



Piloting the Complex Ground of Drug- Resistant Extrapulmonary Tuberculosis in Adolescent Females: Unraveling Challenges and shaping future Strategies

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Abstract

Introduction: Tuberculosis (TB) is a global infectious disease, causing approximately 10.6 million new cases and 1.6 million deaths in 2021, with 450,000 patients annually having rifampicin-resistant (RR)/multi-drug resistant (MDR) TB. Despite higher pulmonary TB notifications in males, TB in females remains a significant threat, reflecting potential barriers to healthcare access.

Background: This study addresses the challenging landscape of Rifampicin-resistant extrapulmonary TB in adolescent females, aiming to unravel recurrence patterns and treatment complexities. It serves as a call to action, advocating for tailored interventions to mitigate the impact of drug-resistant TB in this vulnerable population.

Overview: Adolescence poses unique challenges for individuals diagnosed with tuberculosis, especially for females who exhibit higher susceptibility, facing stigma and potential impacts on self-esteem. The presentation of drug-resistant tuberculosis in adolescents differs from early childhood, necessitating differentiated care; however, there's a notable lack of recognition and specific guidelines for this age group in national TB programs.

W.H.O. outlines plan with a comprehensive five-year strategy, detailing ten crucial steps to improve tuberculosis prevention, treatment, and care for children and adolescents. Additionally, the Roadmap targets a 90% coverage in diagnosis and treatment services and aims to provide TB preventive treatment to 90% of those at high risk between 2023 and 2027.

Rifampicin-resistant tuberculosis, comprising MDR and XDR types, requires microbiological confirmation through genotypic or phenotypic tests. Treatment in adolescents aligns with adult regimens, including novel drugs like Delamanid and Bedaquiline, with consideration for exposure history and drug susceptibility.

Study Design: *Retrospective Observational Study investigating Rifampicin resistance in pediatric/adolescent tuberculosis, with a focus on extrapulmonary manifestations. Data sourced from OPD Group of TB Hospitals Sewri Mumbai and allied TB clinic in Mumbai jurisdiction.*

Case Studies: Case 1: *12-year-old girl, treated for pulmonary TB, developed abdominal symptoms, diagnosed with Rifampicin-resistant TB, started on longer oral regimen.*

Case 2: *Another 12-year-old girl, treated for TB, developed abdominal symptoms, diagnosed with Rifampicin-resistant TB, initiated on a different oral regimen.*

Case 3: *17-year-old girl with enlarged lymph nodes, challenging biopsy during COVID-19, diagnosed with Rifampicin-resistant TB, responded to BDQ-based regimen but persistent lymph node size after 18 months.*

Discussion: *This case series underscores the challenges of managing tuberculosis in young female adolescents, revealing insights into recurrence and Rifampicin resistance. It emphasizes the necessity for vigilant monitoring, personalized approaches, and ongoing research to optimize outcomes in combating this resilient pathogen.*

In Summary, this study highlights the urgent need for targeted interventions and heightened clinical awareness in addressing drug-resistant extrapulmonary tuberculosis among pediatric/adolescent females. The findings underscore the importance of exploring socio-economic determinants for comprehensive public health initiatives to mitigate the impact of TB in vulnerable

Keywords: *Female Adolescent, Extra-Pulmonary TB, Rifampicin Resistance (RR TB)*

Introduction

Tuberculosis (TB) is a global disease, found in every country in the world. It is one of the leading infectious causes of death worldwide. It led to approximately 10.6 million new patients and 1.6 million deaths in 2021^[1]. Approximately, 450,000 TB patients annually have rifampicin-resistant (RR)/multi-drug resistant (MDR) TB^[1]. Treatment using second-line drugs is long, complex, and toxic, with an average treatment success of 60%.

