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Extensively drug-resistant tuberculosis in a young child after travel to India

Nicole Salazar-Austin, **Alvaro A Ordonez**, **Alice Jenh Hsu**, **Jane E Benson**, **Mahadevappa Mahesh**, **Elizabeth Menachery**, **Jafar H Razeq**, **Max Salfinger**, **Jeffrey R Starke**, **Aaron M Milstone**, **Nicole Parrish**, **Eric L Nuermberger**, and **Sanjay K Jain**

Department of Pediatrics (N Salazar-Austin MD, A A Ordonez MD, A M Milstone MD, S K Jain MD), Center for Tuberculosis Research (N Salazar-Austin, A A Ordonez, E L Nuermberger MD, S K Jain), Center for Infection and Inflammation Imaging Research (A A Ordonez, S K Jain), Department of Pharmacy (A J Hsu PharmD), Russell H Morgan Department of Radiology and Radiological Science (J E Benson MD, M Mahesh PhD), Department of Hospital Epidemiology and Infection Control (A M Milstone), Department of Pathology (N Parrish PhD), and Department of Medicine (E L Nuermberger), Johns Hopkins University School of Medicine, Baltimore, MD, USA; Howard County Health Department, Columbia, MD, USA (E Menachery MD); Maryland Department of Health and Mental Hygiene, Laboratories Administration, Baltimore, MD, USA (J H Razeq PhD); National Jewish Health Mycobacteriology Laboratory, Denver, CO, USA (M Salfinger MD); and Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA (Prof J R Starke MD)

Abstract

Extensively drug-resistant (XDR) tuberculosis is becoming increasingly prevalent worldwide, but little is known about XDR tuberculosis in young children. In this Grand Round we describe a 2-year-old child from the USA who developed pneumonia after a 3 month visit to India. Symptoms resolved with empirical first-line tuberculosis treatment; however, a XDR strain of *Mycobacterium tuberculosis* grew in culture. In the absence of clinical or microbiological markers, low-radiation exposure pulmonary CT imaging was used to monitor treatment response, and guide an individualised drug regimen. Management was complicated by delays in diagnosis, uncertainties about drug selection, and a scarcity of child-friendly formulations. Treatment has been successful so far, and the child is in remission. This report of XDR tuberculosis in a young child in the USA

Correspondence to: Dr Sanjay K Jain, Johns Hopkins, University School of Medicine, 1550 Orleans Street, CRB-II, Room 1·09, Baltimore, MD 21287, USA, sjain5@jhmi.edu.

See Online for video

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Contributors

NS-A and SKJ were the primary physicians and managed the patient. NS-A and SKJ also did the scientific literature searches and wrote the initial draft. AJH was the clinical pharmacist and helped in paediatric dosing and formulations. JEB provided clinical reporting for CT and MM calculated the radiation dose. AAO did the CT image analyses. ELN and JRS were consultants for clinical management. NP processed microbiological specimens, isolated the organism, and did the MGIT and TREK assays. JHR and MS were responsible for the agar proportion assays. AMM helped with infection control and EM was in charge of directly observed treatment with the Health Department. NS-A and SKJ wrote the initial report and all coauthors participated in the editing of the report.

Declaration of interests

All other authors declare no competing interests.

highlights the risks of acquiring drug-resistant tuberculosis overseas, and the unique challenges in management of tuberculosis in this susceptible population.

Introduction

Extensively drug-resistant (XDR) tuberculosis is becoming increasingly prevalent worldwide. XDR tuberculosis is caused by bacterial strains that are resistant to isoniazid and rifampicin (multidrug resistant [MDR]), any fluoroquinolone, and at least one of three injectable second-line drugs (ie, amikacin, kanamycin, or capreomycin). XDR tuberculosis is very difficult to treat and associated with high mortality, especially in HIV-infected patients.[1] XDR tuberculosis has been reported in 105 countries and is estimated to cause about 10% of cases of MDR tuberculosis.[2] Although XDR tuberculosis is being increasingly reported, especially in urban areas in tuberculosis-endemic countries such as India, the absence of validated standards for drug-susceptibility testing (DST) remains a major challenge to diagnosis.[3] Since international travel is becoming more common, the possibility of acquiring tuberculosis during travel and importation into low-prevalence settings is increasing. Moreover, active tuberculosis is a prominent disease in travellers, although definitive attribution of infection to the travel event is made difficult by the wide range of latency periods.[4,5]

