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Scientific letter

Shorter treatment for nonsevere pediatric tuberculosis: a single-center case series in a low-burden country

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The development and implementation on a global scale of shorter all-oral regimens for both drug-sensitive and drug-resistant tuberculosis (TB) is one of the main goals of the World Health Organization End TB Strategy, also in children. The SHINE trial recently demonstrated that a 4-month treatment was non-inferior to a 6-month regimen in symptomatic children with nonsevere smear-negative TB in Sub-Saharan Africa and India, and associated lower health care costs.[1] Nonsevere TB included peripheral lymph-node disease or respiratory disease confined to one lobe, without cavities, miliary pattern, complex pleural effusion, or clinically significant airway obstruction. The trial criteria allowed the inclusion of HIV-infected patients, but pregnant adolescents, infants aged <3 months, and patients with other types of extra-pulmonary disease or suspected or known drug resistance were excluded. An identical 4-month treatment regimen for HIV-negative adults with culture-negative TB disease (a rough equivalent for nonsevere TB) had been previously recommended, albeit with very low certainty in the evidence.[2] The new pediatric short treatment regimen was later endorsed by the World Health Organization,[3] but no clinical experiences with the new regimen have been reported to date. We present our use of the short regimen in a low-burden TB country.

We present a case series of 12 children diagnosed with nonsevere pulmonary TB as per the SHINE trial criteria[1] at a referral pediatric center in Barcelona (Spain) between September 2021 and May 2023 who received the 4-month treatment regimen, and compare them with a historical consecutive series of 21 children (diagnosed between March 2016 and August 2021) who met the same diagnostic criteria and were treated for 6 months. In our center, the diagnosis of TB is based on epidemiological, clinical, radiological and microbiological findings according to published consensus criteria,[4] and TB is classified as microbiologically confirmed or unconfirmed, intrathoracic or extrathoracic, and severe or nonsevere, based on published consensus definitions.[5] Our local protocol was updated in September 2021 to include the 4-month treatment regimen for all patients diagnosed with TB who fulfill the SHINE trial criteria.[1] It also includes a low-dose chest computed tomography scan in all cases with clinical-radiological suspicion of pulmonary TB. In this study, both groups received daily standard anti-TB therapy (isoniazid, rifampicin, and pyrazinamide, with or without ethambutol in the intensive phase; isoniazid and rifampicin in the continuation phase) at recommended doses, which did not change during the study period.[6] The groups differed only in the duration of the continuation phase (2 or 4 months). Directly observed treatment was not used. Adherence to anti-TB treatment was reinforced through a nurse-led educational intervention and was assessed by means of a written questionnaire in both groups.[7] Missing more than 10% of prescribed doses prompted an extension of TB treatment to ensure the missed doses were recovered. Follow-up visits were conducted every 1-2 months during anti-TB treatment and every 6-12 months thereafter at least until 2 years had elapsed since TB cure. Vital status was subsequently confirmed through Public Health databases. All patients were prospectively included in the Registry of the Spanish Pediatric TB Research Network, approved by the local ethics committee (ref. PIC 103-16). Informed consent was obtained from parents or legal guardians at diagnosis, as was informed assent in patients aged >11 years. All statistical analyses were performed with SPSS V24 (IBM; Armonk, NY) by means of the Chi Square test or the Mann-Whitney test, with statistical significance defined as a p-value <0.05.

At diagnosis, all patients presented symptoms consistent with TB and/or abnormal chest X-rays. None of the patients was HIV-infected. Adherence was above 90% of daily doses in all cases, except in 3 patients that required treatment extensions due to excessive missed doses (2 in the short treatment group and 1 in the control group). No significant differences were observed between the groups except in the duration of the continuation phase, the total duration of treatment, and the follow-up time after treatment completion (*Table 1*). All patients in both groups were cured and no severe adverse events, cases of TB relapse, TB-associated sequelae, or death were observed after a median (interquartile range) follow-up of 1.3 (1.3-1.8) years in the short treatment group and 3.7 (3.0-5.3) years in the control group.

In contrast to the SHINE trial, we could not use the dispersible fixed-dose combinations of anti-TB drugs, as they were not available in Spain until July 2023.[8,9] Also, only one of the patients in our series presented with peripheral lymph-node TB as compared to 32% in the SHINE trial. Ethambutol use was more frequent in the 4-month group, but it is unlikely that this had any impact on outcomes, since *Mycobacterium tuberculosis* strains were sensitive to the rest of first-line drugs in all cases. Also, similar proportions of unfavourable outcomes with and without ethambutol were reported in the SHINE trial.[1] The observational nature of the study, the short follow-up time after treatment completion in some patients in the short treatment group, and the fact that microbiological diagnosis was not attempted in some cases are limitations of this study.

