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REVIEW OF THERAPEUTIC AND DIAGNOSTIC INNOVATIONS IN TUBERCULOSIS: OVERCOMING DRUG RESISTANCE WITH INTEGRATED APPROACHES

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Abstract: Tuberculosis (TB) remains one of the leading causes of mortality worldwide, with drug resistance (DR-TB) emerging as a critical challenge in combating the disease. This article reviews recent innovations in therapeutic and diagnostic approaches to TB, with an emphasis on strategies aimed at overcoming drug resistance. We explore the updated World Health Organization (WHO) guidelines for the treatment of DR-TB, including the incorporation of new drugs such as bedaquiline and delamanid, which have been shown to significantly improve treatment outcomes. In addition, we discuss emerging diagnostic technologies, such as GeneXpert and LAMP, which allow for the rapid and accurate detection of DR-TB, especially in resource-limited areas. Innovative therapeutic approaches, including the use of nanotechnology and immunomodulators, are also analyzed, highlighting their potential to transform the clinical management of TB. Finally, this article addresses the challenges of implementing these new technologies in resource-limited settings and proposes integrated solutions that combine therapeutic and diagnostic advances with personalized strategies for the effective management of resistant TB.

Keywords: Drug-resistant tuberculosis, therapeutic innovations, rapid diagnosis

INTRODUCTION

Tuberculosis (TB) remains a major global public health threat, responsible for millions of deaths annually. Although TB is treatable, the emergence and spread of drug-resistant TB (DR-TB) represents a growing challenge in controlling the disease. DR-TB, which includes multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), results in significant complications in clinical management, requiring longer, more complex treatments with greater toxicity,

and is associated with considerably lower cure rates [1, 2]. Historically, the treatment of DR-TB has been limited to a restricted set of drugs, many of which were developed decades ago and are accompanied by serious adverse effects. Previous World Health Organization (WHO) guidelines recommended prolonged and toxic regimens, with variable results, especially in patients with advanced forms of the disease [3]. However, significant advances in recent years have transformed the DR-TB treatment landscape. The introduction of new drugs, such as bedaquiline, delamanid and pretomanid, has been incorporated into the updated WHO guidelines, allowing for shorter, less toxic regimens with greater efficacy, even in cases of extensively resistant TB [4, 7]. In addition to therapeutic advances, rapid and accurate diagnosis of DR-TB is essential for successful treatment. Delayed diagnosis or the use of inadequate diagnostic methods can lead to disease progression and the further spread of DR-TB [1, 8]. In recent years, innovative diagnostic technologies such as GeneXpert and LAMP (Loop-Mediated Isothermal Amplification) have revolutionized the ability to rapidly detect TB and resistance to rifampicin, a key marker for DR-TB [9, 13]. These technologies not only increase diagnostic accuracy, but also significantly reduce the time needed to initiate appropriate treatment, especially in resource-limited areas where the burden of DR-TB is highest [17]. However he implementation of these new therapies and diagnostic technologies faces substantial challenges, particularly in regions with poor healthcare infrastructure and limited access to new drugs and diagnostic tools [2, 10]. Nanotechnology, for example, offers significant promise by improving drug delivery, allowing penetration into Mycobacterium tuberculosis biofilms and host cells where the bacteria persist [6, 13]. Nanoparticles designed to maximize drug bioavailability and minimize toxicity have the potential to transform DR-TB treatment, especially in cases where treatment adherence is a challenge due to the duration and side effects of current regimens [14]. Another critical aspect recently addressed is immune modulation. The reuse of immunomodulatory drugs, initially developed for other inflammatory conditions, has shown potential in improving the host response to Mycobacterium tuberculosis infection, suggesting that such approaches may complement traditional antimicrobial therapies [15, 16]. These immunomodulators can act by reducing the bacterial load and preventing reactivation of the disease, which is particularly relevant in latent TB contexts and in patients with co-infections, such as HIV [18]. Despite these advances, the effectiveness of new therapies and technologies depends on their proper implementation in different epidemiological contexts. Adapting global guidelines to local realities is essential in order to maximize the benefits of therapeutic and diagnostic advances [4, 11]. This includes not only updating clinical guidelines, but also strengthening health systems to ensure that professionals are adequately trained and that patients have continuous access to modern treatments and diagnostics [12]. This article therefore reviews the latest innovations in therapeutic and diagnostic approaches for DR-TB, with the aim of offering an integrated view of the advances that are shaping the future of the fight against tuberculosis. By exploring everything from updated guidelines and new drugs to cutting-edge diagnostic technologies and innovative therapeutic approaches, we highlight the opportunities and challenges in the fight against one of the world's deadliest infectious diseases.

