DRUG-RESISTANT TUBERCULOSIS AMONG URBAN THAI CHILDREN: A 10-YEAR REVIEW

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Abstract. Drug-resistant tuberculosis (DR-TB) has become an increasing public health concern. We conducted this retrospective chart review to determine the risk factors, susceptibility patterns, and clinical outcomes of children with DR-TB treated at the Queen Sirikit National Institute of Child Health, Bangkok, Thailand. Susceptibility results were available for 78 of the 91 patients (85.7%) with positive cultures for *M. tuberculosis*. Sensitivity of tuberculin skin testing for overall culture-confirmed tuberculosis with a cut-off point of 10 mm for human immunodeficiency virus (HIV)-uninfected cases was 76.9%. Using a 5-mm induration cut-off-point for tuberculin skin testing for HIV-infected cases, sensitivity was only 14.3%. Resistance to at least one anti-tubercular drug was found in 22 cases (28.2%), with streptomycin resistance being the most common (21.7%), followed by isoniazid (11.5%), rifampicin (5.1%), and ethambutol (5.1%). Multi-drug resistance (MDR) was observed in 3 cases (3.8%). A history of previous TB treatment and bone and joint involvement were associated with a significantly higher percentage of DR-TB: 18.2% *vs* 1.8% (p=0.0078) and 22.7 *vs* 1.8% (p=0.0018), respectively. Case fatality rates were 1.7% and 4.5% for drug-susceptible and DR-TB, respectively. Due to the high rate of resistance, streptomycin is not recommended as first time treatment of childhood tuberculosis in Thailand.

Keywords: childhood tuberculosis, drug-resistant tuberculosis (DR-TB), susceptibility pattern of *M. tuberculosis*, anti-tubercular drugs, tuberculin skin testing (TST)

INTRODUCTION

Tuberculosis (TB) has been regarded as a "disease of poverty" (WHO, 2011a). There were an estimated 9 million new cases of TB in 2013, of which 3.5% multi-drug-resistant (WHO, 2014). Childhood tuberculosis comprises approximately 6% of the total incident cases (WHO, 2012). Each year, there are an estimated 550,000 cases of TB and at least 80,000 deaths due to TB among children world-wide (WHO, 2014). Furthermore, the slow progress in controlling drug-resistant TB (DRTB) problem is a cause for concern as this has become a major threat to successful TB

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treatment and control programs worldwide (Zumla *et al*, 2012). Thailand has a high TB burden (WHO, 2011b). In country report 2010, the proportions of multi-drug resistant tuberculosis (MDR-TB) among newly diagnosed and retreated cases in Thailand were 1.7% and 35%, respectively (WHO, 2011b). Little information is available about the burden of DR-TB among the pediatric population in Thailand, and is likely to be under reported due to the lower likelihood of obtaining TB cultures from respiratory or other clinical specimens, among children. In most pediatric TB cases treatment is not guided by antimycobacterial susceptibility patterns. Therefore, it is essential to periodically monitor and make available local susceptibility data about *Mycobacterium tuberculosis* (MTB) in order to guide selection of appropriate empirical treatment for pediatric cases. Therefore, the objective of this study was to determine the proportion of antimycobacterial resistance, clinical characteristics, and outcomes of culture-proven cases of childhood tuberculosis.

MATERIALS AND METHODS

The Queen Sirikit National Institute of Child Health (QSNICH) (Children's Hospital), Bangkok is a public tertiary medical center for pediatric patients. The hospital provides both in- and out-patient care, with a capacity of 426 beds, and has all pediatric specialties and subspecialties. The hospital delivers medical services to approximately 350,000 outpatients and 15,000 in patients per year. As with many other urban health centers in Bangkok, directly observed therapy for tuberculosis has not been routinely implemented at QSNICH.

We conducted a hospital-based retrospective, descriptive study of children aged ≤18 years diagnosed with microbiologically confirmed TB. To identify cases, the log book of the microbiological laboratory, QSNICH was reviewed for the period of 2001-2010. Mycobacterial cultures and susceptibility testing were performed at the Bureau of Tuberculosis, Department of Disease Control, Ministry of Public Health, using solid egg-based culture media (Löwenstein-Jensen) and the proportion method, respectively. The medical records of cases with positive MTB cultures were obtained from the medical record department, QSNICH. Relevant data about demographics, clinical characteristics, susceptibility patterns, and treatment outcomes were recorded using a specific study form.

