Adherence to Latent Tuberculosis Infection Treatment in a Population with a High Number of Refugee Children

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ABSTRACT

BACKGROUND: Refugee populations in the US have a higher reported prevalence of latent tuberculosis infection (LTBI). The objective of this study was to assess adherence to LTBI treatment in refugee and non-refugee children living in Rhode Island.

METHODS: This was a retrospective review of LTBI patients seen in the Hasbro Pediatric Tuberculosis Clinic between August 2009 and September 2011.

RESULTS: Of 120 patients with LTBI, 93% were foreign-born and 30% were refugees. Overall, 94 children (78.3%) completed therapy. Higher rates of treatment completion were seen among patients who were female, referred within the same hospital system, used an interpreter, and did not report side effects. Refugees attended more scheduled visits compared to non-refugees (p=0.019).

CONCLUSIONS: Overall rates of completion of LTBI treatment were high in this population. Better adherence to clinic visits, likely due to the increased support and care coordination provided to the refugee children, improved treatment completion rates.

KEYWORDS: immigrant, refugee, TB prevention, adherence

BACKGROUND

According to the World Health Organization, tuberculosis (TB) is the number one infectious killer worldwide.[1] An estimated 1 million children became ill with TB in 2014, and 140,000 died from the disease.[1]

Individuals who have positive TB screening tests with no symptoms suggestive of TB disease or radiographic findings associated with active tuberculosis have latent tuberculosis infection (LTBI). Adults with LTBI have about a 10% risk of developing clinical TB disease over their lifetimes. Compared to adults, children with LTBI have more years at risk to develop TB disease. It has also been suggested that their immature immune system places young children at increased risk of developing of active disease if infected with TB.[2,3] For this reason, younger children with TB disease are also more likely to develop severe life threatening forms of TB.[4] Therefore, identifying and treating children with LTBI is a vital part of TB control and prevention.

In the US, foreign-born persons accounted for 66% of cases with TB disease in 2014.[2] Being born in a TB endemic country is a risk factor for TB infection in children.[5] Refugee populations, in particular, have a higher prevalence of LTBI and therefore are at higher risk of developing active TB disease if not identified and treated.[3] Screening and treatment of populations at highest risk of developing active TB disease is critical to TB control in a low-incidence country such as the US.

A 9-month course of Isoniazid (INH) is the gold standard of treatment for LTBI in children in the US.[6] Historically, levels of adherence to LTBI treatment in industrialized countries are low.[7]

There is a paucity of data regarding LTBI treatment adherence in populations in the US with a high number of refugee children. Successful outcomes in this high-risk population require adherence to, and completion of treatment. One recently published report estimated LTBI treatment completion rates among refugee children in the US in 2010 to be only 30%.[8]

The purpose of this study was to assess rates of adherence to LTBI treatment in children seen in the Hasbro Pediatric Tuberculosis Clinic, in which a third of the patients are referred by the Pediatric Refugee Health Program (PRHP).

METHODS

Study Site

In Rhode Island, LTBI treatment can be provided by the child's primary care physician, or children can be referred to the Pediatric Tuberculosis Clinic at Hasbro Children's Hospital (HCH), the only pediatric hospital in the state of Rhode Island. This study included patients who attend the Hasbro Pediatric Tuberculosis Clinic. This clinic performs evaluations and treatment for all pediatric patients referred with a positive TB screening test (TBST) – either tuberculin skin test (TST) or interferon-gamma release assay (IGRA).

The Pediatric TB Clinic and the PRHP are part of the same Pediatric Primary Care Clinic at HCH. The PRHP was founded in 2007 to improve access and better address the needs of pediatric refugee patients by providing a medical home. Initial comprehensive screening evaluation is performed within 30 days of arrival to the United States and

follows CDC screening guidelines for refugees.[9] Robust collaboration exists with the Dorcas International Institute of Rhode Island, which is the Voluntary Resettlement Agency (VOLAG). They notify PRHP of incoming pediatric refugees to arrange timely initial evaluation. All newly arrived Rhode Island pediatric refugee patients are evaluated at the PRHP. The clinic evaluates between 42-90 refugee children annually. Also available at the initial screening are pediatric dental residents who insure follow up dental care. A trauma-informed child psychologist also screens and provides mental health care in the same location. The nurse for the Pediatric TB Clinic is also the nurse for the PRHP, which provides continuity for refugee patients. Most importantly, the PRHP works very closely with medical interpreters, most of whom are former refugees who provide services as Community Health Workers (CHW). The refugee CHW provides culturally appropriate care coordination. The children continue their pediatric primary care at HCH Pediatric Primary Care clinic by the same provider who performed initial comprehensive intake evaluation, thus creating a seamless transition from initial screening to a primary care medical home.

Patients with positive TBSTs are referred to the Pediatric TB Clinic for evaluation from the Providence Health Centers, Rhode Island public or private school systems, the Rhode Island Department of Health, community pediatricians or from primary or specialty clinics within HCH. The Pediatric TB Clinic treats between 50-90 children with LTBI each year.