Childhood tuberculosis constitutes 10–20% of all tuberculosis in high-burden countries,[6] and accounts for 8–20% of tuberculosis-related deaths.[7,8] However, since most children are sputum microscopy smear negative, and culture (when done) is not as sensitive as in adults, the burden of childhood tuberculosis and drug-resistant tuberculosis are probably underestimated. In particular, little is known about XDR tuberculosis in young children (aged ≤5 years), with only five reports with outcomes published worldwide.[9–11] Moreover, young children are a susceptible population, with unique difficulties associated with the management of tuberculosis. Diagnosis is challenging because of the paucibacillary nature of infection and difficulties in obtaining appropriate clinical specimens, leading to diagnostic uncertainties and delays.[12–16] Similarly, assessing response to treatment is particularly challenging in young children. Clinical response can sometimes be noted with suboptimal regimens, and microbiology cannot be used to monitor culture-negative disease. In this Grand Round, we report a case of XDR tuberculosis in a young child in the USA, after a 3 month visit to India. A recent study[15] from this region in children younger than 5 years reported that four (57%) of the seven tuberculosis cases for which culture confirmation was possible, were due to drug-resistant strains. In view of the absence of clinical or microbiological markers, CT imaging was used to monitor response to an individualised drug regimen for XDR tuberculosis.

Case presentation

A previously healthy 2-year-old girl from the USA presented with a 2 week history of daily high fevers after a 3 month visit to India. On arrival in India, she was immunised with BCG. She stayed with her grandparents in an urban area and attended a local day-care facility. During the last week of her visit, she developed fevers that continued after her return to the

USA. Clinical assessment showed a temperature of 39·9°C, tachycardia (172 beats per min), blood pressure of 95/49 mm Hg, tachypnoea (44 breaths per min), peripheral capillary oxygen saturation (SpO_2) of 100% (in room air), weight of 12·7 kg, and no adventitious lungs sounds. Blood, urine, throat, and stool cultures were negative, as were malaria smears. The QuantiFERON-TB Gold In-Tube test (Cellestis, Chadstone, VIC, Australia) was positive and chest radiography showed a left lower lobe infiltrate. The concentration of C-reactive protein was high (12·1 mg/dL). A left lower lobe infiltrate and hilar adenopathy were seen on CT imaging (figure 1A; video 1). HIV testing was negative. Gastric aspirates were obtained for mycobacterial smear microscopy and culture on sequential days. Acid-fast bacilli stains were negative; however, in view of the high clinical suspicion, the child was started on first-line tuberculosis treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol. The child improved clinically with resolution of fevers after 4 weeks, a decline in inflammatory markers, and weight gain (figure 2).

At 4 weeks, acid-fast bacilli were detected in one of four gastric aspirate cultures (Mycobacteria Growth Indicator Tube [MGIT] 960, Becton Dickinson, Sparks, MD, USA). Although the AccuProbe (GenProbe, San Diego, CA, USA) test was negative, subsequent 16S rRNA sequencing[17] of the MGIT culture pellet identified it as a *Mycobacterium tuberculosis* complex. Chest radiography at 10 weeks showed a persistent left lower lobe infiltrate. Mycobacterial growth on Middlebrook 7H11 and Löwenstein-Jensen solid media was poor, and 12 weeks passed before final identification and preliminary DST results identified the isolate as XDR *M tuberculosis* (table 1). At this time, clinical assessment revealed a temperature of 38·2°C, heart rate of 126 beats per min, blood pressure of 100/57 mm Hg, respiratory rate of 20 breaths per min, SpO_2 of 100% in room air, bodyweight of 14·1 kg, with decreased air entry and end-expiratory wheeze in the left lower lung field. CT imaging showed worsening infiltrate, several necrotic areas, and partial obstruction of the left main bronchus (figure 1B; video 2). Gastric aspirates were repeated, central venous access established, and the child started on an individualised drug regimen for XDR tuberculosis (25 mg/kg per day intravenous streptomycin, 20 mg/kg per day linezolid, 150 mg/kg per day para-aminosalicylic acid [PAS], 20 mg/kg per day cycloserine, 50 mg per day clofazimine, and vitamin B6). The child was discharged home 5 days after admission to the hospital. The drugs were given at home by a trained nurse or a parent, and directly observed by a nurse from the local health department.

