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# Community-Based Therapy for Children With Multidrug-Resistant Tuberculosis

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## ABSTRACT

**OBJECTIVES.** The goals were to describe the management of multidrug-resistant tuberculosis among children, to examine the tolerability of second-line antituberculosis agents among children, and to report the outcomes of children treated for multidrug-resistant tuberculosis in poor urban communities in Lima, Peru, a city with high tuberculosis prevalence.

**METHODS.** A retrospective analysis of data for 38 children <15 years of age with multidrug-resistant tuberculosis, either documented with drug sensitivity testing of the child's tuberculosis isolate or suspected on the basis of the presence of clinical symptoms for a child with a household contact with documented multidrug-resistant tuberculosis, was performed. All 38 children initiated a supervised individualized treatment regimen for multidrug-resistant tuberculosis between July 1999 and July 2003. Each child received 18 to 24 months of therapy with  $\geq 5$  first- or second-line drugs to which their *Mycobacterium tuberculosis* strain was presumed to be sensitive.

**RESULTS.** Forty-five percent of the children had malnutrition or anemia at the time of diagnosis, 29% had severe radiographic findings (defined as bilateral or cavitary disease), and 13% had extrapulmonary disease. Forty-five percent of the children were hospitalized initially because of the severity of illness. Adverse events were observed for 42% of the children, but no events required suspension of therapy for >5 days. Ninety-five percent of the children (36 of 38 children) achieved cures or probable cures, 1 child (2.5%) died, and 1 child (2.5%) defaulted from therapy.

**CONCLUSIONS.** Multidrug-resistant tuberculosis disease among children can be treated successfully in resource-poor settings. Treatment is well tolerated by children, and severe adverse events with second-line agents are rare.

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### Key Words

tuberculosis, multidrug resistance, international child health

### Abbreviations

MDR-TB—multidrug-resistant tuberculosis  
DST—drug susceptibility testing  
ITR—individualized treatment regimen  
NTP—National Tuberculosis Program  
DOTS—directly observed therapy, short course

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**D**ESPITE AGGRESSIVE INTERNATIONAL efforts, tuberculosis remains a leading infectious cause of death, with an estimated 8.8 million incident cases per year.<sup>1</sup> In 2000, an estimated 884 000 (10.7%) of these cases occurred among children <15 years of age.<sup>2</sup> Global tuberculosis-control efforts have been threatened by the emergence of multidrug-resistant tuberculosis (MDR-TB), defined as strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin. MDR-TB is estimated to cause  $\geq 4\%$  of new tuberculosis cases in the developing world.<sup>3</sup> The incidence of primary drug resistance is similar among adult and pediatric cases.<sup>4-7</sup>

The traditional strategy of directly observed therapy, short course (DOTS), uses diagnosis of active tuberculosis through smear microscopy alone and administration of standard, first-line, drug regimens given under direct observation. Although first-line therapy cures most cases of drug-sensitive tuberculosis, the strategy does not use mycobacterial culture, drug susceptibility testing (DST), or second-line antituberculosis drugs. Therefore, with the DOTS strategy, detection and appropriate treatment of MDR-TB are often delayed. Moreover, the use of first-line medications to treat MDR-TB may select for more-resistant strains.<sup>8-11</sup> Despite successful implementation of the DOTS strategy in Peru, a 1999 survey found MDR-TB in 3% of new adult tuberculosis cases (primary resistance) and for 12.3% of adults with previously treated tuberculosis (acquired resistance).<sup>12</sup>

In 1996, Socios en Salud Sucursal Peru, a nongovernmental organization, began collaborating with the Ministry of Health of Peru to develop a community-based strategy for the diagnosis and treatment of MDR-TB within the context of the National Tuberculosis Program (NTP). The result was DOTS-Plus, a strategy within the existing DOTS program in which the diagnosis of MDR-TB is made through mycobacterial culture and DST. Once cases of MDR-TB are diagnosed, treatment uses a combination of first- and second-line antituberculosis drugs to which the patient's tuberculosis has documented sensitivity.<sup>13-15</sup> Cure among adult patients with highly resistant strains of *M tuberculosis* in the initial cohort in the program exceeded 80%, comparable to results achieved in referral centers in developed countries.<sup>16-21</sup>

