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ORIGINAL ARTICLE

Compliance with treatment of latent Tuberculosis infection in healthcare workers

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Abstract

Healthcare workers (HCW) are at higher risk of exposure to tuberculosis than the general population, thus screening upon start of employment and periodically thereafter for latent tuberculosis (TB) infection is required for work clearance in healthcare institutions. Treatment of latent TB infection (LTBI) is recommended in HCW, especially those with conditions that increase the risk of progression to active tuberculosis but despite evidence of benefit, adherence to treatment remains suboptimal. We undertook a retrospective study of healthcare employees at a large, academic, tertiary care institution in the United States and found that only 73% were compliant with treatment of LTBI. Side effects and duration of therapy were major reasons for lack of adherence. Closer follow up during the treatment course, and the use of alternative regimens such as the combination of isoniazid and rifapentine under direct observation for a shorter duration may improve compliance rates in healthcare workers in the future.

Key words

Latent tuberculosis and diagnosis and therapy; Health personnel; Medication adherence; Isoniazid and therapeutic use; Rifampin and therapeutic use

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Introduction

Health care workers (HCW) are at risk of exposure to and infection with tuberculosis (TB) in the workplace. An important part of any comprehensive tuberculosis control program is periodic screening of healthcare workers for early detection and treatment of latent tuberculosis infection (LTBI). Once LTBI has been identified, and active tuberculosis ruled out, treatment of LTBI is recommended to reduce the risk of developing active tuberculosis in the future, particularly in individuals who have immunocompromising conditions that may increase the risk of progression to active TB. Active TB can develop in 5%–10% of persons who get infected with *M. tuberculosis*, typically after a latency of 6–18 months, but this can occur even after decades in the form of reactivation of LTBI in some persons. Treatment during latency prevents TB during treatment and afterward.[1] Despite evidence showing benefits of LTBI treatment, compliance in HCW remains inadequate. We undertook a retrospective study to examine adherence rates with LTBI treatment at our academic medical centre.

Methods

Setting

The University of Wisconsin Hospital is a 536-bed, acute care tertiary referral hospital. There are 7400 employees of the hospital and clinics. The hospital averages 1785 new employees per year. The organization has a large solid organ and bone marrow transplant program, a children's hospital and is a level I trauma centre.

Usual Practice

All hospital employees are required to undergo a tuberculin skin test (TST) administered by Employee Health Services (EHS) before beginning employment. Employees who have prior documented positive TST are excluded from TST testing. The test is administered by injecting 0.1 ml of 5-TU purified protein derivative (PPD) intradermally into the forearm, and is read 48-72 hours later. The induration required for a TST result to be read as positive for a new employee varies between 5-15mm depending on their risk factors, with almost all requiring at least 10 mm of induration to be considered a positive test result. An induration of 10 mm or greater is considered a positive TST for all continuing healthcare workers who undergo an annual TST. If the first TST is negative, it is repeated two weeks later to examine for a booster effect. All employees with a positive TST undergo a symptom screen and a chest radiograph to evaluate for the presence of active or previous tuberculosis. Treatment of LTBI is strongly encouraged by EHS, but is not required. The employee has the option to seek treatment either through EHS or through his or her own physician. If care at EHS is chosen, close follow up and frequent monitoring for side effects is undertaken. Follow up protocols if under treatment by other providers are at their discretion.

Two changes in standard of care occurred during the study period. First, midway during the time frame of the study, the recommended length of treatment for LTBI with isoniazid (INH) was extended from 6 months to 9 months duration, based on guidelines from the Center of Disease Control (CDC). The interferon gamma release assay (IGRA), a serum-based test, was also approved as a screening test for LTBI during the latter part of the study period. Although the IGRA is not routinely performed for employee screening at our facility, this is an acceptable alternative to standard tuberculin skin testing.

Study Population

A retrospective cohort study was performed on all hospital employees at the University of Wisconsin Hospital who had a positive TST (defined as 10 or greater mm) between 2004-2010. Hospital volunteers with a positive skin test were not included in our study. Demographic data and information regarding compliance were collected by reviewing files obtained from employee health services. Employees with a positive TST whose files lacked details regarding treatment were contacted by email to request this information. Employees who did not respond to the first email were sent a subsequent email in an attempt to complete the missing information.

Data Collection

We collected data on the following: demographics, country of birth, manner of patient contact (e.g. direct versus indirect), type of screening test used (e.g. IGRA versus TST), PPD measurement, imaging (e.g. chest x-ray), clinical symptoms (e.g. presence of respiratory illness), laboratory tests (e.g. liver function

tests), pregnancy, vaccination with Bacillus Calmette-Guerrin vaccine (BCG) and site of treatment (e.g. employee health versus primary provider).