Data were analyzed using descriptive statistics. The primary outcomes of interest were susceptibility patterns for each anti-mycobacterial agent, except pyrazinamide because it was not part of the routine anti-mycobacterial susceptibility testing at our center. For clinical and outcome variables, mean (standard deviation/SD) and median (interquartile range/IQR) values were calculated for continuous variables where appropriate and frequencies were measured for categorical variables. Univariate analyses were used to compare clinical characteristics and treatment outcomes between those with and without drug resistance. All statistically significant testing was two-tailed, with significance level set at $p < 0.05$. All analyses were conducted using SPSS version 15 (SPSS, Chicago, IL).

RESULTS

From January 1, 2001, through December 31, 2010, 91 cases with culture-proven tuberculosis were identified from a total of 786,017 children aged 0-18 years who

Table 1
Clinical characteristics by susceptibility pattern of culture-proven tuberculosis in Thailand.

	Drug-susceptible TB, *n* (%)	Multi-drug-resistant-TB	*p*-value	Any drug resistant-TB *n* (%)	*p*-value
Total number (%)	56 (100)	3 (100)		22 (100)	
Male, *n* (%)	32 (57.1)	2 (66.7)	0.745	11 (50)	0.568
Age (mean+SD)	64.77 + 59.57	61.67 + 47.98	0.929	64.55 + 52.17	0.987
HIV infection	5 (9)	0	0.588	2 (9)	0.982
History of TB contact	29 (51.8)	1 (33.3)	0.533	13 (59)	0.56
Tuberculin test ≥10 mm (*n*=49)[a]	26 (68.4)[a]	3 (100)	0.07	9 (40.9)	0.659
Previous treatment	1 (1.8)	0	N/A	4 (18.2)	0.0078
Fever	29 (57.8)	0	N/A	6 (27.3)	0.0501
Organ involvement:					
Lung	31 (55.4)	0	0.061	7 (31.8)	0.061
Pleura	0	1 (33.3)	1.32	2 (9)	0.131
Bones and joints	1 (1.8)	2 (66.7)	6.24	5 (22.7)	0.0018
Lymph nodes	7 (12.5)	0	0.514	2 (9)	0.671
Central nervous system	2 (3.6)	0	0.739	1 (4.5)	0.84
Cardiovascular system	2 (3.6)	0	0.739	0	0.369
Skin	0	0	N/A	1 (4.5)	0.108
Disseminated infection	13 (23.2)	0	0.344	6 (27.3)	0.707
Outcomes:					
Incomplete treatment	7 (12.5)	1 (33.3)	0.477	10 (45.5)	0.0015
Complications	1 (1.8)	0	0.815	3 (13.6)	0.327
Relapse	2 (3.6)	0	0.514	1 (4.5)	0.322
Death	1 (1.8)	0	0.815	1 (4.5)	0.787
Loss to follow-up	4 (7.1)	1 (33.3)	0.407	8 (36.4)	0.308

[a]Tuberculin skin test was performed in 49 children, 38 with drug susceptible-TB and 11 with drug resistant TB.
HIV, human immunodeficiency virus; TB, tuberculosis.

received care at QSNICH, yielding an estimated annual hospital-based incidence of 11.6 per 100,000 population. However, only 78 cases (85.7%) had medical records and anti-mycobacterial susceptibility testing results available for analysis.

Demographics and clinical characteristics of culture-proven tuberculosis cases by susceptibility pattern are shown in Table 1. Twenty-two isolates (28.2%) were resistant to at least one first-line antitubercular drug. Single DR-TB was the most common (*n*=16) followed by MDR-TB [resistant to at least both isoniazid (INH) and rifampicin] and other types of drug resistance (*ie*, more than one drug, but no INH or rifampicin resistance). Despite being the most common feature, fever was not a consistent finding, and was identified in only 35 cases (44.8%). The proportions presenting with acute (<14 days), subacute (14 days-3 months),

Table 2
Types and major organ involvements in culture-confirmed childhood tuberculosis cases.

