

Tuberculous Meningitis: Impact of Timing of Treatment Initiation on Mortality

Jaime Soria,^{1,5} Alfredo Chiappe,^{2,5} Jorge Gallardo,² Joseph R. Zunt,³ and Andres G. Lescano⁴

¹Division of Infectious Diseases, University of Kentucky, Lexington, Kentucky, USA, ²Department of Infectious Diseases, Hospital Nacional Dos de Mayo, Lima, Peru, ³Departments of Neurology, Global Health, Medicine (Infectious Diseases), and Epidemiology, University of Washington, Seattle, Washington, USA, ⁴Emerge, Emerging Diseases and Climate Change Research Unit, School of Public Health and Administration, Universidad Peruana Cayetano Heredia, Lima, Peru, and ⁵Northern Pacific Global Health Research Fellows Training Consortium, University of Washington, Seattle, Washington, USA

We conducted a retrospective cross-sectional study of adult hospitalized patients with confirmed tuberculous meningitis to determine the impact of the timing of treatment initiation on mortality. The mortality of tuberculous meningitis patients was high and was associated with delay in initiation of treatment, older age, HIV infection, and higher disease severity at admission.

Keywords. meningitis; tuberculosis; mortality.

Mycobacterium tuberculosis (MTB) caused ~1.2 million deaths in 2019 [1]. Peru is one of the countries with the highest prevalence of tuberculosis globally, where nearly 60% of tuberculosis infections are concentrated in Lima, mainly in the metropolitan area. In 2018, Peru reported 31 668 new cases of tuberculosis [2]. About 2% of people with tuberculosis (TB) infection in Peru had tuberculosis of the central nervous system (CNS), most often manifested as meningitis or tuberculoma [3].

Tuberculous meningitis is the clinical form of tuberculosis with the highest mortality, around 50% in studies published worldwide [4]. The clinical spectrum of tuberculous meningitis is quite broad, ranging from chronic headache or subtle psychiatric changes to sudden severe meningitis that progresses to coma. Unlike other forms of tuberculosis, the involvement of the CNS is considered a medical emergency. Severe inflammation, including vasculitis within the CNS, can be rapidly progressive and generate severe and irreversible sequelae in a matter of hours or days [5].

The diagnosis of tuberculous meningitis is notably difficult due to its frequent insidious onset, nonspecific manifestations, and the difficulty of detecting MTB in cerebrospinal fluid (CSF). Thus, diagnosis and initiation of treatment are often based on clinical suspicion [6].

Multiple factors associated with the increased mortality of tuberculous meningitis have been described, including isolation of MTB in the CNS, worse severity of symptoms on admission, co-occurrence of a cerebrovascular accident, seizures, involvement of cranial nerves, older age, alteration in mental status, delayed initiation of treatment, interruption of treatment, and HIV co-infection [7–9].

A delay in the diagnosis and treatment of CNS infections is usually associated with worse prognosis and higher mortality [10]. This also applies to tuberculous meningitis, but the impact of the delay before the start of tuberculosis treatment leading to increased mortality is not well understood, with prior reports including unconfirmed cases or variable case definitions.

The objective of this study was to determine the impact of the timing of initiation of treatment on the mortality of patients with tuberculous meningitis.

METHODS

We conducted a retrospective cohort study of adult patients with confirmed diagnosis of tuberculous meningitis admitted to the “Dos de Mayo” public hospital (HNDM; acronym in Spanish), a tertiary care facility in Peru. Patients were identified through review of hospitalization records from 2006 to 2015. Patients were excluded if records were incomplete or they had a diagnosis other than tuberculous meningitis. Only confirmed cases of tuberculous meningitis were considered in the final analysis.

CSF cytochemistry analyses were conducted at the HNDM laboratory. Confirmed tuberculous meningitis was defined as clinical evidence of meningitis with MTB detection in CSF via acid-fast bacillus (AFB) smear, CSF culture, or commercial nucleic acid amplification test. Detection of MTB in CSF was performed using the Ziehl-Neelsen stain following the technical standards of the Peruvian National Institute of Health (PNIH). CSF culture was performed using a modified Ogawa medium. Drug susceptibility tests for *M. tuberculosis*, including to second-line drugs, were carried out in the mycobacterial national reference laboratory of the PNIH.

Severity of disease at admission was classified according to the British Medical Research Council (BMRC). Delay in treatment initiation was defined as proposed by Sheu et al. [9]: time elapsed from day of admission to day of treatment initiation above the median time of all cases.

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Correspondence: Jaime Soria, MD, 740 S Limestone—L241, Lexington, KY 40536 (jaime.soria@uky.edu).

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Mortality analysis used a Poisson family generalized linear model (GLM) to identify factors associated with in-hospital mortality. Relative risk (RR) was reported. Statistical analyses were performed with Stata, version 12.0 (College Station, TX, USA), and statistical significance was determined at the $P < .05$ level.

