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Short communication

Latent tuberculosis infection in the outpatient general medicine clinic: Efficacy of a nurse-run electronic directly observed treatment program

Susan Levine *, David Fraulino, Philip Krupka, Sruti Velamakanni

University of Connecticut Health Center, 263 Farmington Ave, MC 8021, Farmington, CT 06030, USA

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ABSTRACT

Tuberculosis (TB) is a leading cause of infectious death worldwide, with nearly 2 billion currently infected globally. While the largest burden of active TB resides in low to middle-income countries, the US contributes to the global epidemic and can play a significant role in interrupting the spread of TB by recognizing and treating latent TB infection (LTBI). The vast majority of active TB in the US originates from the reactivation of LTBI.

This cross-sectional study examines the prevalence of LTBI in a general medicine practice and explores the efficacy of a primary care nurse-run electronic directly observed therapy (eDOT) treatment program. 1221 patients were screened for the presence of historical risk factors for LTBI. Of those screened, 192 were offered QuantiFERON-TB Gold Plus (QFT-Plus) testing and a CXR if indicated, resulting in 35 being offered treatment for LTBI. After an initial provider visit to decide on the treatment regimen, patients received weekly nurse calls to verify adherence, assess for side effects and answer additional patient questions. Provider follow-up appointments occurred at the midpoint and completion of treatment.

33 (94%) of patients with LTBI completed treatment. Patients found the nurse calls very helpful to reassure them about their treatment and to address treatment concerns.

Primary care providers are particularly well-positioned to identify and treat LTBI. Screening is simple and treatment is generally well tolerated. Utilization of a nurse-run eDOT) program can be quite helpful in facilitating adherence and treatment completion.

1. Introduction

Tuberculosis (TB) is a leading cause of infectious death worldwide. Nearly 2 billion are currently infected globally, with 9.9 million incident cases yearly, claiming 1.5 million lives (Furin, et al., 2019). The World Health Organization (WHO) has identified targets to reduce global TB deaths by 95% by 2035. Coordinated efforts focus on early detection, prevention, community engagement, and research (World Health Organization, The End TB Strategy, Published 2015).

While the largest burden of global TB resides in low to middle-income countries, the US contributes to the global TB epidemic and can play a significant role in interrupting the spread of TB by recognizing and treating latent TB infection (LTBI). LTBI is defined as infection with mycobacterium tuberculosis detected as a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) without evidence of active TB disease including symptoms, radiologic changes or microbiologic evidence of infection (Behr, et al., 2021).

It is estimated that 4% of the US population (13 million) have LTBI (Centers for Disease Control Latent Tuberculosis Infection: A Guide for Primary Health Care Providers, Published 2020). Identifying and treating LTBI in the US may significantly impact active TB disease rates given that over 85% of active TB in the US originates from reactivation of LTBI (LoBue and Mermin, 2017) with 71% of these cases occurring in non-US-born (Filardo et al., 2022). While previous screening has focused on new arrivals, in recent years more US TB disease diagnoses have occurred among foreign-born individuals greater than 10 years after arriving in the US (Tsang et al., 2017). The US Preventive Task Force (USPSTF) and Centers for Disease Control (CDC) recommend screening at-risk populations (US Preventive Services Task Force, 2023). At-risk populations include individuals born in or former residents of countries with increased TB prevalence, and persons who have lived in high-risk congregant settings or are immunosuppressed.

Treatment of LTBI has become more accepted and potentially more attractive to primary care providers in that newer regimens are shorter and well tolerated. The 2020 LTBI treatment guidelines include National Tuberculosis Controllers Association (NTCA) and Centers for Disease

* Corresponding author.
E-mail address: slevine@uchc.edu (S. Levine).

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Control (CDC) recommended treatment regimens and comprise 3 preferred and 2 alternative treatment regimens. Rifamycin-based regimens, including 3 months of once-weekly isoniazid (INH) plus rifapentine (RPT) (3HP), 4 months of daily rifampin (RIF) (4R) or 3 months of daily INH plus RIF (3HR) are preferred because of their efficacy, safety and higher completion rates. Regimens of 6 or 9 mo of daily INH (6H) or (9H) are alternative regimens. Although efficacious they have higher toxicity and lower completion rates (Sterling, et al., 2020).

Although screening guidelines for identifying patients at risk of having LTBI exist, they are not consistently followed. The primary purpose of this study was to evaluate the efficacy of a general medicine nurse-run LTBI electronic directly observed therapy (eDOT) program. A secondary outcome was to estimate the prevalence of LTBI in a general medicine practice and suggest strategies to increase screening.

