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Research Paper

Pediatric Multidrug-resistant Tuberculosis in Kyiv City, Ukraine

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ABSTRACT

Few reports have described pediatric Multidrug-resistant Tuberculosis (MDR-TB) in the former Soviet republics, despite the fact that these countries have the highest proportion of TB cases that are MDR. We aimed to examine pediatric MDR-TB in Ukraine. This retrospective cohort study included all children <18 years of age who started undergoing MDR-TB treatment between January 1, 2011 and July 31, 2016 at Kyiv City Pediatric TB Hospital. From each child's clinical chart, we abstracted demographic and clinical data. Using Fisher's exact test, we compared characteristics between children with microbiologically confirmed vs. probable (i.e., clinically diagnosed) MDR-TB. The study population included 20 children with a median age of 5 years. At diagnosis, 12 (60%) had intrathoracic lymphadenopathy as their only radiographic abnormality, and two (10%) were asymptomatic. Children with confirmed MDR-TB were more likely to be adolescents or have radiologic abnormalities in addition to intrathoracic lymphadenopathy. Median treatment duration was 20 months. Eighteen (90%) children were treated successfully. The remaining two were transferred to another facility, and their final outcomes were unknown. The excellent outcomes in this cohort are consistent with high treatment success rates for pediatric MDR-TB reported in other parts of the world.

1. INTRODUCTION

Every year around the world, an estimated 25,000–32,000 children <15 years of age become ill with Multidrug-resistant Tuberculosis (MDR-TB) [1,2], which is caused by strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, the two most powerful anti-Tuberculosis (TB) drugs. Relatively few cases of pediatric MDR-TB have been reported in the literature. A recent systematic review and meta-analysis reported only 975 cases [3], of which more than two-thirds were from South Africa. Few reports have described pediatric MDR-TB in the former Soviet republics [4–6]—despite the fact that this part of the world has the highest proportion of TB cases that are MDR [7].

According to estimates from the World Health Organization (WHO), Ukraine has the world's third highest MDR-TB incidence per 100,000 persons. The WHO estimated that in 2016, Ukraine had 21,000 new MDR-TB cases [7], of which only 7778—including 142 children <18 years of age—were diagnosed and reported to the Ukrainian National TB Program (UNTP) [8]. More than a third of Ukraine's MDR-TB cases can be further classified as pre-Extensively Drug-Resistant (pre-XDR), and >10% as XDR [9]. Pre-XDR strains of *M. tuberculosis* have additional resistance to either a fluoroquinolone or a second-line injectable agent (amikacin, capreomycin, and kanamycin); XDR strains have additional resistance to both a fluoroquinolone and a second-line injectable agent.

Ukraine's MDR-TB epidemic is complicated by the country's high prevalence of Human Immunodeficiency Virus (HIV) infection. In 2016, there were an estimated 240,000 People Living with HIV (PLWH), including approximately 5000 children <15 years of age, in Ukraine [10]. Of the 240,000 PLWH, 40% were receiving antiretroviral therapy (ART) (10). PLWH accounted for 21% of newly diagnosed cases of TB in Ukraine [7]. HIV coinfected persons comprised 16–22% of recently described cohorts of adults in Ukraine with MDR-TB [9,11], and one study showed that HIV coinfection without ART was the strongest predictor of MDR-TB poor treatment outcome [11].

Despite the country's high MDR-TB burden, few reports have described the treatment of this disease in Ukraine [11,12]. Two recent studies showed that only 18–22% of adults treated for MDR-TB achieved treatment success, defined as cured or treatment completion [11,12]. This rate is far lower than the global treatment success rate of 54% among adults [7]. According to the pediatric MDR-TB meta-analysis mentioned earlier, 78% of children with MDR-TB achieve treatment success [3]; but children from the former Soviet republics were underrepresented in this sample.

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Given the poor outcomes of adults with MDR-TB in Ukraine, we decided to examine whether children with MDR-TB in Ukraine had worse outcomes than children in other countries. We therefore conducted this study to examine the presentation, treatment, and outcomes of pediatric MDR-TB in Ukraine.