Disease	DS-TB *n* (%)	SDR-TB *n* (%)	ODR-TB *n* (%)	MDR-TB *n* (%)
Total	56 (100)	16 (100)	3 (100)	3 (100)
Pulmonary TB	31 (55.3)	6 (37.4)	1 (33.3)	0
Disseminated TB				
Pulmonary TB with TB meningitis	1 (1.8)	0	0	0
Pulmonary TB with TB lymphadenitis	4 (7.1)	4 (25)	0	0
Pulmonary TB with TB pleurisy with lymphadenitis	1 (1.8)	0	0	0
TB of pleura with TB of spine	0	1 (6.3)	0	0
Pulmonary TB with TB of spine with lymphadenitis	2 (3.6)	0	0	0
Pulmonary TB with abdominal TB with lymphadenitis	2 (3.6)	0	0	0
Miliary TB with lymphadenitis	1 (1.8)	0	0	0
Miliary TB	2 (3.6)	0	0	0
Extrapulmonary TB				
TB pleurisy	0	1 (6.3)	0	1 (33.3)
TB bone and joint	1 (1.8)	1 (6.3)	1 (33.3)	2 (66.7)
TB lymphadenitis	7 (12.4)	2 (12.4)	0	0
TB pericarditis	2 (3.6)	0	0	0
TB meningitis	2 (3.6)	1 (6.3)	0	0
TB skin	0	0	1 (33.3)	0

TB, tuberculosis; DS, drug susceptable; SDR-TB, single-drug-resistant tuberculosis; MDR-TB, multi-drug-resistant tuberculosis; ODR-TB, other types of drug-resistant tuberculosis; resistance to more than one anti-tubercular drug other than simultaneous isoniazid and rifampicin resistance.

or chronic (>3 months) fever and without fever were 17.9%, 21.8%, 5.1% and 55.1%, respectively. The sensitivities of tuberculin skin testing (TST) for culture-confirmed tuberculosis using a cut-off of 10 mm for all cases and human immunodeficiency virus (HIV)-uninfected cases were 71.4%, and 76.9%, respectively. For HIV-infected cases, the sensitivity of the TST using a 5-mm induration cut-off was only 14.3%.

The most common site of infection was pulmonary (n=38; 48.7%), followed by isolated tuberculous lymphadenitis (n=9; 11.5%), and concomitant pulmonary tuberculosis and tuberculous lymphadenitis (n=8; 10.2%). Tuberculous meningitis was identified in 3 cases (3.8%). All three cases of MDR-TB exhibited extrapulmonary manifestations: one with TB pleurisy and two with tuberculosis of the bones and joints (Table 2). Among the drug-resistant strains, streptomycin resistance was the most prevalent (21.7%), followed by INH (11.5%), rifampicin (5.1%), and ethambutol (5.1%) (Table 3). MDR-TB was observed in 3 cases (3.8%). A history of previous antitubercular treatment and/or bone and joint involvement was significantly more common among DR-TB cases than drug-susceptible tuberculosis (DS-TB) cases: 18.2% *vs* 1.8% (p=0.0078) and 22.7 *vs* 1.8% (p=0.0018) for DR-TB and DSTB, respectively. All subjects received

Table 3
Drug susceptibility patterns of *M. tuberculosis* in cases.

Pattern of resistance	Khummin (2009)	Lapphra *et al* (2013)	Punpanich *et al* (2001)	Present study
Settings	Provincial Hospitals	Tertiary Center	Tertiary Center	Tertiary Center
Type of cases	Unspecified	Children	Children	Children
Sample size[a]	391	53	171	78
Study period	2006 - 2008	2008 - 2011	1991 - 2000	2001 - 2010
Any drug resistance[b]	128 (33.7)	18 (34)	51 (29.8)	22 (28.2)
Isoniazid	98 (25.1)	11 (20.1)	26 (15.2)	9 (11.5)
Rifampicin	77 (19.7)	3 (5.7)	23 (13.5)	4 (5.1)
Ethambutol	63 (16.1)	0	13 (7.6)	4 (5.1)
Pyrazinamide	N/A	5 (10.2)[d]	N/A	N/A
Streptomycin	89 (22.8)	4 (8.2)[d]	35 (20.5)	17 (21.7)
Single drug	43 (10.9)	13 (24.5)	25 (14.6)	16 (20.5)
Two drugs	14 (3.6)	2 (3.8)	23 (13.4)	2 (2.6)
Three drugs	20 (5.1)	N/A	10 (5.8)	2 (2.6)
Four drugs	48 (12.3)	N/A	N/A	2 (2.6)
Multi-drug[c]	60 (15.3)	3 (5.7)	16 (9.4)	3 (3.8)

