneXpert y MTBDRplus facilitan el diagnóstico rápido, y la terapia preventiva con isoniazida podría reducir la progresión a TB activa en contactos cercanos.

Conclusión: en conjunto, los hallazgos subrayan la importancia de combinar métodos diagnósticos avanzados, una evaluación integral del contexto epidemiológico y estrategias de soporte adicionales para enfrentar los desafíos de la MDR-TB en niños y adolescentes. Esta combinación de enfoques puede guiar en la toma de decisiones clínicas y fortalecer la capacidad para identificar y tratar eficazmente a los jóvenes con riesgo de MDR-TB.).

Palabras clave: Tuberculosis; Multirresistente; Adolescente; Niño; Agentes Antituberculosos; Tuberculosis/ Diagnóstico.

INTRODUCTION

Tuberculosis is an infectious disease caused by the etiological agent Mycobacterium tuberculosis, which mainly affects the respiratory tract but can invade other organs and tissues. It is currently one of the diseases with the highest morbidity and mortality rates in the world.[1]

Tuberculosis is currently treatable, but the problem lies in the misuse or non-compliance with antibiotic treatment, which leads to resistance to treatment and has given rise to a new problem: multidrug-resistant tuberculosis, now considered a global public health problem.[1]

To eradicate tuberculosis, it is essential to strengthen tuberculosis control programs regarding detection, follow-up, and control of cases to interrupt the epidemiological chain.[2]

Adolescents and children are at high risk of developing tuberculosis. The clinical forms are similar to those seen in adults, with cavitary disease in the apices and pleurisy. Significant biological changes mark Childhood and adolescence. In adolescence, there is also an increased risk due to early sexual activity, the presence of unwanted pregnancies, and a higher risk of contracting human immunodeficiency virus (HIV) infections.[2]

Infection with HIV or other diseases that cause immunodeficiency increases the likelihood that infected patients will develop tuberculosis and are at greater risk of death.[3]

Young people aged 10 to 24 could constitute an essential but neglected group in global tuberculosis control. While infants and young children are often exposed to tuberculosis at home by caregivers, adolescents spend more time outside the house, where they may face a higher risk of exposure to M. tuberculosis infection. Unlike young children, adolescents are at risk of infection from peers of the same age.[4]

Adolescents may first be identified for tuberculosis after exposure to M. tuberculosis as part of a contact investigation. Second, they may develop signs or symptoms that could be consistent with a diagnosis of tuberculosis. Third, they may be referred based on the results of an investigation that requires a comprehensive evaluation for tuberculosis.[5]

The first step for healthcare personnel is to screen for tuberculosis using a combination of medical history and a thorough physical examination, along with imaging and microbiological tests (smear microscopy, mycobacterial culture, and/or polymerase chain reaction (PCR) tests, among others).[5]

In most adolescents, tuberculosis is intrathoracic, defined as parenchymal lung disease (infiltrates, cavitations, miliary disease), pleural effusions, or intrathoracic lymphadenopathy (hilar mediastinal). The most common symptoms are cough, fever, and weight loss. Chest X-ray findings reflect changes in pathogenesis that occur with the patient's age; adolescents more frequently present with cavitations and pleural effusions and less regularly with intrathoracic lymphadenopathy or miliary disease, as seen in children.[5]

Drug resistance is a condition in which the presence of Mycobacterium tuberculosis resistant to first- and/or second-line antibiotics is confirmed in vitro, which represents a serious problem for the health of the patient, their environment, and society in general.[6]

The World Health Organization defines drug resistance into five groups:

- Single-drug resistant tuberculosis: This is the disease caused by M. tuberculosis that is resistant to only one drug, usually isoniazid or rifampicin.
- Multi-drug resistant tuberculosis: Resistance is expressed to more than one antituberculosis drug but not simultaneously to isoniazid and rifampicin.
- Multidrug-resistant tuberculosis (MDR-TB): This is when resistance to at least isoniazid and rifampicin is present, with or without the addition of resistance to other drugs.
- Pre-extensively drug-resistant tuberculosis (pre-XDR TB): Resistant to at least isoniazid and rifampicin, along with resistance to one of the two anti-TB fluoroquinolones, levofloxacin and moxifloxacin.
- Extensively drug-resistant tuberculosis (XDR-TB): This is PRE-XDR TB with the addition of resistance to at least Bedaquiline and/or Linezolid, which, together with fluoroquinolones, form group A of the WHO treatment regimen for MDR-TB. This form of tuberculosis is the most clinically and epidemiologically serious due to the difficulties in both diagnosis and treatment.
- Resistant tuberculosis (TR-TB) or pan-resistant tuberculosis is resistant to all first- and second-line

drugs (fluoroquinolones, injectables, thioamides, cycloserine, and PAS). [6,8]

The confirmed diagnosis of rifampicin- and isoniazid-resistant TB is subject to microbiological confirmation from clinical samples or isolated cultures using genotypic or phenotypic drug susceptibility testing, which can be difficult in children and adolescents.

In the absence of rapid molecular drug susceptibility testing or patients with culture-negative tuberculosis, a diagnosis of bacteriologically confirmed multidrug-resistant or extensively drug-resistant TB may be made, or in the absence of clinical improvement (i.e., resolution of symptoms and weight gain) after two months of first-line treatment with adherence (provided that the risk of misdiagnosis of another chronic lung disease is low).[5]

The recommended TB diagnosis goal recommended by international organizations is to identify the causative agent and a minimum drug susceptibility profile, primarily for isoniazid and rifampicin, for all bacilliferous patients.[8]

This isn't easy to achieve in developing countries, although progress is being made toward this goal, primarily through rapid molecular methods. Therefore, pending the widespread dissemination of rapid screening methods for multidrug-resistant tuberculosis, surrogate markers continue to be used, such as treatment failure, loss to follow-up, relapse, close contact with bacteriologically diagnosed multidrug-resistant tuberculosis, immunosuppression, tuberculosis in healthcare workers, and vulnerable populations.[8]

Resistance to anti-Mtb drugs is reported at the program level in two categories: patients with and without previous treatment. In the first case, infection is assumed to have occurred through contact with DR-TB. In the second case, resistance is acquired mainly due to actual or covert monotherapy that selects naturally resistant mutants of the bacillus.[8]

Resistance in patients without previous treatment represents a serious epidemiological situation, as it implies that drug-resistant tuberculosis is being transmitted in the community.

It is usually detected after treatment failure (persistence of positive culture at four months of standard treatment), prolongs the transmission period, and can amplify initial resistance.

The essential determining factor of drug-resistant tuberculosis is actual or covert monotherapy, and the main element that allows its existence to be suspected is treatment failure in standardized treatment regimens.[9]

The resistance that develops to antituberculosis drugs is determined by mutations in the genome of Mycobacterium tuberculosis, which appear spontaneously or are induced by the selective precision of the drugs.[10]

Patients undergoing inadequate treatment regimens may, in the presence of subtherapeutic drug concentrations, generate a proliferation of strains with these phenotypic resistance mutations, which can be transmitted through the air to other people who develop drug-resistant tuberculosis without having previously received any treatment.[10]

To date, it is known that mutations in the gene encoding the beta subunit of RNA polymerase (rpoB gene) confer resistance to rifampicin and that mutations in the catalase-peroxidase gene (katG gene) and in the promoter region of the enoyl-ACP reductase gene (inhA gene) are associated with resistance to isoniazid.[10]

In addition, there are mutations in other genes responsible for resistance to other antituberculosis drugs, such as pyrazinamide (pncA gene), aminoglycosides (rrs), and fluoroquinolones (gyrA).[10]

Currently, diagnostic tests include direct examination of sputum smears with Ziehl-Neelsen staining for detecting acid-fast bacteria, either by fluorescence microscopy or both microscopy methods, liquid or solid culture. This culture is considered the standard reference test for diagnosing tuberculosis but is a complex and time-consuming process.[11]

In 2008, the WHO validated using the Genotype MTBDRplus (GTPlus) assay for the rapid and simultaneous detection of M. tuberculosis complex and resistance to rifampicin and isoniazid from cultures or clinical pulmonary samples with positive smear microscopy. The test is based on a polymerase chain reaction (multiplex PCR), which generates various amplification products (probes) that recognize the most common genetic mutations associated with resistance to isoniazid and rifampicin through reverse hydration. These results are obtained in approximately 8 hours.