2. MATERIALS AND METHODS

This retrospective cohort study took place in Kyiv City, Ukraine's capital. In 2016, Kyiv City accounted for 401 (5%) of the country's 7778 notified cases of MDR-TB [8]. The study population consisted of all children <18 years of age who began undergoing MDR-TB treatment between January 1, 2011 and July 31, 2016 at Kyiv City Pediatric TB Hospital. This 130-bed hospital treats the majority of childhood TB cases in Kyiv City with the exception of TB–HIV-coinfected cases, most (but not all) of which are referred to Kyiv City's Pediatric HIV Hospital. In addition, some adult TB hospitals accept a limited number of pediatric patients.

All children included in this study were referred to Kyiv City Pediatric TB Hospital by primary care providers. Children were identified at the primary care level through two ways: (1) passive case finding, meaning that the child presents for evaluation of symptoms, or (2) active case finding, also known as contact investigation. According to the UNTP, every newly diagnosed case of TB should prompt a contact investigation, in which the children in the affected household are brought to a primary care facility for a tuberculin skin test and, if indicated, imaging. If these tests suggest TB, the child is referred to a TB hospital for further management [13,14].

At the time of the study, UNTP guidelines recommended hospitalization for the entire course of MDR-TB treatment and the following regimen construction: ≥4 likely effective drugs, including a second-line injectable agent, for an intensive phase of ≥8 months, followed by ≥3 likely effective drugs for a continuation phase of ≥12 months [13,14]. "Likely effective" means that the Drug Susceptibility Test (DST) performed on the patient's strain indicates susceptibility to the drug, and no known close contacts have documented resistance to the drug [15,16]. An exception to the "likely effective" rule was pyrazinamide, which the UNTP recommended to be included in the regimen regardless of DST result.

Prior to treatment initiation, all children in this cohort were screened for HIV, hepatitis A, and hepatitis B. Treatment monitoring consisted of baseline and monthly acid-fast smear, mycobacterial culture, and liver function tests. Chest X-Rays (CXRs) were performed every 3 months. Children underwent chest CT scans when CXR findings were equivocal. To detect Adverse Drug Events (ADEs) other than hepatotoxicity, clinicians performed complete physical examinations on young children, and nurses asked older children and adolescents whether they were experiencing specific ADEs. If the examination or symptom screen was positive, appropriate follow-up tests, such as audiometry, were obtained. At the time of this study, DST in Kyiv was performed with the proportional method for first-line drugs, ofloxacin, levofloxacin, moxifloxacin, capreomycin, kanamycin, amikacin, ethionamide, cycloserine, and *para*-Aminosalicylic Acid (PAS). Xpert MTB/RIF (Cepheid, Sunnyvale, USA) was not routinely performed.

We included children with confirmed MDR-TB or probable MDR-TB. Following expert consensus definitions [17], we defined confirmed MDR-TB as signs and symptoms consistent with TB disease and isolation of *M. tuberculosis* from the child with genotypic or phenotypic resistance to at least isoniazid and rifampicin, and probable MDR-TB as signs and symptoms consistent with TB disease and a probable source case with confirmed MDR-TB. From each child's clinical chart, we abstracted date of birth; sex; comorbidities; vital status of parents; presence of alcohol abuse in the household; whether the case was identified through household contact tracing; presenting symptoms; height and weight at the time of treatment initiation; results of baseline and monthly monitoring exams, DSTs, and imaging; doses and duration of antibiotics; ADEs; and treatment outcome. We classified age- and sex-adjusted body mass index *Z*-score according to WHO standards [18,19]; disease severity according to the Wiseman criteria [20]; and hepatotoxicity according to definitions published by the U.S. National Institutes of Health [21]. Radiograph findings were abstracted from reports by pediatric radiologists.

We classified treatment outcomes according to expert consensus definitions [17]. For children with confirmed MDR-TB, a successful treatment outcome was "cure," which denotes completion of prescribed treatment with resolution of clinical symptoms, improvement of radiological abnormalities, and conversion of positive microbiological tests to negative. For children with probable MDR-TB, a successful treatment outcome was "probable cure," which denotes completion of prescribed treatment with resolution of clinical symptoms and improvement of radiological abnormalities. Children with probable MDR-TB did not have any positive microbiological tests, so conversion of these tests from positive to negative was not required to achieve a successful outcome. We assigned "transfer" as the outcome for children whose care was transferred to another facility during treatment and whose final outcome was unknown. Using SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA), we performed Fisher's exact test to compare characteristics between children with confirmed and probable MDR-TB.