[a]Only those with available susceptibility patterns were included; [b]only those with microbiological-proven drug resistant strains; [c]*Mycobacterium tuberculosis* with resistance to at least two anti-tubercular drugs, isoniazid and rifampicin; [d]among a total of 49 cases tested for pyrazinamide and/or streptomycin.

conventional anti-tubercular treatment from the TB clinic at QSNICH. None of the study subjects received directly observed therapy. Fifteen point four percent of the subjects were lost to follow-up. DR-TB cases were significantly less likely to complete their treatment course than their non-DRTB counterparts (54.5% *vs* 87.5%; p=0.0015). No significant differences in resistance were seen for age, gender, clinical presentation, or HIV serostatus. Case fatality rates were 1.8% and 4.5% for DS- and DR-TB, respectively (Table 1).

DISCUSSION

M. tuberculosis infection causes significant morbidity and mortality for children, especially those living in resource-limited environments. Serious and life-threatening infection can occur unless appropriate antimycobacterial treatment is instituted promptly, with at least two drugs to which the pathogens are susceptible. Nevertheless, limited data are available regarding susceptibility patterns of MTB in developing countries, especially for young children, due to the pauci-bacillary nature of the infections and difficulties in obtaining specimens.

Although it has been estimated that one-third of the world's population is affected by tuberculosis (WHO, 2015), the exact burden of childhood tuberculosis is difficult to quantify. The major obstacles to estimating the burden of childhood tuberculosis include nonspecific clinical manifestations, lack of standard case definition, difficulty in isolating the causative pathogen, and limited access to sensitive diagnostic testing (WHO, 2012). One

study from developed countries found culture-proven childhood TB was seen in 19% (ECDC, 2011) and another is 54% of cases (Rahman *et al*, 2012).

Despite an infectious process, more than half of our study cases did not present with fever. Among those with fever, the majority presented with subacute onset fever, although acute onset fever of less than 2 weeks duration was not unusual.

According to World Health Organization worldwide estimates, 3.7% of new cases and 20% of previously treated cases have MDR-TB (WHO, 2013). In our study, having a history of previous treatment with anti-TB drugs was significantly more common among those with DR-TB than those with DS-TB. The rate of MDR-TB in our study was similar to a study among children at another tertiary center in Bangkok conducted from 2008 to 2011 (Lapphra *et al*, 2013). However, the rate of MDR-TB was substantially lower than that for adults (Khummin, 2009) and for previous unpublished studies of children at our center between 1991 and 2000 (Punpanich *et al*, 2001). The major difference between the current findings and a previous report (Punpanich *et al*, 2001) was the lack of a significant association between MDR-TB and HIV infection status. This is probably due to the expanded coverage with and access to antiretroviral therapy among HIV-infected patients in Thailand during the past decade (WHO, 2007). We were unable to explain the reason for high rate of streptomycin resistance (21.7%), which has remained relatively unchanged at our center since the previous decade (20.5%) (Punpanich *et al*, 2001). We were unable to find studies of the cause of streptomycin resistance. Previous studies from Thailand have reported streptomycin resistance rates of 2.1%-22.8% (Boonsarngsuk *et al*, 2009; Khummin, 2009; Reechaipichitkul *et al*, 2011; Manosuthi *et al*, 2012; Lapphra *et al*, 2013). Molecular genetic analysis suggests slow-growing mycobacteria have a higher chance of developing streptomycin resistance than other Eubacteria, such as *E. coli*, due to the presence of only one 16S rRNA gene copy rather than multiple copies of rRNA operons. Therefore, only one nucleotide change is sufficient to confer resistance among *M. tuberculosis*, but more than one nucleotide change is necessary for other type of Eubacteria (Musser, 1995).