Patient Consent

The study was approved by the Ethics Committee of the Universidad Peruana Cayetano Heredia. Due to the retrospective study design, the requirement for signed patient consent was waived.

RESULTS

A total of 263 adult patients with confirmed or probable diagnosis of tuberculous meningitis were identified; 68 had microbiologically confirmed tuberculosis and were included in the analysis.

Most patients with confirmed tuberculous meningitis were male (76.5%), with a median age (range) of 35 (18–72) years. A third of the patients had a history of tuberculosis infection.

At admission, the most common symptoms were headache (87.5%), fever (78.1%), and altered level of consciousness (73.9%). The symptoms were present from a few days to months; 51 (75.0%) reported symptoms for >7 days before hospitalization (Table 1).

Twenty-eight (41.2%) patients also had a diagnosis of HIV infection; 11 were diagnosed during hospitalization and had not known their HIV status before admission. Six patients reported taking antiretroviral therapy, but all had a detectable viral load (56 087–284 153 copies/ mL) at the time of tuberculous meningitis diagnosis.

The diagnosis was confirmed in 65 (95.6%) patients via a positive CSF culture, and 3 (4.4%) had a positive CSF PCR test for MTB. Only 3/65 (4.6%) patients had a positive CSF AFB smear. Additionally, 36 patients had a positive culture for MTB in biological samples outside the CNS. Evidence of drug susceptibility was obtained in 28 culture samples; half [14] were resistant to at least 1 drug (mainly isoniazid or rifampicin), and 5/14 (35.7%) were resistant to both isoniazid and rifampicin. Resistance was associated with a slight increase in mortality, although without statistical significance (RR, 1.15; 95% CI, 0.50–2.63).

Table 1. Demographic and Clinical Characteristics by Outcome

	Total (n = 68)	Survived (n = 34)	Died (n = 34)	P
Age, y ^a	35 (18–72)	33 (18–72)	38 (18–71)	.26
Male	52 (76.5)	26 (76.5)	26 (76.5)	1.00
HIV infection	28 (41.2)	12 (35.3)	16 (47.1)	.46
CD4 <200	14/18 (77.8)	5/7 (71.4)	9/11 (81.8)	1.00
TB history	22 (32.3)	9 (26.5)	13 (38.2)	.44
MDR-TB history	5 (7.35)	1 (2.94)	4 (11.8)	.35
TB contact	21 (30.8)	10 (29.4)	11 (32.4)	1.00
Alcoholism/drug addiction	15 (22.1)	8 (23.5)	7 (20.6)	1.00
Symptoms >7 d	51 (75.0)	25 (73.5)	26 (76.5)	1.00
Weight loss	34 (50.0)	15 (46.9)	19 (59.4)	.45
Headache	56 (87.5)	30 (93.8)	26 (81.3)	.25
Fever	50 (78.1)	24 (75.0)	26 (81.3)	.76
Altered level of consciousness	48 (73.9)	22 (68.8)	26 (78.8)	.41
Focal neurologic deficits	27 (42.2)	9 (29.0)	18 (54.6)	.05
BMRC stage				.04
I	25 (36.8)	15 (44.1)	10 (29.4)	
II	28 (41.2)	16 (47.1)	12 (35.3)	
III	15 (22.1)	3 (8.8)	12 (35.2)	
WBC >10 000 cells/uL	22/67 (32.8)	10/33 (30.3)	12/34 (35.3)	.79
Hyponatremia	54/59 (91.5)	29/30 (96.7)	25/29 (86.1)	.19
CSF analyses				
Protein	368 ± 738.5	453 ± 1002.5	272 ± 149.1	.33
Glucose	30.0 ± 14.6	31.2 ± 15.9	28.8 ± 13.4	.49
Hypoglycorrhachia	62/62 (100.0)	31/31 (100)	31/31 (100)	1.00
Leucocytes	224 ± 360.2	285 ± 437	164 ± 254	.16
Mononuclear cells, %	81.1 ± 25.6	82.1 ± 26.0	80.0 ± 25.5	.73
ADA	16.6 ± 13.5	15.3 ± 9.7	17.8 ± 16.5	.47
ADA >9 UI	41/59 (69.5)	20 (69.0)	21 (70.0)	1.00

Data are presented as No. (%), median (range), or median ± SD.

Abbreviations: ADA, adenosine deaminase; BMRC, British Medical Research Council; CSF, cerebrospinal fluid; MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis; WBC, white blood cell count.

Initial treatment for 57 (83.8%) patients included a standard combination of 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol). Eight (11.8%) patients received second-line drug treatment due to suspected resistance. Three patients (4.4%) did not receive antituberculous treatment; 2 of these died during hospitalization. Additionally, 58 (87.8%) received steroids, mainly dexamethasone.

