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REVIEW

Current strategies for the treatment of MDR-TB in children and adolescents

Estrategias actuales para el tratamiento de la TB-MDR en niños y adolescentes

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ABSTRACT

Introduction: the article addressed the challenge posed by drug-resistant tuberculosis, particularly in its multidrug-resistant form (MDR-TB). It explained how this variant of the disease required more extensive, toxic and costly treatments compared to susceptible tuberculosis, critically affecting vulnerable populations such as children and adolescents.
Development: he explained that treatments for MDR-TB could be standardized or individualized, the latter being more effective but historically long and with multiple adverse effects. He explained that, until 2018, treatments required at least five second-line drugs for 24 months. He also described the standard two-phase treatment for tuberculosis (intensive and consolidation), and how the emergence of resistance to fluoroquinolones and aminoglycosides worsened the results. The article highlighted the impact of newer drugs, such as bedaquiline, delamanid, clofazimine, linezolid and pretomanid, which allowed for shorter, completely oral regimens with less toxicity. He clarified that, although bedaquiline showed great efficacy, its long half-life presented risks if treatment was abandoned or cross-resistance existed.
Conclusion: he concluded that MDR-TB constituted a significant challenge for healthcare systems, especially in contexts such as Argentina, where access to medicines, pediatric formulations and adequate diagnostics was limited. Finally, he emphasized the importance of specific research in children and adolescents to improve quality of life, strengthen healthcare policies and move towards more equitable and effective care.

Keywords: Tuberculosis; Resistance; Bedaquiline; Children; Treatment.

RESUMEN

Introducción: el artículo abordó el desafío que representa la tuberculosis resistente a los medicamentos, particularmente en su forma multidrogo resistente (TB-MDR). Explicó cómo esta variante de la enfermedad exigió tratamientos más extensos, tóxicos y costosos en comparación con la tuberculosis sensible, afectando de manera crítica a poblaciones vulnerables como niños y adolescentes.
Desarrollo: explicó que los tratamientos para TB-MDR podían ser estandarizados o individualizados, siendo estos últimos más eficaces pero históricamente largos y con múltiples efectos adversos. Detalló que, hasta 2018, los tratamientos requerían al menos cinco fármacos de segunda línea durante 24 meses. También describió el tratamiento estándar de la tuberculosis en dos fases (intensiva y de consolidación), y cómo la aparición de resistencia a fluoroquinolonas y aminoglucósidos empeoró los resultados. El artículo destacó el impacto de fármacos más recientes, como bedaquilina, delamanid, clofazimina, linezolid y pretomanid, que permitieron esquemas más cortos, completamente orales y con menor toxicidad. Aclaró que, aunque bedaquilina mostró gran eficacia, su larga vida media presentó riesgos si se abandonaba el tratamiento o existía resistencia cruzada.

Conclusión: concluyó que la TB-MDR constituyó un reto significativo para los sistemas de salud, especialmente en contextos como el argentino, donde el acceso a medicamentos, formulaciones pediátricas y diagnósticos adecuados fue limitado. Finalmente, subrayó la importancia de investigaciones específicas en niños y adolescentes para mejorar la calidad de vida, fortalecer las políticas sanitarias y avanzar hacia una atención más equitativa y efectiva.

Palabras clave: Tuberculosis; Resistencia; Bedaquilina; Niños; Tratamiento.

INTRODUCTION

Tuberculosis treatment regimens must contain multiple drugs to which the body is sensitive to cure tuberculosis and prevent the selection of drug resistance. Compared to treatment for drug-sensitive tuberculosis (tuberculosis caused by M. tuberculosis strains not suspected or confirmed to be drug-resistant), treatment for MDR-TB is longer and more complex, toxic, and costly.[1]

MDR-TB regimens can be standardized (all patients are treated with the same regimen) or individualized (patients receive only drugs to which laboratory tests confirm susceptibility).

Individualized regimens have higher treatment success rates; however, until 2018, all regimens used at least five second-line drugs for up to 24 months. This arduous regimen resulted in significant drug toxicity, suboptimal adherence, and substantial losses during follow-up.[2,3]

Tuberculosis treatment consists of two phases

The first is the initial phase: in which drugs are administered daily to quickly eliminate most of the bacillary population and achieve bacteriological conversion in the shortest possible time. Isoniazid, Rifampicin, pyrazinamide, and ethambutol are administered daily.