Among children, the diagnosis and treatment of MDR-TB pose additional challenges. The diagnosis of active tuberculosis among children is difficult because of the lack of a standardized reliable case definition.<sup>22,23</sup> Clinical presentation is variable and often subtle. Lower bacillary loads, which are common in pediatric tuberculosis, render microbiologic confirmation difficult. Up to 50% of children may remain smear- and culture-negative despite the presence of active disease.<sup>24-26</sup> As a result, the identification of drug resistance, and thus the definitive diagnosis of MDR-TB, is particularly problematic among children.<sup>27</sup>

Previously we reported favorable intermediate outcomes for 16 children treated with supervised individualized treatment regimens (ITRs) for MDR-TB in Peru.<sup>28</sup> One of the limitations of that early series was the MDR-TB case definition used by the NTP. Because DST confirmation of multidrug resistance was required for initiation of MDR-TB therapy, many children with suspected MDR-TB could not receive appropriate therapy until they progressed to culture-positive disease. As described in that report, the NTP changed the programmatic definition of "presumed pediatric MDR-TB" to allow for the empiric treatment of drug-resistant tuberculosis among children who had clinical evidence of tuberculosis and a known contact with MDR-TB. In the present study, we present the diagnosis, management, and treatment outcomes for a larger group of children with MDR-TB in Peru.

## METHODS

### Patient Population

In this retrospective case series, we reviewed the clinical records of children who began ITRs for MDR-TB between July 1999 and July 2003. These children initiated therapy on the basis of the following criteria: (1) clinical and radiographic evidence of active tuberculosis infection and (2) either documented failure of a DOTS regimen containing multiple first-line agents or household contact with a patient with confirmed MDR-TB. Contact investigation in the households of patients with MDR-TB is conducted as part of the DOTS and DOTS-Plus programs.<sup>29</sup>

All children underwent a baseline history and physical examination, chest radiography, tuberculin skin testing, and laboratory evaluation (including complete blood count, urea nitrogen and creatinine measurements, liver function tests, and albumin measurement). Samples were obtained from induced sputum, if the child could cough, or through early-morning gastric aspiration. Specimens were sent to the National Mycobacteriology Reference Laboratory. Isolates of any positive cultures were then sent to the Massachusetts State Laboratory Institute for DST for the following first- and second-line antituberculosis agents: isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin, kanamycin, capreomycin, cycloserine, ethionamide, and ciprofloxacin. Other agents, including rifabutin, amikacin, gatifloxacin, levofloxacin, *p*-aminosalicylic acid, clarithromycin, and amoxicillin/clavulanate, were tested when clinically indicated. DST methods were described previously.<sup>16</sup> Informed consent for enrollment in the collaborative treatment program was obtained from the parents of all patients, according to the institutional review board guidelines approved by Harvard Medical School (Boston, MA).

## Treatment Strategy

ITRs consisted generally of 5 to 7 drugs to which the *M tuberculosis* strain was sensitive. The regimens were designed according to the DOTS-Plus algorithm that we described elsewhere.<sup>30</sup> First, children received any orally administered, first-line agents to which the isolate was sensitive. Second, all regimens included an injectable agent for a minimum of 6 months after culture conversion and an orally administered quinolone for the duration of therapy. Children who did not yet have 5 drugs in their regimen received additional second-line drugs (ethionamide, cycloserine, or *p*-aminosalicylic acid). If a strain was so highly resistant that the child's regimen still contained <5 drugs, then additional agents with known antituberculous activity (eg, amoxicillin/clavulanate or clofazimine) were added.

When the DST pattern for the child was unknown, an empiric regimen was designed on the basis of the resistance pattern of the source case's isolate, with consideration of the agents the child had received previously. Regimens were adjusted if DST results for the child's isolate became available. All children received supplemental pyridoxine. Pediatric dosage guidelines are described in the Partners in Health *DOTS-Plus Handbook*.<sup>31</sup>

Each patient was assigned a community health worker, who provided all doses received outside the health center hours. Twice-daily dosing was observed 6 days per week throughout the course of treatment. Dosages were adjusted regularly to reflect weight gain. Monthly specimens were collected for mycobacterial culture, and serial radiographic monitoring was performed every 6 months throughout treatment. Nutritional and economic support was provided.

