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Admissions by tuberculosis in a regional reference Center. A complex and worrying scenario

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Objectives: *To characterize clinical aspects, evaluate the diagnostic opportunity, and identify factors associated with mortality in patients hospitalized for tuberculosis (TB).* ***Methods:*** *Retrospective study of patients admitted for TB to a Regional Hospital in Chile between 2011 and 2019.* ***Results:*** *142 TB events required hospitalization in this period (38.2% of total cases). All risk groups were identified, with a significant increase in patients with diabetes mellitus. The pulmonary location was the most frequent (71.1%), followed by disseminated forms (16.2%). The sensitivity of microscopy smear in cases of pulmonary TB (isolated or combined) was 78.8% and lower in cases of bronchoalveolar lavage (58.3%). PCR was only occasionally applied (< 10%) with a sensitivity of 100% in sputum samples. Its use increased progressively and reached a positivity of 33% (6 out of 18 cases) in cases with negative sputum staining. The median time between symptom onset and diagnosis was prolonged (9 weeks), and 32.5% of all regional events were diagnosed at the hospital. Dose adjustments (22.1%), corticosteroid use (25%), and treatment interruptions were frequent (11%). Lethality reached 19%, and by multivariate analysis, only shock was associated with a fatal outcome.* ***Conclusions:*** *In this case series, the diagnosis of TB cases was delayed, scarcely diagnosed by molecular methods, highly concentrated at the hospital level, required admission in a large percentage of cases, and had a high case-fatality rate.*

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Key words: *Tuberculosis; Diagnosis; Polymerase Chain Reaction; Radiology; Mortality.*

Ingresos por tuberculosis en un hospital regional. Un escenario complejo y preocupante

Objetivos: *Caracterizar aspectos clínicos, evaluar la oportunidad diagnóstica e identificar factores asociados a mortalidad en pacientes ingresados por tuberculosis (TB).* ***Métodos:*** *Estudio retrospectivo de pacientes ingresados por TB a un Hospital Regional en Chile entre el 2011 y 2019.* ***Resultados:*** *Un total de 142 eventos de TB requirieron hospitalización en el período (38,2% del total). Todos los grupos de riesgo fueron identificados con un aumento significativo de los pacientes con diabetes mellitus. La localización pulmonar fue la más frecuente (71,1%), seguida de la forma diseminada (2 o más sitios; 16,2%). La sensibilidad de la tinción de expectoración en casos de TB pulmonar (aislada o combinada) fue de 78,8% y más baja en casos de lavado broncoalveolar (58,3%). La PCR fue sólo ocasionalmente aplicada (< 10%)*

con una sensibilidad del 100% en muestras de expectoración. Su uso aumentó progresivamente en el período y el incremento diagnóstico de TB en casos con tinción negativa de expectoración estudiados con PCR fue de 33% (6 de 18 casos). La mediana entre inicio de síntomas y el diagnóstico fue prolongada (9 semanas) y el 32,5% de los eventos regionales fueron diagnosticados en el hospital. Los ajustes de dosis (22,1%), uso de corticoides (25%) e interrupciones del tratamiento fueron hechos frecuentes (11%). La letalidad alcanzó 19% y en el análisis multivariado sólo la aparición de shock se asoció a un desenlace fatal. ***Conclusiones:*** *En esta serie de casos, el diagnóstico de casos de TB fue tardío, infrecuentemente diagnosticado por métodos moleculares, concentrado en la atención terciaria, requirió hospitalización en un gran porcentaje de casos y tuvo una elevada letalidad.*

Palabras clave: *Tuberculosis; Diagnóstico; Reacción en Cadena de la Polimerasa; Radiología; Mortalidad.*

Tuberculosis (TB) is a re-emerging disease in Chile in the context of budget cuts, a high prison population, and an increased HIV/AIDS incidence rate[1,2]. For treated patients, lethality and follow-up loss rates remain high[2]. We analyzed admissions for this disease in a regional reference hospital over a long period and before the SARS-CoV-2 pandemic to know the associated group risks, diagnostic studies, management features, their outcome, and possible factors associated with mortality.