Since the child initially improved on standard first-line treatment, the gastric aspirate smears were negative at the time of initiation of XDR tuberculosis treatment, and cultures remained negative subsequently. Low-radiation exposure pulmonary CT imaging was used to assess the response to treatment 6 weeks after initiation of XDR tuberculosis treatment (appendix). Imaging revealed a marked reduction in the lesion volume (figure 2) with resolution of necrotic areas (figure 1C; video 3). The improvement in CT imaging was corroborated by consistent weight gain noted over the next few months, but which lagged behind CT results by 10 weeks (figure 2). After 6 months of treatment, CT imaging showed resolution of the infiltrate, with some residual fibrosis (figure 1D; video 4). On the basis of these results, which suggested that the chosen regimen was indeed effective, streptomycin was spaced to thrice weekly (from daily dosing) at 6 weeks, and then discontinued at 6 months. Linezolid, PAS, cycloserine, and clofazimine were continued. Close clinical and laboratory monitoring

and age-appropriate hearing and vestibular testing were done. No side-effects other than hypothyroidism (attributed to PAS and that needed treatment with levothyroxine) and bronze skin discolouration (attributed to clofazimine) developed. The child received 18 months of directly observed treatment for XDR tuberculosis, and remains well in remission. However, follow-up will continue to ensure treatment has been successful.

Review and discussion

Travel-associated tuberculosis

Results from studies suggest that 0·9–2·7% of travellers presenting to health-care facilities with illness after travel have active tuberculosis.[18,19] In one study, 5·5% (two of 36) of children (aged ≤16 years) with travel-associated illness requiring hospital admission had active tuberculosis.[20] Transmission of infection has been reported on aeroplanes.[21] Although the overall risk is low (0·05 per 100 000 passengers), travellers on flights from tuberculosis-endemic areas in Africa or India had a seven times higher risk of acquiring tuberculosis, because flights originating from these regions were more likely to have passengers with tuberculosis.[22] The risk of transmission in travellers to tuberculosis-endemic areas is similar to that in the local population, with an incidence rate of 2·8 per 1000 person-months of travel for tuberculosis infection and 0·6 per 1000 person-months of travel for active tuberculosis disease.[23] However, the risk is increased substantially when travelling for 90 days or longer.[24–27] Moreover, children visiting friends and relatives overseas have a high risk of acquiring infection.[28] In one study[29] of children (aged ≤6 years), travel to tuberculosis-endemic countries in the preceding 12 months increased the risk of acquiring tuberculosis infection by almost four times. More than half (55%) of the 105 children who travelled to tuberculosis-endemic countries had stayed with their grandparents, presumably as travellers visiting friends and relatives. BCG vaccination and isoniazid prophylaxis have been suggested for the prevention of travel-associated tuberculosis, but no consensus has been reached on whether and how they should be used.[30,31]

Diagnosis

Young children are rarely able to produce sputum, and therefore three consecutive early morning gastric lavage specimens have long been regarded as the standard of care. However, some clinicians will forego obtaining invasive specimens because of their low yield. The sensitivities of different specimens and methods to diagnose pulmonary tuberculosis in children vary (table 2). Smear microscopy is the most widely available, but has a low sensitivity with a yield of less than 10% reported in most studies. Culture is the gold-standard method, with a wide range of sensitivities reported, but most studies report a sensitivity of 10–30%. GeneXpert (Xpert MTB/RIF, Cepheid, Sunnyvale, CA, USA) is an automated, cartridge-based test that detects *M tuberculosis* and rifampicin resistance. GeneXpert has high sensitivity for the detection of adult pulmonary tuberculosis,[39] and WHO has widely recommended its use. Although GeneXpert is significantly more sensitive than smear microscopy alone, culture is more sensitive.[14,32,37] In one study investigating pulmonary tuberculosis in children, GeneXpert failed to detect as many as 40% of culture-positive cases.[37] Sputum induction has been shown to be safe, and as effective as gastric aspirates for the diagnosis of tuberculosis.[33–35,38] However, one study reported that gastric

lavage had better yields.[16] The assessment of alternative patient samples, including nasopharyngeal aspirate and stool, is continuing.[36,40] Multiple specimens are helpful at achieving the maximum yield.[16,38,41] Urine tests for mycobacterial lipoarabinomannan by both ELISA and lateral flow were reported to be sensitive in adults with advanced HIV disease, but had low sensitivity and specificity in children.[42,43]

In 2014, a review reported that the risk factors for acquiring MDR tuberculosis in children are similar to adults, but that many children with drug-resistant tuberculosis go undetected.[44] The infrequency with which mycobacterial cultures and DST are done because of difficulties in obtaining appropriate specimens and low yields might be a reason for the low detection rate. GeneXpert can rapidly detect common rifampicin resistance mutations with the intent of being able to more rapidly initiate second-line treatment. Although GeneXpert is an important contribution to the rapid detection of drug resistance, it is less sensitive than liquid culture in children. Furthermore, a report has suggested that the current version of GeneXpert might not detect a substantial proportion of strains that could be resistant to rifampicin.[45]