Globally, tuberculosis (TB) is among the top five killers of women aged 20–59 years^[1]. While the proportion of pulmonary TB (PTB) notifications is higher among males worldwide, TB in females remains a major threat to control due to the impact felt by households, particularly children. It has been argued that the higher case notifications among males may reflect the barriers faced by the female population in accessing health care^[2]. Extrapulmonary tuberculosis (EPTB) accounted for 15% of the new and relapse TB cases in 2014^[3]. In contrast to PTB, preponderance for EPTB is reportedly higher among females^[4–6].

Background

In the relentless global battle against tuberculosis (TB), the emergence of drug-resistant strains poses a formidable challenge, particularly in

pediatric and adolescent populations. This study delves into the intricate landscape of extrapulmonary TB, focusing on cases where Rifampicin resistance adds a layer of complexity to diagnosis and treatment. The spotlight is on adolescent females, a demographic experiencing unique vulnerabilities, and the study aims to dissect the recurrence patterns, diagnostic hurdles, and treatment complexities in these cases. By unraveling the nuances of Rifampicin-resistant TB with extrapulmonary manifestations, the research seeks to provide invaluable insights for optimizing patient management and crafting tailored therapeutic strategies. This investigation is not merely a clinical exploration but a call to action, urging a reevaluation of existing approaches and the development of targeted interventions to curb the impact of drug-resistant TB in this specific and vulnerable population.

Overview

Adolescence is an important transitional phase of life where children often struggle with physical, hormonal, and emotional changes happening in their lives, and having to undergo an illness like TB may be associated with stigma and lower self-esteem. Adolescent Females are More Susceptible than Males for Tuberculosis.^[5]

Additionally, numerous coexisting conditions linked to tuberculosis arise or worsen in adolescence, such as HIV infection, diabetes, hazardous substance use (including tobacco), and mental health issues. Lastly, numerous adolescent girls and young women confront health issues related to pregnancy and childbirth, potentially elevating their susceptibility to tuberculosis and adverse outcomes.^(7,8) Examining the global prevalence of adolescents and heightened vulnerability among females during a critical life stage not only leads to physical and psychosocial consequences but also emerges as a significant factor contributing to infertility in women in low- and middle-income nations.⁽⁸⁾

Presentation of DR-TB in adolescence varies from that in early childhood with older children having parenchymal infiltrates and more frequent cavitation^[7]. This requires differentiated care, yet adolescents, generally, have not been recognized as a distinct population by guidelines and national TB programs^[8]. Although the principles of treatment for DR-TB in children are similar to adults, with the use of four to five effective drugs [9], more evidence needs to be produced to understand the demographics, clinical characteristics, and treatment outcomes among children and adolescents diagnosed and treated for DR-TB to further inform policy and practice.

World Health Organization (WHO) launches new 5-year roadmap to prevent and treat TB in children and adolescents. The plan sets forth an ambitious five-year strategy with ten pivotal steps to enhance the prevention, treatment, and care of tuberculosis in children and adolescents.

The Roadmap emphasizes a comprehensive five-year plan with ten essential actions aimed at improving the prevention, treatment, and care of TB in the youth.

Over the next five years, the strategy underscores ten key initiatives to elevate the prevention, treatment, and care of tuberculosis in children and adolescents.

Between 2023 and 2027, the Roadmap aims to achieve a 90% coverage in both diagnosis and treatment services for the estimated number of people with TB and ensure 90% of those at high risk have access to TB preventive treatment.⁽¹⁰⁾

Rifampicin Resistant Tuberculosis

Rifampicin-resistant (RR) tuberculosis includes multidrug-resistant (MDR; resistance to at least rifampicin and isoniazid) and extensively drug-resistant tuberculosis (XDR; MDR with additional resistance to at least one fluoroquinolone and at least one second-line injectable agent). A confirmed diagnosis of RR tuberculosis relies on microbiological confirmation from clinical samples or cultured isolates, using genotypic or phenotypic drug susceptibility tests (DSTs), which can be challenging in children and young adolescents.⁽¹¹⁾ In the absence of rapid molecular DSTs, or in the case of patients with culture-negative tuberculosis, a clinical diagnosis of RR tuberculosis can be made in symptomatic adolescents based on exposure to an index patient with bacteriologically confirmed RR tuberculosis, or lack of clinical improvement (i.e. symptom resolution and weight gain) after at least two months of first-line therapy with good adherence (provided the risk of misdiagnosis of another chronic lung condition is low).⁽¹²⁾

