

# Paediatric tuberculosis in Singapore: a retrospective review

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## ABSTRACT

**Background** Tuberculosis (TB) is a major cause of mortality and morbidity in the world. Each case represents ongoing transmission and has a significant public health burden. We aim to examine the clinical profile of paediatric TB and compare pulmonary TB (PTB) with extrapulmonary TB (EPTB) in Singapore.

**Methods** A retrospective study of patients admitted to KK Women's and Children's Hospital, Singapore from January 2008 to September 2017 with active TB was undertaken. The clinical characteristics and outcomes of patients with PTB and EPTB were compared.

**Results** Seventy-five patients were diagnosed as having active TB (49 (65%) with PTB and 26 (35%) with EPTB). Patients with EPTB were more likely than those with PTB to be younger (median age 5.1 (IQR 1.2–10.2) years vs 10.1 (IQR 3.5–13.5) years), immunodeficient (35% vs 6%), with a lower haemoglobin count (median 11.2 (IQR 10.2–11.9) g/dL vs 12.0 (IQR 10.5–13.9) g/dL), lower recovery rate (27% vs 57%) and required longer duration of treatment (median 12 (IQR 9–12) months vs 6 (IQR 6–9) months). Common clinical presentations of both PTB and EPTB were significant fever (27%), cough (33%) and weight loss (32%). Overall mortality was 8% with septic shock responsible for three of the six deaths.

**Conclusion** EPTB is more common in the younger age group and is associated with a lower recovery rate.

## INTRODUCTION

Tuberculosis (TB) remains a major cause of morbidity and mortality in the world. Following the introduction of the Singapore Tuberculosis Elimination Programme in 1997, the incidence of TB declined from 57 per 100 000 residents in the 1990s to a low of 35 per 100 000 residents in 2007. In 2016 the incidence of TB was 38.7 per 100 000 residents in Singapore; children aged <19 years contributed only 2.1% of the total TB population. The majority (84%) of cases had pulmonary TB (PTB) with or without extrapulmonary involvement, while the remainder (17%) had extrapulmonary TB (EPTB) exclusively.<sup>1</sup>

The presentation of TB in children can range from non-specific symptoms to a severe clinical presentation, which makes diagnosis challenging. Although PTB is the most common form, all other organs can be

## What is already known on this topic?

- ▶ Diagnosis of paediatric TB (PTB) can be challenging as presentation ranges from non-specific symptoms to a severe clinical presentation. The proportion of extrapulmonary TB (EPTB) has increased in the adult population. However, little is known about the global impact of paediatric EPTB.

## What this study hopes to add?

- ▶ Common clinical presentations involving a third of patients with both PTB and EPTB were significant fever, cough and weight loss. Patients with EPTB were more likely to be immunodeficient. EPTB is more common in the younger age group and is associated with a lower recovery rate.

involved as well.<sup>2 3</sup> Globally, in 2014 almost 10 million people developed TB, of which EPTB represented almost 15% of the overall cases of TB.<sup>4</sup> In adults the proportion of EPTB to PTB has increased due to a decrease in PTB rates.<sup>5</sup> However, little is known of the global impact of paediatric EPTB due to difficulties in paediatric TB case detection and low notification rates.<sup>6</sup> The last published review of paediatric TB in Singapore was by Paul in 1967, which focused on the fatality of tuberculous meningitis. With the changing demographics in Singapore, a new review of paediatric TB is needed.<sup>7 8</sup> The aims of this study were to examine the clinical profile and treatment outcomes of paediatric TB and to compare PTB with EPTB.

## METHODS

### Setting

Kandang Kerbau (KK) Women's and Children's Hospital (KKH) is the largest tertiary paediatric hospital in Singapore with approximately 350 paediatric beds, and accounts for 54% of paediatric admissions nationally (based on market trends; Corporate Communications, KKH). We collected data on all

patients who were admitted for TB investigation in KKH from January 2008 to September 2017. Approval was obtained from the centralised institution review board of Singhealth Research.