The median time from admission to initiation of treatment (range) was 3 (0–19) days. Among cases with a delay in treatment initiation, an alternate bacterial etiology was initially suspected in 13/28 (46.4%), and they received antibiotic treatment without activity against MTB. However, due to a worsening clinical picture or new laboratory results, diagnosis of tuberculous meningitis was reconsidered, and antituberculous treatment initiated. An average of 2.1 additional days of delay in treatment initiation occurred due to administrative issues, including medication unavailability. The median time to treatment initiation in patients with BMRC grade III (stupor or coma, abnormal movements, or severe focal neurologic deficit) was 3 days. Patients with BMRC grade I had a slightly longer delay (median, 3.5 days), which was not statistically significant.

Half of the patients (34) died during hospitalization. The median time to initiation of treatment among those who survived was 2 days, compared with 5.5 days among the deceased ($P = .03$). In multiple regression analysis, treatment initiation after the third day was significantly associated with higher mortality (RR, 1.7; 95% CI, 1.09–2.67) even after adjusting for age, sex, HIV co-infection, and severity of tuberculous meningitis (Table 2).

DISCUSSION

Tuberculous meningitis was associated with high mortality (50.0%), similar to previous reports [4]. Delay of treatment initiation >3 days after admission was associated with a 70% increase in mortality. Factors contributing to delayed treatment

initiation included delays in diagnosis and unavailability of medications. We observed delays in performing the CSF studies for diagnostic purposes, mainly due to administrative issues or inability of the patient to cover costs.

Prior studies evaluating the relationship between delayed initiation of treatment and mortality reported that starting treatment >5 days after admission was associated with a worse prognosis, defined as death or severe disability ($P = .037$) [9]. Gu et al. reported that patients with the worst prognosis initiated treatment for tuberculous meningitis 15.9 days after onset of symptoms, compared with 12.6 days for those with the best prognosis; however, this association was not significant ($P = .176$) [7]. Hosoglu et al. reported that initiation of tuberculosis treatment >3 weeks after onset of symptoms was significantly associated with increased mortality; this analysis included cases with interrupted treatment [8]. Likewise, Verdon et al. reported that initiating treatment 3 days after admission to an intensive care unit was strongly associated with higher mortality ($P = .003$) [11].

To decrease time from hospitalization to treatment initiation, hospitals with limited resources to perform molecular diagnostic assays for tuberculous meningitis could consider including routine CSF examination findings, such as elevated cell count between 0 and 1500/mm³, high concentration of proteins, and low glucose concentration [6]. Although detection of acid-fast bacilli on CSF smear has a low sensitivity (10%–20%), the sensitivity can be increased by performing repeated studies or increasing the volume of CSF obtained during the lumbar puncture [12]. The amount of mycobacteria in the CSF may be higher in those patients with laboratory confirmation of tuberculous meningitis and could also be related to increased mortality [13]. Molecular tests such as nucleic acid amplification have a higher sensitivity [14] but are often unavailable in places with limited resources. In such settings, clinical suspicion typically guides initiation of treatment.

Table 2. Risk Factors Associated With Death During Hospitalization

	Bivariate Analysis		Multiple Regression Analysis		
	RR	<i>P</i>	RR	95% CI	<i>P</i>
Male	1.00	1.00	0.89	0.55–1.46	.65
Age >40 y	1.85	.01	1.62	1.01–2.58	.04
HIV infection	1.26	.32	1.67	1.05–2.64	.03
History of tuberculosis	1.29	.29			
Alcoholism/drug addiction	0.91	.78			
Glasgow <14	1.71	.01			
Focal neurologic deficits	1.64	.04			
BMRC II	1.07	.84	0.91	0.50–1.63	.76
BMRC III	2.00	.01	2.00	1.19–3.37	.01
ADA >9 UI/L	1.01	.36			
MDR-TB	1.15	.74			
Tuberculosis outside CNS	1.31	.40			
Initiation of treatment after third day	1.70	.03	1.65	1.06–2.58	.03

Abbreviations: ADA, adenosine deaminase; BMRC, British Medical Research Council; CNS, central nervous system; MDR-TB, multidrug-resistant tuberculosis.

Two caveats of this study were that many of the antibiotic resistance patterns were not available during hospitalization and that information regarding long-term outcomes following discharge was unavailable, as patients continued their treatment in health care centers in their jurisdictions. Consequently, the conclusions of this study were limited to in-hospital mortality, and we were unable to evaluate if higher levels of resistance were associated with increased mortality. Despite the limited number of patients enrolled in the study, one strength is that all patients had a laboratory-confirmed diagnosis, which limits ascertainment bias in the analysis and conclusions of the study.

We have shown that delayed initiation of treatment was associated with increased mortality. Mortality due to tuberculous meningitis was high and was associated with older age, HIV co-infection, and worse disease severity at the time of admission. The management of tuberculous meningitis requires an early diagnosis, using a combination of clinical and laboratory criteria that allow the timely recognition and treatment of patients with a high probability of tuberculous meningitis.

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