Risk Factors for In-Hospital Mortality Among Children With Tuberculosis: The 25-Year Experience in Peru

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KEY WORDS

pediatrics, childhood tuberculosis, tuberculin skin testing, mortality, global health

ABBREVIATIONS

CI—confidence interval

HR—hazard ratio

ISN—Instituto de Salud del Niño

TB—tuberculosis

TST—tuberculin skin testing

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WHAT'S KNOWN ON THIS SUBJECT: Because most childhood tuberculosis cases are sputum smear-negative, diagnosis relies largely upon clinical presentation, tuberculin skin testing, and chest radiograph. Diagnostic limitations contribute to treatment delays and high mortality. However, childhood tuberculosis (TB) mortality risk factors are not well documented.

WHAT THIS STUDY ADDS: This study demonstrates that false-negative TST is common in children with active TB and is associated with increased risk of death. A negative TST should not delay anti-TB therapy. Improved diagnostic modalities are urgently needed in resource-limited settings.

abstract

OBJECTIVE: We examined factors associated with in-hospital death among children with tuberculosis (TB). We hypothesized that a negative response to tuberculin skin testing (TST) would predict decreased survival.

METHODS: This retrospective cohort comprised 2392 children ages 0 to 14 years hospitalized with TB at a Peruvian referral hospital over the 25-year study period. Detailed chart abstraction captured clinical history including TB contacts, physical examination findings, diagnostic data, treatment regimen, and hospitalization outcome. We used Cox proportional hazards regression analyses to determine risk factors for mortality.

RESULTS: Of 2392 children, 2 (0.1%) were known to be HIV-positive, 5 (0.2%) had documented multidrug-resistant TB, and 266 (11%) died. The median time from hospitalization to death was 16 days (interquartile range: 4–44 days). Reaction of <5 mm induration on TST predicted death in a multivariable analysis (hazard ratio [HR]: 3.01; 95% confidence interval [CI]: 2.15–4.21; $P < .0001$). Younger age, period of admission, alteration of mental status (HR: 3.25; 95% CI: 2.48–4.27; $P < .0001$), respiratory distress (HR: 1.40; 95% CI: 1.07–1.83; $P = .01$), peripheral edema (HR: 1.97; 95% CI: 1.42–2.73; $P < .0001$), and hemoptysis (HR: 0.57; 95% CI: 0.32–1.00; $P = .05$) were associated with mortality. Treatment regimens that contained rifampicin (HR: 0.47; 95% CI: 0.33–0.68; $P < .0001$) were associated with improved survival.

CONCLUSIONS: Negative reaction to TST is highly predictive of death among children with active TB. In children with clinical and radiographic findings suggestive of TB, a negative TST should not preclude or delay anti-TB therapy. *Pediatrics* 2012;130:e373–e379

Childhood tuberculosis (TB) has been called a “hidden epidemic.”¹ Approximately 1 million children develop active TB annually, comprising up to 25% of the total TB caseload in high-burden countries.^{2,3} Yet because global TB policy has historically focused on the more infectious sputum smear-positive cases, only 0.6% to 3.6% of reported TB cases globally comprise children.^{4,5} In addition to underreporting of cases, the low public health priority allocated to childhood TB is associated with delays in diagnosis and treatment of 2 to 10 weeks.^{6,7} The combination of underreporting and treatment delays may contribute higher to childhood TB mortality.⁸

For decades, children have been underrepresented in TB research, and pediatric treatment protocols are largely extrapolated from research in adults.^{9,10} Yet the natural history and clinical presentation of TB in children differ markedly from adults. Young children are particularly susceptible to the more lethal hematogenous disease forms, including miliary and central nervous system TB.¹¹ Approximately one-third of children have extrapulmonary disease.¹² Importantly, due to the paucibacillary nature of childhood TB, bacteriologic confirmation is achieved in only 20% to 30% of probable TB cases.^{13–17} However, Marais et al¹⁸ have reported bacteriologic confirmation in 77% of children with advanced intrathoracic disease.

Although tuberculin skin testing (TST) is a cornerstone of diagnosis in many settings, up to 10% of immunocompetent children with culture-confirmed TB may have false-negative responses to TST.^{19,20} False-negative TST may also result from recent viral or bacterial infection, recent live virus vaccine, HIV infection, hypoproteinemia and malnutrition, metabolic derangements, immunosuppression, and severe stress.²¹ Many of these conditions are also risk factors for developing TB disease. Because TST status is often included in the

diagnostic algorithm for childhood TB, a false-negative TST could result in harmful treatment delays. A TST reaction <5 mm of induration has been associated with increased risk of death in HIV-positive adults with TB.²²

We examined the risk factors for in-hospital mortality among 2392 children hospitalized with TB in Peru over a 25-year period. In particular, we hypothesized that a negative response to TST would predict decreased survival.

