

Epidemiology of Tuberculosis in pediatrics and variables associated with loss to follow-up

Epidemiología de la Tuberculosis en pediatría y variables asociadas a pérdida en el seguimiento

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What do we know about the subject matter of this study?

Tuberculosis is a serious public health problem. Loss to follow-up is a critical issue that can lead to death and increases the risk of developing drug-resistant TB.

What does this study contribute to what is already known?

This article describes a pediatric cohort with tuberculosis. It identifies the absence of symptoms at the first consultation as a risk factor for loss to follow-up.

Abstract

Loss to follow-up (LTFU) in tuberculosis (TB) patients endangers their lives, facilitates disease transmission, and contributes to the development of drug resistance. **Objective:** To describe the epidemiology of a cohort of children diagnosed with TB in a high-complexity pediatric hospital and to identify variables associated with LTFU. **Patients and Method:** A retrospective cohort study was conducted at a tertiary care hospital in Buenos Aires, Argentina. Patients aged ≥ 30 days to ≤ 16 years diagnosed with TB during 2022–2023 were included. Patient characteristics were compared based on whether they experienced LTFU. STATA 18 was used for statistical analysis. **Results:** 197 patients met the inclusion criteria. The median age was 11 years (IQR 7–14). 79% consulted due to symptoms, while 20% did so due to contact with a TB case. TB was classified as exclusively pulmonary in 60%, extrapulmonary in 11%, and both in 29%. Microbiological confirmation was obtained in 59% of cases. Drug resistance was identified in 5% of patients. 19% experienced LTFU. In the multivariate analysis, patients who did not report symptoms compatible with TB at the first consultation had a higher risk of LTFU (ORa 3.27, 95%CI 1.55–6.88; $p = 0.030$). **Conclusions:** In this cohort of children with TB, a high rate of microbiological confirmation was observed. 19% were lost to follow-up. TB diagnosed in children who did not report symptoms at the first consultation was identified as a risk factor for LTFU.

Keywords:
Mycobacterium tuberculosis;
Pediatrics;
Follow-up Studies;
Epidemiology;
Adherence

Introduction

Globally, tuberculosis (TB) continues to be a serious problem¹. In Argentina, the number of TB cases is on the rise, and the proportion of patients lost to follow-up (LTFU) is alarming. Argentina has committed to ending TB by 2030 within the framework of the Sustainable Development Goals (SDGs)².

In 2024, Argentina reported a total of 16,647 TB cases, equivalent to a notification rate of 35.4 per 100,000 inhabitants. This represents an increase of 8.3% compared to 2023 and marks the fourth consecutive year of sustained increase in case notification. The analysis of the period between 2009 and 2024 shows that 2024 was the year with the highest absolute number of cases, the highest rate, and the fastest growth rate, with an average annual variation of 11%³.

In those under 20 years of age, the notification rate was 19.8 per 100,000 in 2024, an increase of 15.1% compared to 2023. In the pediatric population, there has been a sustained increase of 5.4% per year since 2017, which intensified after the pandemic, with an acceleration of 12.7% per year from 2020 to the present. In 2022, the success rate achieved in this group was 58.1%, with 12.9% presenting LTFU³.

Pediatric TB presents specific challenges in diagnosis, treatment, and follow-up due to factors such as difficulty in obtaining diagnostic samples, nonspecific clinical presentations, and socioeconomic barriers that affect access and adherence to treatment^{4,5}.

LTFU is a critical problem that compromises efforts to control the disease and puts patients' lives at risk, while increasing the likelihood of developing drug-resistant TB (DR-TB)^{6,7}. The objective of this study is to describe the epidemiology of a cohort of children diagnosed with TB in a high-complexity pediatric hospital and to identify variables associated with LTFU.

Patients and Method

Design

Retrospective cohort study. The inclusion criteria were age ≥ 30 days and ≤ 16 years, having been diagnosed with TB at *Hospital Pediátrico Juan P. Garrahan*, a tertiary care facility located in the Autonomous City of Buenos Aires, Argentina. The study was conducted between January 1, 2022, and December 31, 2023. Patients with initial suspicion of TB who were later ruled out were excluded.