## Adverse Events

All children were monitored for adverse events daily by community health workers, weekly by nurses, and monthly by a physician. Routine laboratory monitoring included transaminase measurements, monthly creatinine and electrolyte measurements for patients receiving injectable agents, and quarterly thyroid-stimulating hormone measurements for patients receiving *p*-aminosalicylic acid or ethionamide. Patients receiving injectable agents for >6 months underwent audiometry, and young children receiving ethambutol underwent ophthalmology evaluation. Adverse events were managed aggressively, with reliance on dosage adjustments and supportive therapy whenever possible.<sup>31</sup> Changes to the MDR-TB regimen were avoided unless serious or refractory reactions occurred. An algorithmic approach to the management of adverse reactions to MDR-TB therapy is available in the Partners in Health *DOTS-Plus Handbook*.<sup>31</sup>

## Outcome Measures

The duration of MDR-TB therapy was 18 to 24 months, with a minimum of 12 consecutive months with nega-

tive cultures. Patients who met this criterion and exhibited sustained radiographic and clinical improvement, defined as weight gain and resolution of presenting symptoms, were defined as cured. Treatment failure was defined as the presence of persistent positive cultures after 9 months of therapy. Death was defined as death resulting from any cause during the treatment or follow-up period.

For the 14 children who had not completed therapy at the time of analysis, intermediate treatment outcomes were defined as follows: 12 months of consecutive negative cultures with sustained clinical improvement, good outcome or probable cure; failure to achieve 12 months of consecutive negative cultures, poor outcome or probable failure. After completion of therapy, children continued to receive twice-yearly clinical follow-up visits with a pediatric pulmonologist.

## Data Collection

Baseline characteristics, clinical and radiographic data, laboratory values, and all reported adverse events were abstracted from the clinical records with the use of a structured instrument. With respect to adverse events, any resulting changes in the treatment regimen were noted, when applicable. Data were analyzed with an Excel (Microsoft, Redmond, WA) database.

## RESULTS

Between July 1999 and July 2003, a total of 1359 patients with MDR-TB were enrolled in ITRs that included second-line drugs. Of these, 39 (3%) were children 0 to 14 years of age (Table 1). All children who completed  $\geq 4$  weeks of therapy were included in the analysis; unfortunately, 1 HIV-negative child with highly advanced disease died as a result of respiratory failure only 10 days after initiation of the ITR. Therefore, our cohort included the remaining 38 cases of pediatric MDR-TB. The age distribution of patients was bimodal, with 7 patients <4 years of age and 27 patients >9 years of age. Nearly one half of the patients had coexisting medical conditions, predominantly malnutrition (29%) and anemia (39%). Two patients were coinfecting with HIV and 5 had concurrent extrapulmonary tuberculosis, including 1 HIV-infected child with miliary disease.

Although 9 patients were referred promptly to the DOTS-Plus program after diagnosis of active tuberculosis, the mean period from tuberculosis diagnosis to initiation of ITR was 9.4 months (range: 0–46 months). At the time of initial evaluation, patients had been exposed to a median of 5 antituberculosis drugs. Thirty-four children (87%) had received first-line agents previously, 19 (49%) had received injectable agents, and 9 (23%) had received second-line agents. Two thirds (26 of 38 children) had documented failure of  $\geq 1$  standard regimen containing first-line agents before enrollment in an ITR for MDR-TB. Notably, 20 (74%) of the 27 children with