To our knowledge, this is the first experience with the short treatment regimen for nonsevere pediatric TB in a low-burden country. Children in our series presented with less severe forms of TB than those in the SHINE trial, mostly due to very early diagnosis through contact tracing. A few of them even presented without symptoms or with normal chest X-rays. TB diagnosis was based in epidemiological history (contact with a smear-positive index case in 61% of patients), clinical and radiological findings, and almost universally positive immunodiagnostic tests. TB was confirmed in one third of the patients in whom microbiological diagnosis was attempted, as compared to only 14% in the SHINE trial.[1] This comprehensive diagnostic workup largely

precludes the misdiagnosis of TB in a child from a low-burden TB region, an aspect that has been criticized in the SHINE Trial.[10] The use of computed tomography scans, albeit controversial, was also useful in confirming the TB diagnosis and allowed for a better assessment of radiological severity criteria.[11] Finally, pre-existing comorbidities such as HIV co-infection and malnutrition were rare. In this scenario, the outcomes were excellent in both groups, as previously reported.[12] We were unable to assess long-term sequelae in our study. A recent systematic review on post-pediatric pulmonary TB sequelae reported radiological findings in 7% to 49% of patients, but clinical symptoms (such as coughing or wheezing) were observed in only 1%.[13] However, the studies included in the analysis were diverse and dated, revealing a gap in knowledge regarding post-TB lung function in children. Nonetheless, it is anticipated that children with non-severe TB would be at very low risk of developing sequelae.

Recent data from the Spanish Pediatric TB Research Network estimate that nonsevere TB represents almost two thirds of pediatric TB cases in Spain.[14] It is likely that these children could benefit from the 4-month regimen, potentially increasing adherence and quality of life, and decreasing toxicity and costs. Almost 2 years after the publication of the SHINE trial, several national guidelines have been updated with the new 4-month treatment regimen for nonsevere cases.[6,15-17] Our observational results are consistent with those of the SHINE trial and support the rapid implementation of the short treatment in low-burden TB countries using active case finding strategies, provided that a comprehensive diagnostic workup and close follow-up of the patients are available.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Authors´ contributions

AN-J conceptualized and designed the study, and drafted the initial manuscript; AG, CF and GR collected and analyzed data; CL and MM assisted with data interpretation. All authors participated in the clinical assessment of the patients, reviewed and revised the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

References

1. Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, et al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children. N Engl J Med 2022;386:911-22. https://doi.org/10.1056/NEJMoa2104535.
2. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. 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:e147-95. https://doi.org/10.1093/cid/ciw376.
3. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/9789240046764. Accessed May 31 2024.
4. Graham SM, Ahmed T, Amanullah F, Browning R, Cardenas V, Casenghi M, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. J Infect Dis 2012;205:S199-208. https://doi.org/10.1093/infdis/jis008.

5. Wiseman CA, Gie RP, Starke JR, Schaaf HS, Donald PR, Cotton MF, et al. A proposed comprehensive classification of tuberculosis disease severity in children. Pediatr Infect Dis J 2012;31:347–52. https://doi.org/10.1097/INF.0b013e318243e27b.

6. Baquero-Artigao F, del Rosal T, Falcón-Neyra L, Ferreras-Antolín L, Gómez-Pastrana D, Hernanz-Lobo A, et al. Update on the diagnosis and treatment of tuberculosis. An Pediatr (Engl Ed) 2023;98:460-9. https://doi.org/10.1016/j.anpede.2023.03.009.

7. Guix-Comellas EM, Rozas-Quesada L, Velasco-Arnaiz E, Ferrés-Canals A, Estrada-Masllorens JM, Force-Sanmartín E, et al. Impact of nursing interventions on adherence to treatment with antituberculosis drugs in children and young people: A nonrandomized controlled trial. J Adv Nurs 2018;74:1819–30. https://doi.org/10.1111/jan.13692.

8. Noguera-Julian A, Buonsenso D, McKenna L, Seddon JA, Ritz N. Availability of fixed-dose, child-friendly formulations of first-line tuberculosis drugs in Europe. Eur Respir J 2021;58:2101196. https://doi.org/10.1183/13993003.01196-2021.

9. Noguera-Julian A, Latre C, Flores Á. Availability of paediatric dispersible fixed-dose combinations of tuberculosis drugs in Spain. Eur Respir J 2024;63:2400104. https://doi.org/10.1183/13993003.00104-2024.

10. Kumar K, Mathew JL. World Health Organization Guideline on the Management of Tuberculosis in Children: Critical Appraisal, Concerns, and Caution. Indian J Pediatr 2023;90:811-6. https://doi.org/10.1007/s12098-023-04584-y.

11. Tonne EO, Fosbøl MØ, Poulsen A, Nygaard U, Højgaard L, Borgwardt L. Imaging modalities for pulmonary tuberculosis in children: A systematic review. Eur J Radiol Open 2022;10:100472. https://doi.org/10.1016/j.ejro.2022.100472.

12. Ziemele B, Ranka R, Ozere I. Pediatric and adolescent tuberculosis in Latvia, 2011-2014: case detection, diagnosis and treatment. Int J Tuberc Lung Dis 2017;21:637-45. https://doi.org/10.5588/ijtld.16.0270.

