

Predicting Non-Completion of Treatment for Latent Tuberculous Infection

A Prospective Survey

Fred K. Shieh, Graham Snyder, C. Robert Horsburgh, John Bernardo, Claire Murphy, and Jussi J. Saukkonen

Pulmonary Center, Boston University School of Medicine; and Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts

Treatment of latent tuberculosis (TB) infection (LTBI) is essential for the elimination of TB in the United States, but treatment is often not completed. Little is known about patients' reasons for not completing treatment. We hypothesized that certain health beliefs, lifestyle, and clinic- and regimen-related barriers to provision of care could predict non-completion of LTBI treatment.

Methods: We administered a survey in English, Chinese, or Spanish to patients with LTBI at the first TB clinic visit. Using χ^2 and logistic regression analysis, we assessed demographics, TB risk factors, and survey responses as predictors of non-completion of 6 mo of isoniazid.

Results: 217 patients, 90% foreign-born, completed the survey, and 28.6% of which finished at least 6 mo of isoniazid under usual clinic conditions. Multivariate analysis identified two independent predictors of non-completion: low risk perception of progressing to active TB without LTBI treatment (odds ratio [OR], 0.31 [0.13–0.72], 95% confidence interval [CI]), $p = 0.007$, accounting for 20% of non-completers, and not wanting venipuncture (OR, 0.43 [0.22–0.85], 95% CI), $p = 0.015$, accounting for 37% of non-completers. Another 18% shared both predictors; thus these two predictors accounted for 75% of non-completers in total.

Conclusions: Patients assess LTBI treatment risks and inconveniences relative to low perceived benefits at treatment outset. Predictors of LTBI treatment non-completion are identifiable at the first visit. Targeting TB high-risk individuals, minimizing inconveniences, further education, and use of diagnostic tests with improved specificity for TB may address these concerns.

Keywords: isoniazid; latent tuberculosis infection; prospective survey

As the incidence of tuberculosis (TB) disease has decreased in the United States, the diagnosis and treatment of latent TB infection (LTBI) has assumed increasing importance. Standard LTBI treatment is daily isoniazid for 6 to, preferably, 9 mo, with completion rates often ranging from 20 to 60% for 6 mo of isoniazid (1, 2). Limited objective information is available regarding factors influencing adherence to LTBI treatment. We hypothesized that barriers to the provision of TB care, related to regimen or clinic, or in beliefs regarding tuberculosis or health and lifestyle in general, could be identified at the outset of treatment. We have presented preliminary findings from this study previously in the form of an abstract (3).

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Correspondence and requests for reprints should be addressed to Jussi J. Saukkonen, M.D., Pulmonary Center, 80 East Concord Street, R-304, Boston, MA 02118. E-mail: jsaukk@bu.edu

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METHODS

Human Studies Approval

The Institutional Review Board of Boston University Medical Campus approved this study and the surveys employed. Participation in the study was voluntary and not linked to treatment.

TB Clinic Usual Procedures

The study setting was a Boston, MA academic medical center's TB clinic. TB physicians and nurses provided TB screening, verbal and written patient education, including treatment risks and benefits (using interpreters as needed), and treatment of LTBI (1). Baseline serum transaminases were determined in all patients. An initial visit for usual medical care, including time in the clinic, Radiology, Pharmacy, and the Clinical Laboratory, typically lasted approximately 3 to 4 h. At follow-up visits with a nurse, patients were clinically assessed for toxicity and given a 1-mo medication refill, as well as additional education. These visits usually lasted between 30 and 60 min. Serum transaminases were monitored periodically in those at increased risk for isoniazid-induced hepatitis and in those over 35 yr of age. Patients referred from specific neighborhood health centers returned there to nurse-staffed TB follow-up clinics by pre-arrangement. While primary care physicians may have provided initial referrals, they were generally not involved in treatment of LTBI within this system.