**TABLE 1** Baseline Characteristics of 38 Children

Characteristic <sup>a</sup>	No. of Patients (%)	Median (Range)
Gender		
Male	17 (45)	
Female	21 (55)	
Age, y		11 (2–14)
Weight, percentile for age <sup>b</sup>		25 (<3–95)
Albumin, g/dL		4.1 (2.7–5.7)
Hematocrit, %		37 (25–47)
Children with previous or current coexisting conditions <sup>c</sup>	17 (45)	
Anemia	12 (39)	
Malnutrition	11 (29)	
HIV coinfection	2 (6)	
Other	5 (13)	
Observed respiratory difficulty <sup>d</sup>	8 (21)	
Severe chest radiographic findings <sup>e</sup>	11 (29)	
Extrapulmonary tuberculosis	5 (13)	
Pleural effusion	2 (5)	
Gastrointestinal	2 (5)	
Skeletal (Pott's disease)	1 (3)	
Meningoencephalitis	1 (3)	
Miliary	3 (8)	
Time from first TB diagnosis to ITR, mo		6.5 (0–46)
No. of drugs exposed to previously		5 (0–8)
No. of patients with DST results available within 3 mo after initiation	28 (74)	
No. of drugs to which <i>M tuberculosis</i> strain was resistant <sup>f</sup>		
All drugs		4 (1–13)
First-line drugs		4 (1–5)
Second-line drugs		0 (0–6)
Injectable agents		1 (0–4)
No. of patients with documented household contacts with MDR-TB	27 (71)	

<sup>a</sup> Data on some characteristics were missing for some patients. Data on baseline weight were available for 31 patients, hematocrit for 31 patients, albumin for 29 patients, and time from initial tuberculosis diagnosis for 37 patients.

<sup>b</sup> According to Centers for Disease Control and Prevention clinical growth charts.

<sup>c</sup> Anemia was defined for age and gender, and malnutrition was defined as weight for age or weight for length of <5th percentile, wasting, or edema. Other coexisting conditions included giardiasis (2 patients), gastritis (1 patient), hepatitis (1 patient), recurrent urinary tract infections (1 patient), and an intrathoracic mass of unknown cause in a HIV-coinfected patient.

<sup>d</sup> Defined as dyspnea, respiratory rate of >95th percentile for age, or accessory muscle use.

<sup>e</sup> Defined as bullae, bronchiectasis, bilateral cavitory lesions, or miliary pattern.

<sup>f</sup> The drugs tested for all patients were isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin, kanamycin, capreomycin, amikacin, ciprofloxacin, levofloxacin, cycloserine, and ethionamide. First-line drugs included isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. Second-line agents included kanamycin, capreomycin, amikacin, ciprofloxacin, levofloxacin, cycloserine, and ethionamide. Injectable agents included streptomycin, kanamycin, capreomycin, and amikacin.

known household contacts with MDR-TB had received and failed  $\geq 1$  standard first-line treatment regimen.

Thirty patients had positive cultures; DST of 28 *M tuberculosis* strains revealed resistance to a median of 4 drugs (range: 1–11 drugs). In 3 (11%) of those 28 cases, the drugs to which a patient's strain demonstrated resistance were identical to the drugs to which that patient had been exposed previously. The 1 child with resistance to a single drug did not have DST results available until the 11th month of therapy. DST of available source cases' strains demonstrated resistance to a median of 5

drugs (range: 2–9 drugs). DST results were available for both the patient and an adult household contact with MDR-TB in 17 cases. Resistance patterns were identical for only 1 adult-child pair (6%). Resistance patterns correlated except for 1 resistant drug for 8 pairs (47%). Resistance patterns differed by  $\geq 2$  drugs for 8 adult-child pairs (47%). In several cases, however, consideration of drugs to which the child had been exposed previously accounted for the differences in adult and child resistance patterns.

Seventeen of the 38 children were hospitalized initially, because of either the severity of illness or social and economic difficulties in the home (Table 2). Otherwise, all therapy was administered and supervised on an ambulatory basis. The 38 patients received regimens with a median of 6.5 drugs (range: 5–9 drugs).