Variables analyzed

All patients who met the inclusion criteria were identified from the hospital's epidemiological records. Medical records were reviewed and the follow-

ing data collected: sex, age, origin, underlying disease, reason for consultation, anatomical location of TB, chest X-ray findings, history of BCG vaccination, results of complementary studies [tuberculin skin test (PPD), smear microscopy, culture, Xpert MTB/RIF], sensitivity to first-line drugs, characterization of the index case, requirement for hospitalization, indicated anti-TB regimen, incidence of major adverse reactions to anti-TB drugs, treatment abandonment, and disease course.

Definitions

- Tuberculosis disease: primary or extra-primary involvement caused by *Mycobacterium tuberculosis* (Mtb) diagnosed by a physician who has decided to initiate anti-TB treatment, with or without bacteriological confirmation⁸.
- According to anatomical location, TB disease was classified as:
 - Pulmonary TB: bacteriologically confirmed or clinically diagnosed TB affecting the lung parenchyma, the tracheobronchial tree, and the intrathoracic lymph nodes (mediastinal and/or hilar), even without pulmonary abnormalities revealed by imaging studies. Pulmonary TB with miliary pattern is included^{8,9}.
 - Extrapulmonary TB: bacteriologically confirmed or clinically diagnosed TB affecting organs other than the lungs^{8,9}. Pleural TB was classified within this group.
 - Pulmonary and extrapulmonary TB: bacteriologically confirmed or clinically diagnosed TB with involvement compatible with the definition of pulmonary TB as well as extrapulmonary TB.
- Drug-resistant TB: TB disease caused by a strain of the Mtb complex that is resistant to any anti-TB drug¹⁰.
- Completed treatment: bacteriologically confirmed or clinically diagnosed TB case that completed the indicated treatment^{9,11}.
- Treatment abandonment: bacteriologically confirmed or clinically diagnosed TB case that completed treatment for at least one month and subsequently did not attend follow-up visits for at least two months⁹.
- Recovered treatment abandonment: patient with a history of treatment abandonment who then restarts and completes treatment¹¹.
- Relapse: a patient who has already completed a full course of TB treatment and was declared cured and is diagnosed with a recurrent episode (either a new relapse or a new episode of TB caused by reinfection)¹¹.

- Loss to follow-up (LTFU): a bacteriologically confirmed or clinically diagnosed TB case for which treatment was indicated and whose patient subsequently failed to attend follow-up for at least 2 months and up to the start date of the research protocol¹¹.
- Co-habitant: a person who shared the same enclosed living space as the index case for one or more nights or during frequent or prolonged daytime periods during the 3 months before the start of the current treatment¹⁰.

Microbiological aspects

For microbiological diagnosis, samples were sent to the microbiology laboratory, where direct examination was performed using Auramine-O or Ziehl-Neelsen staining and culture in BD MGIT 960 liquid media and solid media (Stonebrink media). Identification was performed using the BD MGIT TBc Identification Test[®] rapid chromatographic immunoassay. Rifampicin and isoniazid sensitivity tests were performed using the BD MGIT 960 system, and resistant isolates were referred to the “ANLIS Malbrán” National Reference Center for confirmation and sensitivity testing to other anti-TB drugs.

Molecular diagnosis using the Xpert[®] MTB/RIF assay (in addition to culture) was requested for patients with extrapulmonary TB or suspected drug resistance based on clinical and epidemiological history and symptom severity.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as medians and interquartile ranges (IQR). The characteristics of patients who presented LTFU were compared with those who presented good adherence (categories “complete treatment” and “undergoing treatment”). For the study of variables associated with LTFU, patients referred to other institutions were excluded. A univariate analysis was performed using the chi-square test to compare categorical variables, and the Rank sum test was used for continuous variables. A logistic regression model was then developed, manually incorporating the variables that were significant in the univariate analysis or that had greater clinical relevance. A *p*-value < 0.05 was considered significant. The strength of the association between variables was estimated using odds ratios (OR) and their 95% confidence intervals. Stata version 18 software was used.

