INT J TUBERC LUNG DIS 28(9):407–409
© 2024 The Union http://dx.doi.org/10.5588/ijtld.24.0232

EDITORIAL

The hidden burden of miliary TB in children and adolescents

More than 1.2 million children develop TB every year,[1] and it is recognised as a top-10 cause of under-5 mortality in TB-endemic areas.[2] Disseminated disease manifesting as miliary TB, with or without TB meningitis or other central nervous system (CNS) TB pathology, is often the 'final terminal pathway', especially in young and vulnerable children.[3] Because the occurrence of miliary TB and TB meningitis in young children (<5 years) reflects local TB transmission, its occurrence has been used as an indicator of the annual infection rate in children, which informed earlier TB incidence estimates using the 'Styblo rule'.[4] However, in most high TB incidence settings, miliary TB is grossly under-detected, and data on its occurrence are not routinely recorded or reported.

This issue of the Journal includes a scoping review by Buonsenso et al.,[5] which addresses this knowledge gap by assessing all peer-reviewed publications from 1950–2023 for children and adolescents (<19 years of age) with miliary TB. The study defined miliary TB as the presence of radiological and/or pathological evidence indicating the presence of small 'miliary' lesions in at least one organ, and summarises clinical presentation, diagnostic test performance, treatment regimens and reported outcomes.[5] All study types were considered, but no clinical trials could be identified, and the available information came from observational studies, small case series and case reports. A total of 257 publications reported data for 1,883 patients with miliary TB. Data quality was variable, and key data points were collected inconsistently. Reported symptoms were non-specific, with fever (63%) being most common, followed by cough (30%), neurological symptoms (22%) and reported weight loss (22%). The results of TB infection testing were informative when positive, but sensitivity was suboptimal for both the tuberculin skin test (47%) and the interferon-gamma release assay (72%), precluding its use as a 'rule-out' test. Miliary TB was most frequently detected on chest X-ray (CXR), although in some instances, miliary lesions were missed on CXR and only detected on high-resolution computed tomography (CT). Given the disseminated nature of miliary disease, ultrasound, which can detect splenic micro-abscesses in addition to other thoracic and extra-thoracic findings suggestive of TB, may be informative in adults and children.[6–8] However, more information is required, and the optimal use of point-of-care devices is an area of active investigation.

Microbiological confirmation was achieved in 56% of patients, with the highest yield from sputum and gastric aspirates. The yield from stool in young children unable to expectorate sputum was lower (~50%), but it is recognised as a valuable sample in settings where other respiratory specimens are hard to collect.[9] Cerebrospinal fluid (CSF) was collected in only a small proportion of children (62/1,883; only 3%) and the microbiological yield was >50% (32/62 children) with the use of culture and/or nucleic acid amplification testing (NAAT). Although this is likely a selective group, it had a remarkably high rate of CSF microbiological positivity, which provides important information for clinical management and follow-up. Even if microbiological testing is negative, collecting CSF has value, as cell counts and chemistry analysis provide additional clues suggestive of TB or other forms of meningitis, but CSF is often not collected in high TB incidence settings with limited resources. Some laboratories are also reluctant to test non-sputum samples if local equipment suppliers specify 'sputum only' testing as a warranty pre-condition, or if the testing of non-sputum specimens is not covered by government health insurance schemes.[10,11] A basic commitment from all TB control programmes should be to ensure access to appropriate TB diagnostics that are free of charge, irrespective of disease manifestation.

Of 924 children with miliary TB, 367 (40%) were reported to have CNS involvement. However, the number of children who underwent a lumbar puncture (62 children) and/or neurological imaging (105 children) was very low. CNS involvement could have been missed, as many patients with confirmed CNS involvement did not display any overt CNS symptoms. The fact that overt symptoms are frequently absent in patients with early CNS involvement is well documented.[12] Only 69 children had magnetic resonance imaging (MRI), of whom 64 (93%) showed tuberculomas or other CNS pathology, similar to findings in adults with miliary TB.[12] Given the high rates of CNS disease in people with miliary TB, a routine lumbar puncture (LP) with CSF culture and/or WHO-approved NAAT is recommended in the 'Clinical standards for drug-susceptible TB in children and adolescents',[13] especially in infants with miliary TB. However, LP results may be normal in the presence of CNS tuberculomas on contrasted CT or MRI, and vice versa.[12,14] Given the high rate of abnormal CSF and CNS imaging findings in patients with miliary TB, it is advised that all children and adolescents with miliary TB on CXR should be treated as presumptive TB meningitis, if CSF assessment and neuroimaging are not locally available or done and CNS involvement therefore not excluded with certainty.