### Patient identification and data collection

A patient list with the code tuberculosis was generated using the International Classification of Disease (ICD9CM or ICD10AM from 2012 onwards). Patients who were treated for active TB were included, while latent TB cases were excluded. Data pertaining to demographic profile, clinical presentation, investigations and treatment of selected cases were collected from case notes, electronic records and the infectious disease database.

### Case definitions

Both microbiologically proven cases and non-microbiologically proven cases were included. Microbiologically proven cases were defined as those with a positive TB culture and/or TB PCR. Non-microbiologically proven cases were defined as those with a negative TB culture or PCR but positive TB smear, tuberculin skin test, interferon gamma release assay (IGRA) in the presence of a clinical diagnosis of TB or suggestive chest X-ray (CXR). EPTB was defined as any active TB case involving organs other than the lungs and pleurae. Multiorgan TB was defined as active TB involving two or more organs and was considered EPTB. CNS TB (subset of EPTB) was defined as TB meningitis or meningoencephalitis.

Close contact was defined as living in the same household or in frequent contact with a case of smear-positive PTB. Immunodeficiency was either primary immune disorders or secondary to an underlying disease or immunosuppressive drugs. Definitions of symptoms were adapted from the South African Guidelines 2013<sup>9</sup>:

- ▶ Significant cough was defined as cough duration of  $\geq 14$  days
- ▶ Significant fever was defined as temperature  $\geq 38^\circ\text{C}$  for  $\geq 14$  days
- ▶ Significant weight loss was defined as  $\geq 1$  kg for  $\geq 1$  month. Weight loss was further expressed as a percentage of body weight at diagnosis
- ▶ Fatigue was defined as patient's or parents' complaint of reduced playfulness or lethargy

In our centre, the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK) is the preferred type of IGRA used for children aged  $\geq 2$  years because of the lower rate of indeterminate results compared with QuantiFERON-TB Gold and QuantiFERON-TB In-tube.<sup>10</sup> A tuberculin skin test (TST) might be performed when the T-spot is not available (ie, out of office hours). A positive TST was defined as a reading of  $\geq 10$  mm at 48 hours. All patients had CXR performed and reported by in-house radiologists. All our patients had microbiological investigations. Consecutive fluid specimens were sent for acid-fast bacilli (AFB) smear and culture, using the automated MGIT960 system for liquid growth and Lowenstein–Jensen slants

for solid growth.<sup>10 11</sup> Multidrug-resistant TB (MDR-TB) was defined as resistance to both rifampicin and isoniazid.

### Statistical analysis

Analysis was carried out using SPSS Version 19 (IBM, Armonk, New York, USA). Categorical data were expressed as counts and percentages and continuous data were expressed as median and interquartile ranges (IQR). Differences between categorical data were analysed by  $\chi^2$  tests or Fisher's exact test when cell sizes were less than 5. Differences between continuous data were analysed by the Mann–Whitney test. All statistical tests were two-tailed and a p value  $< 0.05$  was statistically significant.

### RESULTS

Seventy-five patients were included, of which 49 (65%) had PTB and 26 (35%) had EPTB (5 lymphatic, 7 CNS, 1 pericardial, 2 gastrointestinal, 1 eye, 2 musculoskeletal and 8 multiorgan TB). All cases of CNS TB were TB meningitis. Of the eight patients with multiorgan TB, two had pulmonary and CNS involvement and one patient each had CNS and lymphatic involvement; gastrointestinal and musculoskeletal involvement; pulmonary and gastrointestinal involvement; pulmonary and lymphatic involvement; gastrointestinal, lymphatic and musculoskeletal involvement; and gastrointestinal and pulmonary involvement.

