Journal of Kathmandu Medical College, Vol. 11, No. 4, Issue 42, Oct.-Dec., 2022

Drug resistant paediatric tuberculosis: An emerging but neglected global threat

Shah BK

Basant Kumar Shah, Paediatric Pulmonologist, Telemedicine Unit – Medicine Sans Frontiers, Toronto, Ontario, Canada.

Tuberculosis (TB) is a leading cause of infection related death and remains a major public health threat globally.[1] World Health Organisation (WHO) report estimates that around 10 million people fell ill with TB in 2020. They have also estimated around 1.3 million deaths in patients without Human Immunodeficiency Virus (HIV), and an additional >200,000 TB deaths in those with HIV.[2] Therefore, TB is still a leading cause of morbidity and mortality in both adults and children with HIV.[3] Paediatric TB is often more challenging to diagnose and manage compared to TB in adults. It is difficult to diagnose TB in children due to its pauci-bacillary nature; there are challenges in obtaining sample and limited availability of diagnostic tests/facilities further complicates it. This leads to lower rates of microbiological confirmation of TB and hence underreporting of total disease burden.[4] According to the published reports, it has been estimated that 1.1 million children developed TB in 2020 and more than 230,000 of them died.[2]

Access this article online

Website: www.jkmc.com.np

DOI: https://doi.org/10.3126/jkmc.v11i4.50794

HOW TO CITE
Shah BK. Drug resistant paediatric tuberculosis: An emerging but neglected global threat. J Kathmandu Med Coll. 2022;11(4):247-9.

Submitted: Feb 17, 2022
Accepted: Nov 08, 2022
Published: Dec 30, 2022

Address for correspondence

Dr. Basant Kumar Shah
Paediatric Pulmonologist,
Telemedicine Unit – Medicine Sans Frontiers,
Toronto, Ontario, Canada.
E-mail: basantkshah@gmail.com

ISSN: 2019-1785 (Print), 2091-1793 (Online)

Drug-resistant TB (DRTB) is one of the worst forms of TB. It is a neglected global health problem and has received increasing concerns in recent times. The WHO has classified DRTB into five categories on the basis of resistance to various classes of available anti-tubercular drugs – Isoniazid resistant TB, Rifampicin resistant TB and Multi drug resistant (MDR) TB, plus pre-extensively drug resistant TB (pre-XDR-TB) and extensively drug resistant TB (XDR-TB).[5] Worldwide, 150359 people with MDR/RR-TB were enrolled for the treatment in the year 2020, which is a decrease by 15% from the total of 177,100 in 2019. The WHO concerningly reports this level of enrolment was equivalent to only about one in three of the people who develop MDR/RR-TB each year.[2] The challenge with DRTB is that it cannot be detected solely on clinical basis, it needs laboratory confirmation with advanced tests like culture and drug sensitivity, molecular tests and/or genomic sequencing technologies.[6] The DRTB remains grossly underdiagnosed and underreported due to various factors which contribute to diagnostic difficulties in children. This possesses additional challenges to the health care personnel, institutions and organisations to address DRTB in children.[2]

The WHO Global TB report has listed countries with high burdens of MDR-TB. Unfortunately, there remains a wide gap between estimated MDR/RR-TB cases and the number of cases enrolled in MDR/RR-TB treatment in most of these high burden countries.[2] In patients with MDR/RR-TB commenced on treatment, global treatment success ranges from approximately 59% to 80% in some countries.[2,7] As previously discussed, DRTB cases are more likely to be undiagnosed and underestimated in children than in adults due to lower rates of microbiological confirmation. It is worrying that there are no precise and reliable data on DRTB in children and most of the estimates are based on mathematical modelling.[8] In a recent study published by Song et al., out of 23,652 paediatric TB patients, the proportions of DR-TB, MDR-TB, mono-resistant TB, polydrug resistant TB, extensive drug-resistant TB were 13.59%, 3.72%, 6.07%, 1.61% and 0.44% respectively.[9]

The development of drug resistance in children with TB has a different mechanism compared to adults. DRTB in young children are typically acquired from other DRTB case, mostly from close contact adults. This is unlike the resistance mechanism induced in adult TB where resistance develops from intrinsic changes in *Mycobacterium tuberculosis* in the patient itself.[10,11] This also highlights the importance of contact tracing and source identification for each case of childhood TB, both for case management as well as transmission prevention. Practically, source identification is much more challenging in countries with high TB prevalence.[12] It is very important to have high index of clinical suspicion for TB and be aware of DRTB for clinicians practicing in high TB burden region. In resource limited countries, TB is still diagnosed clinically on the basis of clinical features and epidemiological risk factors; with addition of laboratory and radiological support if available.[13] As discussed earlier, microbiological confirmation may not be always possible, and a negative investigation may not always rule out TB. Most of the national guidelines recommend induced sputum as the preferred method for specimen collection, however it may not be possible in young children and infants; there is also a risk of spreading infection due to aerosolisation with sputum induction. Early morning gastric samples are recommended for sample collection in such young children and infants whom sputum collection is difficult. Like adults, children may develop wide range of clinical manifestation: pulmonary or extrapulmonary TB (TB meningitis, abdominal TB, miliary of disseminated TB); these heterogenous clinical presentation further add to the diagnostic challenge. Therefore, the clinicians need to choose appropriate investigations to support and/or confirm the diagnosis.[5,14]