Employees were considered to have direct patient contact if they provided medical services, came in close contact with patients or performed technical support functions essential to medical care. We did not consider foodservice workers and custodians to have direct patient contact. Country of birth was categorized as either foreign or US born. A TST result was considered large if the induration measured over 20mm and small if it measured between 10-20mm. An employee was considered compliant if INH was taken for at least 6 months if recommended to do so. Conversely, if treatment was contraindicated and not recommended employees were also considered to be compliant. Partial compliance was defined as an employee taking INH for at least 4 months but less than 6 months, and non compliance was defined as INH therapy for less than 3 months or not at all.

The study was submitted to the Institutional Review Board and considered exempt from review.

Statistical analysis

We undertook descriptive analyses of factors associated with compliance. Univariate analyses were done using Chi-square test for categorical variables and Student's t-test for continuous variables. A two-sided P value of equal to or less than 0.05 was considered statistically significant. We undertook logistic regression analysis to examine factors independently associated with compliance. Statistical analyses were done using StatsDirect software (StatsDirect Inc, Cheshire, UK).

Results

A total of 105 hospital healthcare workers tested positive for LTBI between 2004 and 2010. Of these, 57 (54%) were female and 48 (46%) were male. None of these employees had current or previous active tuberculosis. Sixty-five (62%) received treatment at EHS, while the remainder (38%) sought treatment with their own physician or did not contact a provider about treatment options. We were unable to find compliance data for 7 of the 65 (10.8%) employees who initiated treatment at EHS and 17 of the 40 (42.5%) employees who did not follow up at EHS. This left us with a pool of 81 employees from whom compliance data was available. Of these, 58 were seen at EHS and 23 were not. Of the 81 health care workers for which compliance data was available, 54 (67%) were compliant, 5 (6%) were partially compliant and 22 (27%) were noncompliant. Risk factor analyses were restricted to the 81 employees for whom compliance data was available. For analyses, we considered partially compliant employees (n= 5) to be compliant.

None of the HCWs in our study were found to have active tuberculosis. Seven subjects had abnormalities on their chest X-ray such as calcified granulomas and calcified lymph nodes, but no chest X-ray finding was consistent with active TB. Of the seven people with abnormal chest X-rays, six complied with treatment. There were no pregnant patients in our cohort although one subject who was contemplating pregnancy was noncompliant with therapy. Five health care workers had elevated liver function tests, all of whom were fully compliant with their healthcare provider's recommendations (e.g. they either did not initiate INH or stopped taking it once liver tests results rose to greater than three fold above normal on treatment). Data on BCG vaccination was incomplete as patients were often unable to recall whether they had ever been vaccinated for tuberculosis. Nevertheless, 63 health care workers reported having received BCG vaccine. Univariate analyses and logistic regression did not identify any statistically significant factors associated with poor compliance.

Discussion

We found that 73% of our employees were fully compliant with treatment for latent TB infection. This may overestimate the true compliance rate, because compliance data was available for only 81 (77%) of the 105 employees and it is possible that employees who were lost to follow up may not have taken the recommended course of treatment for LTBI in its entirety. Assuming all twenty-four patients were non-compliant with treatment, compliance rate in our cohort would decrease to 56%. Although compliance remains suboptimal, our results are slightly more favourable compared with other studies that have examined this issue. In these studies, summarized in Table II, treatment regimens for LTBI in healthcare workers have completion rates ranging from 0.8-90%.[2-10] For example, in the Barrett-Conner[2] study three decades ago, only 41.3% of patients who had a positive

Table I. Descriptive statistics of study population

	Complied (%)	Noncompliant (%)	Number for whom Compliance data available (%)	Total # (%)
Total Population of Study	59 (73)	22 (27)	81	**105**
Foreign Birth	36 (72)	14 (28)	50 (62)	**66 (63)**
Born in USA	23 (74)	8 (26)	31 (38)	**39 (37)**
Male	25 (69)	11 (31)	36 (44)	**48 (46)**
Female	36 (80)	9 (20)	45 (56)	**57 (54)**
Treatment at EHS	41 (71)	17 (29)	58 (72)	**65 (62)**
Treatment Not at EHS	18 (78)	5 (22)	23 (28)	**40 (38)**
Direct Patient Care	27 (81)	6 (19)	33 (46)	**48 (46)**
No Direct Patient Care	26 (67)	13 (33)	39 (54)	**57 (54)**
Positive IGRA Test	2 (100)	0(0)	2 (29)	**2 (29)**
Negative IGRA Test	5 (100)	0 (0)	5 (71)	**5 (71)**
PPD Induration <20mm	35 (74)	12 (26)	47 (59)	**66 (63)**
PPD Induration >20mm	23 (70)	10 (30)	33 (41)	**38 (37)**
Abnormal Chest Radiograph	6 (86)	1 (14)	7 (9)	**10 (10)**
Normal Chest Radiograph	53 (72)	21 (28)	74 (91)	**95 (90)**
Respiratory Illness	1 (33)	2 (67)	3 (4)	**4 (4)**
No Respiratory Illness	60 (76)	19 (24)	78 (96)	**101 (96)**
Liver Test Elevated	5 (100)	0 (0)	5 (6)	**5 (5)**
Normal Liver Test/ No Liver Test	55 (72)	21 (28)	76 (94)	**100 (95)**
History of BCG	23 (74)	8 (26)	31 (49)	**44 (53)**
No History of BCG	24 (75)	8 (25)	32 (51)	**39 (47)**