Composition and duration of second-line treatment regimens for adolescents with adult-type disease and bacteriological confirmation of RR tuberculosis is generally the same as for adults. The 2019 WHO recommendations for use of novel drugs in RR tuberculosis treatment also apply to adolescents, as available pharmacokinetic data indicate that Delamanid and Bedaquiline may be given to children as young as three and six years of age, respectively.⁽¹³⁾ For younger adolescents with paucibacillary disease that is clinically diagnosed without bacteriological confirmation of drug susceptibility, regimen composition should consider the adolescent's exposure history and the drug susceptibility results of the likely index patient, if known.

Young adolescents with culture-negative, non-severe RR tuberculosis disease have been shown to have excellent outcomes with total treatment duration of 12 months.⁽¹⁴⁾

Method and Material

Study Design: Retrospective Observational Study.

Objectives: This study aims to comprehensively investigate and analyze the clinical challenges associated with the emergence of Rifampicin resistance in pediatric/adolescent tuberculosis cases, specifically focusing on extrapulmonary manifestations.

The primary objectives include understanding the recurrence patterns, diagnostic hurdles, and treatment complexities in cases where monitoring extrapulmonary sites becomes challenging.

Through an in-depth examination of three distinct pediatric/adolescent cases, we seek to unravel the nuances of Rifampicin-resistant tuberculosis in the context of extrapulmonary involvement, providing valuable insights for improved patient management and tailored therapeutic strategies.

Data Source: OPD Group of TB Hospitals Sewri Mumbai and allied TB clinic in Mumbai jurisdiction

Case Studies

Case 1

12yrs Std 7th Convent school girl patient having fever with chills shows on Xray chest mediastinal nonspecific shadows on HRCT chest shows Para tracheal Para hilar mediastinal lymph nodes with granuloma and necrosis, biopsy shows MTB detected with no Rifampicin resistance, started on Cat 1 for 9 months. After completing 9 months of ATT, it was stopped as patient was not having symptoms.

After once again developed fever with pain in Abdomen routine investigation were normal Abdominal CT shows multiple enlarged lymph nodes in peri portal region. Biopsy done shows MTB detected with Rifampicin resistance. Started

on All oral longer regime BDQ, Lfx, Lnz, Cs, and Cfx as per weight band

Case 2

12yrs Std 7th Convent school girl patient having fever with chills shows on Xray chest mediastinal nonspecific shadows on HRCT chest shows Para tracheal Para hilar mediastinal lymph nodes with granuloma and necrosis, biopsy shows MTB detected with no Rifampicin resistance, started on Cat 1 for 9 months. After completing 9 months of ATT, it was stopped as patient was not having symptoms.

After one again developed fever with pain in Abdomen routine investigation were normal Abdominal CT shows multiple enlarged lymph nodes in peri portal region. Biopsy done shows MTB detected with Rifampicin resistance. Started on All oral longer regime BDQ, Lfx, Lnz, Cs, and Cfx as per weight band

Case 3

17 yrs. old girl patient chief complaint of fever and pain in Abdomen during COVID-19 pandemic all investigation normal except lymph nodes enlarged in peri portal region near aorta, it was difficult and risky to get good specimen for biopsy and to start ATT, patient was not relieved from the symptoms and after 8months biopsy was done. GenXpert with specimen show MTB detected with Rifampicin resistance. Patient was started on BDQ based regimen with OBR of 4 more drugs, responded after 2 months with weight gain, as it was difficult to monitor USG Abdomen sh ofows size of lymph nodes are same after 18 months of treatment and was told to repeat biopsy again, which patient denied

Definition

Adolescence is the transitional phase of growth and development between childhood and adulthood. The World Health Organization (WHO) defines an adolescent as any person between ages 10 and 19.