METHODS

The study received approval from the institutional review boards of the Instituto de Salud del Niño (ISN) in Peru and Partners Healthcare in Boston, Massachusetts.

Setting and Study Population

With an incidence and prevalence of 126 and 136 per 100 000 population, respectively, in 2007, Peru has among the highest TB rates in the Americas.⁵ In the hyperendemic shantytowns of Lima, the prevalence may exceed 350 per 100 000.²³ The ISN in Lima is the largest pediatric referral center in Peru.

For this retrospective cohort analysis, we included all children aged 0 to 14 who were hospitalized at ISN with TB disease between January 1, 1973, and December 31, 1997. Only partial medical records for patients admitted after 1997 were available to the investigators, so the cohort was limited to the 25-year period for which complete data were available. All children with a recorded admission date, discharge date, and outcome of hospitalization were included in the analysis.

Children presented for care via outpatient referral, emergency department visit, or inpatient transfer. An extensive diagnostic workup was routinely performed, including history and physical examination, TST and chest radiograph, sputum smear microscopy and culture

when possible, or gastric aspirate samples for children too young to cough. Other diagnostic studies, including lumbar puncture, thoracentesis, and surgical biopsy, were performed when appropriate. Drug susceptibility testing was not routinely available during the study period.

Data Collection

Detailed chart abstractions were performed by Spanish-fluent clinicians with expertise in childhood TB by using a standardized instrument developed by the investigators. Variables included demographic information, history and physical examination data, laboratory and microbiology results, disease classification, treatment, and adverse event data. Chest radiographs were interpreted by 1 of the study authors, a pediatric pulmonologist, and coded by using a standardized system developed by the investigators. If multiple chest radiographs were available, the admission chest radiograph was used. Likewise, if more than 1 value for a laboratory test was recorded in the chart, only admission laboratory values were used for analysis. Outcome was recorded as death or survived at the time of hospital discharge. As data collection was based solely on hospital medical records, there was no post-hospitalization follow-up or matching with vital registries. Data were entered into a Microsoft Access database.

Exposure Definitions

A negative TST was defined as a reaction of <5 mm of induration by Mantoux testing, performed at admission. Children with admission weight less than the third percentile per age were considered to be underweight, a proxy for undernutrition.²⁴ Respiratory distress was defined by the presence of tachypnea, chest wall retractions, or nasal flaring. We defined central nervous system TB, miliary/disseminated disease,

and gastrointestinal/peritoneal TB as severe extrapulmonary disease due to high associated mortality. A confirmed TB diagnosis required demonstration of acid-fast bacilli on smear microscopy, a positive mycobacterial culture, or histopathologic findings consistent with TB. Otherwise, TB diagnosis was made on clinical grounds (clinical TB), based on TB exposure history, clinical and radiographic findings, and TST results. The investigators did not interpret or alter a clinical TB diagnosis made by the treating clinicians as documented in the medical record.

Statistical Analysis

Kaplan-Meier survival analyses were used to estimate the time from admission to death. For patients who did not reach the end point of death, the data were censored at the time of hospital discharge. We used Cox proportional hazards regression models to conduct multivariable analyses. The final multivariable model was derived through a backward deletion strategy with the main exposure, TST result, forced into the final model.²⁵ Specifically, we began with all potential predictors of mortality (ie, possible confounders) in the model and removed them 1 variable at a time, starting with those with the highest *P* values. We retained in the final multivariable model those variables whose removal altered the hazard rate for TST result by 10% in either direction or predicted mortality at a *P* value < .05. Age was examined as a categorical variable with three 5-year intervals (0–4, 5–9, and 10–14 years). To account for potential confounding due to changes in clinical practices over time, admission year was divided into 5-year groups and examined as a categorical variable.

Missing Data

In general, a condition or symptom was presumed to be present if it was noted in the chart and absent if there was no

note in the chart. Missing values for TST result (eg, positive or negative) and admission weight percentile were multiply imputed for multivariable analysis. Imputation was conducted with Markov Chain Monte Carlo methods (SAS MI procedure; SAS Institute Inc, Cary, NC) by using covariate and outcome data.²⁶ All statistical analyses were performed by using Statistical Analysis Software, version 9.12 (SAS Institute).

