Perinatal transmission and cure of extensively drug-resistant tuberculosis in an infant

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We describe a rare case of perinatally acquired extensively drug-resistant tuberculosis in an infant. The infant was successfully treated with an individualised all-oral multidrug regimen containing delamanid, a drug rarely described in the treatment of perinatal tuberculosis.

Keywords. Drug-resistant tuberculosis, perinatal tuberculosis.

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Study synopsis
What the study adds. This brief report offers insight into a clinical case of perinatally acquired extensively drug-resistant tuberculosis (XDR-TB), and outlines the individualised treatment plan that led to a successful treatment outcome.
Implications of the findings. The report highlights the need for evidence-based guidance on XDR-TB in this paediatric population, as well as further research on preventive strategies for mitigating mother-to-child transmission of TB.

Tuberculosis (TB) is the leading cause of death from a curable infectious disease worldwide.[1] Multidrug-resistant (MDR)/rifampicin-resistant (RR)-TB (MDR/RR-TB) remains a significant public health concern, with increasing case notifications globally and an estimated 410 000 people who developed MDR/RR-TB in 2022.[1]

The World Health Organization (WHO) updated its definitions for drug-resistant (DR)-TB to reflect the expanded access to oral bedaquiline-containing regimens for RR-TB treatment.[2] MDR-TB is defined as disease caused by *Mycobacterium tuberculosis* resistant to rifampicin and isoniazid (INH), both core drugs used in the treatment of drug-sensitive TB.[1,2] Pre-extensively drug-resistant TB (pre-XDR-TB) now describes MDR-TB with additional resistance to fluoroquinolones (levofloxacin or moxifloxacin),[1,2] while XDR-TB is now defined as resistance to rifampicin, INH, fluoroquinolones, and at least one other group A drug (i.e. bedaquiline or linezolid).[1,2]

Although TB is generally transmitted by inhalation of droplet nuclei containing *M. tuberculosis*, mother-to-child transmission may also occur. This may happen as a result of haematogenous dissemination via the umbilical vein during the antenatal period, through aspiration of infected amniotic fluid or genital secretions during the intrapartum period, or through inhalation of infected droplet nuclei during the postpartum period.[3]

A 3-month-old male infant was referred to a specialised DR-TB unit in KwaZulu-Natal Province, South Africa (SA). He was born at 31 weeks' gestation via normal vertex delivery in November 2021, weighed 1 320 g and had Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. He did not receive BCG vaccination at birth because

his mother had pre-XDR-TB disease during pregnancy. He was HIV exposed, received HIV prophylaxis (nevirapine) and TB preventive therapy (TPT) (INH 5 mg/kg/d) after delivery, and was exclusively formula fed.

At 2 months of age, the infant was taken to his primary healthcare facility with a history of fever, and was found to have a temperature of 38.3°C. He was treated as an outpatient and received single doses of ceftriaxone and paracetamol. Subsequent outpatient visits were required for nonspecific complaints of diarrhoea, and progressive respiratory symptoms including cough and wheeze. Two weeks later, at 10 weeks of age, he developed signs of respiratory distress and was admitted to a regional mother-and-child hospital for further investigation.

Physical examination at admission revealed features of respiratory distress, bilateral expiratory wheezes, and no hepatosplenomegaly. Initial blood investigations showed anaemia (haemoglobin concentration 6.6 g/dL), raised inflammatory markers (C-reactive protein 33 mg/L, erythrocyte sedimentation rate 37 mm/h), and a negative *Toxoplasma gondii*, rubella, cytomegalovirus and herpes simplex virus screen. HIV polymerase chain reaction and COVID-19 rapid antigen tests were negative. Blood, urine and stool culture revealed no pathogens, and the results of cerebrospinal fluid analysis were normal. Chest radiography showed bilateral diffuse reticulonodular infiltrates and features of mediastinal lymphadenopathy. Abdominal ultrasonography revealed no hepatic complex, lymphadenopathy or features suggestive of TB. Initial Xpert MTB/RIF Ultra assay (Cepheid, USA) on gastric aspirate detected *M. tuberculosis* complex and a mutation in the *rpoB* gene, confirming rifampicin resistance.