The Institutional Review Board (IRB) of The Miriam Hospital, USA approved this study and waived informed consent. Consistent with ethics standards for retrospective studies in Ukraine, in lieu of IRB approval, we obtained written permission to conduct this research from the chief medical officer of Kyiv City Pediatric TB Hospital.

3. RESULTS

During the years of this study, 20 children were treated for MDR-TB at Kyiv City Pediatric TB Hospital. All children met the criteria for either confirmed or probable MDR-TB. The median age of the study participants was 5 years [Interquartile Range (IQR): 4–14.25 years]. Table 1 summarizes the demographic and clinical characteristics of the study participants. Thirteen (65%) were identified through contact tracing. At the time of diagnosis, 12 (60%) had intrathoracic lymphadenopathy as their only radiographic abnormality (on CXR or CT scan), and two (10%) were asymptomatic. Four (20%) were classified as having severe disease: a 1-year-old had necrotic lymph node disease with adjacent bronchopneumonia, one 16-year-old had bilateral infiltrates, and two 16-year-olds had lung cavities (Table 2). None of the children had signs or symptoms of extrathoracic disease.

Table 1 | Comparison of baseline characteristics between children with confirmed MDR-TB vs. children with probable MDR-TB

Characteristics	Confirmed MDR-TB (*n* = 5)	Probable MDR-TB (*n* = 15)	All MDR-TB (*n* = 20)	Two-sided *p*-value[a]
Age 13–18 years	5 (100.0)	3 (20.0)	8 (40.0)	0.008
Female sex	3 (60.0)	8 (53.3)	11 (55.0)	0.79
One or both parents deceased	2 (40.0)	7 (46.7)	9 (45.0)	0.60
Alcohol abuse present in the household	2 (40.0)	12 (80.0)	14 (70.0)	0.26
HIV infection	0 (0)	3 (20.0)	3 (15.0)	0.54
Identified through contact tracing	2 (40.0)	11 (73.3)	13 (65.0)	0.29
Asymptomatic at the time of presentation	0 (0)	2 (13.3)	2 (10.0)	1.00
BMI *Z*-score ≤2 at treatment initiation[b]	0 (0)	3 (20.0)	3 (15.0)	0.54
Radiologic abnormalities other than intrathoracic LAN	5 (100.0)	3 (20.0)	8 (40.0)	0.004
Severe disease	2 (40.0)	2 (13.3)	4 (20.0)	0.25
Documented resistance in addition to isoniazid and rifampicin[c]				
Ethambutol	1 (20.0)	10 (66.7)	11 (55.0)	0.13
Pyrazinamide	2 (40.0)	6 (40.0)	8 (40.0)	1.00
Streptomycin	5 (100.0)	13 (86.7)	18 (90.0)	1.00
Ofloxacin	1 (20.0)	2 (13.3)	3 (15.0)	1.00
Kanamycin	0 (0)	4 (26.7)	4 (20.0)	0.53
Capreomycin	0 (0)	1 (6.7)	1 (5.0)	1.00
Amikacin	0 (0)	1 (6.7)	1 (5.0)	1.00
Ethionamide	1 (20.0)	6 (40.0)	7 (35.0)	0.61
Para-aminosalicylic acid	0 (0)	1 (6.7)	1 (5.0)	1.00
Pre-XDR or XDR-TB[d]	2 (40.0)	4 (26.7)	6 (30.0)	0.61

[a]The *p*-value refers to comparisons between children with confirmed MDR-TB vs. children with probable MDR-TB, which were performed using Fisher's exact test. [b]A child with a *Z*-score ≤2 has a BMI that is more than two standard deviations below average for age and sex. [c]DST results are of the presumed source case for children with probable MDR-TB. There were no cases with documented resistance to levofloxacin, moxifloxacin, or cycloserine. [d]Two children with probable MDR-TB and no children with confirmed MDR-TB had XDR-TB. DST, drug susceptibility test; HIV, human immunodeficiency virus; LAN, lymphadenopathy; MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