Childhood TB in itself is also an indicator of recent TB transmission in community which warrants contact tracing and source identification in addition to the clinical management. This is more important in DRTB to prevent transmission of drug resistant TB in the community. There are national and regional guidelines and resources published for the management of drug resistant TB in adults and children.[5,13] There have been major changes in the approach to DRTB treatment in last decade. The recently published TB guidelines describe the treatment protocol for MDR-TB with multiple sensitive anti-tubercular drugs; and recommends the use oral drugs wherever feasible.[5]

The challenges faced by clinicians treating DRTB in children are not only limited to diagnostic difficulties, but also extends to the limited access to drugs, absence of child friendly drug formulations, potential drug interactions and limited availability of in vivo pharmacokinetic data.[6] Until recently, the treatment course for DRTB used to be much longer (as long as two years), but there are newer and ongoing studies to evaluate shorter course of treatment as well. Bedaquiline and Delaminid are two new oral drugs approved for treatment of MDR-TB in children which have the potential to shorten the duration of treatment.[5] DRTB treatment is associated with higher incidence of drug related adverse effects likely due to multiple drugs and prolonged duration of therapy. In addition, it also increases the financial and psychosocial burden including fear for social stigma on the patient and family. This becomes more relevant to patients with HIV and DRTB co-infection.[15,16]

From the global health point of view, there is an urgent need of coordinated efforts to strengthen partnership among various stakeholders involved in addressing the burden of tuberculosis. It is imperative to improve the capacity to identify and diagnose children with tuberculosis and improve the quality and compliance of treatment to prevent evolution and transmission of DRTB in community. Clinico-epidemiological studies on mechanism and transmission dynamics for MDR-TB, surveillance activities targeted to high risk and susceptible population, and drug resistance surveys may be useful in formulating future programs and policies to control DRTB in children.

Conflict of interest: None
Source(s) of support: None

REFERENCES

1. MacNeil A, Glaziou P, Sismanidis C, Maloney S, Floyd K. Global epidemiology of tuberculosis progress toward achieving global targets – 2017. MMWR Morb Mortal Wkly Rep. 2019;68(11);263-6. [PubMed | Full Text | DOI]
2. World Health Organisation (WHO). Global tuberculosis report 2021 [internet]. Geneva: WHO; 2021. [Full Text]
3. Ford N, Matteelli A, Shubber Z, Hermans S, Meintjes G, Grinsztejn B, et al. TB as a cause of hospitalisation and in-hospital mortality among people living with HIV worldwide: A systematic review and meta-

analysis. J Int AIDS Soc. 2016;19(1):20714. [PubMed | Full Text | DOI]

4. World Health Organisation (WHO). Roadmap for childhood tuberculosis: Towards zero deaths [internet]. Geneva: WHO; 2013. [Full Text]
5. World Health Organization (WHO). WHO consolidated guidelines on tuberculosis: Module 4: Treatment: Drug-resistant tuberculosis treatment [internet]. Geneva: WHO; 2020. [Full Text]
6. Koch A, Cox H, Mizrahi V. Drug-resistant tuberculosis: Challenges and opportunities for diagnosis and treatment. Curr Opin Pharmacol. 2018;42:7-15. [PubMed | Full Text | DOI]
7. Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ, et al. Outcome of pulmonary multidrug-resistant tuberculosis: A 6-yr follow-up study. Eur Respir J. 2006;28(5):980-5. [PubMed | Full Text | DOI]
8. Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: A mathematical modelling study. Lancet Glob Health. 2017;5(9):e898-e906. [PubMed | Full Text | DOI]
9. Song WM, Li YF, Liu YX, Liu Y, Yu CB, Liu JY, Li HC. Drug-resistant tuberculosis among children: A systematic review and meta-analysis. Front Public Health. 2021;9:721817. [PubMed | Full Text | DOI]
10. Becerra MC, Swaminathan S. Commentary: A targets framework: Dismantling the invisibility trap for children with drug-related tuberculosis. J Public Health Policy. 2014;35(4):425-454. [PubMed | Full Text | DOI]
11. Dheda K, Gumbo T, Maartens G, Dooley KE, Murray M, Furin J, et al. The lancet respiratory medicine commission: 2019 update: epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug resistant and incurable tuberculosis. [PubMed | Full Text | DOI]
12. Sun SJ, Bennett DE, Flood J, Loeffler AM, Kammerer S, Ellis BA. Identifying the sources of tuberculosis in young children: A multistate investigation. Emerg Infect Dis. 2002;8(11):1216-23. [PubMed | Full Text | DOI]
13. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official american thoracic society/infectious diseases society of america/ centres for disease control and prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017;64(2):111-5. [PubMed | Full Text | DOI]
14. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Executive summary: Official american thoracic society/centers for disease control and prevention/infectious diseases society of america clinical practice guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63(7):853-67. [PubMed | Full Text | DOI]
15. Furin J, Isaakidis P, Reid AJ, Kielmann K. 'I'm fed up': Experiences of prior anti-tuberculosis treatment in patients with drug-resistant tuberculosis and HIV. Int J Tuberc Lung Dis. 2014;18(12):1479-84. [PubMed | Full Text | DOI]
16. Isaakidis P, Rangan S, Pradhan A, Ladomirska J, Reid T, Kielmann K. 'I cry every day': Experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. Trop Med Int Health. 2013;18(9):1128-33. [PubMed | Full Text | DOI]