Study Enrollment

Individuals 18 or more years of age prescribed at least 6 mo of daily isoniazid only for LTBI, and who spoke English, Spanish, or Chinese, were included in the study. Patients were excluded if they were prescribed medication other than isoniazid for treatment of LTBI, had treatment delayed, or were suspected to have or had TB disease. From July 14, 2002 to September 28, 2003, 217 subjects were voluntarily enrolled, with a refusal rate of eligible patients of approximately 30%.

Survey Administration

The survey was pilot-tested before the study, measured 4.0 on the Microsoft (Redmond, WA) Word Flesch-Kincaid English readability scale, which uses the formula $(0.39) (\text{total words}/\text{total sentences}) + 11.8 (\text{total syllables}/\text{total words}) - 15.59$ to yield a number corresponding to a United States educational grade level. The survey was also translated into Chinese and Spanish. During the enrollment period, eligible patients were approached after the initial TB clinic evaluation and patient education had been concluded. There was no time limit in which to complete the written survey, but typically respondents were finished within 10 min. Answers were kept confidential from clinic staff.

Data Analysis

We used χ^2 analysis to determine significance of variables relative to the primary study endpoint, completion of 6 mo of isoniazid within 9 mo, using the EpiInfo, July 2002 (CDC, Atlanta, GA) statistical program. For multivariate regression analysis, the adjusted relative risks of completion were estimated using a log-binomial model with the GENMOD procedure in SAS version 9.1 (Cary, NC).

RESULTS

Respondent Demographics and TB Risk Factors

Surveys were completed by a total of 217 individuals: 148 in English, 22 in Spanish, and 47 in Chinese. The respondents were

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF 217 SURVEY PARTICIPANTS

Demographic	Variable	Number	Percentage	Completed treatment (%)	
Sex	Male	96	44.2	30.1	
	Female	118	54.4	29.4	
	Unknown	3	1.4	0.0	
Age	< 35 yr	112	51.6	29.4	
	≥ 35 yr	100	46.0	31.3	
	Unknown	5	2.3	20.0	
Race	White	45	20.7	25.6	
	Black	75	34.6	28.8	
	Asia/Pacific Islander	67	30.9	35.0	
	Race not identified	30	13.8	23.3	
	Unknown	21	9.7	28.6	
Place of Birth	U.S.-born	21	9.7	28.6	
	Foreign-born	196	90.3	29.3	
	Asia/Pacific Islands	77	35.5	32.4	
	Latin/South America	70	32.3	29.6	
	Africa	35	16.1	36.4	
	Europe	9	4.2	16.7	
	Unknown	5	2.3	50.0	
	TB risk factor	Foreign-born, TB-endemic country	179	82.5	31.5
		Outside United States in past 5 yr, TB-endemic country	80	36.9	27.3
Contact of active TB case		11	5.1	33.3	
Recent converter		15	6.9	16.7	
Predisposing medical condition		8	3.7	16.7	
Resident, high risk setting		5	2.4	20.0	
New immigrant, A/B TB		13	6.0	46.2	
None recorded		20	9.2	27.8	

Definition of abbreviations: A/B TB = old/active TB; TB = tuberculosis.

90% foreign-born and included a substantial proportion of racial minorities (Table 1). There were more women among survey participants (54.4%, versus 44.2% men). A majority of participants were under the age of 35 (52%), with a median age of 34 yr. Participant demographics were similar to those of patients with LTBI who were offered treatment at this clinic (4). The most common TB risk factor was foreign-birth in a TB endemic country. Approximately one third of participants received their follow-up at neighborhood health centers.

Completion of LTBI Treatment

A total of 29.0% completed at least 6 mo of isoniazid, with 19.4% completing the full 9-mo course and 9.2% completing between 6 and 9 mo of treatment. Nearly two-thirds (65.9%) of the participants self-discontinued treatment either by declaration or by not returning to the clinic within 3 mo. Another 5.3% had treatment discontinued by a TB provider due to adverse events, including itching, rash, fatigue, malaise, headache, dizziness, nausea, abdominal discomfort, and diarrhea.