Adverse events were reported for 16 patients (42%) (Table 3). Approximately one third experienced symptoms of gastritis, such as nausea, vomiting, and abdominal discomfort. For these children, symptoms responded to splitting of ethionamide into divided doses or supportive therapy. Four patients exhibited psychiatric side effects, such as depression, anxiety, or hallucinations; these symptoms were managed with cycloserine dose reduction plus pharmacotherapy, including selective serotonin reuptake inhibitor antidepressants, anxiolytics, and antipsychotics. Three children exhibited hypothyroidism and were treated with levothyroxine until therapy was completed. High-frequency hearing loss was observed for 2 of 30 patients. An asymptomatic creatinine level elevation to 0.5 mg/dL above baseline was noted for 1 patient during the 22nd month of therapy; creatinine levels returned to baseline 1 month after use of the injectable agent streptomycin was suspended. No

**TABLE 2** Clinical Course and Outcomes in 38 Children

	No. of Patients (%)	Median (Range)
Hospitalized at initiation	17 (45)	
Length of hospitalization, mo		6 (1–20)
No. of drugs in regimen		6.5 (5–9)
Orally administered first-line agents		1 (0–2)
Orally administered second-line agents		4.5 (2–6)
Injectable agents		1 (1–2)
Time to culture conversion, mo <sup>a</sup>		1 (1–7.5)
All outcomes		
Good	36 (95)	
Poor	2 (5)	
Final outcomes	34	
Cure	32 (94)	
Failure/death	1 (3)	
Lost to follow-up monitoring <sup>b</sup>	1 (3)	
Intermediate outcomes	4	
Probable cure	4 (100)	
Probable failure	0 (0)	

<sup>a</sup> Positive cultures were obtained for 30 patients.

<sup>b</sup> Defaulted after 13 months of therapy; patient had been culture-negative for 12 consecutive months.

**TABLE 3 Adverse Events Among 38 Children**

Adverse Events	No. (%)
Any adverse events	16 (42)
Hearing loss <sup>a</sup>	2 (7)
Nephrotoxicity	1 (3)
Gastritis	12 (32)
Psychiatric effects	4 (11)
Hypothyroidism	3 (8)
Joint/musculoskeletal	0 (0)
Other <sup>b</sup>	2 (5)
Events requiring dosage adjustments	3 (20)
Events requiring cessation of therapy for >5 d	0 (0)

<sup>a</sup>Data were available for 30 patients. Both cases involved mild, high-frequency, conductive, hearing loss determined with audiometry.

<sup>b</sup>Other adverse events included a hypersensitivity rash (1 patient) and hypokalemia (1 patient).

joint or musculoskeletal complaints were reported. For 3 children, dose adjustments were made to mitigate adverse events. However, there were no adverse events that required suspension of therapy for >5 days.

When a child initiated the ITR with a positive culture, conversion was achieved in a median of 1 month (range: 1–7.5 month). Overall, good outcomes were achieved for 95% of patients. Of the 34 patients who completed therapy, 32 were cured; 1 patient experienced therapy failure and died, and 1 patient was lost to follow-up monitoring after 13 months, after having remained culture-negative for 12 consecutive months. The child who died had massive hemoptysis and tested HIV-negative. He had experienced failure of 3 empiric courses of therapy, which resulted in a strain of tuberculosis that demonstrated resistance to 13 drugs. Of the 4 patients who had not completed treatment at the time of analysis, all demonstrated negative cultures for  $\geq 12$  consecutive months and were defined as having probable cures.

Outcomes were similar for children with culture-proven MDR-TB and those classified as having presumed MDR-TB in the absence of available DST results. Of the 27 children with documented MDR-TB, 25 (93%) achieved cures (21 children) or probable cures (4 children), 1 (3.5%) died, and 1 (3.5%) defaulted from treatment. Of the 10 children diagnosed as having presumed MDR-TB on clinical grounds alone, all achieved cures. The child with documented resistance to isoniazid alone also achieved a cure.