Article submitted 1 May 2024. Final version accepted 2 May 2024.

Table. Implementation and research priorities in children and adolescents with miliary TB.

Implementation priority	Motivation
Improved diagnostic access	Diagnostic access for children with miliary TB remains poor in most high TB incidence settings, given non-specific presentation and limited awareness among front-line healthcare workers; recent TB contact is rarely solicited; high-quality CXR are often unavailable or not funded by the TB programme; huge barriers to CSF collection and NAAT often not used to test CSF
Optimal use of available treatment	Given the high rates of TBM/CNS TB disease in children with miliary TB, empiric treatment should be as for TBM. Higher doses of rifampicin are important to optimise CSF penetration
Research priority	
A more protective vaccine	Although BCG offers protection against disseminated forms of disease in young children, its protection is incomplete and wanes in time.
Better diagnostic tools	A rapid point-of-care screening test to improve TB detection, especially in vulnerable young children. Use of ultramobile CXR with computer assisted detection of miliary TB or point-of-care ultrasound. Enhanced tools for early accurate TBM diagnosis. A multi-centre observational study with CSF collection to evaluate for TBM and MRI to evaluate for both TBM and other CNS TB pathology, to determine the true frequency and extent of CNS TB in children with miliary TB.
A stronger treatment evidence base	Better treatment is essential to reduce high rates of morbidity and mortality associated with miliary TB. New evidence regarding optimal TBM therapy, including optimal rifampicin dosage and the inclusion of levofloxacin as a fourth drug, should guide empiric treatment. Steroids are recommended in TBM, but the role of steroids in miliary TB needs to be determined. In children with miliary TB following exposure to an RR/MDR-TB source case, or with confirmed RR/MDR-TB disease, physicians should carefully consider the CSF penetration of second-line drugs and optimal treatment duration.
Reducing post-TB sequelae	Permanent neurological sequelae are common, especially with delayed diagnosis. Improving the quality of life in children with post-TBM sequelae requires further study, especially in resource-limited settings.

CXR = chest X-ray; CSF = cerebrospinal fluid; NAAT = nucleic acid amplification tests; TBM = tuberculous meningitis; CNS = central nervous system; BCG = bacilli Calmette-Guérin; MRI = magnetic resonance imaging; RR/MDR-TB = rifampicin/multidrug-resistant TB.

In the review by Buonsenso et al., pre-1995 studies reported very high death rates (42%) in miliary TB cases, especially in those with CNS involvement (65%).[5] After 1995, this declined to 15% without and 20% with CNS disease, presumably due to improved early diagnosis and treatment.[5] However, the morbidity and mortality associated with miliary TB remains unacceptably high. It is important to emphasise that miliary TB and TB meningitis are best prevented. Neonatal bacille Calmette-Guérin (BCG) vaccination remains important to reduce the risk of disseminated TB in young children and should be universally delivered at birth (aiming to protect every single infant) in high TB incidence settings.[15] In the study by Buonsenso et al.,[5] only 29% of patients had a known BCG vaccination status, of whom 40% were vaccinated. The other major intervention to reduce miliary TB and TB meningitis risk is the provision of TB preventive treatment (TPT) following close TB contact,[16] especially in young child contacts who are at high risk of severe disseminated TB.

Unfortunately, high rates of morbidity and mortality persist, even in children with relatively mild disease at presentation, and despite receiving standard 12-month TB meningitis treatment as currently advised by the WHO.[17,18] Of particular concern is the low CSF drug concentrations achieved with standard doses of rifampicin, a crucial TB drug with important bactericidal and sterilising activities.[10,11,18] It is now well established that rifampicin doses of up to 30 mg/kg are well tolerated and safe.[19] Given the difficulty with which rifampicin crosses the blood-brain barrier, it is imperative to maximise rifampicin exposure for enhanced CSF penetration and to consider the addition of either ethionamide (or prothionamide) or a fluoroquinolone (levofloxacin or moxifloxacin) as a fourth drug, instead of ethambutol, which is weakly bactericidal and does not penetrate the CSF.[18,20] A 6-month, 4-drug regimen consisting of isoniazid (15–20 mg/kg), rifampicin (20–30 mg/kg), pyrazinamide (30–40 mg/kg) and levofloxacin (15–25 mg/kg) should provide optimal treatment for drug-susceptible miliary TB or TB meningitis,[10] given good bactericidal activity and CSF penetration. This regimen is currently being evaluated in the SURE trial,[21] which also assesses the use of low-dose aspirin to improve neurodevelopmental outcomes.