Predictors of LTBI Treatment Non-Completion

Demographic and TB risk factors did not predict failure to complete treatment of LTBI. The completion rates by survey language were not significantly different.

Regimen and Clinic-related Barriers to Care

Concern about venipuncture, which approximately half of respondents either did not want or were unsure if they wanted, was a significant predictor of treatment non-completion by univariate analysis (relative risk [RR], 0.63 [0.39–1], 95% confidence interval [CI], $p = 0.048$) and by multivariate analysis (odds ratio [OR], 0.43 [0.22–0.85], 95% CI, $p = 0.015$). This view alone accounted for 20% of non-completers and was a shared predictor among 18% of all non-completers (Table 2).

Health Beliefs

Univariate predictors of treatment non-completion included not having a primary care physician (RR, 0.48 [0.25–0.87], $p = 0.013$) and not valuing regular visits to a health care professional for health maintenance (RR, 0.27 [0.07–0.85], $p = 0.019$) (Table 3). Patients who perceived a low risk for developing active TB without LTBI treatment were significantly less likely to complete LTBI treatment (RR, 0.35 [0.18–0.67], $p = 0.001$). This was also true for those who completed only the English version of the survey (RR, 0.26 [0.10–0.62], 95% CI, $p = 0.001$). Multivariate analysis also identified low TB risk perception as a significant predictor of treatment non-completion (OR, 0.31 [0.13–0.72], 95% CI, $p = 0.007$). This view alone accounted for 37% of non-completers and was a shared predictor among 18% of all non-completers. The majority of respondents felt that they were not infected with TB, and believed that BCG vaccine would prevent the development of TB, but these views did not predict failure to complete treatment. Reluctance to have venipuncture, and perception of low TB risk, as both independent and shared predictors, accounted for 75% of non-completers.

DISCUSSION

From a broad array of patients' health-related concerns, we identified two predictors of non-completion of 6 mo of isoniazid for treatment of LTBI by multivariate analysis, which together accounted for 75% of non-completers. Patients who perceived a low risk of progressing from LTBI to TB disease were significantly less likely to complete 6 mo of isoniazid. Patients with LTBI may perceive the threat, or severity of illness, from TB disease as potentially high, but their risk of disease incidence as low (5). Low risk perception alone was a predictor of non-completion among 37% of non-completers. This view is likely related to the finding that only 25% of our survey participants (Table 3) unequivocally accepted the diagnosis of LTBI.

TABLE 2. REGIMEN- AND CLINIC-RELATED POTENTIAL BARRIERS TO TREATMENT OF LATENT TUBERCULOSIS INFECTION

Category	Survey Issues	Answer	Response (%)	Completion (%)	Barrier	RR	95% CI	p Value
Regimen	The number of clinic visits would be difficult for me.	Agree/Not sure	57.14	26.79	Yes	0.804	0.525–1.238	0.320
		Disagree	42.86	33.33	No			
	I am worried the TB medication may be bad for me.	Agree/Not sure	69.07	26.12	Yes	0.746	0.485–1.180	0.207
		Disagree	30.93	35.00	No			
	I would prefer to take 3 pills 2 times a week.	Agree/Not sure	64.71	26.45	Yes	0.759	0.493–1.192	0.228
		Disagree	35.29	34.85	No			
	I do not want my blood taken.	Agree/Not sure	50.26	21.88	Yes	0.63	0.394–0.997	0.048*
		Disagree	49.74	34.76	No			
	I would like to be paid to finish the TB medicine.	Agree/Not sure	45.86	25.30	Yes	0.827	0.512–1.319	0.429
		Disagree	54.14	30.61	No			
If the medicine were mailed to me I would take it.	Agree/Not sure	75.26	30.07	Yes	1.087	0.664–1.877	0.753	
	Disagree	24.74	27.66	No				
Clinic	The amount of time I spent at the clinic today was too long.	Agree/Not sure	65.00	26.15	Yes	0.763	0.500–1.186	0.227
		Disagree	35.00	34.29	No			
	I want to go to a TB clinic closer to home.	Agree/Not sure	74.50	28.19	Yes	0.799	0.522–1.277	0.339
		Disagree	25.50	35.29	No			
	I would prefer to go to an evening clinic.	Agree/Not sure	51.74	28.85	Yes	0.965	0.629–1.482	0.87
		Disagree	48.26	29.90	No			
	I am worried about time waiting for medicine at the pharmacy.	Agree/Not sure	67.51	28.57	Yes	0.871	0.569–1.370	0.543
		Disagree	34.49	32.81	No			
	The TB clinic staff listens to me and cares about my health.	Agree	88.27	29.48	No	1.032	0.511–1.829	0.925
		Not sure/Disagree	11.73	30.43	Yes			
Do you get other health care in this building or nearby?	Yes	40.51	29.11	No	1.036	0.673–1.622	0.874	
	No	59.49	30.17	Yes				