Patients and Methods

Study design. Retrospective observational study using medical records of patients hospitalized for tuberculosis (2011-2019) of any form at the Valdivia Regional Hospital in southern Chile.

Patient detection and inclusion/exclusion criteria. Patients were identified using the registry of the Regional Reference Laboratory, including only confirmed cases by culture or PCR (Xpert MTB /RIF; Cepheid or RealAccurate® Quadruplex Mycobacteria PCR Kit; PathoFinder®, Maastricht, The Netherlands). We included patients with a negative culture and a positive PCR if associated with another compatible finding[3]. As some patients were admitted more than once, every admission was considered an event, and these events were included if TB led to admission, if it was detected as a nosocomial complication, if provoked hospitalization due to complications, or to secure therapy. Patients diagnosed and managed on an outpatient basis or hospitalized for causes unrelated to TB during treatment were omitted.

Variables analyzed. Clinical, microbiological, imaging, and therapeutic information was obtained from medical records for each event. Events were classified as pulmonary, extrapulmonary, or disseminated forms. Timing to diagnosis (symptoms onset to diagnosis, [SOD]) and timing from diagnosis to treatment were calculated. The condition at discharge from treatment was classified according to international standards. Deceased patients were analyzed by the authors in order to evaluate an attributable or associated TB death.

Statistical analysis and ethical aspects. Data was analyzed using nonparametric methods. The study of mortality risk factors was done by calculating the Odds Ratio. For the multivariate analysis, a binary logistic regression method was applied. The Scientific Ethics Committee of the Valdivia Health Service approved this work.

Results

Between 2011 and 2019, 142 admissions with confirmed TB were observed in 139 patients in our regional Hospital (3 patients had more than one admission). Six of these events were diagnosed by molecular methods (95.8% by culture and 4.2% by PCR). These events compromised 38.2% of all confirmed TB cases in our Region. Except for one pulmonary case linked to *M. bovis,* the remaining 141 infections were linked to *M. tuberculosis*.

General features of the 139 affected patients and causes of hospitalization

In this series, primarily men (73.4%) with a median age of 52 years (IQR 38-64) were in-

Table 1. General features of 139 patients with TB, Hospital Base de Valdivia, Chile 2011-2019

Variable	n	%
Demographic and social features		
Male gender	102	73.4%
Elderls	30	21.6%
Aboriginal people	21	15.1%
Immigrant	3	2.2%
Healthcare personnel	2	1.4%
Homeless	21	15.1%
Inmate	10	7.2%
Consumption		
Current tobacco smoking	42	30.2%
Heavy alcohol consumption	52	37.4%
Illicit drugs abuse	9	6.5%
Monthly income		
No income	62	44.6%
Minimal wage	54	38.8%
Comorbid conditions		
Diabetes mellitus	24	17.3%
COPD/Asthma/fibrosis*	14	10.1%
Liver cirrhosis	15	10.8%
Child-Pugh A	4	2.9%
Child-Pugh B	9	6.5%
Child-Pugh C	2	1.4%
Chronic kidney disease	4	2.9%
Leukemia/lymphoma	2	1.4%
Cancer	2	1.4%
Rheumatoid arthritis /Systemic Lupus Erythematous	3	2.2 %
HIV/AIDS	6	4.3%
Immunesuppressive drugs		
Costicosteroids	5	3.6%
Methotrexate	2	1.4%
Mycophenolate	1	0.7%
Fludarabine	1	0.7%
Infliximab	0	0.0%
Previous TB	9	6.4%
Treated	7	5.0%
Non treated	1	0.7%
Therapy abandonment	1	0.7%
Past exposure to a pulmonary TB case	21	14.8%
Tuberculin test (past or recent)		
Positive	4	2.9%
Negative	5	3.6%

*COPD: Chronic obstructive pulmonary disease; HIV/AIDS: Human immunodeficiency virus/ Acquired immunodeficiency syndrome.