The second phase: is the consolidation phase, which aims to reduce the number of persistent bacilli to prevent relapse after treatment is completed. Although daily administration of the drugs is recommended, a continuation phase can be administered on non-consecutive days, provided that the treatment is directly observed. This phase lasts four months and consists of isoniazid and rifampicin. [4,5]

Fluoroquinolones and aminoglycosides form the backbone of such regimens, and treatment outcomes are significantly worse in people infected with tuberculosis strains that show resistance to one or both of these classes of drugs. However, introducing new or repurposed drugs, such as Bedaquiline, Clofazimine, and Linezolid, has revolutionized the efficacy of more extended regimens, eliminating the need for injectable drugs and promising shorter, all-oral regimens.[6]

Fluoroquinolones play an essential role in treating MDR-TB/rifampicin-resistant tuberculosis and are also important for protecting second-line drugs such as bedaquiline. Since the discovery of Rifampicin in the 1970s, only two new classes of anti-tuberculosis drugs have been developed: diarylquinolines (Bedaquiline) and nitroimidazopyranos (derivatives of Metronidazole: Delamanid and Preromanid, which are not yet available in Argentina). Bedaquiline (Bdq) is an inhibitor of Mtb ATP synthase, which has an average terminal elimination half-life of 5,5 months, resulting in antibacillary levels almost twice the standard recommended treatment time. For this reason, it should be noted that any regimen that includes Bdq for the standard treatment time (6 months) carries a risk of selecting resistant mutants in the event of resistance to the other drugs used. The same risk is encountered when treatment is discontinued. The first 6 months with Bdq could be considered an initial phase of MDR/XDR TB treatment. Bdq has been used for 12 months in patients with XDR-TB without increased toxicity. It has also been combined with Delamanid (Dlm) for periods of 6 and 12 months in patients with extensive resistance profiles or who cannot use other drugs due to adverse reactions.[7,8,9]

Pretomanid, also a nitroimidazopyran derivative, has only been approved in the US and Europe for use in the BPal regimen (Bdq, Pretomanid, Lzd) under operational research conditions in patients over 14 years of age.

Delamanid (Dlm) is a nitroimidazopyran that alters mycobacterial cell wall synthesis and respiration. Based on studies of early bacterial activity and bacteriological conversion at 2 months of treatment, it was recommended as an antituberculosis drug. The WHO recently recommended the use of Dlm in children of all ages.[10]

In many countries, including Argentina, drug-resistant tuberculosis represents a significant challenge for the public health system. This disease disproportionately affects children and adolescents, a vulnerable population that requires specialized care and effective treatment strategies. The proposed research addresses this priority by providing specific data and management strategies tailored to current epidemiological characteristics.

The study provides solid knowledge of the epidemiology, risk factors, and improved treatment practices for drug-resistant tuberculosis in adolescents and children. This includes evaluating therapies and early diagnosis

strategies.

The fundamental purpose is to improve clinical management in public health by providing scientific evidence. It also seeks to reduce the burden of the disease and improve clinical outcomes and quality of life for affected patients.[11]

In summary, the proposed research on drug-resistant tuberculosis in adolescents and children not only responds to a critical public health need but also promises to generate valuable and applicable knowledge that could significantly impact public health and the quality of life of a vulnerable population.[12]

DEVELOPMENT

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis, which is mainly transmitted through the air. Effective treatment of this disease requires the administration of multiple drugs to which the microorganism is sensitive to cure the disease and prevent the development of drug resistance.[13] The complexity of treatment increases significantly in cases of drug-resistant tuberculosis (DR-TB), especially in its multidrug-resistant form (MDR-TB), which is defined as resistance to at least isoniazid and rifampicin, the two most potent anti-tuberculosis drugs.