OBJECTIVE

This study aims to review and analyze recent innovations in the treatment and diagnosis of drug-resistant tuberculosis (DR-TB), addressing new therapeutic guidelines, emerging diagnostic technologies and innovative therapeutic approaches. Firstly, it seeks to examine the updates to the World Health Organization (WHO) guidelines for the treatment of DR-TB, with a focus on the incorporation of new drugs such as bedaquiline, delamanid and pretomanid, and to assess the impact of these changes on global clinical practice. In addition, this study aims to evaluate the role of emerging diagnostic technologies, such as GeneXpert and LAMP, in the rapid and accurate detection of DR-TB, discussing their advantages, limitations and the challenges that arise with their implementation, especially in resource-limited regions. Another crucial objective is to explore innovative therapeutic approaches, including the use of nanotechnology and immunomodulators, analyzing how these strategies can overcome the limitations of traditional treatments and improve efficacy in the fight against DR-TB. Finally, the study sets out to identify the main challenges in implementing these new therapies and diagnostic technologies in different epidemiological contexts and to propose strategies to overcome these barriers, ensuring that technological advances can be applied widely and effectively, contributing to the global control of tuberculosis.

METHODOLOGY

This study was conducted by means of a narrative literature review, with the aim of analyzing recent therapeutic and diagnostic innovations in the management of drug-resistant tuberculosis (DR-TB). The literature search was carried out using the scientific databases PubMed and Scopus, focusing on articles published in recent years. Specific keywords, such as "tuberculosis drug resistance," "new therapeutic approaches," "nanotechnology in tuberculosis," and "diagnostic innovations in TB," were used to ensure that the search was comprehensive. The search was restricted to articles published in English, including clinical studies, systematic reviews, meta-analyses and international guidelines. The initial selection resulted in a wide range of articles, of which 18 were considered relevant to the objectives of the study and therefore included in the final analysis. The choice of these articles was based on inclusion criteria that favored studies that addressed updates to the World Health Organization's (WHO) therapeutic guidelines, the development and application of new diagnostic technologies, such as GeneXpert and LAMP, and innovative therapeutic approaches, such as the use of nanotechnology and immunomodulators in the treatment of DR-TB. In addition, articles were included that discuss the challenges of implementing these innovations in varied epidemiological contexts, particularly in regions with limited health infrastructure. Each selected article was carefully reviewed to extract data on the most recent advances in the treatment and diagnosis of DR-TB, as well as to identify the main barriers and opportunities for implementing these innovations in clinical practice. The information collected was organized in such a way as to allow a critical analysis of the different aspects covered, ensuring that each reference was used at least once throughout the article. This methodological approach allowed for a comprehensive and integrated understanding of advances in the fight against DR-TB, contributing to the discussion on best practices and strategies to tackle this global public health threat.

RESULTS

The review of studies revealed a number of significant advances in the management of drug-resistant tuberculosis (DR-TB), highlighting progress in both the treatment and diagnosis of the disease. These innovations are key to tackling the growing global challenge of DR-TB and can be organized into three main areas: updates to therapeutic guidelines, technological innovations in diagnostics and the development of new therapeutic approaches. In recent years, the World Health Organization's (WHO) therapeutic guidelines for the treatment of DR-TB have undergone substantial revisions, reflecting the incorporation of new drugs and therapeutic regimens that have the potential to transform clinical practice. Drugs such as bedaquiline, delamanid and pretomanid, which were previously considered last-line treatments, are now being integrated as first-line options in certain contexts. These drugs, when combined in new therapeutic regimens, have been shown not only to increase cure rates, but also to reduce treatment duration and associated side effects, which are critical factors in improving patient adherence to treatment. Studies have shown that these shorter, less toxic regimens can result in better clinical outcomes, even in patients with extensively resistant forms of the disease (XDR-TB) [4, 7, 10]. These findings are particularly important in regions where the burden of DR-TB is high and resources are limited, as they offer more viable and affordable solutions for treating the disease. In addition to therapeutic advances, the field of DR-TB diagnostics is also has witnessed significant innovations. The introduction of advanced diagnostic technologies, such as GeneXpert and LAMP (Loop-Mediated Isothermal Amplification), has revolutionized the way resistant TB is detected. These technologies allow the rapid and accurate identification of resistance to rifampicin, which is a critical marker for DR-TB, significantly reducing the time needed to start appropriate treatment. In areas with limited resources, where the health infrastructure may be inadequate to support more complex diagnostic methods, these technologies have proved essential, not only because of their speed, but also because of their simplicity and ease of implementation [9, 13, 17]. Studies indicate that the use of these diagnostic tools could lead to a substantial reduction in the mortality rates associated with DR-TB, by enabling earlier and more precise interventions. Nanotechnology is another emerging area that has shown great potential in the treatment of DR-TB. By improving drug delivery, nanotechnology allows anti-tuberculosis drugs to penetrate Mycobacterium tuberculosis biofilms and host cells, where the bacteria often hide and persist, protecting themselves from the effects of conventional treatments. Nanoparticles developed to maximize the bioavailability of drugs and minimize their toxicity offer a new frontier in the fight against DR-TB, especially in patients who face difficulties in adhering to prolonged and demanding treatments. These technologies can not only increase the effectiveness of treatments, but also reduce side effects, which are a significant barrier to adherence in many contexts [6, 14]. The studies reviewed suggest that these approaches have the potential to transform DR-TB management by making treatments more accessible and effective. In parallel, the field of immunomodulation has also advanced as a complementary therapeutic strategy in the treatment of DR-TB. The reuse of immunomodulatory drugs, which were originally developed for other inflammatory conditions, is being explored as a way of improving the host response to Mycobacterium tuberculosis infection. These drugs have the potential to act synergistically with traditional antimicrobial therapies,