With respect to comorbidities, one child had diabetes mellitus, one had cerebral palsy, and three had HIV infection. One of the HIV-infected children, a 5-year-old girl, was receiving ART at the time of her MDR-TB diagnosis. Another child, a 4-year-old girl, had known HIV infection, but her mother had refused ART. At the time of her TB diagnosis, her CD4+ cell count was 26/mm^3. The medical team convinced her mother to agree to ART, which began 2 weeks after the initiation of MDR-TB therapy. The last child, a 3-year-old girl, screened positive for HIV infection at the time of her MDR-TB diagnosis. Her initial CD4+ cell count was 1475/mm^3. ART was started 1 month after the initiation of the MDR-TB therapy. None of the children had hepatitis A or B.

Compared with children with probable MDR-TB, children with confirmed MDR-TB were more likely to be adolescents (ages 13–18 years) or have radiologic abnormalities in addition to intrathoracic lymphadenopathy (Table 1).

Table 2 details the regimen composition, ADE, and treatment outcome for each child. Almost all regimens used in this cohort were based on the DST of the presumed source case as most children lacked an isolate on which to perform the DST. All children were hospitalized for the entirety of the MDR-TB therapy. Median treatment duration was 20 months (IQR: 20–20 months). All children received a fluoroquinolone; seven (35%) children did not receive an injectable agent. Five of the 20 children (25%) experienced hepatotoxicity [21]. In four of the five children, the anti-TB regimens were suspended for a week, at which point repeat testing showed improvement in transaminitis. Medications were then restarted one at a time, hepatotoxicity resolved, and the children tolerated the remainder of their prescribed regimens. The fifth child, a 16-year-old boy with grade-3 hepatotoxicity, did not tolerate reinitiation of pyrazinamide. One of the 11 (9%) children who received cycloserine experienced hallucinations. Cycloserine was discontinued in this 14-year-old male with resolution of the hallucinations. One week later, cycloserine was restarted at the same dose and continued through the end of the therapy without recurrence of hallucinations. One of the 13 (8%) children who received an injectable agent had hearing loss. This child was a 15-year-old male, and he reported difficulty hearing, which was confirmed on audiometry, at the end of the 8-month intensive phase. Because audiometry was not routinely performed, it is unknown how many other children may have had undetected hearing loss. Two children experienced rashes—one to kanamycin, and the other to PAS. For this reason, these medications were discontinued during the first month of treatment.

Four of the five (80%) children with confirmed MDR-TB achieved cure; 14 of 15 (93%) children with probable MDR-TB achieved probable cure. The remaining children were transferred to another facility with unknown final treatment outcomes. One child was transferred after 3 months, and the other was transferred after 15 months (Table 2).

4. DISCUSSION

Compared with adults with MDR-TB in Ukraine, the children in our cohort had much better treatment outcomes [11,12]. This finding is consistent with those conducted in other settings that have reported higher rates of MDR-TB treatment success in children compared with adults [3]. Most of the children in our cohort were identified through contact tracing, just less than half had intrathoracic lymphadenopathy as their only radiographic abnormalities, and 10% were asymptomatic at the time of diagnosis. These findings suggest that early diagnosis and initiation of anti-TB therapy