## DISCUSSION

The establishment of the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the Green Light Committee for Access to Second-Line Antituberculous Agents has provided new opportunities to treat MDR-TB in resource-poor countries.<sup>32,33</sup> However, there remains insufficient evidence regarding optimal treatment protocols, diagnostic testing, and infection control in community-based settings. Several issues specific to pediatric MDR-TB have only begun to be addressed in the litera-

ture, notably the safety of second-line antituberculosis agents.<sup>34</sup> A consensus statement by the multinational Stop TB Working Group, which outlined a MDR-TB research agenda, noted that “the field of paediatric MDR-TB is relatively unexplored, and the clinical management of MDR-TB in children needs to be further assessed in terms of safety and efficacy.”<sup>35</sup>

The existing literature on childhood MDR-TB is limited largely to case reports.<sup>36–38</sup> Schaaf et al<sup>39</sup> reported the treatment of 36 children with active MDR-TB with 2 or 3 drugs for 9 to 18 months in South Africa. Of this group, 54% were cured, 10% died, 15% defaulted from treatment, and the rest were still undergoing treatment. As noted, similar outcomes were described for adults with MDR-TB.<sup>30</sup>

The present report includes, to our knowledge, the largest group of children undergoing MDR-TB treatment described in the literature to date. The percentage of cures in this community-based treatment program (94%) was at least as high as any reported for a referral hospital setting and was higher than that for adults enrolled in the DOTS-Plus program in Peru. Favorable outcomes were achieved despite a high rate of baseline comorbidity (45%), advanced disease, and high-grade drug resistance. The most prevalent coexisting conditions in this group of children, namely, anemia and malnutrition, have been identified as risk factors for poor treatment outcomes among adults.<sup>16</sup>

Although operational considerations have been discussed elsewhere,<sup>28</sup> several points are worthy of note. First, the good outcomes described here reflect the excellent treatment adherence produced by daily supervised therapy, most of which was delivered on an outpatient basis. Adherence is also critical in preventing amplification of drug resistance, a phenomenon that has been described for children.<sup>40,41</sup> In fact, children in 7 (41%) of the 17 adult-child pairs demonstrated resistance to additional drugs, compared with their adult contacts; these were drugs to which the children had been exposed previously, which suggests that resistance was acquired before enrollment in the DOTS-Plus program. Second, the largely outpatient nature of the program offers essential cost savings in resource-poor settings and also decreases the risk of nosocomial MDR-TB, which was reported among HIV-infected Peruvian adults.<sup>42</sup> This is especially relevant for older children with adult-type, reactivation, pulmonary tuberculosis, as was common in this group.<sup>43</sup>

The frequency of culture-positive, cavitary, pulmonary disease, which is not classically associated with pediatric tuberculosis, likely reflects progression of disease while children received ineffective therapy with first-line agents. This may be understood as a consequence of initial programmatic reluctance to consider resistance patterns of the source cases when culture-negative pediatric patients presented with both active

tuberculosis disease and adult MDR-TB contacts. Indeed, Schaaf et al<sup>39</sup> reported a median delay of 246 days to the initiation of appropriate therapy for children with MDR-TB when the DST pattern of the source case was not taken into account, compared with only 2 days when the MDR-TB source case was considered in making the diagnosis; these delays contributed to increased morbidity and mortality rates.

Comparison of resistance patterns for adult-child pairs reveals no consistent correlation. Minor discrepancies may reflect variability of DST results for second-line agents.<sup>44</sup> Other authors demonstrated correlations of 60% to 70% in the resistance patterns of adult-child pairs with MDR-TB; in several cases, transmission was confirmed with restriction fragment length polymorphism analysis.<sup>45-47</sup> Although the current series suggests that the resistance pattern of the child's strain often differs from that of the purported source case, excellent outcomes were achieved even for children for whom no DST results were available. This may reflect the efficacy of the conservative algorithm (more drugs at higher doses) used to design the ITRs.<sup>30</sup> The significance of discrepant resistance patterns for adult-child pairs remains unclear. However, when DST results were not available for the child's isolate, the source case's strain served to guide the design of the empiric regimen.

Experience with the use of second-line antituberculosis agents among children has been limited, raising concerns regarding potential adverse events. The absence of serious adverse events in this group of children is reassuring. As noted elsewhere, children seem to tolerate combination chemotherapy for MDR-TB well.<sup>24,47</sup> A previous report of adverse events among adults receiving similarly aggressive ITRs noted ~3 times the rates of gastritis and psychiatric effects, compared with those observed for the children in this series.<sup>48</sup> Interestingly, only 1 (9%) of 11 children <10 years of age experienced any adverse events. Although young children may be less able to articulate complaints, the current series suggests a remarkable ability to tolerate regimens that include second-line agents. Still, the importance of close monitoring by community health workers, nurses, and physicians is worthy of emphasis.