Definition of abbreviations: 95% CI = 95% confidence interval; RR = relative risk; TB = tuberculosis.

Non-acceptance of LTBI diagnosis may also reflect fear of therapeutic consequences: adverse effects, follow-up visits, hidden costs, or stigma (6–8). BCG vaccination, likely received by the majority of our foreign-born study population, is often thought to cause or confound a positive tuberculin skin test (TST) result (8, 9), although considerable epidemiologic evidence is available to enhance the interpretation of TST results in those vaccinated (1, 9–12). Furthermore, only 6.3% of survey participants categorically doubted the protective efficacy of BCG (Table 3), likely further contributing to the perception of low TB disease risk. Patients who perceive low risk of progressing to TB disease are likely to see little benefit in LTBI treatment.

The most significant patient concern associated with LTBI treatment was reluctance to have venipuncture, expressed by approximately half of the survey participants. This alone was a predictor of non-completion in 20% of non-completers. This view was expressed before actually having venipuncture, which was performed in the Clinical Laboratory at a separate location. Venipuncture seems to have been a greater issue for patients than concern about isoniazid toxicity, which, although held by the majority of survey participants, was not associated with failure to complete treatment (Table 3). Historically, a significant

proportion of our TB clinic patients have been considered at risk for isoniazid hepatotoxicity, leading to the transaminase-monitoring regime described. Current CDC/ATS recommendations suggest that clinical rather than biochemical monitoring may be employed in most patients without risk factors for hepatotoxicity undergoing LTBI treatment (1). This practice, rather than a wider-ranging biochemical monitoring policy, may enhance adherence to treatment of LTBI.

There were several potential limitations to our study. Other reasons for failure to complete may have emerged after treatment initiation and were not detected in this study. Among those who did not return for follow-up visits, there might have been some with adverse events associated with non-adherence to treatment of LTBI (8, 14, 15). The threshold for stopping isoniazid due to adverse events is likely to differ between providers and patients. Adverse events have been reported to occur in 14 to 18% (14, 16), but in our study were relatively infrequent and rarely treatment limiting. Patient education may have varied among multiple clinic providers. Three languages were used for the performance of this study, with small accrual in two of the three groups. A larger study may have permitted the identification of language group-specific risks for non-completion. While

TABLE 3. GENERAL AND TB HEALTH BELIEFS AND LIFESTYLE ISSUES AS POTENTIAL BARRIERS TO TREATMENT OF LATENT TUBERCULOSIS INFECTION