During the admission, a telephonic discussion with the specialised DR-TB unit revealed that the infant's mother was receiving treatment for microbiologically confirmed pre-XDR-TB. This information led to the decision that the infant be started on an age- and weight-appropriate regimen comprising linezolid (LZD), clofazimine (CFZ), terizidone (TRD), delamanid (DLM) and para-aminosalicylic acid (PAS) (Table 1). Prior to treatment commencement, his haemoglobin concentration was optimised to 10.5 g/dL. When the mother's extended drug susceptibility testing (DST) showed an XDR-TB resistance pattern, with resistance to bedaquiline (BDQ), the infant was kept on the initial regimen because of his improving clinical condition. He completed 15 months of treatment, with resolution of the initial clinical features, and remained with serially negative mycobacterial culture results from diagnosis onwards.

Approximately 4 months before conception, in November 2020, the infant's mother had been diagnosed with MDR-TB and commenced on the basic long MDR/RR-TB regimen, which comprised LZD, BDQ, levofloxacin (LFX), CFZ and TRD. She received treatment for 6 months and was then lost to follow-up. She was re-diagnosed with pre-XDR-TB at an antenatal care visit at 28 weeks' gestation, with positive smear microscopy for acid-fast bacilli on sputum and positive culture for *M. tuberculosis*. She was recommenced on the same drug regimen 3 weeks before delivery. At the time, she remained on antiretroviral therapy with a suppressed viral load and a CD4 cell count of 149 cells/μL.

In January 2022, 3 months after recommencing treatment, her sputum culture remained positive for TB, and extended DST showed XDR-TB.

Perinatal TB is an umbrella term that encompasses both congenital and postnatal acquisition of TB.[3] Although each has distinct transmission characteristics for diagnosis, differentiation of the two forms of perinatal TB is mainly of epidemiological importance, as both are managed using the same approach.[4] The updated diagnostic criteria for congenital TB includes proven TB lesions and at least one of:[3,5] (*i*) lesions in the first week of life; (*ii*) a primary hepatic complex or caseating hepatic granuloma; (*iii*) TB infection of the placenta or the maternal genital tract; and (*iv*) exclusion of the possibility of postnatal transmission by thorough investigation of contacts, including the infant's hospital attendants, and by adherence to existing recommendations for treating infants exposed to TB.

Diagnosis of TB in the paediatric population is difficult owing to the paucibacillary nature of the disease, difficulty in obtaining good-quality respiratory tract specimens, low sensitivity of microbiological assays on sputum and gastric aspirate specimens, and the risk of misdiagnosis due to overlap of nonspecific TB symptoms with other common childhood diseases.[6] For these reasons, it is recommended that treatment be based on the DST profile of the likely source patient until DST results for the child are available.[7]

In the case of the infant in our report, there was insufficient information to confirm congenitally acquired TB, as the placenta was not sent for histopathological evaluation. In addition, abdominal ultrasonography performed during admission did not suggest any features of hepatomegaly or abdominal TB pathology. It is possible that transmission may have occurred during delivery or the postnatal period, owing to the delayed symptom presentation at 2 months of age. However, it was established that the mother and infant had had minimal contact during the neonatal period, including only two contact sessions with appropriate use of personal protective equipment by the mother. The infant had remained in the care of his grandmother while the mother received her DR-TB treatment in an inpatient setting. On thorough screening by symptoms and microbiological investigations, all close contacts of the mother and infant, including the grandmother, were negative for TB.

It is important to note that INH TPT was probably ineffective in this case because the mother had confirmed *inhA* and *katG* gene mutations, and phenotypic INH resistance. There are limited data on TPT for RR-TB. The use of LFX for MDR-TB preventive therapy is recommended; however, evidence gaps on TPT for patients exposed to pre-XDR- and XDR-TB strains persist.[8]

Two serial gastric aspirate specimens were sent for Xpert Ultra testing on consecutive days before treatment commencement, both of which detected *M. tuberculosis* complex with rifampicin resistance. All subsequent specimens sent for genotypic and phenotypic testing did not detect TB.