Table 1 describes the differences between PTB and EPTB. Patients with EPTB were younger (median age 5.1 years (IQR 1.2–10.2) vs 10.1 years (IQR 3.5–13.5),  $p=0.03$ ), were more likely to be immunodeficient (35% vs 6%,  $p<0.01$ ) and had a lower haemoglobin level (median 11.2 g/dL (IQR 10.2–11.9) vs 12.0 g/dL (IQR 10.5–13.9),  $p=0.01$ ). Common clinical presentations of both PTB and EPTB were significant fever (27%), cough (33%) and weight loss (32%). However, only 20 (27%) of our patients presented with  $\geq 2$  significant symptoms. Patients with PTB were more likely to have significant cough whereas those with EPTB were more likely to present with significant fever and/or lymphadenopathy (table 1). Twenty-eight patients (37%) had positive TB contact (26 household contacts and 2 school contacts). Only four patients (5%) had  $\geq 2$  significant symptoms and a positive contact history.

An abnormal CXR was found in 51 patients (68%) with the following changes: pulmonary infiltrates ( $n=24$ , 32%), hilar adenopathy ( $n=7$ , 9%), miliary ( $n=4$ , 5%), lobar collapse ( $n=3$ , 4%), pleural changes ( $n=2$ , 3%), cavitation ( $n=2$ , 3%), widened mediastinum ( $n=1$ , 1%) and a combination of these changes ( $n=8$ , 11%). Patients with PTB were more likely to have an abnormal CXR than those with EPTB (84% vs 39%,  $p<0.01$ ).

More than half of the patients with PTB and EPTB had microbiologically proven disease (53% and 73%, respectively). T-Spot was performed in 41 (55%) patients: 32 (78%) positive, 6 (15%) negative and 3 (7%)

**Table 1** Comparison of pulmonary and extrapulmonary TB

	<b>Pulmonary n=49 (%)</b>	<b>Extrapulmonary n=26 (%)</b>	<b>P values</b>
Median age (years)	10.1 (IQR 3.5–13.5)	5.1 (IQR 1.2–10.2)	0.03
Gender			
Males	25 (51)	14 (54)	0.82
Females	24 (49)	12 (46)	
Nationality			
Singapore residents	37 (76)	16 (62)	0.21
Non-Singapore residents	12 (24)	10 (38)	
Received BCG vaccine	41 (89)	19 (76)	0.14
Comorbidities			
Immunodeficient	3 (6)	9 (35)	<0.01
Not immunodeficient	46 (94)	17 (65)	
Contact history			
Positive contact	22 (45)	6 (23)	0.06
No contact history	27 (55)	20 (77)	
Symptoms			
Significant fever	9 (19)	11 (48)	0.01
Significant cough	22 (51)	3 (14)	<0.01
Significant weight loss	18 (39)	6 (27)	0.34
Median weight loss (% body weight)	10.6 (IQR 5.8–20.0)	16.3 (IQR 13.6–40.6)	0.29
Fatigue	2 (4)	2 (8)	0.60
Lymphadenopathy	2 (4)	8 (31)	<0.01
≥2 symptoms stated above	14 (29)	5 (23)	0.61
No symptom stated above	22 (45)	11 (42)	0.83
Haematological results			
Median haemoglobin (g/dL)	12.0 (IQR 10.5–13.9)	11.2 (IQR 10.2–11.9)	0.03
Median white blood cells (x10 <sup>9</sup> /L)	11.2 (IQR 7.5–15.6)	10.2 (IQR 7.6–12.0)	0.15
Median platelet count (x10 <sup>9</sup> /L)	376.5 (IQR 281.5–451.0)	377.0 (IQR 339.5–507.0)	0.38
Median ESR (mm/hour)	40.0 (IQR 15.0–85.0)	34.0 (IQR 19.0–54.5)	0.61
Median CRP (mg/L)	36.0 (IQR 16.5–84.4)	32.4 (IQR 8.6–69.3)	0.43
Immunological results			
Positive TST	20 (41)	6 (23)	0.10
Positive IGRA	20 (41)	12 (46)	0.80
Microbiological			
Microbiologically proven	26 (53)	19 (73)	0.10
Not microbiologically proven	23 (47)	7 (27)	
Microbiological results			
≥1 site/sample positive AFB smear	13 (27)	7 (28)	0.89
≥1 site/sample positive AFB culture	24 (49)	15 (58)	0.47
≥1 site/sample positive TB PCR	14 (40)	12 (60)	0.15
Abnormal CXR	41 (84)	10 (39)	<0.01
Treatment outcome			
Recovered	28 (57)	7 (27)	0.01
Death	2 (4)	4 (15)	0.17
Relapsed	1 (2)	1 (4)	-