Compared to drug-sensitive tuberculosis, treatment for MDR-TB is considerably more protracted, more toxic, and more expensive. In addition, it can be standardized or individualized according to the sensitivity profile of the infecting strain. Although individualized regimens show better therapeutic success rates, historically, they involved the use of five or more second-line drugs over up to 24 months, leading to high toxicity, poor adherence, and high rates of loss to clinical follow-up.[13]

Traditionally, fluoroquinolones and aminoglycosides were the mainstay of treatment for MDR-TB. However, resistance to these drug classes has been associated with poorer clinical outcomes. Introducing new drugs, such as bedaquiline, clofazimine, and linezolid, has enabled the development of shorter, more effective, all-oral treatment regimens, eliminating the need for injectable drugs.[14,15]

The World Health Organization (WHO) has prioritized the development of new treatments based on combinations with drugs such as bedaquiline (Bdq), delamanid (Dlm), and pretomanid, with promising results. Bdq, a diarylquinoline that inhibits M. tuberculosis ATP synthase, has a prolonged terminal half-life, favoring its antibacillary action beyond the standard treatment period. However, this characteristic may also increase the risk of selecting resistant strains if treatment is interrupted or combined with ineffective drugs.[8] Delamanid, on the other hand, is a nitroimidazopyran that inhibits mycobacterial cell wall synthesis and bacterial respiration. It has demonstrated efficacy in early bacteriological conversion and has recently been recommended by the WHO for use in children of all ages.[16,17] Pretomanid, another member of the same class, has been approved in the US and Europe as part of the BPaL regimen (Bedaquiline, Pretomanid, and Linezolid) in patients over 14 years of age in operational research settings.[18,19]

The standard treatment for drug-sensitive tuberculosis consists of two phases: an intensive two-month initial phase with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a four-month consolidation phase with isoniazid and rifampicin. This regimen aims to reduce the initial bacterial load and prevent relapse. Daily or three-times-weekly supervised administration is recommended in both cases to ensure treatment adherence.[20,21]

In countries such as Argentina, drug-resistant TB poses a growing challenge for public health systems, especially in vulnerable populations such as children and adolescents. This age group requires specific diagnostic and therapeutic strategies due to reduced access to health services, difficulty obtaining diagnostic samples, and limited availability of appropriate pediatric formulations. Research on this population is essential to generate scientific evidence to improve clinical management and reduce disease burden.[18,19]

This study addresses this need by proposing the analysis and evaluation of the best available practices for the early diagnosis and effective treatment of MDR-TB in children and adolescents. The ultimate goal is to improve clinical outcomes and quality of life for patients by implementing evidence-based strategies adapted to the local epidemiological context.

CONCLUSIONS

Drug-resistant tuberculosis, especially multidrug-resistant tuberculosis (MDR-TB), is currently one of the most significant challenges in infectious disease control worldwide. The need to use multiple drugs for prolonged periods, together with high levels of toxicity and the cost of treatment, seriously compromise therapeutic adherence and clinical outcomes, especially in vulnerable populations such as children and adolescents. In this regard, a comprehensive approach to MDR-TB must consider both the microbiological and pharmacological characteristics of the disease and the social, economic, and health factors that affect access to timely diagnosis and treatment.

Advances in research and the development of new therapeutic alternatives have led to a significant change in the treatment paradigm for MDR-TB. The introduction of drugs such as bedaquiline, delamanid, clofazimine,

linezolid, and pretomanid has enabled the design of shorter, less toxic, all-oral regimens without the need for injectable medications. These advances substantially improve clinical efficacy, tolerability, and quality of life for patients, especially those with extensive resistance or adverse reactions to conventional therapies.

Despite these achievements, significant challenges remain, particularly in resource-limited settings such as Argentina. The restricted availability of new drugs, the lack of specific pediatric formulations, and the limited infrastructure for timely sensitivity testing hinder the effective implementation of new therapeutic regimens. In addition, strict surveillance is needed to prevent the emergence of strains resistant to new drugs, such as bedaquiline, and rigorous clinical monitoring and integrated disease control strategies are required.

In this context, research focused on MDR-TB in adolescents and children becomes a priority. This population group has clinical and social characteristics requiring a differentiated diagnosis, clinical management, and follow-up approach. Generating specific scientific evidence in this field optimizes treatment regimens, improves clinical outcomes, and strengthens public health policies, ensuring equitable access to safe and effective treatments.

In conclusion, the fight against drug-resistant tuberculosis in children and adolescents requires a multidisciplinary approach supported by therapeutic innovation, strengthening of the health system, and the production of local knowledge. Only in this way will it be possible to reduce the disease's burden and substantially improve the quality of life of affected patients.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

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