RESULTS

Characteristics of the Study Population

Of 2393 children hospitalized with a diagnosis of active TB during the study period, 1 was excluded for missing discharge date. Thus, the final cohort comprised 2392 children. The median hospital stay was 70 days (range: 0.5–334 days). The baseline characteristics are shown in Table 1. The median age was 9 years (interquartile range, 5–12), and half (50.2%) were girls. Two patients (0.1%) were known to be HIV-positive, and 1966 (82.2%) children were ill for >4 weeks at the time of admission.

A total of 2274 (95.1%) and 2147 (90.0%) children had complete data on TST status and weight, respectively. We

excluded from univariable analysis 5 children with infeasible values for weight. At the time of admission, 890 children (41.5% of those with weight data) had an admission weight less than third percentile for age. Most (88.6%) had abnormal findings on chest auscultation, and over half (51.6%) exhibited respiratory distress. TB diagnosis was confirmed in 1290 (53.9%) children, including 985 (41.2%) with positive acid-fast smear, 708 (29.6%) with positive mycobacterial culture, and 122 (5.1%) with histopathologic findings consistent with TB. A negative response to TST was common (42.6%) among both children with and without confirmed TB (41.5% and 43.8%, respectively, *P* = .26) and was more prevalent among children who were underweight at admission than among children who were not underweight (55.1% vs 44.9%, respectively, *P* < .0001). Of 11 children who underwent drug-susceptibility testing, 5 had documented multidrug-resistant TB.

Forty-two percent (*n* = 1013) of children presented with exclusively pulmonary disease. Of the 1304 children with extrapulmonary TB, a majority (76.5%) had both pulmonary and extrapulmonary manifestations. The most common extrapulmonary localizations were central nervous system (447, or 18.7% of cohort), lymphadenitis (14.1%), pleural effusion (14.5%), and gastrointestinal/peritoneal TB (10.6%); 428 children (17.9%) had miliary TB. Note that disease localization categories were not mutually exclusive.

Mortality

Two hundred sixty-six children (11.1%) died. Mortality was highest in children <1 year of age (46.9%), decreasing to 3.2% by 14 years of age (Fig 1). Children with both pulmonary and extrapulmonary disease had higher mortality (17.0%) than those with pulmonary (7.4%) or extrapulmonary (6.9%) disease alone

TABLE 1 Baseline Characteristics of 2392 Children Hospitalized With TB

Variable	<i>n</i> (%)
Age, y	
0–4	544 (22.7)
5–9	786 (32.9)
10–14	1062 (44.4)
Gender	
Girl	1192 (49.8)
Boy	1200 (50.2)
Overcrowding/poor sanitation in home	1526 (63.8)
BCG vaccinated	1369 (57.2)
Previous TB disease	88 (3.7)
TB contacts	
Intradomiciliary	1250 (52.3)
Extradomiciliary	187 (7.8)
Illness duration >4 wk	1966 (82.2)
Emergency admission	1003 (41.9)

FIGURE 1
Mortality by age.

(Table 2). Among disease localizations, high mortality was seen with meningitis (28.4%), gastrointestinal or peritoneal TB (24.0%), and miliary disease (20.8%). Mortality is plotted by year of admission in Fig 2.

Factors Associated With Survival

Figure 3 shows the survival patterns stratified by TST. Significant predictors of death in univariable analysis are shown in Table 3. A negative TST was associated with a nearly fivefold increase in the rate of death (hazard ratio [HR]: 4.97; 95% confidence interval [CI]: 3.55–6.96; $P < .0001$).

In the multivariate model, negative TST remained an independent predictor of death (HR: 3.01; 95% CI: 2.15–4.21; $P < .0001$); other significant predictors

included younger age (0–4 years; 5–9 years), respiratory distress, altered mental status, hemoptysis, and peripheral edema. Rifampicin-containing regimens remained an independent predictor of improved survival, relative to regimens without rifampicin. Comparing children whose diagnosis was microbiologically confirmed with children receiving a clinical diagnosis, survival did not significantly differ in multivariate analysis. Mortality also varied significantly by period of admission.

DISCUSSION

The current analysis represents, to our knowledge, the largest detailed clinical cohort of childhood TB reported since the advent of TB chemotherapy. In addition to reinforcing important epidemiologic concepts, a number of notable clinical findings were revealed.