In early 2001, the WHO approved a rapid, automated molecular diagnostic test, the Xpert MTB/RIF assay, which can detect tuberculosis and rifampicin resistance simultaneously. [6]

This automated molecular method integrates DNA extraction, real-time PCR genomic amplification, semi-quantitative detection, and detection of rifampicin resistance in the rpoB gene.[1]

This test provides results in 2 hours so that patients can start the appropriate treatment even on the same day.[11]

According to the 2015 WHO guidelines, molecular diagnostic tests should be used where there is a high incidence of tuberculosis, in patients with HIV infection, and when there is a high suspicion of multidrug-resistant tuberculosis. These tests provide rapid results compared to traditional culture methods, which require an average of 4 weeks to obtain a result. However, phenotypic testing is recommended to confirm the molecular

test result.[1]

METHOD

A systematic review of the literature published in scientific journals was conducted to compile all the evidence available to answer the question posed.

To this end, an exhaustive literature search was conducted using search engines such as PubMed, Epistemonikos, Google Scholar, Open Athens, Tripdatabase, Cochrane, and Scielo.

A search used keywords such as multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis, adolescent, children, diagnostic, and antituberculosis drugs.

Once the bibliography was obtained, the question was answered: When should MR-TB be suspected in children and adolescents?

The objective was to obtain the information necessary for the early diagnosis of MR-TB in children and adolescents, to identify molecular tests that allow for rapid diagnosis, and to highlight current treatments.

The study population consisted of adolescents and children diagnosed with multidrug-resistant tuberculosis. Literature was obtained and analyzed for diagnosis and treatment, and the drugs currently available for the treatment of MDR-TB in children and adolescents.

Inclusion criteria

- Literature focused exclusively on tuberculosis in adolescents and children.
- Literature with information on rapid diagnostic methods for MDR-TB.
- Literature on the diagnosis of MDR-TB in the pediatric population.

Exclusion criteria

- Exclusion of literature on adult patients with MDR-TB
- Literature that did not address MDR-TB in adolescents and children
- Literature on patients who have experienced adverse effects related to previous antituberculosis treatment.
- Literature on adolescents with HIV diagnosed with TB The scope of the study was in a university context, carried out at the Inter-American Open University, with data obtained from scientific literature published in renowned scientific virtual biomedical databases.

Data Analysis Plan

The data analysis plan was based on a systematic search of articles for the research. Articles were selected by title, followed by the abstract. Once selected, a detailed search was generated using filters with inclusion and exclusion criteria, thus providing articles on MDR-TB in children and adolescents.

RESULTS

Multidrug-resistant tuberculosis (MDR-TB) in children and adolescents presents significant challenges in diagnosis and clinical treatment. This review compiles the findings of eight relevant studies focusing on diagnostic methods, risk factors, and the clinical presentation of MDR-TB in the pediatric population. Below are comparisons of the diagnoses, along with a compilation of the individual characteristics of each study.

Radiological findings as markers of MDR-TB

In Indonesia, a comparative study of children with drug-sensitive tuberculosis (DS-TB) and those with MDR-TB highlights that MDR-TB frequently presents with consolidations (68 %) and pulmonary cavitation (29 %), as well as fibrosis (42 %).[14] These radiographic findings contrast with less severe patterns seen in DS-TB, suggesting that severe radiographic features may be a marker of MDR-TB in children.