Ethical considerations

This study complied with all laws and regulations in force regarding ethical evaluation guidelines. The protocol was approved by the Research Coordina-

tion Office (research protocol number 1664), which included evaluation and approval by the institution’s Ethics Committee. Data collection was carried out using coded identifications to protect the identity of the patients.

Results

A total of 197 patients were included (Table 1). The median age was 11 years (IQR 7-14), and 53% were female (*n* = 105). Regarding place of residence, 133 patients (67.5%) lived in the Province of Buenos Aires, 58 (29.5%) in the Autonomous City of Buenos Aires, and 6 (3%) in other provinces of Argentina. Foreign patients accounted for 7 patients (3.5%).

A total of 54 patients (27%) had some comorbidity (Table 1). 18 patients (9%) had a history of previous treatment: 17 had abandoned treatment, and one had relapsed. The latter was a 10-year-old patient who had presented with pleural TB two years earlier and had completed 6 months of treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol. Her relatives had not completed the contact study, and she had a relative with active TB at the time of diagnosis of recurrent TB.

Regarding vaccination, 93 patients had a history of BCG vaccination in their medical records, of whom 91 (98%) had it recorded in their health card or presented a vaccination scar, while 2 patients had not received the vaccine.

Regarding the reason for consultation, 156 patients (79%) attended due to symptoms compatible with TB, 40 (20%) due to a history of contact with a confirmed case, and 1 patient was evaluated in the context of a relapse. Close contact with a patient diagnosed with TB was identified in 113 patients (57%), distributed among cohabitants (*n* = 88, 78%), close non-cohabitant contacts (*n* = 18, 16%), and schoolchildren (*n* = 7, 6%).

TB was classified as pulmonary in 118 patients (60%), extrapulmonary in 21 (11%), and both in 58 (29%). 11 patients (6%) had central nervous system (CNS) involvement, 4 of them associated with another location. Table 1 shows a complete description of the sites of extrapulmonary infection.

Chest X-ray abnormalities were observed in 177 patients (90%). Microbiological confirmation was obtained in 115 patients (59%), of whom 63 (32%) were smear-positive, and 104 (53%) had *Mtb* isolated in culture. The Xpert MTB/RIF test was performed on 45 samples, of which 20 were positive (44%). Isoniazid resistance was detected in 6 patients (3%), rifampicin resistance in 2 (1%), and multidrug resistance in 2 cases (1%).

Table 1. Demographic, clinical, radiological and treatment characteristics of the cohort (n = 197)

Variable	n (%)
Age in years (median, IQR)	11 (7-14)
Female sex, N (%)	105 (53)
Comorbidities, N (%)	
None	143 (73)
Asthma	13 (6)
Down syndrome	8 (4)
Neurological disease	6 (3)
Oncohematological disease	5 (2,5)
Human immunodeficiency virus infection	5 (2,5)
Solid organ transplant	4 (2)
Rheumatologic disease	3 (1,5)
Congenital heart disease	2 (1)
Chronic liver disease (non oncologic, non solid organ transplant)	2 (1)
Other ^a	6 (3)
Anatomical classification, N (%)	
Pulmonary	118 (60)
Extrapulmonary	21 (11)
Pulmonary and extrapulmonary	58 (29)
Extrapulmonary involvement (n = 79), N (%)	
Lymph node	18 (23)
Pleural	17 (21)
Osteoarticular	7 (9)
Central nervous system	7 (9)
Abdominal	7 (9)
Laryngeal	2 (2,5)
Erythema nodosum	2 (2,5)
More than one extrapulmonary site	19 (24)
Chest imaging findings, N (%)	
Exclusive pulmonary involvement	
Bilateral without cavities	109 (55,5)
Unilateral without cavities	18 (9)
Cavitary TB	23 (12)
Miliary TB	7 (3,5)
Pleural effusion	
Without parenchymal involvement	
Unilateral	3 (1,5)
Bilateral	0 (0)
With parenchymal involvement	
Unilateral	16 (8)
Bilateral	1 (0,5)
Normal	20 (10)
Treatment regimens ^b , N (%)	
HRZE ₂ HR ₄	124 (63)
HRZE ₂ HR ₇₋₁₀	42 (21)
HRZ ₂ HR ₄	5 (3)
Other regimens	26 (13)