Treatment and monitoring

The basic principles for treating XDR tuberculosis are similar to those for treating MDR tuberculosis.[46,47] Tuberculosis drugs are chosen from five groups of drugs in a stepwise manner. The treatment regimen includes at least four drugs to which the isolate is regarded as susceptible, although five drugs are generally used for XDR tuberculosis. Surgery is considered in some situations, although good success with medical management alone has been reported in children.[48] In view of the genotypic and phenotypic evidence of resistance to isoniazid, rifampicin, and pyrazinamide, the child's improvement on standard first-line tuberculosis treatment in this report was attributed to monotherapy with ethambutol. Reports from the early 1960s suggested that adult patients with tuberculosis receiving monotherapy with ethambutol showed an initial bacteriological (but not radiological) improvement, followed by treatment failure because of the development of drug resistance.[49] Streptomycin was included on the basis of initial phenotypic susceptibility results, and its established activity against *M tuberculosis*.[50] Moreover, although the *rrs* mutation detected in the child's isolate confers resistance to several aminoglycosides, it does not seem to confer cross-resistance to streptomycin.[51] PAS and cycloserine were chosen because of their favourable susceptibility results. Furthermore, PAS has historically been used in combination with streptomycin with good outcomes.[52,53] Linezolid was included because it has been shown to be highly effective in adults with refractory XDR tuberculosis[54] and was well tolerated in a series describing treatment of 18 children with drug-resistant tuberculosis.[48] Finally, clofazimine was included on the basis of evidence suggesting efficacy in treating drug-resistant tuberculosis.[55] In view of the high minimum inhibitory concentration for ethionamide (2·5 μg/mL), and challenges in achieving sufficient serum concentrations in young children (maximum serum concentration [C_{max}] ≥5 μg/mL),[56] ethionamide was not included. As a result of discordant initial (genotypic and phenotypic) susceptibility results, and because no subsequent isolate was available for testing, ethambutol was not included. Delamanid and bedaquiline were considered; however, because of their unknown safety profile and the absence of pharmacokinetic data and child-friendly formulations, they were

not used. Treatment of tuberculosis in young children is complicated by the scarcity of child-friendly drug formulations.[57] Commercial PAS and cycloserine had to be custom formulated (opened, re-weighed, and unit dosed) and given with child-friendly foods (eg, apple sauce and chocolate pudding).[57] Clofazimine, a hard-gel capsule, was swallowed whole by the child.

Historically, response to treatment for pulmonary tuberculosis is assessed clinically, by monitoring symptoms and weight gain, and by testing monthly sputum samples for smear or culture conversion. However, this assessment is particularly challenging in children with paucibacillary disease, in which clinical response can be seen with suboptimal regimens, and microbiology cannot be used to monitor culture-negative disease. Radiological imaging, especially chest radiography, is often used as complementary evidence of adequate treatment response. Compared with culture, which needs weeks or months, imaging is rapid and correlates well with disease progression and efficacy of tuberculosis treatments in animals[58–60] and human beings.[61–63] Serial CT imaging has been shown to be a good marker of response to tuberculosis treatments in adults.[64,65] Although CT imaging has not yet been used to serially monitor tuberculosis treatments in young children, a retrospective study in infants diagnosed with pulmonary tuberculosis reported that CT imaging provided better visualisation of parenchymal lesions and lymphadenopathy than chest radiography.[66] Chen and colleagues[63] reported that CT imaging could be better than conventional (sputum) microbiology for monitoring response to MDR tuberculosis treatments in adults. In this study, quantitative changes in lesion volumes on CT imaging were predictive of treatment responses at both 2 and 6 months after initiation of treatment. Moreover, quantitative changes in ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET, which is a sensitive measure of metabolic activity, not only predicted treatment responses earlier, but also predicted long-term treatment outcomes. Pathogen-specific imaging techniques in development could have the potential to more precisely predict treatment response.[67,68] CT is often perceived to deliver high levels of radiation. However, technological developments and the design of customised protocols for paediatric patients (dose modulation, lower tube voltage, and iterative reconstruction) have significantly lowered radiation exposure. For example, the effective dose for each chest CT in this child was 0·4–0·7 mSv, which is equivalent to 2 or 3 months of natural background radiation. Moreover, no sedation was needed because scan times were short (3 s). Low-radiation exposure protocols are routinely used for children at Johns Hopkins Hospitals, and could be applied more universally, including in developing countries.[69]