Table 2. Clinical findings among pulmonary TB events. Hospital Base de Valdivia, Chile 2011-2019

Parameter	n	%
In events with isolated pulmonary involvement (n = 101)		
Cough	93	92.1%
Sputum	78	77.2%
Fever	62	61.4%
Weight loss	78	77.2%
Cough + fever + weight loss	52	51.5%
Diaphoresis	38	37.6%
Hemoptysis	16	15.8%
Shortness of breath	49	48.5%
Pleuritic pain	14	13.9%
Undernourihsed	61	60.4%
Focal lung findings	40	39.6%
Respiratory rate ≥ 30/min	13	12.9%
Pulse oximetry < 93%	24	23.8%
In all events with pulmonary TB (isolated or combined) Chest X-ray (n = 120)		
Bilateral compromise	94	78.3%
Bilateral upper lung compromise	91	75.8%
Upper right lung quadrant compromise	100	83.3%
Upper left lung quadrant compromise	103	85.8%
Lower right lung quadrant compromise	86	71.7%
Lower left lung quadrant compromise	86	71.7%
Cavitation	51	42.5%
Consolidation pattern	66	55.0%
Lung infiltrates	105	87.5%
Apical residual lung lesions	40	33.3%
Pleural effusion	28	23.3%
Pneumothorax	7	5.8%
Chest computed tomography (n = 67)		
Bilateral compromise	54	81.8%
Upper right lung lobe compromise	54	80.6%
Upper left lung lobe compromise	57	85.1%
Middle lobe compromise	49	73.1%
Lower right lung compromise	48	71.6%
Lower left lung compromise	53	79.1%
Cavitation	35	52.2%
Consolidation pattern	29	43.9%
Lung infiltrates	57	86.4%
Apical residual lung lesions	23	34.8%
Pleural effusion	20	30.3%
Lung nodes	18	27.3%
Bronchiectasias	31	47.0%

Table 3. Sensitivity of smear microscopy and PCR* of different brands for diagnosis of pulmonary TB (isolated or combined with other form), Hospital Base de Valdivia, Valdivia, Chile 2011-2019

Sample site	Culture positive n	Positive AFB**/ requested	%	Positive by Xpert-MTB-RIF / requested (%)	Positive by RealAccurate / requested (%)
Sputum	104	82/104	78.8%	6/6 (100%)	4/4 (100%)
BAL***P	25	14/24	58.3%	4/7 (57.1%)	4/5 (80%)
Overall	129	96/128	75%	10/13 (76.9%)	8/9 (88.9%)

*PCR: polymerase chain reaction; **AFB: Acid fast bacilli: ***BAL: Bronchoalveolar lavage.

Table 4. Clinical and microbiologic features in events of pleural TB, Hospital Base de Valdivia, Chile 2011-2019

Parameters	n (%)
In events with isolated pleural TB	
Cough	6 (66.7%)
Sputum	3 (33.3%)
Shortness of breath	7 (77.8%)
Weight loss	5 (55.6%)
Diaphoresis	6 (66.7%)
Fever	7 (77.8%)
Undernourished	2 (22.2%)
Pleural effusion at physical exam	9 (100%)
Pleuritic pain	6 (667%)
Chest X-ray or CT findings*	
Pleural effusion	9 (100%)
Cavitation	0 (0,0%)
Consolidation	0 (0,0%)
Lung infiltrates	2 (22.2%)
Apical residual lung lesions	2 (22.2%)
Pleural fluid analysis (n requested)	Median; IQR values
Adenosin deaminase (n = 4)	50.8 U/L; 42.2-65.5 U/L
Protein concentration (n = 7)	50 g/L; 42-52 g/L
Cell count (n = 8)	1,661/μL; 339-3 175 /μL
% mononuclear cells (n = 7)	93%; 90-98%
Pleural lactate dehydrogenase (n = 5)	770 U/L; 219-1,435 U/L
Diagnostic studies in all events with pleural TB (isolated or combined)	
Diagnostic yield in pleural fluid	
AFB: positive smear /n**	1/11 (9.1%)
Culture: positive /n	8/11 (72.7%)
PCR: positive/n***	3/3 (100%)

*CT: computed tomography; **AFB: Acid fast bacilli; ***PCR: Polymerase chain reaction.