Category	Survey Issues	Answer	Response (%)	Completion (%)	Barrier	RR	95% CI	p Value
Health Beliefs and Lifestyle	It is OK to use street drugs.	Agree	10.26	25.00	Yes	0.825	0.329–1.625	0.624
		Not sure/ Disagree	89.74	30.29	No			
	Seeing a doctor or nurse regularly keeps me healthy.	Agree	88.61	32.40	No	0.268	0.073–0.846	0.019*
		Not sure/ Disagree	11.39	8.70	Yes			
	I take medicine when a doctor recommends it.	Agree	91.41	35.29	No	1.229	0.583–2.159	0.570
		Not sure/ Disagree	8.59	28.73	Yes			
	I would like to see a doctor about other health problems.	Agree/Not sure	86.87	30.81	No	0.781	0.430–1.594	0.487
		Disagree	13.13	26.92	Yes			
	I may lose money when I come to clinic.	Agree/Not sure	43.43	29.37	Yes	0.987	0.635–1.518	0.952
		Disagree	56.57	29.46	No			
	My boss or teacher may not let me come to the clinic.	Agree/Not sure	41.07	27.54	Yes	1.010	0.609–1.648	0.970
		Disagree	58.93	27.27	No			
Do you have a primary care physician?	Yes	72.22	34.27	No	0.478	0.249–0.867	0.013*	
	No	27.78	16.36	Yes				
Do you have children or others who need you at home?	Yes	52.79	28.85	Yes	0.958	0.623–1.477	0.846	
	No	47.21	30.11	No				
TB beliefs	I will take all the medication against TB I have been given.	Agree	88.61	30.73	No	0.708	0.306–1.427	0.375
		Not sure/ Disagree	11.39	21.74	Yes			
	I might get sick with TB if I do not take medicine.	Agree	69.19	37.23	No	0.352	0.177–0.665	0.001*
		Not sure/ Disagree	30.81	13.11	Yes			
	I am not infected with TB.	Agree/Not sure	74.24	28.57	Yes	0.971	0.608–1.625	0.909
		Disagree	25.76	29.41	No			
	More information about TB would help me take the TB medicine.	Agree/Not sure	85.57	30.72	Yes	1.434	0.739–3.110	0.318
		Disagree	14.43	21.43	No			
	A videotape about TB would help me understand treatment.	Agree/Not sure	82.11	30.13	Yes	1.280	0.708–2.524	0.442
		Disagree	17.89	23.53	No			
	The vaccine against TB will protect me from getting TB disease.	Agree/Not sure	93.68	29.78	Yes	1.787	0.641–6.458	0.332
		Disagree	6.32	16.67	No			
Did you receive the TB vaccine (also called the BCG vaccine)?	Yes	47.64	24.18	Yes	0.733	0.462–1.150	0.179	
	Don't know/No	52.36	33.00	No				

Definition of abbreviations: 95% CI = 95% confidence interval; RR = relative risk; TB = tuberculosis.

some studies have found demographic associations (8, 14) with failure to complete isoniazid LTBI treatment, we did not, and this appears to be an inconsistent finding (1).

We have shown that at the first clinic visit patients have specific views regarding the risks, inconveniences, and benefits of LTBI treatment, which are associated with treatment non-adherence. Further studies are needed to determine whether the identified predictors can be generalized, or if others emerge. The overall treatment completion rate was low in this study and was no better for the highest TB risk groups, although similar rates have been reported elsewhere (2, 8, 14, 17, 18). Efforts to treat LTBI

are more likely to succeed in patients who perceive a greater risk from TB than the risks and inconveniences of the treatment regimen, necessitating lucid LTBI patient education addressing these concerns. Our findings also reinforce current recommendations to target individuals at high risk of TB for testing and treatment (1). Improved diagnostic tests are now becoming available, which can more accurately draw a distinction between BCG-vaccinated individuals and TB-infected individuals, for example, such as assays of *in vitro* IFN- γ release in response to *Mycobacterium tuberculosis*-specific antigens (19). Such measures and eventually shorter treatment regimens will likely

improve LTBI treatment acceptance and adherence. Nevertheless, since many patients fail to return for even the first follow-up visit, it is critical to understand and address patient concerns and beliefs at the outset, even before the first brief TB clinic visit. It may be helpful to promulgate a message of greater benefit than risk in LTBI treatment to communities with high proportions of those at greatest risk from this disease and to their health providers.

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