Outcomes

Treatment success is dependent on several factors such as host immunity, extent of drug resistance, and disease severity. However, favourable outcomes, which are defined as cure or treatment completion, are much lower (16–44%) in patients with XDR tuberculosis than in those with MDR tuberculosis. Furthermore, very high mortality (98%) was reported by Gandhi and colleagues[1] in highly immunosuppressed adults with XDR tuberculosis and HIV co-infection. Data for treatment outcomes of XDR tuberculosis in young children are scarce, although case reports and expert opinion suggest they are likely to do better than adults.[70] Five reports (three pulmonary and two meningitis) of XDR tuberculosis in children younger

than 5 years with outcomes, have been published worldwide.[9–11] One patient with tuberculosis meningitis died, but the other four were either cured or had culture conversion and were continuing treatment at the time the report was published. The children were reported to have tolerated the drugs well, with PAS-induced hypothyroidism being the most common side-effect. Liver toxic effects were reported in one child with both first-line and optimised treatment regimens. All diagnoses were delayed by 1 month to 1 year. Optimum duration of treatment for XDR tuberculosis in young children is not known; however, experts and guidelines recommend 18 months after culture conversion.[46]

In this report, no immediate contacts who were tested were reported to have active disease. Genotyping confirmed that the isolate was of east African Indian lineage, with no match to any previous isolate from the USA. Tuberculosis in young children is considered non-infectious,[71] and adult patients with MDR tuberculosis are rendered non-infectious after 2 weeks of appropriate treatment.[72] However, much debate occurred regarding the risk of this child to the general public, and the implications of public contact tracing, since current diagnostics cannot distinguish tuberculosis infection with resistant versus susceptible strains. A then 4-year-old sibling, who had extensive initial contact with the child described in this report, showed no signs of infection (negative QuantiFERON-TB testing initially and 6 months later) or disease. No other household member acquired infection, and all of them remain disease free.

In summary, this report of XDR tuberculosis in a young child in the USA highlights the risks of acquiring drug-resistant tuberculosis overseas. Empirical first-line treatment resulted in initial resolution of symptoms, but enabled disease progression. In view of the absence of clinical or microbiological markers, CT imaging was used to monitor and optimise an individualised XDR-tuberculosis drug regimen. Imaging showed marked improvement by 6 weeks, corroborated by consistent weight gain. However, the improvement in weight gain lagged behind CT imaging by 10 weeks, suggesting that CT imaging can serve as a rapid biomarker to monitor tuberculosis treatments. Treatment was complicated by the scarcity of child-friendly drug formulations and evidence-based dosing recommendations for some drugs, and controversy regarding the infectious risk of the child to the general public. Although treatment is complete, and the child is now in remission, this report highlights the unique difficulties associated with the management of drug-resistant tuberculosis in young children, a susceptible population for whom challenges in diagnosis, monitoring, and treatment could have fatal results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Search strategy and selection criteria

We identified data by searching PubMed for articles published in English with the terms “children” AND “tuberculosis” AND “diagnosis” AND “microbiology” between April 1, 2010, and Sept 5, 2015. Additional searches included the search terms “travel” AND “associated” AND “tuberculosis” (all articles until Sept 5, 2015), and “imaging” AND “tuberculosis” AND “therapy” OR “treatment” AND “correlates” OR “monitoring” (between April 1, 2010, and Sept 5, 2015). We reviewed identified articles and other relevant references from hand-searching of records.