13. Igbokwe V, Ruby LC, Sultanli A, Bélard S. Post-tuberculosis sequelae in children and adolescents: a systematic review. Lancet Infect Dis 2023;23:e138-e150. https://doi.org/10.1016/S1473-3099(23)00004-X.

14. Hernanz-Lobo A, Noguera-Julian A, Gamell A, López-Suárez A, Soriano-Arandes A, Espiau M, et al. Prevalence and clinical characteristics of children with nonsevere tuberculosis in Spain. Pediatr Infect Dis J 2023;42:837-43. https://doi.org/10.1097/INF.0000000000004016.

15. Kainz K, Brinkmann F, Bogyi M, Feiterna-Sperling C, Götzinger F, Mädel C, et al. Tuberkulose – Update 2022. Monatsschr Kinderheilkd 2023;171:553-64. https://doi.org/10.1007/s00112-023-01768-w.

16. British Association for Paediatric Tuberculosis. Clinical Guidance: Care of children and young people exposed to or infected with tuberculosis. BAPT 2023. Available at: http://bapt.uk/wp-content/uploads/2023/04/BAPTguidance11thApril2023.pdf. Accessed May 31, 2024.

17. American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021, 786-813. Updated on Nov 28, 2022.

Table 1. Demographic and clinical characteristics at TB diagnosis, and treatment details of the two groups of patients included in this study. Data are shown as n (%) or median (interquartile range).

	4-month treatment (n=12)	6-month treatment (n=21)	*p*-value
Female sex	4/12 (33)	10/21 (48)	0.424
Age at TB diagnosis (years)	4.6 (2.3-12.2)	3.6 (1.9-9.8)	0.525
Born to a Spanish family[a]	3/12 (25)	8/21 (38)	0.703
Born in Spain	11/12 (92)[b]	21/21 (100)	0.364
Pre-existing comorbidities[c]	2/12 (17)	1/21 (5)	0.538
TB assessment in contact tracing studies	8/12 (67)	12/21 (57)	0.719
Malnutrition at diagnosis[d]	0/12 (0)	1/21 (5)	1.000
Symptomatic at TB diagnosis	8/12 (67)	13/21 (62)	1.000
Chest X-ray findings[5]			0.877
Normal	3/11 (27)	2/21 (9)	
Ghon focus	3/11 (27)	14/21 (67)	
Ghon complex	5/11 (45)	5/21 (24)	

Computed tomography findings[5] Ghon complex	11/11 (100)	20/20 (100)	1.000
Non-complex pleural effusion	0/12 (0)	5/21 (15)	0.133
Peripheral lymphadenitis	1/12 (8)	0/21 (0)	0.364
Positive TST (induration ≥5mm)	10/10 (100)	20/21 (95)	1.000
TST induration (mm)	15 (15-20)	20 (15-21)	0.359
Positive QuantiFERON-*TB* Gold Plus (Cellestis/Qiagen, Hilden, Germany)	12/12 (100)	18/21 (86)	0.284
Microbiologically-confirmed TB[e]	4/12 (33)	6/16 (37)	1.000
Inclusion of ethambutol in the intensive phase of treatment	12/12 (100)	17/21 (81)	0.271
Intensive phase duration (weeks)	8.9 (8.7-9.7)	8.9 (8.6-9.3)	0.441
Continuation phase duration (weeks)	9.3 (8.9-10.1)	17.6 (17.4-17.7)	<0.001
Total treatment duration (weeks)	18.6 (17.9-19.8)	26.6 (26.3-27.1)	<0.001
Adverse events[f]	4/12 (33)	3/21 (14)	0.377
Follow-up time after completion of treatment (years)	1.3 (1.3-1.8)	3.7 (3.0-5.3)	<0.001

TB, tuberculosis; TST, tuberculin skin test

[a]Family origin: Spain (n=11), Latin America (n=11), Asia (n=5), Morocco (n=4), and Sub-Saharan Africa (n=2).

[b]Only 1 patient born in Sub-Saharn Africa.

[c]Pre-existing comorbidities: obesity (n=2) and autism spectrum disorder (n=1).

[d]Defined as a weight-for-length Z-score below -2 in children <5 years of age, and as a body mass index-for-age Z-score below -2 in children >5 years of age, as per the WHO Child Growth Standards (available at: https://www.who.int/tools/child-growth-standards).

[e]At least 3 respiratory samples were obtained, most commonly gastric aspirates, and assessed both by liquid culture and molecular techniques (Xpert MTB/RIF Ultra; Cepheid, Sunnyvale,

California, USA). All respiratory samples were smear-negative; all identified strains were fully susceptible to first-line anti-TB drugs. Microbiological diagnosis was not attempted in 5 cases because the *Mycobacterium tuberculosis* strain of the index case was known to be pansensitive at child diagnosis.

[f]Including: paradoxical reaction (n=2), febrile seizures (n=2), self-limited abdominal pain (n=2), and self-limited non-symptomatic hypertransaminasemia (n=1).