Epidemiological risk factors

Close contact with patients with resistant TB and a history of treatment with antituberculosis drugs are prominent risk factors. A study in South Africa shows that 45,2 % of children with MDR-TB had previously been treated for TB, and 76,4 % had had close contact with a known TB case.[15] The same study in Ethiopia also shows that a history of previous treatment is a significant risk factor; in their study, the prevalence of resistance was 13,9 % in children previously treated and 2,3 % in those who had not been treated.[16]

Rapid diagnostic methods

The arrival of rapid tests such as GeneXpert MTB/RIF and the MTBDRplus linear probe test has led to the fast and accurate detection of MDR-TB. In a study conducted on GeneXpert in Nepal, sensitivity was 98,6 %, and specificity was 100 %, with results available in less than two hours, compared to the 75 days required

by conventional tests.[17] MTBDRplus showed a sensitivity of 99,3 % for rifampicin and 88,5 % for isoniazid, highlighting its usefulness in settings with a high burden of MDR-TB.[18]

Impact of HIV and Malnutrition on Treatment Outcomes

HIV coinfection and malnutrition were factors associated with poorer outcomes in children with MDR-TB. A meta-analysis revealed that among coinfected children, those who did not receive antiretroviral therapy (ART) during TB treatment had a success rate of 56 %, compared to 82 % of children who did receive ART.[19] Malnutrition was also associated with unfavorable treatment outcomes, underscoring the need for comprehensive management that includes nutritional status.

Prevention through Isoniazid Therapy

In terms of prevention, a study in Peru showed that pediatric contacts of MDR-TB cases who received isoniazid (INH) had a lower incidence of progression to active TB, even when the index case was MDR-TB. This finding suggests that INH may have a role in preventing the progression of latent infection, especially in high-exposure settings.[20]

DISCUSSION

The results of this review highlight the need for a multidimensional approach to the suspicion and early diagnosis of MDR-TB in children and adolescents. The results show that specific clinical characteristics and epidemiological determinants should be considered warning signs for healthcare professionals who have to deal with the diagnosis of MDR-TB, particularly in high-burden areas.

Radiology and risk factors: Chest radiology patterns (consolidation, fibrosis, and cavitation) provide clues to the suspicion of MDR-TB. This clue, combined with a set of risk factors (previous contact with resistant TB cases, previous anti-TB treatment, etc.), can help increase clinical suspicion. However, it should be noted that although radiology alone may indicate suspicion, it should not be decisive; from a clinical point of view, the medical and epidemiological history of cases should be considered independently.[14,15]

Advances in diagnostic tests: The emergence of rapid diagnostic tests for MDR-TB, such as GeneXpert and MTBDRplus, has dramatically changed the diagnosis of this disease in children and adolescents. The possibility of obtaining results within a few hours also makes it possible to start appropriate treatment quickly, which is key to controlling the progression of the disease and reducing transmission. These technologies should be introduced with the same regularity in regions with high MDR-TB prevalence, as well as in high-risk groups, which include children who are in direct contact with known cases of resistance.[18,17]

Coinfection and nutritional status: HIV coinfection and malnutrition have been identified as important determinants of treatment response in children with MDR-TB. This highlights that adequate clinical care should consist of administering antituberculosis drugs and, when necessary, nutritional support strategies and the initiation and/or possible reinforcement of ART in coinfected patients. Combining these factors in care may be a way to improve adherence and reduce morbidity.[19]

Role of Isoniazid Prevention: Finally, preventive therapy with INH for contacts of MDR-TB cases appears to have the potential to limit progression to active TB. However, the results are still preliminary; they could (inform) future public health policies that include the administration of INH to high-risk pediatric (populations) (populations) living in areas with high MDR-TB prevalence and limited resources for implementing other forms of prevention.[20,21]

CONCLUSION

Taken together, the results obtained and discussed suggest both the advisability of implementing combinations of more advanced and comprehensive diagnostic tests, the description of the epidemiological context, and complementary support strategies to address the problems posed by MDR-TB in children and young people, but also the need to combine all of these to not only provide clinicians with adequate tools for decision-making but also to strengthen the capacity for detection and treatment of young people at risk of MDR-TB).

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CONFLICT OF INTERES

The authors declare that there is no conflict of interest.

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