Given that the most widely used pediatric TB diagnostic algorithms use TST as major criteria, a negative TST may lead to delays in diagnosis and treatment.²⁷ Yet a surprisingly high percentage of children in the current cohort (42.6%) had a negative TST upon admission. Several reported causes of false-negative TST may contribute to higher mortality and therefore explain this association. First, overwhelming TB has itself been associated with anergic TST.²¹ Second, both HIV infection and

malnutrition have been associated with increased TB mortality.^{28–30} Finally, TST may not become positive until 3 months after infection, yet infants and young children may progress to severe disseminated TB disease during this time window.¹¹ In our analysis, anergic TST (<5 mm induration) was a robust independent predictor of in-hospital mortality. The association between TST and mortality did not change when history of BCG vaccination was included in the model. Furthermore, a negative TST was equally common among children with bacteriologically confirmed TB, indicating that this finding is not due to misdiagnosis of TB disease and death due to another untreated illness. In children with clinical and radiographic findings suggestive of TB, a negative TST should not preclude or delay anti-TB therapy, and preexisting factors that could lead to a negative TST result should be thoroughly assessed and treated.

Severe protein-energy malnutrition has been reported as an independent predictor of mortality in HIV-infected children with TB and among adults with miliary TB.^{30,31} In the current study, underweight status was associated with mortality in univariable but not multivariable analysis; however, we cannot rule out malnutrition as a risk factor for mortality. Malnutrition profoundly affects cellular immune function, the key host defense against TB. A negative TST result may be a proxy for the impaired immune function resulting from malnutrition. We found that the HR for undernutrition was attenuated when TST result was included in the model. This is not surprising given that impaired immune status, represented by a negative TST result, is 1 mechanism through which malnutrition may increase TB mortality.

Microbiologic or pathologic confirmation of TB diagnosis was achieved in a relatively high proportion (54%) of cases. High rates of bacteriologic confirmation

TABLE 2 Mortality Among 2392 Children, by Disease Localization

	n	Number died (%) ^a
Pulmonary only	1013	75 (7)
Extrapulmonary only	306	21 (7)
Pulmonary and extrapulmonary	998	170 (17)
Extrapulmonary localization		
Meningoencephalitis	447	127 (28)
Miliary/disseminated	428	89 (21)
Lymphadenitis	338	27 (8)
Pleural effusion	347	15 (4)
Gastrointestinal or peritonitis	254	61 (24)
Pericarditis	32	2 (6)
Skeletal	61	3 (5)

^a A total of 266 children died (11% of total cohort).

FIGURE 2
Mortality by year of admission.

FIGURE 3
Kaplan-Meier estimates of the proportion of patients with TB surviving to hospital discharge.

have been reported for children in other highly TB endemic regions, suggesting that an aggressive diagnostic approach can yield significant benefit.¹⁸ This is particularly relevant in the era of drug-resistant TB, where isolation of the organism is paramount for accurate diagnosis and treatment. Overall, mortality was high both in children with a confirmed (bacteriologic) diagnosis (9.7%) and those receiving a clinical diagnosis (12.8%), and confirmation of diagnosis was not a significant predictor of survival

in multivariable analysis. We found that hemoptysis was protective against TB death. This may be a chance finding or hemoptysis may be a proxy for pulmonary disease, which tends to have a lower mortality rate than extrapulmonary disease.

A notable finding is the declining mortality rate in the first 2 decades of the study period, followed by fewer hospitalizations and concurrent increase in the in-hospital mortality rate during the 1990s, as elucidated in Fig 3. This

may reflect a shift toward community-based directly observed treatment, short-course management in Peru in the early 1990s, when less ill children were more likely to be treated in an ambulatory setting. The emergence of HIV and multidrug-resistant TB may have played a role in the mortality increase in later years.

We attempted to minimize measurement bias through detailed chart abstraction, followed by validation of the data through a thorough audit of the chart abstraction in 10% of patients. However, the retrospective nature of this study makes this difficult to rule out entirely. For example, if treating clinicians were especially vigilant about recording conditions or symptoms in the sickest individuals, this could have inflated HRs for some risk factors because conditions were presumed to be absent if they were not noted in the chart. Our cohort comprised a referral hospital population, and thus findings may be less applicable in a community-based setting. The historical nature of the cohort may detract from generalizability, as standards of care for TB have changed over time. Finally, it is unknown whether our results are generalizable to settings of high HIV prevalence and multidrug-resistance.

