Comparing the epidemiology and clinical characteristics of childhood tuberculosis through active and passive case finding

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ABSTRACT

Background: Childhood tuberculosis can be found via passive case finding (PCF) - diagnosing a child presenting with symptoms - or active case finding (ACF) - discovering a child through contact tracing.

Design/Methods: We performed a retrospective cohort study of all patients diagnosed with tuberculosis disease from 01/01/2012-12/31/2019 at a United States tuberculosis clinic. We compare clinical, radiographic, microbiologic and epidemiological characteristics of patients found via PCF and ACF.

Results: Of 178 eligible patients, 99 (55.6%) were diagnosed via PCF. Patients found via PCF were older (mean 8.91 vs 6.06 years, p= 0.003) and non-US-born. Patients found via PCF had more extrapulmonary disease (44.5% vs 2.6%, OR 30.8 [95%CI: 7.2-132.5]), severe intrathoracic findings (39% vs 10%, OR 5.77 [95%CI: 2.50-13.29]) and accounted for all 14 severe extrathoracic cases. They also had less isolated hilar/mediastinal adenopathy (OR 0.31 [95%CI: 0.11-0.87]) and were more often cultured (89% vs 37%, OR 13.79 [95%CI: 6.35-29.97]). However, culture yield was similar (PCF 59.1% vs ACF 55.2%, OR 1.17 [95%CI: 0.50-2.74]).

Conclusions: Patients found via PCF were older and had more severe manifestations. ACFs more often had isolated intrathoracic adenopathy and less extensive pulmonary parenchymal involvement, and minimal extrathoracic disease. Clinicians need to be aware that clinical and radiographic presentations in children differ between PCF and ACF.

BACKGROUND

- Tuberculosis (TB) in childhood arises as a result of transmission from an adult with pulmonary TB.
- Childhood TB can be found via passive case finding (PCF), diagnosing a symptomatic child, and active case finding (ACF), discovering a child through contact tracing.
- Diagnosis of childhood TB can be challenging
  - Microbiologically confirmed in only 15-50%
  - If patients have an abnormal chest X-ray, they are classified as having TB disease even if asymptomatic.
  - In ACF: may not collect specimen if susceptibilities of the source case are known
- As contact tracing is introduced to high burden settings, knowing characteristics in the 2 groups is important so that cases can be recognized faster, and effective treatment begun earlier

Aim: Compare the characteristics of epidemiological, clinical, microbiologic and radiographic findings in pediatric TB patients diagnosed through active case finding and passive case finding

METHODS

- **Design:** Retrospective cross-sectional
- **Inclusion criteria:** Patients with microbiologically-confirmed or clinically-diagnosed TB disease cared for by the Texas Children's Hospital in Houston.
- **Study period:** 2012-2019
- Those who had completed treatment by 12/31/2019 and had complete information, were included for evaluation of treatment outcome.
- If microbiology information was available, *Mycobacteria.bovis* was excluded.

Definitions:

- **Active case finding:** If a child was identified with microbiologically-confirmed or clinically-diagnosed TB after being identified as a contact to an index case, or when a screening was performed for immigration or incarceration
- **Passive case finding:** If a child was identified with microbiologically-confirmed or clinically-diagnosed TB after presenting with symptoms without a known source case being linked to the child at the time of diagnosis
- Severity of disease was based on location of illness, imaging and bacteriology/histopathology per Wiseman *et al.*

Data were entered into a REDCap (Vanderbilt; Nashville, TN) database. Frequencies were calculated for demographics and clinical, microbiologic, radiographic, and laboratory findings. Characteristics of the patients found through PCF and ACF were compared and odds ratio (OR) and 95% confidence intervals (CI) were calculated.

Acknowledgment

We would like to thank our health department colleagues, whose work helped identify the majority of our children and lessened their morbidity.