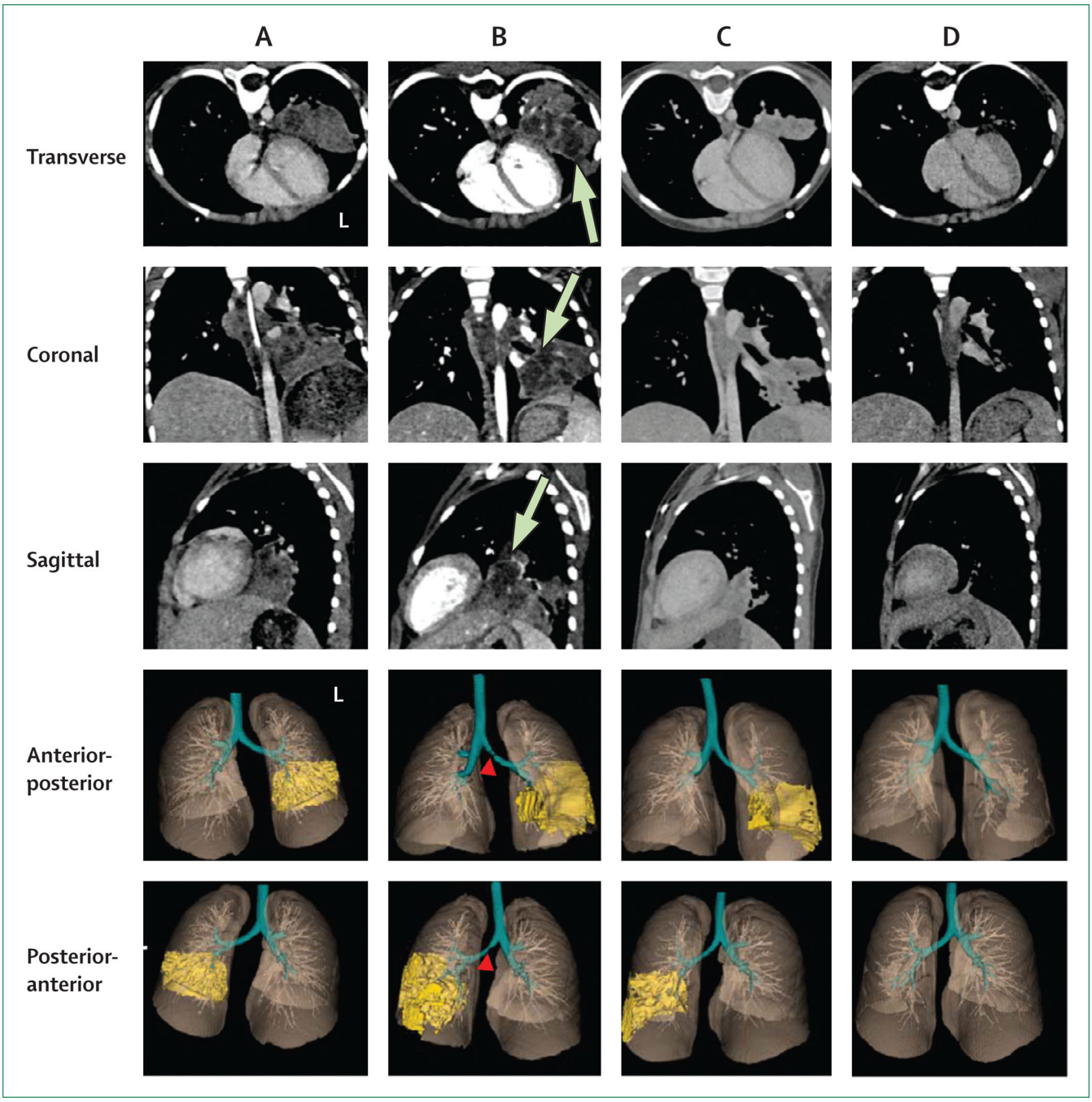

Figure 1. CT imaging

CT imaging with intravenous contrast was done using the Definition FLASH (Siemens, Malvern, PA, USA) using a protocol customised for children. Lung segmentation and visualisation were done using VivoQuant 1·23 (inviCRO, Boston, MA, USA). The transverse, coronal, sagittal, and 3D views of the lung parenchyma and the pulmonary infiltrates in the left lung are shown. Each panel corresponds to CT done at: initiation of first-line tuberculosis treatment (A, day 0); initiation of individualised extensively drug-resistant (XDR) tuberculosis treatment (B, day 90); and 6 weeks (C, day 131) and 6 months

(D, day 270) after initiation of XDR tuberculosis treatment. Several necrotic (hypodense) central areas can be seen in B (green arrows). Note the partial obstruction of the left main bronchus in B (red arrowheads). Marked improvement with resolution of necrotic areas is noted after 6 weeks (C) and near complete resolution of the infiltrate after 6 months (D) of XDR tuberculosis treatment. L = left side.