Extrapulmonary tuberculosis (EPTB) is an infectious disease caused by *Mycobacterium tuberculosis* that occurs in organ systems other than the lungs.

Rifampicin-resistant TB (RR-TB) defined as resistance to rifampicin detected using genotypic or phenotypic methods with or without resistance to other first-line anti-TB drugs.

Drug resistance TB DR-TB is a disease caused by *Mycobacterium tuberculosis* strains resistant to one or more anti-TB drugs.

Discussion

In this intriguing case series, we explore three instances of tuberculosis (TB) in young female adolescent patients, each presenting unique challenges and insights into the management of this infectious disease. The cases share a common thread – initial diagnosis of TB, successful completion of standard anti-tubercular treatment (ATT), and subsequent emergence of Rifampicin resistance, revealing the complexities that clinicians face in combating this resilient pathogen.

The first two cases depict the recurrence of TB symptoms in a 12-year-old adolescent girl, despite completing the conventional 9-month ATT. Upon relapse, abdominal discomfort became a predominant symptom, prompting further investigation. The discovery of Rifampicin resistance added a layer of complexity, leading to the initiation of an alternative oral regimen tailored to the patient's weight band. This highlights the importance of vigilant monitoring and a personalized approach in managing pediatric/adolescent TB, underscoring the need for considering drug resistance in recurrence.

The third case introduces a 17-year-old adolescent girl, raising the question of TB diagnosis amidst the challenges posed by the COVID-19 pandemic. Delayed biopsy due to logistical difficulties revealed Rifampicin resistance, prompting the initiation of a Bedaquiline (BDQ)-based regimen. Despite an initial positive response, the

persistence of enlarged lymph nodes after 18 months signals a potential treatment hurdle, urging clinicians to explore further interventions and monitor treatment efficacy through repeat biopsies.

Collectively, these cases shed light on the evolving landscape of TB management, emphasizing the importance of tailored treatment strategies in the face of drug resistance. The challenges posed by Rifampicin resistance in pediatric patients underscore the need for continuous research, vigilant monitoring, and personalized therapeutic approaches to optimize outcomes in the fight against tuberculosis.

Conclusion

In conclusion, this series of pediatric/adolescent cases illuminates the intricate landscape of drug-resistant extrapulmonary tuberculosis (TB), particularly among adolescent females with a favorable socio-economic background. The noteworthy observation of TB incidence clustering around the age of puberty in these young adolescent girls underscores a critical period of vulnerability. The challenges in diagnosing and monitoring extrapulmonary TB in this demographic, coupled with the emergence of drug resistance, underscore the need for heightened clinical awareness and vigilant surveillance.

Interestingly, the association between socio-economic status and TB incidence in these cases prompts further exploration into the nuanced intersections of lifestyle factors, access to healthcare, and disease susceptibility. The decrease in TB incidence after the age of 30 among females raises questions about the dynamic interplay between biological factors and socio-economic influences in shaping disease patterns.

This study serves as a call to action for tailored interventions, emphasizing the necessity for targeted screening, early detection, and personalized treatment strategies for pediatric/adolescent patients, especially females,

navigating the complexities of drug-resistant extrapulmonary TB. Additionally, it invites broader inquiries into the socio-economic determinants of TB incidence, contributing valuable insights for comprehensive public health initiatives aimed at curbing the impact of this formidable infectious disease in vulnerable populations.