RESULTS

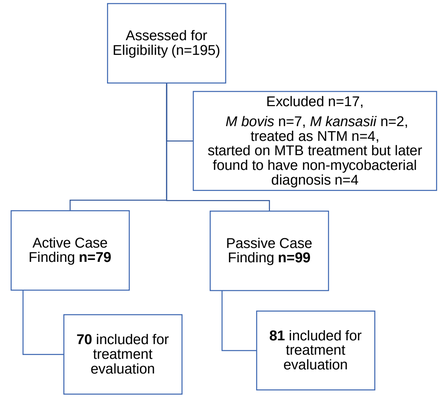

Table 1. Demographics of the Study Population

	Active case finding 79 (44.4%) N (%)	Passive case finding 99 (55.6%) N (%)	OR (95% CI)[a]
Age (median, IQR)	4.11 (IQR 8.73)	10.12 (IQR 14.53)	
Female N (%)	43 (54.4)	50 (50.5)	0.85 (0.47-1.55)
Race/ethnicity N (%)			
Hispanic	42 (53.2)	49 (49.5)	REF
Non-Hispanic Black	20 (25.3)	23 (23.2)	0.99 (0.48-2.0)
Asian	10 (12.7)	22 (22.2)	1.89 (0.8-4.4)
Non-Hispanic White	5 (6.3)	4 (4.0)	0.69 (0.17-2.72)
Multiracial	2 (2.5)	1 (1.0)	0.43 (0.04-4.9)
Region of birth			
United States	65 (82.3)	67 (67.7)	REF
Latin America	6 (7.6)	9 (9.1)	1.46 (0.5-4.32)
Western Pacific Region	2 (2.5)	8 (8.1)	3.88 (0.79-19.0)
South East Asia	2 (2.5)	4 (4.0)	1.94 (0.34-11.0)
Africa	3 (3.8)	9 (9.1)	2.91 (0.75-11.23)
Eastern Mediterranean Region	1 (1.3)	2 (2.0)	1.94 (0.17-21.92)
BCG			
Received	13/77 (16.9)	31/96 (32.3)	2.35 (1.13-4.89)
Not received	64/77 (83.1)	65/96 (67.7)	0.43 (0.20-0.89)
Not documented/Unknown	2	3	-
Underlying medical condition			
None	69 (87.3)	69 (69.7)	0.33 (0.15 – 0.73)
Yes[b]	10 (12.7)	30 (30.3)	3 (1.36-6.61)
History of TB infection	0	8 (8.1)	p=0.009
HIV	0	0	-
Source case known	65 (82.3)[c]	25 (25.3)	0.07 (0.03-0.15)
Parent	22/65 (33.8)	8/25 (32)	0.92 (0.34-2.46)
Grandparent	15/65 (23.1)	4/25 (16)	0.63 (0.19-2.14)
Sibling	3/65 (4.6)	1/25 (4)	0.86 (0.09-8.69)
Other relative	7/65 (10.8)	5/25 (20)	2.07 (0.59-7.27)
Not related	6/65 (9.2)	3/25 (12)	1.34 (0.31-5.83)
Source case found after the patient	2/65 (3.1)[d]	13/25 (52)	34.1 (6.8-171)

BCG: bacille Calmette-Guérin; CI: confidence interval; HIV: Human immunodeficiency virus; IQR: interquartile range; OR: odds ratio; TB: tuberculosis
[a]odds of identification via passive case finding
[b]Underlying comorbidity/condition:
ACF group: 2 with prematurity, 2 with mental health illness/autism/developmental delay, 1 congenital heart disease, 1 splenectomy due to hereditary spherocytosis, 1 tuberous sclerosis, 1 seizure disorder,1 pregnancy, and 1 with history of perinatal HIV exposure. 3 were being treated for TB infection when they developed disease.
PCF group: 8 with asthma or underlying respiratory illness (includes 2 with both prematurity and chronic lung disease and 1 with Down syndrome and chronic lung disease), 6 with mental health disorder/developmental delay, 3 with prematurity, 2 patients with Down syndrome, 1 each with cancer, immunodeficiency, rheumatological disease, inflammatory bowel disease, sickle cell disease who underwent bone marrow transplantation, malnutrition, metabolic disorder, trisomy 18, and 6 with other health conditions not known to be risk factors for TB.

Table 2. Microbiological Information

	Active Case Finding (n=79) N (%)	Passive Case Finding (n=99) N (%)	OR (95% CI) or p-value for Fisher exact
Source case culture positive	64 (81.0)	24 (24.2)	0.17 (0.09-0.32)
Patient culture positive	16 (20.3)	52 (52.5)	4.36 (2.22-8.56)
Microbiological information known from source case or patient	**69 (87.3)**	**59 (59.6)**	**0.21 (0.10-0.46)**