Clinic Procedures

Interpretation of a positive TBST is done based on epidemiological risk according to CDC guidelines.[6] During the period of study, children in Rhode Island were being screened almost exclusively with TSTs as IGRAs were not yet readily available. For patients who have a positive TBST, treatment is provided free to the patient by the Rhode Island Department of Health. After referral to the Pediatric TB Clinic, patients are initially evaluated by a pediatric infectious disease specialist. A follow-up visit is scheduled within a month, with a nurse who assesses the patient for any medication side effects, assesses medication adherence, and disburses refills of medication. Subsequent visits are scheduled every 2 months. Per protocol, patients are instructed to bring their pill bottles with them and pill counts are done at each follow-up visit as an assessment of adherence. During every patient visit, a member of the healthcare team spends 15-20 minutes assessing patient adherence and reinforcing good adherence. If a patient does not attend a scheduled visit, a phone call is made to the patient's residence. Therapy is certified as completed if the patient received 270 doses of INH within 12 months, as defined by the CDC treatment guidelines.[6] Therapy is restarted if ≥14 doses have been missed prior to the completion of at least 6 months of treatment

Data Collection

The study was approved by the Lifespan Institutional Review Board. Medical records of all patients seen in the Hasbro TB clinic between August 2009 and September 2011 were obtained and reviewed. Data collected included country of origin, refugee status, TB exposure history, prior positive TST, comorbidities, LTBI treatment and adherence (including appointments, doses dispensed, pill counts, and reported side effects).

Statistical analysis

Univariate and bivariate analyses using STATA 11 software (StataCorp, College Station, TX) were conducted to examine patient factors, as well as association of these factors among (1) patients who completed treatment and those who did not, and (2) refugee status. T-tests and $\chi 2$ – tests were used, where appropriate, to determine if differences were statistically significant.

RESULTS

One hundred and twenty patients were diagnosed with LTBI from August 2009 to September 2011 (**Table 1**). Fifty-one percent were male, and the median age at first appointment was 12 years (range 1–18 years). Thirty percent (36/120) were refugees, 63% (76/120) had a history of BCG vaccination, and only 6.7% (8/120) were born in the US.

Table 1. Characteristics of children treated for LTBI from 2009 to 2011.

	N=120
Male gender	61 (51%)
Median age at first clinic visit	12 years (range 1–18 years)
Birth region	
Africa	36 (30%)
Caribbean	26 (22%)
Asia	21 (18%)
S. America	20(17%)
US	8 (7%)
Europe	4 (3%)
Middle East	4 (3%)
NR[a]	1 (0.8%)
Refugee	36 (30%)
BCG vaccine	76 (63%)
HIV positive	1 (0.8%)

Footnote. a: NR, not recorded.

The most common reason for performing a TST was immigration from a TB endemic country (62.5%, 75/120). Forty percent (30/75) of these immigrants entered Rhode Island with refugee status and were referred to the Pediatric TB Clinic from the PRHP. Among the other non-refugee patients (immigrant and non-immigrant), six were referred from their primary care provider, 32 from St. Joseph Health Center (which is a non-profit that provides primary care services), 15 from the Providence Community Health Centers, 4 from other hospitals or clinics, 2 from other HCH clinics, and for the remainder no referral source was recorded.

Thirty-eight children had no reason recorded for placement

of the TST; 15 (40%) of these were foreign-born with a US arrival date less than 12 months before the first TB clinic appointment, 8 (15%) had a household contact with a positive TST, 3 (8%) had history of foreign travel, and 3 (8%) had a household contact with active TB. One patient who had HIV infection was screened as part of standard care.

Ninety-four patients (78.3%) completed INH therapy. Eighteen patients did not complete the treatment, and there was no record of either completion or non-completion for the remaining 8 patients. Higher rates of treatment completion were seen among female patients (95% CI 0.805, 0.972), patients referred internally from other HCH clinics (95% CI 0.799, 0.845), patients who used an interpreter (95% CI 0.781, 0.946), and those who did not report side effects (95% CI 0.781, 0.941) (**Table 2**).

Thirty-one refugees (91.2%) completed treatment compared to 83.3% of non-refugee children (p=0.28). Refugees attended more of their scheduled appointments (95.4%), compared with only 82.3% of clinic visits attended by non-refugee children (p=0.019) (**Table 3**). Slightly more non-refugees reported missed doses (86.7%) but the difference compared to refugees (83.3%) was not statistically significant (p=0.3).

Table 2. Factors associated with completion of LTBI therapy in children between 2009–2011.