2. Methods

2.1. Study setting, participants, and design

The Farmington Internal Medicine practice of UConn Health serves a 72% Medicare and Medicaid population. Between February and July 2019, 1221 patients were randomly selected for screening by virtue of having sequentially scheduled appointments with one of six primary care providers. A TB risk assessment was completed on all selected patients by a medical assistant while rooming routine or preventive visits. The assessment was developed by the Connecticut Department of Public Health and the Centers for Disease Control (CT Department of Public Health CT TB Risk Assessment, Published 2019). Answering yes to any one of the following indicated a positive screen: 1. Have you resided in or traveled for over a month to a TB endemic area? 2. Are you immunosuppressed? 3. Have you had close contact with someone with TB?

Positive screens were offered QuantiFERON-TB Gold Plus (QFT-Plus) testing and a CXR if indicated. Patients diagnosed with LTBI had a follow-up visit to discuss treatment options including 3 months of weekly INH/RPT (3HP), 4 months of daily RIF(4R), 3 months of daily INH/RIF (3HR), and/or 6 or 9 months of daily or twice weekly INH (6H/9H) (Sterling, et al., 2020).

After deciding on a treatment regimen, patients were enrolled in a nurse-run eDOT program. In this program, patients received weekly nurse calls to review side effects and assess compliance. Nurse calls occurred on the day of medication administration. Nurses verified that medication was taken completely on the assigned day. A standard message prompt was utilized to consistently review side effects based on the particular treatment regimen selected. Nurses also addressed any additional patient concerns. Provider follow-up appointments with pill counts occurred at the midpoint and completion of treatment.

The study qualified for exemption status by the UConn Institutional Review Board.

2.2. Study outcomes

The primary goal of this study was to assess the efficacy of a nurse-run eDOT program in treating LTBI in a general medicine setting. Therapy completion was the measure to determine efficacy. Therapy completion rates were reported as raw numbers and percentages.

A secondary goal was to estimate the prevalence of LTBI in a general medicine practice. Numbers of individuals with positive screens were tallied to assess prevalence.

3. Results

Patient characteristics are outlined in Table 1.

Of 1221 screened, 192 (15.7%) answered yes to one of the screening questions and qualified for QFT-Plus testing. Of these, 106 (55.2 %) had a negative QFT-Plus, 86 had a positive QFT-Plus(7.0%), 7 (3.6 %) refused testing, 10 (5.2 %) were previously treated for active TB, 8 (4.2 %) had prior recent negative TSTs and 22 (11.5%) were lost to follow-up.

Table 1
Patient characteristics of individuals eligible for LTBI testing as defined by a positive history (hx) (N = 192) and those offered treatment (tx) for LTBI (N = 35).

Characteristics of patients screened (+) by hx N (%)	born/travel/ resided in TB endemic area > 1mo		Currently immuno-suppressed	close contact with TB	
	< 10 years ago	>10 years ago		< 10 years ago	>10 years ago
Female					
age 18–30	45 (46%)	0	1 (1%)	0	0
age 31–50	36 (37%)	4 (4%)	0	0	2 (2%)
Age > 51	2 (2%)	8 (8%)	0	0	0
Total n = 98 (51%)					
Male					
age 18–30	42 (45%)	0	0	0	0
age 31–50	30 (32%)	1 (1%)	0	0	0
age > 51	10 (11%)	5 (5%)	0	0	6 (6%)
Total n = 94 (49%)					

characteristics of patients with LTBI N (%)	born/travel/ resided in TB endemic area > 1mo		Currently immuno-suppressed	close contact with TB	
	< 10 years ago	>10 years ago		< 10 years ago	>10 years ago
Female					
age 18–30	2 (13%)	2 (13%)	0	1 (7%)	0
age 31–50	5 (33%)	4 (27%)	0	0	1 (7%)
age > 51	0	0	0	0	0
Total n = 15 (43%)					
Male					
age 18–30	3 (15%)	0	0	0	2 (10%)
age 31–50	6 (30%)	5 (25%)	0	0	1 (5%)
age > 51	3 (15%)	0	0	0	0
Total n = 20 (57%)					

39 patients were initially deemed eligible for treatment. 4 were discovered to have been previously treated for LTBI leaving 35 to whom treatment was offered. 33 completed treatment (94.3%). 25 patients completed a 3HP regimen. 1 developed nausea to 3HP and subsequently completed biweekly 6H. 2 patients moved out of state and completed 4R. Another 5 patients also moved out of state and completed 3HP after starting in our clinic. Patients who left the state during the study completed their eDOT calls and follow-up physician visits were conducted virtually. One patient refused treatment and another developed a hypersensitivity reaction to 3HP (Fig. 1). The prevalence rate of LTBI was 3.1% and compliance with treatment 94.3%.