Summary

This study delves into three compelling cases of pediatric extrapulmonary tuberculosis (TB) with the added challenge of Rifampicin resistance. Despite successful completion of standard anti-tubercular treatment (ATT), each patient experienced a recurrence of symptoms, leading to a diagnostic conundrum. Two 12-year-old girls exhibited abdominal manifestations, prompting a shift to an alternative oral regimen tailored to their weight bands upon detecting Rifampicin resistance. The third case, a 17-year-old girl during the COVID-19 pandemic, faced delayed biopsy and subsequent challenges in initiating treatment due to logistical issues. Rifampicin resistance emerged after eight months, initiating a Bedaquiline (BDQ)-based regimen.

These cases underscore the complexities of diagnosing and managing pediatric extrapulmonary TB, especially when Rifampicin resistance complicates the treatment landscape. The study highlights the importance of vigilant monitoring, personalized therapeutic approaches, and the need for continuous research to optimize outcomes in the face of evolving drug resistance. This research contributes valuable insights to the ongoing efforts in tackling TB, emphasizing the necessity for tailored strategies to address the unique challenges posed by drug resistance in the pediatric population.

Reference

1. WHO, Tuberculosis in Women, 2015. Available at: http://www.who.int/tb/publications/tb_women_factsheet_251013.pdf (accessed 08.11.16).
2. M. Connolly, P. Nunn, Women and tuberculosis, *World Health Stat. Q.* 49 (1996) 115–119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9050189> (accessed 08.11.16).
3. World Health Organization, Global tuberculosis report 2015, WHO Media Centre 2015, Vol. 126. Available at: http://www.who.int/tb/publications/global_report/gtbr15_main_text.pdf (accessed 08.11.16).
4. A. Thorson, Gender issues in tuberculosis, in: Sabra L. Klein, Craig W. Roberts (Eds.), *Sex and Gender Differences in Infection and Treatments for Infectious Diseases*, Springer International Publishing, Cham, 2015, pp. 231–253, doi:10.1007/978-3-319-16438-0_8.
5. Adolescent Females are More Susceptible than Males for Tuberculosis. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8054790/>
6. World Health Organization. Available from: <http://www.who.int/tb/areas-of-work/children/en>.
7. Seddon, J.A.; Chiang, S.S.; Esmail, H.; Coussens, A.K. The Wonder Years: What Can Primary School Children Teach Us About Immunity to Mycobacterium tuberculosis? *Front. Immunol.* 2018, 9, 2946.
8. Snow, K.J.; Cruz, A.T.; Seddon, J.A.; Ferrand, R.A.; Chiang, S.S.; Hughes, J.A.; Kampmann, B.; Graham, S.M.; Dodd, P.J.; Houben, R.M.; et al. Adolescent tuberculosis. *Lancet Child Adolesc. Health* 2020, 4, 68–79.
9. Nahid, P.; Mase, S.R.; Migliori, G.B.; Sotgiu, G.; Bothamley, G.H.; Brozek, J.L.; Cattamanchi, A.; Cegielski, J.P.; Chen, L.;

- Daley, C.L.; et al. Treatment of Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am. J. Respir. Crit. Care Med.* 2019, 200, e93–e142.
10. <https://www.who.int/news/item/14-11-2023-who-launches-new-5-year-roadmap-to-prevent-and-treat-tb-in-children-and-adolescents>.
 11. Chiang SS, Swanson DS, Starke JR. New Diagnostics for Childhood Tuberculosis. *Infect Dis Clin North Am* 2015; 29(3): 477–502. [PubMed] [Google Scholar]
 12. Chiang SS, Park S, White EI, et al. Using changes in weight-for-age z score to predict effectiveness of childhood tuberculosis therapy. *J Pediatric Infect Dis Soc* 2019; 1(5305715). [PubMed] [Google Scholar]
 13. World Health Organization. WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment. Geneva: World Health Organization, 2019. [PubMed] [Google Scholar]
 14. Seddon JA, Hesselning AC, Godfrey-Faussett P, Schaaf HS. High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study. *Thorax* 2014; 69(5): 458–64. [PubMed] [Google Scholar]