Table 2 | Individual patient characteristics

Age at diagnosis/ sex	Comorbidities	CXR or chest CT findings	AFB smear result	Myco-bacterial culture result	Child's DST result	Presumed source case's DST result	MDR-TB regimen[a]	Adverse drug events	Treatment outcome
3 m/F[b]	None	LAN	Negative	Negative	None	H, R, S, Km, Eto	8ZEOfxPtoPAS/9ZEPtoPAS	Grade 1 hepatotoxicity	Probable cure
1 y/M	None	Necrotic LAN with adjacent broncho-pneumonia	Negative	Negative	None	H, R, S	9ZKmLfxPtoCsPAS/12ZLfxPtoCsPAS	Grade 3 hepatotoxicity	Probable cure
2 y/M[c]	None	LAN	Negative	Negative	None	H, R, Z, S	8ZLfxPtoCsPAS/12ZLfxCsPAS	Rash	Probable cure
3 y/F	HIV	LAN	Negative	Negative	None	H, R	8ZEKmLfxPto/12ZELfxPto	None	Probable cure
4 y/F[b]	None	LAN	Negative	Negative	None	H, R, E, S, Km, Ofx, Eto, PAS	8ZMfxCsClr/5ZMfxCs	Grade 3 hepatotoxicity	Probable cure
4 y/F	HIV	LAN	Negative	Negative	None	H, R, E, S	6ZKmLfxPtoPAS/17ZLfxPtoPAS	None	Probable cure
4 y/M	None	LAN	Negative	Negative	None	H, R, S, Eto	8ZEKmLfxPAS/12ZELfxPAS	None	Probable cure
5 y/F[b]	None	LAN	Negative	Negative	None	H, R, Z, E, S, Km, Cm, Ofx	8ZMfxPtoCsPAS/12ZMfxPtoCs	None	Probable cure
5 y/M	None	LAN	Negative	Negative	None	H, R, E, S, Eto	8ZAmOfxPtoPAS/12ZOfxPtoPAS	None	Probable cure
5 y/F	HIV	LAN	Negative	Negative	None	H, R, E, S, Am, Km, Eto	3ZCmOfxPAS	None	Transfer
6 y/M	None	LAN	Negative	Negative	None	H, R, E, Z, S	8ZKmLfxPtoCsPAS/12LfxPtoCsPAS	None	Probable cure
10 y/M[d]	None	LAN	Negative	Negative	None	H, R, E, Z, S	8ZKmLfxPto/12ZLfxPto	Rash	Probable cure
13 y/F	None	LAN	Negative	Negative	None	H, R, E, Z, S	8ZKmLfxPtoCsPAS/12ZLfxPtoCsPAS	None	Probable cure
13 y/F[e]	None	Infiltrate	Negative	Positive	H, R, E, S	H, R, E, S, Ofx, Mfx	8ZLfxPtoCsPAS/12ZLfxPtoCsPAS	None	Cure
14 y/M	None	Infiltrate	Negative	Negative	None	H, R, E, S	8ZKmMfxPtoCsPAS/12ZMfxPtoCs	Grade 2 hepatotoxicity; hallucinations	Probable cure
15 y/M	None	Pleural effusion	Negative	Positive	H, R, S	H, R, Z, S, Ofx, Lfx	8ZKmMfxPtoCsPAS/12ZMfxPtoCs	Hearing loss	Cure
16 y/F	None	Bilateral infiltrates	Negative	Negative	None	H, R, E, Z, S, Eto	8ZKmLfxPtoCsPAS/12ZLfxCsPAS	None	Probable cure
16 y/F[b]	Cerebral palsy	Cavity	Negative	Positive	H, R, Z, S	H, R, E, Z, S, Km, Ofx	8ZMfxPtoCsPAS/12ZMfxPtoCs	None	Cure
16 y/F[e]	Diabetes mellitus	Cavity	Positive	Positive	H, R, Z, S, Eto	No source case	7ZLfxTrdPASClr/7ZLfxTrdClr	None	Cure
16 y/M	None	Infiltrate	Negative	Positive	H, R, S, Ofx	No source case	8ZEKmLfxPto/7EPtoLfx	Grade 3 hepatotoxicity	Transfer

[a]Standard notation of TB regimens is as follows: the number of months' duration of the intensive phase, each of the drugs used in the intensive phase, a slash (/), the number of months' duration of the continuation phase, and each of the drugs used in the continuation phase. [b]Kanamycin was the only second-line injectable agent at the time of this child's treatment, and there was documented resistance to kanamycin on the presumed source case's drug susceptibility test; therefore, no second-line injectable agents were included in the regimen. [c]Rash was attributed to kanamycin, which was discontinued during the first month of treatment. [d]Rash was attributed to *para*-amino salicylic acid, which was discontinued during the first month of treatment. [e]It is unknown why an injectable agent was not included in this patient's regimen. Am, amikacin; Clr, clarithromycin; Cm, capreomycin; Cs, cycloserine; E, ethambutol; Eto, ethionamide; H, isoniazid; Km, kanamycin; Lfx, levofloxacin; Mfx, moxifloxacin; Ofx, ofloxacin; PAS, para-aminosalicylic acid; Pto, prothionamide; R, rifampicin; S, streptomycin; Tzd, teridazone; Z, pyrazinamide.

occurred in many of these children—thus increasing the probability of treatment success.