volved. A fifth were elders, and other prevalent social factors were detected: aboriginal people and people experiencing homelessness (Table 1). Active smoking and excessive alcohol consumption were common (30.2-37.4%, respectively). A 6.5% declared consumption of illicit substances. Diabetes mellitus, previous chronic pulmonary pathology, and liver cirrhosis (> 10%, Table 1) were prevalent. Only six patients with HIV/AIDS coinfection (4.3%) were detected. The use of immunosuppressive drugs was unusual (< 5%). The median prednisone equivalent dose was 10 mg/day (IQR 10 - 32.5 mg/day). Nine patients had a history of previous TB, 2 of them with therapy abandonment or no treatment. When inquired, exposure to a pulmonary smear-positive patient was frequently positive (21 out of 33), but the global rate was low (Table 1). Of the series, 21 events were diagnosed before admittance (14.8%) and the rest at admission or during hospitalization (n = 121; 85.2%). Events diagnosed after admission represented 32.5% of all TB cases diagnosed in our Region. Reasons for hospitalization in the preadmission diagnosis group included treatment monitoring (n = 7, 33.3%), adverse drug reactions (ADR; n = 5, 23.8%), urinary or intestinal complication or wasting syndrome (n = 6; 28.6%), and prostration, depression or immune reconstitution syndrome (n = 3; 14.3%).

Trends in hospitalizations by risk groups

During the study period, a significant incremental trend was observed for events associated with diabetes mellitus (Spearman +0.72; $p < 0.05$) but not for other risk groups.

TB by localization and SOD

The most frequent location was lung (71.1%), followed by pleural (n = 9; 6.3%), lymph node (n = 4; 2.8%), urogenital (n = 4; 2.8%), vertebral (n = 1; 1.4%), and disseminated forms (n = 23; 16.2%), the latter usually combined with pulmonary TB (91.3%). Pulmonary involvement alone or in combination was present in 122 cases (85.9%). The median SOD was nine weeks.

Pulmonary TB

The series includes 101 events of pulmonary TB without extrapulmonary involvement. In addition to the expected high frequency of cough, expectoration, fever, weight loss, and diaphoresis, a high prevalence of malnutrition and abnormal chest physical findings were prominent in this group. However, hemoptysis was uncommon (Table 2). The median time from SOD was nine weeks for 93 events with available data (IQR 3.9 to 13.7 weeks). For 84 events where the diagnosis was made at or after admission, the median duration from hospitalization to diagnosis was four days (IQR 1-10 days). Image analysis of those with pulmonary TB (isolated or disseminated) indicated a high frequency of bilateral involvement, especially of the upper lobes (75.8%; Table 2). Also, 42.5% had cavitations, and one-third had upper residual lesions. Pleural effusion was present in around 20%, and some presented pneumothorax. Similar results were observed in those with tomographic studies (Table 2) with the addition of bronchiectasis (in 47%) and nodules (27.3%) (Table 2). The overall sensitivity of smear microscopy in sputum samples in events of culture-proven pulmonary TB (isolated or disseminated) was 78.8%, with a lower sensitivity for bronchoalveolar lavage (BAL, 58.3%) (Table 3). Molecular methods were only occasionally applied (< 10% of samples) with a high sensitivity (100%) in the case of sputum samples for either of the two brands applied. The use of molecular tests increased during the study period with an expansion since the introduction during the year 2016 of the Xpert MTB/RIF provided by the Ministry of Health. PCR positivity reached 33% (6 out of 18) in cases with negative sputum staining.

Extrapulmonary and disseminated TB

Extrapulmonary and disseminated forms comprised 41 events (28.9%). An isolated pleural form was observed in 9 events, allowing an exploration of its clinical profile (Table 4). As expected, pleuritic pain (66.7%) and signs of pleural effusion were relevant (100%). Other common symptoms of pulmonary TB were also present, except hemoptysis. Pleural TB events did not present pulmonary consolidation or cavitations and had less frequency of pulmonary infiltrates than pulmonary TB (Table 4; $p < 0.01$). The rate of residual apical lesions was similar. The study of the pleural liquid was developed in a few events, observing elevated ADA, proteins, and % of mononuclear cell values (Table 4).