Continued

Table 1 Continued

	Pulmonary n=49 (%)	Extrapulmonary n=26 (%)	P values
Sequelae	10 (20)	9 (35)	0.18
Lost to follow-up	8 (16)	3 (12)	0.73
Still completing treatment	0 (0)	2 (8)	-
Median duration of treatment (months)	6.0 (IQR 6.0–9.0)	12.0 (IQR 9.0–12.0)	<0.01

AFB, acid-fast bacilli; CRP, C-reactive protein; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; IGRA, interferon gamma release assay; TST, tuberculin skin test.

indeterminate. TST was performed in 31 patients (41%), of which 26 (84%) were positive with a median reading of 14.5 mm (IQR 11.0–20.0). However, there were no significant differences in the percentage of positive smears, cultures, PCR, TST or T-Spot disease between PTB and EPTB. There were no cases of MDR-TB in our cohort.

All patients received isoniazid and rifampicin with pyrazinamide and/or ethambutol. Patients with EPTB needed a longer duration of treatment than those with PTB (median 12 months (IQR 9–12) vs 6 months (IQR 6–9),  $p<0.01$ ). Twelve patients (16.0%) were immunodeficient. Table 2 shows the types of immunodeficiencies in patients with PTB and those with EPTB. Patients who were immunodeficient were also treated for a longer period than immunocompetent patients (median 12 months (IQR 10–12) vs 6 months (IQR 6–9) months,  $p<0.01$ ).

The overall mortality rate was 8.0%. The mortality rate for PTB and EPTB was 4% and 15%, respectively. Event-free survival in patients with PTB compared with those with EPTB was 57% and 27%, respectively ( $p=0.01$ ). Of the four deaths in those with EPTB, two (50%) had TB meningitis. The mortality rate of TB meningitis was 29%. Septic shock accounted for three out of six deaths in both PTB and EPTB. Table 3 describes the details of sequelae, mortality and relapse in cases of PTB and EPTB.

Table 2 Types of immunodeficiencies in pulmonary and extrapulmonary TB

Types of immunodeficiencies	Pulmonary n=49 (%)	Extrapulmonary n=26 (%)
HIV	2 (4)	2 (8)
Malignancy	0 (0)	2 (8)†
Primary immune deficiency	0 (0)	2 (8)‡
Others	1 (2)*	3 (12)§

\*Ebstein–Barr virus-related haemophagocytic lymphohistiocytosis.

†One medulloblastoma on chemotherapy, one neuroblastoma on chemotherapy.

‡Severe combined immunodeficiency.

§One Crohn's disease on immunosuppressant, one juvenile idiopathic arthritis on biologics, one Mendelian susceptibility to mycobacterial disease.

## DISCUSSION

Our study compares the demographics, clinical spectrum, investigation results and outcomes of PTB and EPTB.

The median age of patients with EPTB was significantly younger than those with PTB (median age 5.05 vs 10.10 years,  $p=0.03$ ), which is similar to another study of paediatric TB.<sup>12</sup> EPTB had a lower recovery rate and higher mortality, relapse and sequelae rates compared with PTB. Similar to other studies, this implies that younger children have a higher risk of serious TB.<sup>13 14</sup> The mortality of TB meningitis from our review had decreased drastically from a peak of 60% in 1955.<sup>7 8</sup> A mass BCG vaccination campaign, implemented in 1957, was one of the key interventions that led to a marked decrease in TB mortality rates, especially EPTB and for children aged <5 years.<sup>15 16</sup> A retrospective paediatric study in China showed that EPTB was more prevalent in the BCG unvaccinated group (59% vs 41%,  $p=0.05$ ); our small study failed to show any significant difference.<sup>12</sup> This finding suggests that children who received BCG vaccination have less chance of contracting EPTB.