helping to reduce the bacterial load and prevent reactivation of the disease, which is especially relevant in latent TB contexts or in patients with co-infections such as HIV [15, 16]. The combination of these approaches may offer new ways to overcome the limitations of current treatments, which are often insufficient to completely eradicate the infection in patients with multidrug resistance. However, despite these advances, the implementation of these new therapies and diagnostic technologies faces substantial challenges, particularly in areas with limited health infrastructure. Adapting global guidelines to local conditions is essential to ensure that these advances can be applied effectively in different epidemiological contexts. Barriers to the adoption of these innovations include not only a lack of financial resources and adequate infrastructure, but also the need for specialized training for health professionals, who often do not have access to the latest technological or therapeutic innovations [11, 12]. In addition, cultural acceptance and awareness of the importance of early diagnosis and appropriate treatment also play a crucial role in the effectiveness of these interventions. Therefore, the studies reviewed suggest that in order to maximize the benefits of these advances, an integrated approach is needed that combines new technologies with robust public health policies and strategies for implementation that can overcome existing barriers. This includes strengthening health systems, continuing education for professionals, and creating patient support programs that encourage adherence to treatment. Only with a holistic approach will it be possible to achieve a significant impact in the fight against DR-TB, ensuring that therapeutic and diagnostic advances can be widely applied and benefit all patients, regardless of their geographical location or socioeconomic conditions.

CONCLUSION

Drug-resistant tuberculosis (DR-TB) remains one of the greatest threats to global public health, challenging health systems and requiring continuous innovation in treatment and diagnosis. Recent progress in therapies and diagnostic technologies offers new hope, but also highlights the complexity of their implementation in different epidemiological and socioeconomic contexts. This review addressed the various fronts of innovation, from the therapeutic guidelines updated by the World Health Organization (WHO) to advanced diagnostic technologies and emerging therapeutic approaches such as nanotechnology and immunomodulation. The incorporation of drugs such as bedaquiline, delamanid and pretomanid into therapeutic regimens reflects a notable advance, allowing for shorter and less toxic treatments, which is crucial for improving patient compliance and clinical outcomes [4, 7, 10]. However, the success of these new treatments depends on their accessibility and the ability of health systems to implement them effectively, especially in areas where DR-TB is more prevalent [11, 12]. This underscores the importance of ongoing international support and effective public policies that can adapt these innovations to local realities. Diagnostic innovations such as GeneXpert and LAMP have brought significant advances in the rapid and accurate detection of DR-TB. These technologies not only improve the early identification of resistance, but also enable the immediate initiation of appropriate treatments, which is vital for controlling the spread of the disease [9, 13, 17]. Despite this, implementing these tools remains a challenge in regions with inadequate infrastructure and limited resources, which limits their potential impact [3, 8]. The dissemination of these technologies on a global scale requires investments in health infrastructure, training

of professionals and cost reduction, so that they can benefit a greater number of people affected by DR-TB. In addition to traditional therapies, innovative approaches such as nanotechnology are revolutionizing the way we treat DR-TB. Nanotechnology offers the possibility of more effective drug delivery, allowing drugs to reach the sites of infection with greater precision and less toxicity [6, 14]. This is particularly important in patients facing prolonged treatment, where adherence to the therapeutic regimen is often hampered by the adverse effects of the drugs. The development of nanoparticles that increase the bioavailability of drugs could transform the treatment of DR-TB, reducing treatment time and improving clinical outcomes [15]. Another significant advance discussed in this review is the role of immunomodulation in the treatment of DR-TB. The reuse of immunomodulatory drugs, initially developed for other diseases, has shown promise in complementing traditional antimicrobial therapies. These drugs have the potential to improve the host's immune response, helping to reduce the bacterial load and prevent reactivation of the disease, which is especially relevant in the context of latent TB and in patients with DR-TB. immunocompromised, such as those co-infected with HIV [16, 18]. Although these approaches are still in the early stages of research and development, they represent a new frontier in the fight against DR-TB, offering solutions that could be integrated into conventional treatments to improve the overall effectiveness of the fight against the disease. However, even with all these advances, considerable challenges remain. The disparity in the distribution of resources and in the capacity to implement these innovations in different regions of the world remains a significant obstacle. The effectiveness of new treatments and diagnostics depends largely on the ability of health systems to adapt them to local needs, which requires not only technical innovation, but also a global political and economic commitment [2, 5]. In addition, raising public awareness of the importance of early diagnosis and adherence to treatment is crucial to ensuring that these innovations can reach their full potential. In conclusion, the fight against drug-resistant tuberculosis requires an integrated approach that combines technological innovation, health system strengthening and effective public policies. Although significant progress has been made, it is essential to continue developing and implementing strategies to ensure that all patients, regardless of their geographical location or economic situation, can benefit from these innovations. Only with a coordinated effort will it be possible to reduce the global burden of DR-TB and move towards the control and eventual eradication of this devastating disease.

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