4. Discussion

The prevalence of LTBI in this general medicine setting was 3.1%. 94.3% completed treatment. Although previous estimates are variable, the prevalence of LTBI was a little lower than expected. This discrepancy

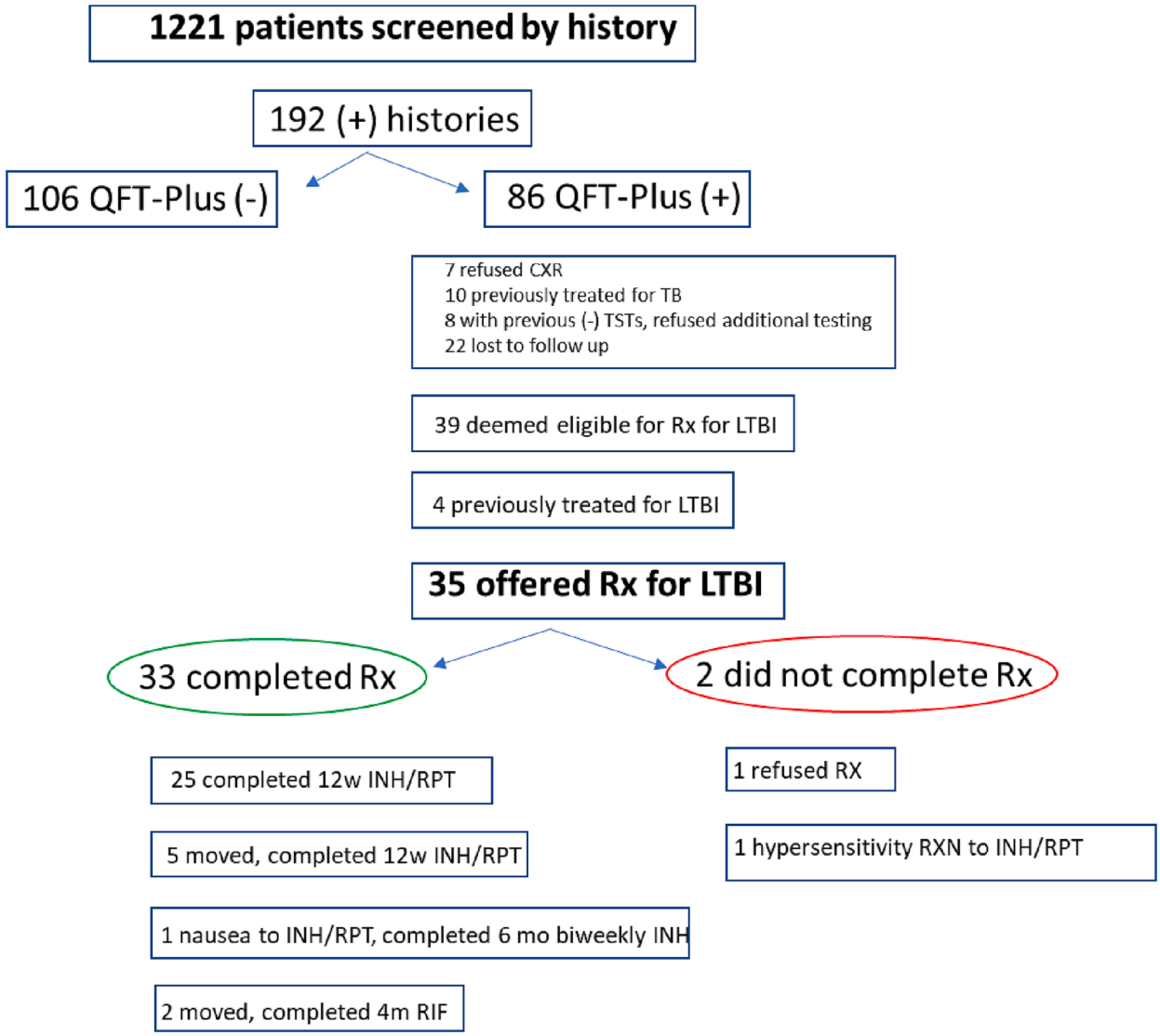

Fig. 1. Outcomes of Patients screening positive for LTBI risk factors and subsequently offered treatment.

may be explained by a small sample size. Additionally, 22 patients were lost to follow-up, 7 refused CXR and 1 refused treatment. In either case, the opportunity exists to identify a significant number of latent TB-infected individuals within the primary care setting.