^aOther comorbidities: cleft lip and palate (1 patient), chronic kidney disease (1 patient), DiGeorge syndrome (1 patient), primary immunodeficiency (1 patient), autoimmune hypothyroidism (1 patient), psoriasis (1 patient). ^bH: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol. Subscripts indicate treatment duration in months.

Table 2. Univariate analysis according to loss to follow-up

Característica		Sin pérdida de seguimiento (n = 146) (N %)	Pérdida de seguimiento (n = 37) (N %)	P
Female sex		77 (53)	19 (51)	0.8
Age in years (median, IQR)		11 (8-13)	10 (2-14)	0.3
Presence of underlying disease		41 (28)	8 (22)	0.5
Place of residence	Autonomous City of Buenos Aires	39 (27)	15 (41)	0.1
	Buenos Aires Province	104 (71)	22 (59)	0.1
Foreign nationality		6 (4)	1 (3)	0.69
Reason for consultation	Contact investigation	24 (16)	15 (41)	< 0.01
	Symptoms	122 (84)	22 (59)	< 0.01
Disease localization	Exclusive pulmonary	85 (58)	25 (68)	0.35
	Exclusive extrapulmonary	14 (10)	5 (14)	0.54
	Pulmonary + extrapulmonary	47 (32)	7 (19)	0.15
Microbiologically confirmed		93 (64)	18 (38)	0.04
Positive smear microscopy		52 (36)	7 (19)	0.05
Drug-resistant tuberculosis*		10 (6)	-	-
Household index case		60 (41)	23 (62)	0.02
Hospitalized		81 (55)	17 (46)	0.35
Major adverse reaction to anti-tuberculosis drugs		23 (16)	2 (6)	0.11
Previous history of treatment default		14 (10)	3 (8)	1

*Drug-resistant tuberculosis: tuberculosis caused by a strain of *Mycobacterium tuberculosis* complex resistant to any anti-tuberculosis drug¹⁰.

During treatment, 111 patients (56%) required hospitalization, with a median length of stay of 12 days (IQR 6-19.25). Table 1 shows the treatment regimens indicated. In patients who completed treatment, the median treatment time was 6 months (IQR 6-10). Adverse events were reported in 27 patients (14%): hepatotoxicity (n = 22), hypersensitivity (n = 2), blood count abnormalities (n = 2), and 1 patient presented with DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome.

At the time of data analysis (October 1, 2024), 140 patients (71%) had completed their treatment at the hospital, while 14 (7%) had been referred to other institutions, and 6 (3%) were still in follow-up. There were no deaths attributable to TB in this cohort.

A total of 37 patients (19%) were classified as LTFU. Among them, 51% were female, and the median age was 10 years (IQR 10-14). The time between the start of treatment and the last recorded visit was 1 month (IQR 0-3.75 months).

In the univariate analysis, statistically significant associations were found between LTFU and the following factors: contact with a confirmed TB case as the reason for the initial consultation (n = 15, 41% vs

n = 24, 16%; p = 0.003) and the fact that the index TB case was a cohabitant (n = 23, 62% vs n = 60, 41%; p = 0.027). In addition, microbiological TB confirmation was associated with lower LTFU (n = 14, 38% vs n=93, 64%; p=0.04). No differences were found in age, sex, origin, underlying disease, clinical TB form, hospitalization due to TB, or history of previous treatment abandonment (Table 2).

In the multivariate analysis, adjusting for the other variables in the model, patients who did not report symptomatic disease at the time of their first consultation had a higher risk of LTFU (ORa 3.27, 95% CI 1.55-6.88, p = 0.03).

Discussion

TB in pediatrics is a growing problem worldwide. In recent years, there has been an increase in the proportion of children under 20 years of age diagnosed with TB in Argentina³.