The paper by Buonsenso et al.[5] is a reminder of how little high-quality evidence we have on this severe form of TB disease. In the Table we present an overview of implementation and research priorities in children and adolescents with miliary TB. Implementation priorities emphasise improved diagnostic access and optimal use of available treatment, while research priorities focus on the development of better diagnostic tools, a stronger evidence-base for optimal treatment, and better strategies to reduce and rehabilitate post-TB sequalae.

B.J. Marais,[1] W.C. Buck,[2] H.S. Schaaf[3]
[1]Sydney Infectious Diseases Institute (Sydney ID) and The Children's Hospital at Westmead, University of Sydney, Sydney, NSW, Australia; [2]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA, USA; [3]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa

Correspondence to: Ben J Marais, Clinical School, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, Sydney, New South Wales 2145, Australia. E-mail: ben.marais@health.nsw.gov.au

Conflict of interest: none declared.

KEY WORDS: tuberculosis; miliary TB; TB management; rifampicin; drug concentrations

References

1 World Health Organization. Global tuberculosis TB report, 2023. Geneva, Switzerland: WHO, 2023.
2 Dodd PJ, et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. Lancet Glob Health 2014;2:e453–459.
3 Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med 2012:367:348–361.
4 van Leth F, van der Werf MJ, Borgdorff MW. Prevalence of tuberculous infection and incidence of tuberculosis: a re-assessment of the Styblo rule. Bull World Health Organ 2008; 86:20–26.
5 Buonsenso et al. Miliary TB in children and adolescents: a scoping review of the literature**.** Int J Tuberc Lung Dis 2024;28(9): 412–418.
6 Allan-Blitz LT, et al. Point-of-care ultrasound for diagnosing extrapulmonary TB. Int J Tuberc Lung Dis 2024;28:217–224.
7 Belard S, et al. Point-of-care ultrasound for tuberculosis and HIV – revisiting focused assessment with sonography for HIV-associated tuberculosis (FASH) protocol and its differential diagnoses. Clin Microbiol Infect 2024;30:320–327.
8 Moretó-Planas L, et al. Point-of-care ultrasound for tuberculosis diagnosis in children: a Médecins Sans Frontières cross-sectional study in Guinea-Bissau. BMJ Open 2023;13: e066937.
9 World Health Organization. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva, Switzerland: WHO, 2022.
10 Hill J, Marais BJ. Improved treatment of children with tuberculous meningitis: acting on what we know. Arch Dis Child 2022;107: 68–69.
11 Ruslami R, et al. Pharmacokinetics and safety/tolerability of isoniazid, rifampicin and pyrazinamide in children treated for tuberculous meningitis. Arch Dis Child 2022;107:70–77.
12 Urs VL, et al. Concurrent central nervous system involvement in immunocompetent adults with pulmonary miliary TB: a prospective analysis. Trans R Soc Trop Med Hyg 2022;116: 344–351.
13 Chiang SS, et al. Clinical standards for drug-susceptible TB in children and adolescents. Int J Tuberc Lung Dis 2023;27: 584–598.
14 Donald PR, Schaaf HS, Schoeman JF. Tuberculous meningitis and miliary tuberculosis: the Rich focus revisited. J Infect 2005;50: 193–195.
15 Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006;367:1173–1180.
16 Casenghi M, et al. Closing the policy-practice gap for tuberculosis preventive treatment. Lancet Child Adolesc Health 2024;8: 315–317.
17 Nataprawira HM, et al. Treatment outcomes of childhood tuberculous meningitis in a real-world retrospective cohort, Bandung, Indonesia. Emerg Infect Dis 2022;28:660–671.
18 Huynh J, et al. Tuberculosis treatment in children: The changing landscape. Paediatr Respir Rev 2020;36:33–43.
19 Dian S, et al. Double-blind, randomized, placebo-controlled Phase II dose-finding study to evaluate high-dose rifampin for tuberculous meningitis. Antimicrob Agents Chemother 2018;62: e01014–1018.
20 Van Toorn R, et al. Short intensified treatment in children with drug-susceptible tuberculous meningitis. Pediatr Infect Dis J 2014;33:248–252.
21 MRC Clinical Trials Unit at UCL, University College London. SURE: A randomised trial of 6 months intensified anti-tuberculosis and 2 months anti-inflammatory treatment of HIV-infected and HIV-uninfected African and Asian children with tuberculous meningitis. London, UK: UCL, 2024.