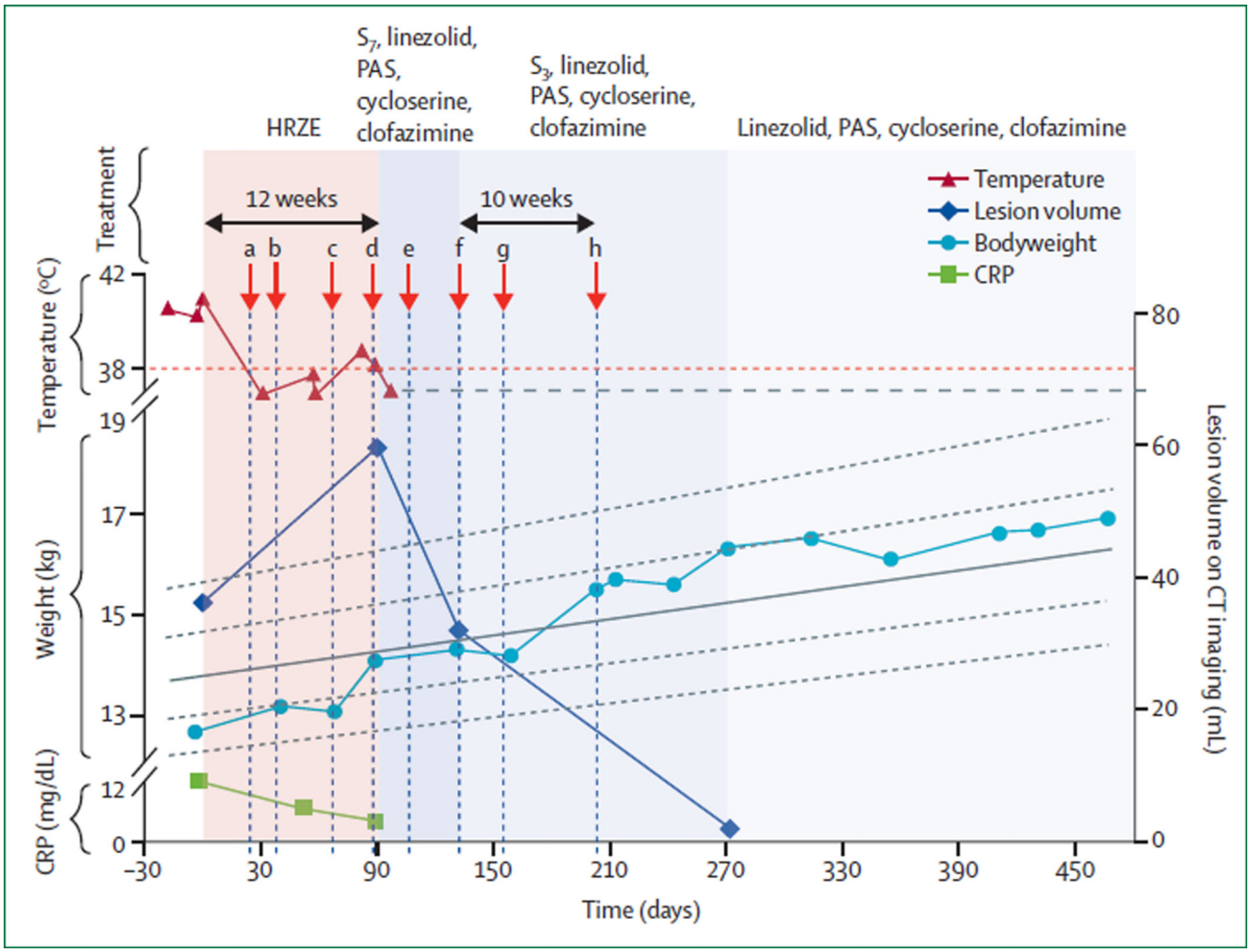

Figure 2. Clinical course

The temperature, total bodyweight, lesion volume on CT imaging, and CRP concentration during the course of the illness and treatment are shown. The dashed red line shows the cutoff for fever; the child's body temperature was not measured daily after it became normal, but she had a healthy body temperature thereafter (represented by the horizontal, dashed grey line). The solid grey line shows mean (0 *Z* score) female weight-for-age growth, and the dashed grey lines correspond to the 1, 0·5, −0·5, and −1 female weight-for-age *Z* scores. Red arrows denote: (a) growth of acid-fast bacilli in liquid broth; (b) identification of *Mycobacterium tuberculosis* complex by 16S rRNA sequencing; (c) persistent left lower lobe infiltrate on chest radiography; (d) Sanger sequencing and initial TREK panel confirming extensively drug-resistant strain; (e) agar proportion results (from the Maryland Department of Health and Mental Hygiene reference laboratory); (f) CT showing substantial reduction in lesion volume; (g) agar proportion results (from the National Jewish Health Mycobacteriology reference laboratory); (h) consistent weight gain. HRZE = isoniazid, rifampicin, pyrazinamide (discontinued at 8 weeks), and ethambutol. S_7 = daily intravenous

streptomycin. S_3 = thrice-weekly intravenous streptomycin. PAS = para-aminosalicylic acid. CRP = C-reactive protein.