	Completed Treatment[a]	95% CI
Gender		
male	79% (46/58)	(0.689, 0.897)
female	89% (48/54)	(0.805, 0.972)
Refugee		
yes	91.2% (31/36)	(0.816, 1.00)
no	83.3% (60/76)	(0.747, 0.919)
Referral source[b]		
outside Hasbro	73% (28/31)	(0.609, 1.00)
within Hasbro	90% (40/55)	(0.799, 0.845)
Interpreter use		
yes	86% (57/66)	(0.781, 0.946)
no	80% (37/46)	(0.710, 0.933)
BCG vaccination		
yes	81% (58/72)	(0.712, 0.889)
no	90% (36/40)	(0.849, 1.00)
Reported Side Effects		
yes	80% (32/40)	(0.676, 0.924)
no	86% (62/72)	(0.781, 0.941)

A total of 94 patients completed therapy, 18 did not complete, and there was no data available for 8 patients.
There was no recorded referral source for 26 patients.

Table 3. Comparison of adherence to LTBI therapy in refugee and non-refugee patients.

	Refugee (n=36)	Non-Refugee (n=76)	p-value
Patients who missed any doses	83.3%	86.7%	0.300
Percent of scheduled appointments attended	95.4%	82.3%	**0.019**

Boldface indicates statistical significance (p<0.05).

DISCUSSION

Adherence to LTBI treatment among patients in North America, the majority of whom were born in TB endemic countries, is sub-optimal.[7,10–12] LTBI treatment adherence rates of children in North America vary, from 28% to 92%.[13–16] In our retrospective review of 120 patients, the majority of whom were born in TB endemic regions, 78% (94/120) overall completed the recommended nine months of INH treatment, and 91% (31/36) of refugees.

The overall rate of completion of LTBI therapy in our clinic population was high. This is consistent with findings reported in the literature from other immigrant populations.[11,14] A study in Los Angeles found that foreign-born adolescents had higher completion rates than their US-born counterparts (82% vs. 71.8%), despite language and cultural barriers.[17] The authors suggested that the higher completion rate among foreign-born adolescents was attributable to greater respect for physician's authority, and likelihood to have known somebody who suffered morbidity or mortality from tuberculosis, which increased the foreign-born adolescents' perceived susceptibility to tuberculosis disease.

Sixty-three percent of the patients had a history of BCG vaccination, but it did not impact treatment completion rates (p=0.84). A study in San Diego reported that 14% of parents in that population attributed their child's positive TST to prior BCG vaccination, which was a barrier to accepting LTBI treatment.[18] Our study did not assess parental perceptions of their child's positive TST.

The refugee children had a completion rate of 91% which is higher than previously reported in a 2010 national review of LTBI treatment among US refugee children.[8] We also observed higher rates of treatment completion among females, those who used an interpreter, those who reported no side effects, and those referred internally within the same hospital system. Factors previously identified as contributing to non-adherence to LTBI treatment in children include: perceived toxicity/somatic complaints, long duration of therapy, failure to understand the importance of treatment, lack of transportation, financial constraints, and parental work conflicts with clinic appointment.[18–20] The overall high rate of completion of LTBI treatment observed in our clinic is likely attributable to employing enablers and incentives as means to overcome barriers and facilitate better adherence. The Pediatric TB Clinic offers free interpreter services.

During every patient visit, a member of the healthcare team spends 15-20 minutes assessing patient adherence and reinforcing good adherence. The Clinic is located along a major highway and patients are provided with free parking vouchers at every visit. Additionally, the hospital is also easily accessible by bus, has a designated bus stop, and patients are given free bus passes. All medications are provided free of charge to patients. Upon completion of therapy, a gift card of $25-$50 is awarded to the child's family. If a patient does not attend a scheduled visit, a phone call is made to the patient's residence.

Comparison of refugee and non-refugee patient adherence revealed that refugee patients were more likely to attend their scheduled appointments than non-refugee children. The most likely explanation for this finding is that the Pediatric TB Clinic works closely with the PRHP. The nurse in charge of scheduling the visits often makes an effort to schedule follow-up visits at the TB clinic at the same day and time that the patients have their regular primary care visits at HCH Primary Care. Most importantly the refugees work closely with the refugee CHW who provides additional social support and works closely with the medical team to ensure that patients are always able to attend their visits.

There were some limitations to this study. First, the sample size was small but as this is the sole pediatric TB clinic for the state of Rhode Island, we feel that our cohort accurately reflects the state's population. Rhode Island is unique for it small geographical size and sole health department for the entire state. It may be more challenging to achieve similar treatment completion rates in larger states where follow-up may be more complex. Second, although the indirect measure of adherence (pill counts) that we used can serve as a proxy for estimating drug ingestion, it has an inherent limitation—the actual ingestion of the dose cannot be proven. Finally, as this was a retrospective study, missing data due to incomplete documentation in medical records could not be recovered.

CONCLUSION

This study demonstrates that high LTBI treatment completion rates can be achieved in a population with a high number of refugees. Historically, inadequate attention and resources have been invested in diagnosis and treatment of LTBI in children despite being at high risk of developing active TB disease. The importance of supporting patients on LTBI treatment cannot be over-emphasized.

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