The clinical presentation of TB in pediatrics is highly variable, ranging from oligosymptomatic to very severe forms. It is estimated that 20% of TB cases in

children are extrapulmonary¹². Disseminated forms or those involving the nervous system are associated with higher morbidity and mortality. In this study, 24% of patients had more than one extrapulmonary involvement, and 6% had nervous system involvement.

The high proportion of patients with confirmed TB in this study is noteworthy. Systematic microbiological studies: direct, culture, and the use of molecular diagnostic techniques improve the yield of diagnostic studies¹².

The study of antibiotic resistance is a fundamental epidemiological surveillance tool. Resistance to first-line drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) identified in this cohort was lower than that reported in previous studies. Berberian et al. reported 9.6% resistance to these drugs in children with TB between 1998 and 2015 at the same institution¹³, which is probably related to the decrease in cases of HIV patients^{14,15}.

The LTFU rate in pediatric patients undergoing TB treatment varies considerably depending on the geographical and socioeconomic context. A study conducted in South Africa reported a LTFU rate of 19%¹⁶, while studies conducted in developed countries show that LTFU can be significantly lower when strategies such as material incentives and structural support are implemented¹⁷. In Argentina, the reported LTFU for the general population is 12.9%, while in this cohort, it was 19%. This finding underscores the difficulty of treatment adherence in the pediatric population with TB in highly complex settings. Other studies conducted in low- and middle-income countries describe higher LTFU among patients undergoing treatment in highly complex hospitals^{18,19}. In this cohort, patients who consulted without symptoms compatible with TB had lower treatment adherence. Similarly, a study conducted in India in 2018 reports the absence of TB symptoms as a predictor of LTFU²⁰.

Other publications list other determinants of LTFU in TB patients, such as sociocultural factors, stigmatization, lack of knowledge about the disease, and the severity of clinical forms^{21,22}. These aspects were not evaluated in this study.

Microbiologically confirmed TB was associated with lower LTFU in the univariate analysis, but when adjusted for other variables, such as the presence of symptoms and the clinical form of the disease, it did not reach statistical significance in the multivariate analysis. However, the importance of diagnostic confirmation for optimizing follow-up measures is highlighted. A study conducted in the city of Buenos Aires found an association between the LTFU of TB contacts with a negative PPD result and the absence of microbiological confirmation in the index case²³. This could be related to whether adults perceive the disease as severe.

Consistent with other studies²⁴, hepatotoxicity was the most common adverse reaction. Although the incidence of adverse reactions was relatively low and was not associated with LTFU, these events could negatively impact treatment adherence. It is essential to implement strategies for monitoring and early management of adverse reactions to prevent treatment abandonment.

Finally, although the TB treatment success rate in this cohort was over 70%, LTFU remains a significant barrier to achieving TB control goals in Argentina³.

The main strengths of this study are the large number of TB patients registered in a short period and the methodical review of clinical and microbiological data in the medical records, which allowed for the exploration of associations between different variables and treatment failure. However, a weakness is that it was conducted in a single high-complexity center, which should be considered when assessing the external validity of the findings. In addition, it has limitations inherent in retrospective studies, such as incomplete recording of data in medical records, and the study design did not allow for an in-depth examination of environmental and social determinants and qualitative variables that could be associated with difficulties in treatment adherence.

Despite this, this study adds updated information on the clinical manifestations and variables associated with LTFU in the pediatric population, which can provide a solid basis for the design and implementation of interventions. Only through a comprehensive approach tailored to the specific needs of the pediatric population can we move toward the goal of ending TB by 2030.

Conclusions

In this retrospective cohort of patients diagnosed with TB, most children had no previous comorbidities. Pulmonary form was the most frequent; however, the high proportion of extrapulmonary TB and TB involving more than one organ is noteworthy. Fifty nine percent of the cases were microbiologically confirmed TB, and 19% of patients had LTFU. In the multivariate analysis, TB diagnosed in children who did not report symptoms at the first consultation was identified as a risk factor for LTFU.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World

Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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