The median duration of symptoms until admission was 5.9 weeks (IQR 3-15.9 weeks), and

Table 5. Description of variables associated with the treatment of tuberculosis events in different forms, Hospital Base de Valdivia, 2011-2019

Parameter	n (%)
Treated cases	136 (95.8%)
Pyridoxine use	4 (3.4%)
Corticosteroids	32 (25%)
Adjuntive therapy for TB	16 (11.7%)
Other reason	18 (12.7%)
Dose adjustment	30 (22.1%)
Low weight	19
Adverse drug reaction	2
Renal failure	3
Combined reasons	6
Treatment interruption	15 (11%)
Due to adverse drug reaction	13
Due to medical complications	2
Evolution	
Improvement	108 (76.1%)
No change	11 (7.7%)
Worsening	23 (16.2%)
Transfer to another center	43 (30.3%)
Deceased	27 (19%)
In-hospital	21 (14.8%)
During treatment after discharge	6 (4.2%)
Cause of death	
Attributable to TB	15
TB associated	7
Not related	2
Incomplete data	3
Readmissions	27 (19%)
Adverse drug reaction	4
TB related complications	14
To secure treatment	5
Not TB related	4

from admission to diagnosis, ten days (IQR 5.5-55 days). Other four events of pleural TB were identified as associated with pulmonary or spinal TB. In global terms, the diagnostic performance of smear microscopy was low (< 10%), but that of culture reached 72%. All three events studied with PCR were positive.

Lymph node TB

Seven events with lymph node TB were identified, four isolated and 3 associated with pulmonary (n = 2) or vertebral (n = 1) TB. Patients presented mainly with fever and enlarged inflammatory cervical, supraclavicular, or axillary lymph nodes without fistula. All cases underwent biopsy.

The culture was positive in 75% when requested, and the histological analysis revealed granulomas in all except 2 events. Positive smear microscopy of fixed tissues was infrequent (2 out of 7, 28%). Median time from SOD was 8.5 weeks (IQR 3.4 to 23 weeks) for events without TB elsewhere.

Urogenital TB

Four events of renal-ureteral and one event of testicular TB were detected. Patients presented different urinary symptoms, such as nycturia, persistent polyaquiuria, or macroscopic hematuria. Median time from SOD was prolonged (53.9 weeks; IQR 36.5-53.9). Four events were confirmed by smear microscopy with positive urine cultures and one by PCR of a bladder biopsy. Two of the patients ultimately required nephrectomy. Renal images revealed hydroureteronephrosis, ureteral stenosis, or ureteral wall thickening and calcifications.

Gastrointestinal TB

Four events with digestive tract TB were detected, all of them associated with pulmonary TB: one with esophageal stenosis and the rest with ileocecal involvement. Two of the latter evolved with ileal perforation after two months, and the remaining case with ileal bleeding two weeks after starting treatment. The event with esophageal TB presented logical dysphagia and concurrent pulmonary TB. CT imaging studies indicated esophagic stenosis with fusiform dilation and ileum involvement in 2 of the three ileocecal events.

Spinal TB

Six events of spinal TB are included, and most occurred in combination with another focus (5/6; 83.3%), mainly with pulmonary TB. Culture, PCR, or association with another proven focus confirmed these events . Images showed spondylodiscitis or collections in all of them.

Miliary TB

These events (not associated with immunosuppression) were identified by chest CT (4.2% of the whole group), and all had pulmonary TB documented by sputum or BAL culture. In two, there was also vertebral involvement.

Immunosuppressed patients

Twelve events were associated with concurrent immunosuppressive conditions (8.5%). Half of them occurred in patients with HIV/AIDS, and all had CD4 lymphocyte counts < 200/μL (median count 40/μL; IQR 20.8-112 μL). Other cases were associated with patients treated with corticosteroids (n = 5, daily prednisone dose 10-40 mg) with or without another associated drug and one case after fludarabine in a patient with leukemia. An *M. bovis* lung infection linked to raw milk consumption in a corticosteroid-treated patient was identified. Of interest, two events of TB in patients with HIV/AIDS occurred in the context of immune reconstitution (one with febrile reactivation and increased pulmonary infiltrates three months after the start of TB treatment, and the other as a *de novo* lymph node TB 10 days after starting antiretroviral therapy).