At the time of treatment commencement, WHO guidance on DR-TB treatment in the paediatric population did not recommend DLM and BDQ for children <3 and <6 years of age, respectively. This has subsequently changed. The patient was discussed with a paediatrician experienced in the management of DR-TB, who suggested an exclusive oral regimen including the use of DLM on this individual case basis. The final drug regimen included LZD, CFZ, TRD, PAS and DLM for a 15-month duration. The patient did not have any adverse drug effects, and this regimen continued until treatment cessation, 15 months later. It is important to note that CFZ could not be counted on as an

Table 1. Summary of drug therapy and microbiological TB findings of the case patient during the course of treatment

	Pre-treatment	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
TB results	15 Feb 2022 Ultra positive Rifampicin resistant TB culture: No growth after 42 days 16 Feb 2022 Ultra positive Rifampicin resistant	LPA (clinical specimen) unsuccessful TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days
Patient weight (kg)	3.36	3.6	3.6	3.6	4.7	5.4	5.7
Drug and formulation							
LZD 20 mg/mL suspension		20 mg/kg daily orally					
DLM 25 mg dispersible tablet		25 mg twice daily orally					
TRD 250 mg capsule dispersed in 10 mL WFI (25 mg/mL) suspension		20 mg/kg daily orally					
PAS granules PAS sodium salt (equal to 4 g PAS acid) sachet		250 mg/kg daily orally					
CFZ 50 mg dispersible tablet		5 mg/ kg daily orally					

TB = tuberculosis; Ultra = Xpert MTB/RIF Ultra (Cepheid, USA); LPA = GenoType MTBDRplus version 2.0 line probe assay (Hain Lifescience, Germany); LZD = linezolid; DLM = delamanid; TRD = terizidone; PAS = para-aminosalicylic acid; CFZ = clofazimine; WFI = water for injection.

effective drug in this regimen because the source patient's DST showed resistance to the drug.

There is limited evidence-based guidance on treatment regimens for MDR/RR-TB in children.[6,7] The WHO recommends exclusive oral regimens for children of all ages.[6] However, neither international nor local guidelines provided recommendations for XDR-TB regimens in paediatric patients at the time when our infant was cared for. Subsequently, in 2022 the WHO updated its DR-TB treatment guidelines, recommending BDQ and DLM for children of all ages.[6]

Owing to the rarity of perinatal MDR/RR-TB, there is no clinical trial evidence to guide optimal treatment in this patient population. A recent case report of confirmed pre-XDR-TB in a premature neonate demonstrated a successful treatment outcome associated with the use of a regimen containing BDQ and DLM. However, the regimen also included a second-line injectable drug, amikacin.[9]

SA guidelines recommend that regimens should consist of at least four drugs to which the organism is likely to be susceptible for the entire duration of therapy, with the possible addition of a fifth drug for the first few months of therapy. In cases of severe disease or with a high bacillary burden, emphasis is placed on the inclusion of WHO group A and B drugs, as well as DLM, in the treatment regimen.[6,7] The treatment duration ranges from a minimum of 6 months to 12 - 18 months, depending on the site and severity of disease, and the extent of drug resistance.[6,7]

In this case, owing to the extensiveness of drug resistance in the presumed index case, the infant was treated with five drugs for a 15-month duration, which included one group A drug (LZD), two group B drugs (CFZ, TRD) and two group C drugs (DLM, PAS). The infant had a successful outcome, achieving treatment completion after 15 months with microbiological, radiological and clinical improvement.

A factor that may have contributed to a good outcome was that the patient received inpatient care for the entire treatment duration, which included scheduled administration of medication and close monitoring by trained healthcare professionals.

Although the delay in diagnosis did not obviously compromise this patient's outcome (in the absence of proper evaluation of post-TB lung disease), a high index of suspicion for perinatally acquired TB ought to have remained on the differential diagnosis in his respiratory illness presentation. Timeous diagnosis and treatment are essential to prevent poor outcomes, as was noted in a previously reported case of congenitally acquired MDR-TB where delayed diagnosis and inadequate drug therapy contributed to mortality.[10]

Although rare, this case emphasises the need for evidence-based guidance for XDR-TB regimens for perinatally acquired TB, as well

	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12	Month 13	Month 14	Month 15
	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: Contaminated	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days	TB culture: No growth after 42 days
	6.1	6.0	6.5	6.6	6.7	8.0	7.5	8	7.5
	200 mg/kg daily orally								

as for studies on preventive strategies for mitigating mother-to-child transmission of TB.

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