Similar to other studies, clinical and laboratory findings, such as tuberculin skin test results and chest X-ray were indistinguishable between DS- and DR-TB (Schaaf *et al*, 2000; Moll *et al*, 2009). Our findings show extrapulmonary TB was more common among MDR-TB cases and could be important clinically. However, due to the small number of MDR cases in our study, this result should be interpreted with caution. A study from South Africa found extrapulmonary TB was common (up to 46%) among MDR-TB pediatric cases (Schaaf *et al*, 2003). Extrapulmonary and disseminated TB were found more frequently among children with HIV co-infection (Mukherjee *et al*, 2011).

Our study supports a previous study that a prior history of TB treatment is more common among those with DR-TB (Yew and Leung, 2008). Our study found a higher risk for complications, relapse rates, fatality, and loss to follow-up/incomplete treatment among DR-TB cases than among DS-TB cases, but the differences did not reach statistical significance.

Using a TST with a cut-off point of 10 mm gave suboptimal sensitivity (71.4%) in our study. Other studies have found sensitivities of 33%-100% (Shingadia and Novelli, 2003; Connell *et al*, 2011). Lower sensitivities are more common in low-

income/high-TB prevalence countries (Connell *et al*, 2011).

The TST in children with HIV-TB coinfection using the recommended cut-off point of 5 mm gave only 14% sensitivity. Other studies have found similarly poor sensitivities of 22%-36% (Liebeschuetz *et al*, 2004; Walters *et al*, 2008; Davies *et al*, 2009) among children with TB-HIV coinfection. Among HIV-infected children with TB, the TST lacks diagnostic value.

To institute appropriate empiric antitubercular therapy for childhood tuberculosis, data regarding local susceptibility patterns should be available to clinicians. In Thailand, the prevalence of TB resistance to any drug is 29.8%-34% (Punpanich *et al*, 2001; Khummin, 2009; Lapphra *et al*, 2013) and MDR occurs in 5.7-16.2% (Punpanich *et al*, 2001; Khummin, 2009; Lapphra *et al*, 2013). In an unpublished study from our center examining culture-confirmed childhood TB between 1991 and 2000, any drug resistance and MDR-TB were identified in 29.8% and 9.4%, respectively (Table 3). Studies among pediatric populations found INH resistance, any drug resistance and MDR among children with TB ranged from 4.6%-9% (Nelson *et al*, 2004; Schaaf *et al*, 2009; Ruwende *et al*, 2011), 6.9%-15.1% (Schaaf *et al*, 2009), and 1%-5.6% (Nelson *et al*, 2004; Schaaf *et al*, 2009; Ruwende *et al*, 2011), respectively. The World Health Organization estimated the global prevalence of MDR-TB was 3.5% (WHO, 2013). It is essential to keep in mind that resistance to at least one anti-TB drug is common, suggesting empiric treatment using a three-drug regimen may not be appropriate for childhood TB in high DR-TB burden countries such as Thailand. Given that the highest and lowest rates of resistance were identified for streptomycin and ethambutol, respectively, our finding supports the current recommendation of empiric antitubercular regimens should includes INH, rifampicin, pyrazinamide and ethambutol rather than INH, rifampicin, pyrazinamide and streptomycin for childhood tuberculosis.

This study includes only data from culture-confirmed tuberculosis cases. Given the low likelihood of obtaining positive cultures from children, our findings may not be generalizable to culture-negative cases, which comprise the majority of childhood TB. In addition, the incidences reported herein are likely to substantially underestimate the true burden of childhood TB in Thailand. Pyrazinamide susceptibility was not available. Due to the small sample size and number of cases of MDR-TB, multivariate analyses examining risk factors for this condition were not feasible. As a result, we were unable to report the adjusted effect estimates of potential risk factors for DR-TB controlling for potential confounding factors.

In summary, the sensitivity of TST for detecting culture-confirmed tuberculosis was low, especially among HIV-infected children. High rates of isoniazid and streptomycin resistance are causes for concern. Previous treatment of TB and involvement of bones and joints were associated with DR-TB. Ethambutol is preferable to streptomycin as a first-line anti-TB regimen, due to the current high rates of streptomycin resistance among Thai children.

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