Table 1

Results of drug susceptibility testing

	Mutation(s)	Likelihood of phenotypic resistance	MGIT (interpretation, critical concentration tested)	TREK Sensititre plates (interpretation, MIC)	Agar proportion* (interpretation, critical concentration tested)	
					Maryland State	National Jewish
Rifampicin	*rpoB* (Ser531Leu)	100%	Resistant, 1 μg/mL	Resistant, ≥16 μg/mL	Resistant, 1 μg/mL	Resistant, 1 μg/mL
Isoniazid	*katG* (Ser315Thr)	100%	Resistant, 0·1 and 0·4 μg/mL	Resistant, 2 μg/mL	Resistant, 1 μg/mL	Resistant, 0·2 and 1 μg/mL
Pyrazinamide	*pncA* (Asp12Glu)	Likely	Resistant, 100 μg/mL	..	..	..
Ethambutol†	*embB* (Met306Ile)	87%	Susceptible, 4 μg/mL	Susceptible, 4 μg/mL	Resistant, 5 μg/mL; susceptible, 10 μg/mL	Susceptible, 7·5 μg/mL
Rifabutin	..	..	..	Resistant, 16 μg/mL	..	..
Amikacin	*rrs* (Ala1401Gly)	100%	..	Resistant, ≥16 μg/mL	..	Resistant, 6 μg/mL
Kanamycin	*rrs* (Ala1401Gly)	100%	..	Resistant, ≥40 μg/mL	Resistant, 6 μg/mL	Resistant, 6 μg/mL
Capreomycin	*rrs* (Ala1401Gly)	>45%	..	..	..	Susceptible, 10 μg/mL
Streptomycin	..	..	Resistant, 1 μg/mL; susceptible, 4 μg/mL	Susceptible, 2 μg/mL	Susceptible, 2 μg/mL	Susceptible, 2 and 4 μg/mL
Moxifloxacin	*gyrA* (Asp94Gly)	100%	..	Resistant, 4 μg/mL	..	..
Ofloxacin	*gyrA* (Asp94Gly)	100%	..	Resistant, 16 μg/mL	Resistant, 2 μg/mL	..
Ethionamide	*InhA* mutation not detected	..	..	Susceptible, 2·5 μg/mL	Susceptible, 10 μg/mL	Susceptible, 10 μg/mL
Cycloserine	..	..	..	Susceptible, 4 μg/mL	..	Susceptible, 60 μg/mL
PAS	..	..	..	Susceptible, 0·5 μg/mL	..	Susceptible, 8 μg/mL
Linezolid	..	..	..	Susceptible, ≤1 μg/mL	..	Likely susceptible, ≤4 μg/mL
Clofazimine‡	..	..	..	Susceptible, ≤0·125 μg/mL	..	Susceptible, 0·25 μg/mL

MIC determinations were done using MGIT and TREK Sensititre plates (ThermoScientific, Oakwood Village, OH, USA) at Johns Hopkins Hospitals (MD, USA). Sanger sequencing (complete panel) was used for molecular detection of drug resistance (Centers for Disease Control and Prevention, Atlanta, GA, USA). All TREK assays were done in duplicate or triplicate, and inoculum size was verified by determination of viable counts. Linezolid and clofazimine susceptibilities were not available (by any method) at the time of initiation of the individualised extensively drug-resistant tuberculosis treatment.

MGIT = mycobacteria growth indicator tube. MIC = minimum inhibitory concentration. PAS = para-aminosalicylic acid.

*Agar proportion drug susceptibility testing was done at the Maryland Department of Health and Mental Hygiene (Maryland State) and the National Jewish Health Mycobacteriology (National Jewish) reference laboratories.

†Breakpoint for ethambutol is 7·5 μg/mL.

‡Assay not clinically validated.

Table 2

Diagnostic yields from clinical specimens in children with pulmonary tuberculosis

	Gastric lavage		Induced sputum	
	One specimen	**Multiple specimens**	**One specimen**	**Multiple specimens**
Smear	2·2% (1·4–6·9)[12,16,32,33]	7·0% (2.3–10·4)[12,16,33]	5·2% (3·5–8·0)[16,33–36]	6·7% (5·3–10)[16,33,35,36]
GeneXpert	4·2%[32]	..	10·4% (3·9–12·6)[14,35–37]	11·4% (5·2–15·1)[14,35–37]
Culture	8·5% (6·1–42·0)[12,16,32,33,38]	15·0% (3·1–66·0)[12,15,16,33,38]	15·0% (3·0–38·0)[14,16,33–36,38]	18·3% (15·1–55·0)[14,16,33,35,36,38]

Data are median % (range).