Results from this cohort also support the WHO's recent recommendation to eliminate the injectable agent for children with culture-negative, non-severe MDR-TB [22]. Seven (35%) children did not receive an injectable agent; three of these children had culture-confirmed disease. Of these seven children, all achieved treatment success.

Hospitalization for the entire treatment course may also have contributed to the good outcomes in this cohort. Nine (45%) children were orphans, and 14 (70%) came from households where alcohol abuse was present—unsurprising findings given the high rates of death and alcohol abuse among adults with MDR-TB in Ukraine [11]. Hospitalization of children for MDR-TB treatment usually is not medically indicated [23]; however, it is possible that hospitalization prevents loss to follow-up in children with social risk factors. Nevertheless, hospitalization during TB treatment—a practice that persists in Ukraine and other former Soviet republics—can cause social and psychological problems in children. Long hospitalizations mean lack of integration into normal family, school, and community environments; few studies have characterized the effect of these disruptions on children. One study from South Africa, where children are hospitalized for the intensive phase of MDR-TB therapy, reported that despite their access to in-hospital schooling, these children experienced academic and social difficulties on return to regular school [24]. This finding also has been reported among children with other chronic illnesses who experienced prolonged school absenteeism [25]. Another study found an association between long pediatric hospitalizations and increased fear and anxiety among both children and their parents [26]. With support from the WHO, the UNTP currently is shifting from a hospital-based to ambulatory-based model of care [27]. However, inpatient treatment remains an option at the physician's discretion. Further work is needed to assess the benefits and harms of this practice, and these benefits and harms must be weighed carefully in each case.

A notable observation from our study is the low number of children treated for MDR-TB at Kyiv City Pediatric TB Hospital—which treats the majority of children in Kyiv City with TB. In 2016, an estimated 21,000 incident MDR-TB cases occurred in Ukraine [7]; however, the UNTP reported only 7778 MDR-TB cases [8]—implying that around 63% cases were undetected and untreated. In fact, Ukraine is among the 10 countries with the largest gaps between the number of patients started on MDR-TB therapy and the best estimates of MDR-TB incidence [7]. Because of the paucibacillary nature of childhood TB and the difficulty of collecting respiratory specimens in young children, microbiological confirmation of childhood MDR-TB is elusive, and the diagnosis is often based on exposure history, clinical presentation, and radiographic findings [28]. As a result, the magnitude of under-diagnosis and under-treatment of MDR-TB is even greater for children than for adults [1]. Only 3–4% of the 25,000–32,000 pediatric MDR-TB cases estimated to occur each year globally are diagnosed and notified to the WHO [29]. Most likely, underdiagnosis and underreporting of pediatric MDR-TB in Ukraine are also high. Therefore, despite the good outcomes in our study population, there are possibly several times as many undiagnosed children in Kyiv City and nationwide who are suffering—and dying [29]—from MDR-TB—a curable disease. To prevent this unnecessary morbidity and mortality, we urgently need more household contact investigations to find children with TB, increased use of preventive therapy for children who have been exposed to MDR-TB cases, and improved diagnostics for pediatric MDR-TB disease [28,29]. All these measures are particularly important in Ukraine, where around 27% of children with TB have MDR-TB [1,7].

A strength of this study is that because 18 (90%) subjects were hospitalized for the entire treatment course, during which they had daily physical examinations and monthly liver panels, we were able to document ADEs carefully. We observed that most children tolerated anti-TB medications well. Of note, a limitation is the lack of routine audiometry for children receiving injectable agents. As audiometry was performed only for children who reported hearing difficulties—which means that the problem was already quite marked—we were unable to detect milder cases of hearing loss. Other limitations of the study were the small sample size and lack of posttreatment follow-up data.

Despite these limitations, this study provides insight into the issues facing children with MDR-TB in Ukraine. Ukraine is the country with the second highest prevalence of transmitted MDR-TB [7], and more studies are needed to better characterize and address the needs of this vulnerable population.

CONFLICTS OF INTEREST

We have no conflicts of interest to declare.

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