Treatment and outcome

A total of 136 of the 142 events were treated (95.8%), and the remaining 6 (4.2%) were not due to a postmortem diagnosis (n = 5; 3.5% of the total group) or transfer to another center (n = 1). In 20 events (14.1%), treatment was initiated before diagnosis confirmation on an empirical basis with a median of -5 days (IQR -16 to -1.5 days). Treatment was initiated after diagnosis in the remaining 116 events (median 0 days; IQR 0-1 day). Analyzing some parameters associated with treatment, frequent dose adjustments and interruptions were revealed (Table 5). The prescription of pyridoxine to prevent peripheral neuropathy was unusual. In addition, 19% suffer readmissions after discharge, either by complications, ADR, or to ensure treatment. Lethality reached 19% of the series, most attributable to or associated with TB. Finally, 30% were transferred to another center within the regional hospital network to complete their treatment.

Corticosteroids use

A total of 32 events (22.5%) received corticosteroids during tuberculosis treatment, either as part of TB treatment (n = 14; 9.9%) or for another concurrent condition (n = 18; 12.7%). Extensive pulmonary involvement and miliary TB led causes associated with TB (n = 5 each one). Corticosteroids were also used for concurrent complications

such as shock or ARDS (n = 5 for each one) or other conditions such as autoimmune diseases (n = 5) or others (n = 3).

ADRs

These complications were detected in 40 treated events (29.4%), and they presented mainly as digestive intolerance (n = 17, 12%), liver compromise (n = 16, 11.3%), or skin allergy (n = 11, 8.1%). Most cases of liver ADRs (13 out of 16) required a temporary suspension of treatment by a median of 11 days (IQR 9 to 16.8 days) but with good tolerance after restarting the same or an adapted treatment (in 12 out of 13 events).

Surgical procedures

A total of 30 events (21.1%) required some kind of surgical procedure, including pleuro-pulmonary, osteoarticular, urogenital, intestinal, or ganglion procedures.

Other therapeutics issues

Nutritional supportive therapy was applied as enteral (32.4%) or parenteral nutrition (3.5%). Four out of 16 events with hemoptysis received codeine (25%), and different sedative drugs were indicated in 15 events with withdrawal syndrome (10% of the series). Liver failure required active management with albumin and diuretics in 8 out of 15 patients with chronic liver damage (53%).

Follow-up and final condition. Patients were classified as cured or treatment completed in 71.1% of events (n = 101). In 27 cases, patients died (19% of the events, most of them attributable or associated with TB; Table 5), and in 13 events, patients were transferred to other Regions without follow-up information (9.2%). One patient abandoned therapy (0.7%).

Factors associated with hospital mortality or during treatment. Of the different factors potentially associated with a fatal outcome by

Table 6. Factors associated with a fatal outcome in admissions by TB, Hospital Base de Valdivia, 2011-2019. Chile

Factor	Deceased n/N*	Non deceased n/N*	Odds Ratio	IC95	p value
Univariate analysis					
No income or minimal wage	27/27	90/115	15.5	0.91-262	0.004**
Hematological neoplasm	2/27	0/112	22.06	1.03-463	0.037**
Undernourished	19/26	56/114	2.8	1.09-7.20	0.031
Weigh < 45Kg	7/12	13/93	8.61	2.37-31.2	0.001
Pleuritic pain	1/27	24/114	0.14	0.19-1.11	0.046
Pneumothorax	4/27	4/109	4.56	1.06-19.6	0.049
TB-related corticosteroids use	6/23	8/114	4.67	1.44-15.15	0.014
Non-TB related corticosteroids use	8/27	10/115	4.42	1.54-12.6	0.007
O2 therapy	20/27	39/115	5.56	2.16-14.3	< 0.001
Mechanical ventilation	13/27	7/115	14.3	4.9-41.9	< 0.001
Shock	15/27	2/114	70.0	14.2-343	< 0.001
Anemia < 12.5 g/dL	22/27	68/114	2.97	1.05-8.4	0.044
Lymphopenia < 1000/μL	17/25	39/111	3.92	1.55-9.9	0.003
Thrombocytopenia	9/27	8/113	6.56	2.23-19.2	0.001
Hyperbilirubinemia	10/24	13/95	4.50	1.65-12.2	0.007
Multivariate analysis			ORa		
Shock			115	13.5-1411	< 0.001