Children with TB rarely present with classical symptoms, as seen in a survey from a high burden community.<sup>17</sup> This is similar to our study in which only 27% of patients presented with  $\geq 2$  out of five significant symptoms listed by the South African Society for Paediatric Infectious Diseases.<sup>9</sup> Marais *et al* stated that the index of suspicion should be increased when symptoms such as prolonged cough for >2 weeks, significant weight loss and fatigue exist together with positive TB contact.<sup>18</sup> Four (5%) of our patients with TB had  $\geq 2$  significant symptoms and a positive contact history. Nevertheless, available scoring systems should not be used for predicting paediatric TB infection as they lack sensitivity and specificity.<sup>19</sup>

An abnormal CXR was seen in 68% of our patients, which was higher than a large-scale multicentre study conducted in India.<sup>20</sup> This can be explained by significant variation between radiologists when interpreting paediatric CXR.<sup>21</sup> Moreover, CXR had a high sensitivity but low specificity for detecting active TB, as many radiological changes seen in TB could be present in other infections.<sup>22</sup>

A positive microbiological culture remains the gold standard for diagnosis of active TB, but is often limited by the prolonged turnover time. In this study the percentage



**Table 3** Outcomes of pulmonary and extrapulmonary TB

		Pulmonary n=49		Extrapulmonary n=26		
		n	%	n	%	
Types of sequelae	Bronchus compression	3	6	Intestinal perforation	1	4
	Bronchiectasis	3	6	Kyphosis	1	4
	Restrictive lung disease	2	4	CNS infarct	1	4
	Complications from underlying condition	2	4	Complications from underlying condition	2	8
Reasons for mortality *	Septic shock	1	2	Septic shock	2	8
	Pulmonary haemorrhage	1	2	Severe cerebral oedema	1	4
				Underlying malignancy	1	4
Reasons for relapse	Reactivation of pulmonary TB with pericarditis (cause unknown)	1	2	Recurrent TB lymphadenitis (cause unknown)	1	4

\*Of four EPTB: two TB meningitis, one pericardial TB, one multiorgan TB.

of patients with eventual positive TB culture (49.0% and 57.5%) was more than those with  $\geq 1$  positive AFB smears (26.5% and 28.0%) in both the PTB and EPTB groups, which could lead to a delay in identification and treatment of active TB disease. Our higher TB culture rates compared with 15.7% in China and 34% in the USA could be due to more aggressive sampling methods or different culture methods.<sup>12 23</sup>

Immunological investigations such as TST and IGRA can aid in the diagnosis of TB, but each has its own limitations. In children aged <4 years, T-Spot is preferred as it has a lower rate of indeterminate results compared with the QuantiFERON-TB test.<sup>24</sup> While IGRA and TST are good predictors of latent TB infection, their sensitivity for active TB infection is much more limited.<sup>25 26</sup> Regardless of TST or IGRA results, treatment for TB should not be delayed if factors are strongly suggestive of TB (contact history, radiological and microbiological).<sup>27</sup>

The limitations of this study were the small sample size and its retrospective nature. It was not powered to correlate the effect of age, gender and symptoms with laboratory results. This study only included patients who received inpatient treatment for TB in KKH, potentially missing the less severe group who received outpatient therapy.

## CONCLUSION

EPTB is more common in the younger age group and is associated with a lower recovery rate. As TB culture has a long turnover time, treatment for TB should not be delayed if other factors are strongly suggestive of TB. Clinicians should have a high index of suspicion for EPTB and should pay special attention to the younger age group.

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