Concerns regarding the use of fluoroquinolones among children have been raised because of the effects of these agents on cartilage growth in animal studies.<sup>49</sup> However, quinolones have been used among children to treat other highly resistant, life-threatening infections, notably chronic *Pseudomonas* infection in cystic fibrosis. Most reports demonstrated a low incidence of reversible arthralgia and a safety profile similar to that for adults.<sup>50-52</sup> The absence of adverse musculoskeletal effects in the current series corroborates the previous analyses. Several authors recommended use of these drugs in selected situations when benefits outweigh risks.<sup>53-55</sup> Because fluoroquinolones are the only orally administered,

second-line agents with bactericidal activity against *M tuberculosis*, their use is essential, and probably lifesaving, for children with MDR-TB disease.

Long-term childhood exposure to daily injectable agents, including aminoglycosides and capreomycin, has raised concerns regarding nephrotoxicity and ototoxicity.<sup>56</sup> In this group of children, hearing loss and nephrotoxicity were both rare and mild, with the incidences being similar to those reported previously for adults.<sup>48</sup>

The most important limitation of this study is that the short follow-up period does not allow assessment of potential long-term adverse events associated with second-line agents. To date, >100 Peruvian children have been enrolled in ITRs for MDR-TB; those who have completed treatment are being monitored for signs of relapse or late-presenting toxicity.

## CONCLUSIONS

We conclude that successful treatment of MDR-TB disease among children is possible in resource-poor settings such as urban Peru. A child who is experiencing failure of DOTS or who has a household contact with known or suspected MDR-TB should be classified as having presumed pediatric MDR-TB. Mycobacterial cultures from sputum, gastric aspirates, or extrapulmonary sites should be pursued aggressively, followed by DST when available. As with adults, prompt treatment should be initiated with multiple first- and second-line agents to which the strain is likely to be sensitive. In cases in which DST results for the child's infecting strain are not available, using the adult source case's resistance pattern to guide therapy is preferable to delaying effective treatment. Adverse events seem to be less common among children than among adults and rarely compromise treatment when managed appropriately.

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## DON'T TAKE THIS LYING DOWN

“Women are still prescribed the equivalent of the rest cure for obstetrical complications, but now it is recommended before birth. It is a standard means of treating just about any pregnancy-related problem in the United States. . . . Indeed, doctors prescribe it for about one in five of all pregnant women, or around 750,000 women a year. . . . There is substantial doubt within the medical profession about the efficacy of bed rest. My own doctors, who were undoubtedly acting in good faith, openly admitted that they were not sure bed rest would increase my amniotic fluid levels. I carried my daughter to term, although no one could tell me if bed rest really helped or not. . . . Ninety-two percent of American obstetricians prescribe bed rest in some form, according to Judith Maloni, a professor at the Bolton School of Nursing at Case Western Reserve University and one of the few researchers of the phenomenon. Dr. Maloni’s investigations reveal that obstetricians in the United States tend to discount both the side effects of bed rest and to believe in its value in the face of evidence to the contrary. (Although bed rest continues to be prescribed almost routinely by some doctors for mothers of multiples at 24 to 28 weeks gestation, a study in 2000 conducted by a professor of obstetrics and gynecology at the University of Adelaide in Australia linked hospitalized bed rest to higher rates of pre-term delivery in mothers of twins.) . . . The lack of research on bed rest’s value for the long shopping list of complications for which it is prescribed, and the lack of recognition of its consequences, is simply astounding. For example, I have yet to hear of a woman on bed rest being offered rehabilitative treatment; I certainly was not. The profession needs to recognize the profound psychological and physical costs of this modern rest cure, and to thoroughly research its putative benefits, before yet another generation of women finds itself staring blankly at the wallpaper.”

Bilston S. *New York Times*. March 24, 2006

Noted by JFL, MD

## Community-Based Therapy for Children With Multidrug-Resistant Tuberculosis

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