RESULTS

Table 3. Clinical Findings

	Active Case Finding (n=79) N (%)	Passive Case Finding (n=99) N (%)	OR (95% CI) or p-value for Fisher exact
Symptoms*			
Asymptomatic	43 (54.4)	0	p=1.0
Fever	16 (20.3)	53 (53.5)	4.54 (2.31-8.92)
Cough	30 (38)	54 (54.5)	1.96 (1.07-3.58)
Hemoptysis	0	8 (8.1)	p=0.001
Weight loss	3 (3.8)	22 (22.2)	7.24 (2.08-25.19)
Night sweats	2 (2.5)	7 (7.1)	2.93 (0.59-14.51)
Decreased energy	2 (2.5)	21 (21.2)	10.37 (2.35-45.73)
Lymphadenopathy	2 (2.5)	25 (25.3)	13.01 (2.98-56.87)
Duration of symptoms	N=77	N=97	
Less than 1 week	8 (10.4)	10 (10.3)	0.99 (0.37-2.65)
8-<30 days	15 (19)	33 (33.3)	2.1 (1.06–4.30)
1-6 months	8 (10.4)	38 (39.2)	5.56 (2.40-12.84)
>6-12 months	1 (1.3)	7 (7.2)	5.91 (0.71-49.12)
> 12 months	0	9 (9.3)	p=0.01
Hospitalized	14 (17.7)	84 (84.8)	26 (11.72-57.7)
ICU admission	0	9 (9.1)	p=0.01
Type of disease			
Isolated Intrathoracic	77 (97.5)	55 (55.6)	0.03 (0.01-0.14)
Isolated Extrathoracic	1 (1.3)	28 (28.3)	30.76 (4.08-231.98)
Both Intrathoracic and Extrathoracic	1 (1.3)	16 (16.2)	15.04 (1.95-116.08)
Site of Disease (Extrathoracic)*			
Lymphadenopathy	1 (1.3)	25 (25.3)	26.35 (3.48-199.43)
CNS	0	10 (10.1)	p=0.005
Abdominal disease	0	4 (4.0)	p=0.13
Ear infection	1 (1.3)	2 (2.0)	1.61 (0.14-18.07)
Bone	0	3 (3.0)	p=0.26
Ocular	0	3 (3.0)	p=0.26
Cutaneous	0	2 (2.0)	p=0.5
Severe TB			
Severe Intrathoracic Disease (imaging/clinical)	8 (10.1)	39 (39.4)	5.77 (2.50-13.29)
Severe abdominal disease	0	4 (4.0)	p=0.13
Solid Organ Disease	0	4 (4.0)	p=0.13
Peritoneal spread	0	1 (1.0)	p=1
Severe based on location of illness	0	14 (14.1)	p=0.0003
CNS	0	10 (10.1)	p=0.005
Tuberculous spondylitis	0	1 (1.0)	1
Ocular disease	0	3 (3.0)	p=0.26

BMI: body mass index; CI: confidence interval; CNS: central nervous system; ICU: intensive care unit; OR: odds ratio; TB: tuberculosis
Missing variables included: 4 (2.2%) missing symptom duration and 17 (9.5%) missing z-scores for weight-for-length/BMI
*do not sum to 100% as some children had > 1 finding

Other key findings

- PCF patients had less isolated hilar/mediastinal adenopathy (OR: 0.18 [95%CI: 0.06-0.51]).
- PCF patients were more likely to have cultures attempted (88.9% vs 36.7%, OR 13.8 [95% CI: 6.35-29.97]). Among the patients who had cultures sent, microbiological confirmation rates were similar (PCF 59.1% vs ACF 55.2%, OR 1.17 [95% CI 0.50-2.74]).
- 5/16 (31.3%) of the ACF patients with microbiological confirmation were asymptomatic, but all had consolidation or cavities on chest X-ray.
- No child had treatment failure.
- Less patients in the PCF group completed therapy in 6 months (OR 0.08 [95%CI: 0.03-0.24] and had 3 drug regimen for initial therapy (OR 0.2 [95%CI: 0.75-0.53]).
- 1 patient in ACF and 7 patients in PCF group had documented drug resistance based on culture and drug susceptibility results from either the child or the likely source case.

CONCLUSIONS

- Children diagnosed via ACF were younger and more likely to be US born.
- Almost all the severe and extrathoracic cases were seen in the PCF group.
- Early diagnosis via ACF prevents more serious forms of TB disease.
- Availability of source case culture and drug susceptibility results for ACF patients allowed for more tailored empiric mycobacterial therapy.
- Clinicians need to be aware that the common epidemiological, clinical and radiographic presentations in children differ between PCF and ACF.

Reference

- Wiseman CA, Gie RP, Starke JR, et al. A proposed comprehensive classification of tuberculosis disease severity in children. *Pediatr Infect Dis J*. 2012;31(4):347-352.