CONCLUSIONS

Given that most cases of childhood TB are managed in community-based

TABLE 3 Factors Associated With In-Hospital Mortality in 2392 Children

	Died	Survived	Univariate			Multivariate		
	<i>n</i> (%)	<i>n</i> (%)	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Gender, girl	140 (52.6)	1052 (49.5)	1.11	0.87–1.41	.41	—	—	—
Age, y								
0–4	125 (47.0)	419 (19.7)	6.10	4.26–8.71	<.0001	3.53	2.40–5.18	—
5–9	101 (38.0)	685 (32.2)	3.30	2.28–4.76	—	2.22	1.52–3.24	<.0001 ^a
10–14	40 (15.0)	1022 (48.1)	—	—	—	—	—	—
Illness duration >4 wk	211 (79.3)	1755 (82.6)	0.73	0.54–0.99	.043	—	—	—
Underweight ^b	106 (63.1)	784 (39.6)	2.09	1.52–2.86	<.0001	—	—	—
History of BCG	121 (45.5)	1248 (58.7)	0.65	0.51–0.82	.0004	—	—	—
Previous TB disease	9 (3.4)	79 (3.7)	0.72	0.35–1.45	.35	—	—	—
Fever	228 (85.7)	1836 (86.4)	0.98	0.69–1.38	.90	—	—	—
Vomiting	140 (52.6)	595 (28.0)	2.45	1.92–3.12	<.0001	—	—	—
Hemoptysis	14 (5.3)	478 (22.5)	0.21	0.12–0.36	<.0001	0.57	0.32–1.00	.05
Wt loss	185 (69.6)	1612 (75.8)	0.75	0.57–0.97	.03	—	—	—
Respiratory distress	149 (56.0)	1085 (51.0)	1.19	0.94–1.52	.16	1.40	1.07–1.83	.01
Altered mental status	145 (54.5)	393 (18.5)	4.30	3.37–5.47	<.0001	3.25	2.48–4.27	<.0001
Peripheral edema	50 (18.8)	143 (6.7)	2.39	1.75–3.28	<.0001	1.97	1.42–2.73	<.0001
Negative TST ^c	163 (61.3)	805 (37.9)	4.97	3.55–6.96	<.0001	3.01	2.15–4.21	<.0001
Confirmation of TB diagnosis ^d	125 (47.0)	1165 (54.8)	0.69	0.54–0.88	.0028	—	—	—
Rifampin-containing regimen	147 (55.3)	1498 (70.5)	0.59	0.46–0.76	<.0001	0.47	0.33–0.68	<.0001
Severe extrapulmonary disease	168 (63.2)	543 (25.5)	4.06	3.17–5.2	<.0001	—	—	—
Year of admission								
1973–1977	57 (21.4)	345 (16.23)	0.48	0.31–0.75	—	0.39	0.22–0.70	—
1978–1982	94 (35.3)	528 (24.8)	0.56	0.37–0.85	<.0001	0.61	0.37–1.00	—
1983–1987	56 (21.0)	735 (34.6)	0.27	0.17–0.43	—	0.34	0.21–0.55	<.0001 ^a
1988–1992	28 (10.5)	389 (18.3)	0.29	0.17–0.43	—	0.37	0.22–0.62	—
1993–1997	31 (11.6)	129 (6.1)	—	—	—	—	—	—

^a *P* value for likelihood ratio test.^b *N* = 2147 for univariable analysis.^c *N* = 2274 for univariable analysis.^d Microbiologic or histopathologic confirmation of TB disease.

settings, our findings may help to identify children requiring more aggressive care and hospitalization. These include young children and children presenting with respiratory insufficiency, alteration of mental status, and peripheral edema. Perhaps more importantly, the strong association between anergic TST and mortality lends new urgency to development and widespread implementation of more effective diagnostic modalities for children.³²

Current World Health Organization guidelines for childhood TB allow for a measure of flexibility and clinical judgment in making the diagnosis.³ Yet the unfortunate reality in many settings is that attempts to make a bacteriologic diagnosis in children are often halfhearted; moreover, children not meeting traditional diagnostic criteria, such as smear positivity and positive TST, are often late to receive appropriate therapy. Our findings suggest that

aggressive attempts to achieve bacteriologic diagnosis pay dividends in settings of high TB burden and that a negative TST should not supplant clinical judgment when clinical and radiographic features suggest TB.

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