Patients who screened positive by history as well as those subsequently found to have LTBI were relatively young. This fact may have hindered our ability to fully capture the effect of more distant exposure. Additionally, the smaller numbers of patients with distant travel and close contact exposures could be complicated by more recent additional TB exposures that were not captured as travel <1 month was not included in the assessment questionnaire. It is unclear if the development of LTBI correlated with age or exposure timeline as the numbers of patients with LTBI in this study were small.

94% of patients completed treatment, most electing a 3HP regimen. All but one patient tolerated treatment and no patients who entered therapy were lost to follow-up. Previous estimates of LTBI treatment completion rates are lower than those found in our study. 3HP completion rates are estimated at 82%, 6H at 63% and 4R at 79%. (Huaman and Sterling, 2019) LTBI completion rate studies vary in their application of eDOT. Some include provider visits on the day of medication administration, others include pill counts during interim provider visits. Our higher completion rates may have been in part explained by a younger population, but are also likely due to ease and completeness of follow-up with our variation of eDOT. Nurse-run eDOT provided additional advantages to providers, freeing them up to focus on the interval in-person visits that reinforced nurse telephone visits. Patients appreciated phone call check-ins and time with nursing to address concerns.

Barriers to testing and treatment of LTBI include disease-specific, patient, provider, and system challenges. While these barriers may seem numerous, many can be easily overcome.

Disease-specific challenges include the fact that the number of individuals with LTBI (~13 million) is vast compared to the number of new cases (<10,000). The TST and IGRA are poorly predictive (5 and 13%) of progression to active disease (Centers for Disease Control Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Published 2020). Another disease-specific barrier includes the notion that long-term immunoreactivity may not reflect continued infection; therefore, decisions about whether to treat distant exposures can be challenging (Behr et al. 2019).

Patient-specific challenges include the fact that it is often difficult to convince well patients to take medications with side effects. Adverse effects of INH include primarily asymptomatic transaminitis, hepatitis, and peripheral neuropathy. Asymptomatic transaminitis often resolves spontaneously. Clinical hepatitis is rare (<1%). Peripheral neuropathy is also rare (<1%), less common in shorter regimens and mitigated by coadministration of vitamin B6. RIF and RPT are associated with lower

hepatotoxicity than extended INH regimens. Cutaneous reactions including pruritus with or without rash are usually self-limiting. Hypersensitivity reactions are quite rare and can include hypotension, anaphylaxis, or nephritis. Gastrointestinal symptoms such as nausea, anorexia, or abdominal pain are rarely severe enough to discontinue therapy, and finally orange-red discoloration of body fluids such as urine or tears; is expected and harmless. Despite these possible complications, regimens are generally well tolerated. Side effects in our study were rare and all but 1 patient completed therapy. Our greater completion rates may in part be due to a relatively younger patient population with fewer potential drug-drug interactions. Weekly nurse calls helped to reassure patients and reinforce adherence.

Provider challenges include time and familiarity with screening and treatment options. Despite USPSTF guidelines, many providers remain unfamiliar with screening recommendations and uncomfortable with prescribing (Szkwarko et al. 2022). Utilizing side effect assessments through standard protocols such as standard message prompts in a nurse-run eDOT program can ensure consistency in treatment assessment.

System challenges can include patient access and practice resources. Access was not an issue as our patients were insured and LTBI treatment was fully covered. Many states have additional resources available thru the public health department to procure medications for uncovered patients. While many practices may lack the nursing bandwidth to institute an eDOT program, our program eliminates the common barrier of wait times to see infectious disease specialists and frees the provider up for other visits. Primary care providers may also be better positioned than specialists to identify LTBI risks.

The efficacy and cost-effectiveness of LTBI screening and treatment compare favorably with other widely accepted preventive strategies including mammography (2011 Lineas et al.) and the use of statins (2016 Chou, et al.). Despite a number of barriers to treatment, primary care providers are well-positioned to play a key role in identifying and treating LTBI. Identifying country of origin or international residence on a problem list or embedding simple screening questions within electronic records will help identify patients eligible for LTBI screening. With additional education or identification of in-office referral sources, as well as utilizing effective and timesaving treatment strategies including a nurse-driven eDOT treatment program, primary care physicians can treat LTBI and contribute significantly to reducing the US burden of active TB disease.

5. Conclusion

Given the prevalence of LTBI, the longitudinal nature of therapeutic relationships and the ease of screening, primary care providers are positioned to identify a large number of patients eligible for screening. A general medicine nurse-run eDOT program is convenient for patients, well-tolerated, and associated with high adherence rates. Expanding the role of LTBI identification and treatment to primary care may significantly reduce US TB disease rates.

CRediT authorship contribution statement

Susan Levine: Conceptualization, Methodology, Data curation. **David Fraulino:** Conceptualization, Data curation. **Philip Krupka:** Data curation. **Sruti Velamakanni:** Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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