*: Incomplete information for some variables;**:0.5 was added to each cell to calculate OR.

univariate analysis, only the presence of shock was independently associated with a fatal outcome by multivariate analysis (ORa 115; IC95 13.5-1411, $p < 0.001$; Table 6).

Discussion

The results of this study are worrying because they reveal that TB continues to be a persistent cause of hospitalization in our Region, that the diagnosis takes several weeks to be made, and that a high percentage of events are diagnosed in the reference hospital and not in primary care with high associated mortality and even postmortem diagnoses. In addition, a low and slow incorporation of PCR techniques is observed for the rapid diagnosis of this disease. The highly concentrated diagnosis in hospitals or emergency rooms was already observed in an evaluation carried out by PAHO in 2012[4] and indicates two fundamental problems: low diagnostic suspicion and difficult access to rapid molecular diagnosis in outpatient settings. Since the revised 2021 Chilean TB guideline, universal molecular diagnosis by PCR is contemplated for all suspected cases. The classical clinical and imaging profile (upper lung compromise and/or cavitations) of our cases associated with the predominance of pulmonary involvement (isolated or combined) should ease diagnostic suspicion at primary care at earlier stages.

We also observed a highly complex scenario in hospitalized patients with almost all risk groups present and with multiple therapeutic needs that included intensive management requirements, high rate of corticosteroid use, dose adjustment requirements, surgical procedures, nutritional supportive care, liver failure or withdrawal syndrome management, development of different ADR with associated therapy interruptions, and readmissions.

Other relevant findings in this study were the high rate of AFB-positive smears in cases of pulmonary and urogenital TB (nearly 80%, in both cases, probably due to late suspicion). In contrast, the sensitivity in cases of lymph node (28%) or pleural TB (< 10%) was low. Culture, molecular, biochemical, and histological information have proven helpful for these forms. This discloses that there is no universal diagnostic strategy and that confirmation of TB must be explored in multiple ways, especially in extrapulmonary forms. Unfortunately, LBA PCR sensitivity was limited in our study (57-80%, according to the brand used), hindering an early diagnosis for those cases where sputum samples were not available. Systematic reviews have informed a pooled sensitivity of 87% for PCR, higher than our results[5].

Events in immunosuppressed patients were not only linked to HIV/AIDS but also to corticosteroids and fludarabine. A high risk has been described for fludarabine in oncohaematological and rheumatologic patients with steroids[6,7]. The limited presence of patients with HIV/AIDS in our series may be secondary to their incorporation into screening programs and treatment of latent infection. On the other hand, corticosteroids can be used therapeutically in TB patients to decrease mortality in cases of meningitis and to decrease morbidity in cases of pleural or peritoneal TB and perhaps in extensive pulmonary or miliary tuberculosis[8-10]. These compounds may also be indicated for underlying autoimmune diseases, adrenal insufficiency, immune reconstitution syndrome, and in selected patients with shock[11,12]. Its use in ARDS is controversial[13].

ADR were frequent in our work, diverse, and in the case of hepatic reactions, they provoked treatment interruptions and sometimes replacement of the original regimen. In Chile, a block suspension of all anti-tuberculous drugs is applied as a norm until liver tests are normalized; then, a sequential reincorporation in staggered doses is attempted, withdrawing the suspicious drug if required. This strategy allows good tolerance in most patients[14].

In univariate analysis, several factors appeared associated with a fatal outcome, but after multivariate analysis, only shock was independently associated with death, in accordance with other reports[15-17].

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