IGRA, interferon gamma-release assay; BCG, bacillus-calmette-guerin; EHS, employee health service.

TST initiated therapy, although the majority (71%) of those completed treatment. LoBue and Cananzaro[6] included health care workers with a positive PPD test and found that only 40% complied with the INH treatment. The study by Camins *et al.*,[3] which was similar to ours in both setting and sample size, found a 55% compliance rate. Gershon *et al.*[5] found that compliance rates of HCW was low (47%), and that HCWs were less likely to initiate LTBI treatment. Interestingly, compliance with LTBI treatment was much higher in studies where more aggressive and systematic approaches were implemented. In the study by Shukla *et al.*,[8] where compliance rate was 80%, there was active follow up, consisting of physician counselling and monthly consultations with nurses from the hospital's occupational health department. In the study by Tavitian *et al.*,[9] a pharmacist-managed TB clinic was created to help improve compliance with treatment of LTBI, which was a dismal 0.8%. The clinic provided monthly medication refills, face to face follow up for the first three months, and monthly telephone interviews until completion of the regimen. Compliance rates improved to 90-100% after the intervention.

Several reasons for noncompliance were noted upon review of employee charts in our institution. While no single major reason was identified, we observed that fear of side effects was a common self reported reason to refuse treatment for LTBI. Side effects commonly reported in the literature and associated with long-term use of INH include malaise, nausea, diarrhoea, hepatitis, arthralgias, paresthesias and rash.[1,3]

Table II. Studies that have examined compliance with latent TB infection treatment among healthcare workers

First Author (Year)	Study Design	Setting/ Location	Number of Healthcare Workers with LTBI	Percent Compliance with LTBI	Possible Risk Factors for Noncompliance
Barrett-Connor[2] (1979)	Cross sectional survey	Multiple medical institutions	310	41	Side effects
Fraser[4] (1994)	Convenience sample	Tertiary care hospital	86	37.5	Side effects
Camins[3] (1996)	Observational study	Urban public hospital	125	55	Non physician healthcare worker
Ramphal-Naley[7] (1996)	Cross sectional survey	Regional medical center	40	43	Right to refusal Side effects
LoBue[6] (1998)	Retrospective cohort	Urban teaching hospital	259	48	NR
Shukla[8] (2002)	Prospective cohort	Urban teaching hospital	404	82	BCG vaccination Side effects
Tavitian[9] (2003)	Interventional study	Hospital-based ambulatory clinic	341	Pre-intervention: 0.8 Post-intervention: 80-100	NR
Gershon[5] (2004)	Retrospective Cohort	Ambulatory tuberculosis clinic	107	47	HCW Old age Female BCG Vaccination
Xu[10] (2012)	Retrospective cohort	Referral centre	210	70	Side effects

Although little is known about the factors influencing HCWs' abilities or decisions to adhere to screening and treatment, a low perceived risk of TB, the voluntary nature of screening programs, adverse drug effects and past history of BCG vaccination have all been associated with non-adherence to LTBI treatment.[8,11] A study by Joseph *et al.*,[12] which involved several focus group discussions involving healthcare personnel, identified several barriers to treatment adherence, including misperception regarding LTBI treatment, misunderstanding regarding TB pathology, and contradictory messages from EHS and other healthcare providers, leading to distrust and lack of confidence in employee health. In our study, we examined a number of factors that may have impacted the decision of an employee to take treatment for LTBI; however we did not find a statistically significant correlation between gender, direct patient care, history of BCG, country of birth, and type of follow up (e.g. employee health compared with other) and compliance with treatment of latent TB infection.

Length of treatment for LTBI has also been identified as a factor that hinders completion of LTBI therapy. Standard of care until recently required 9 months of isoniazid therapy as the preferred regimen which may adversely affect completion rates. Self-supervised daily INH rates have been ≤60% in typical

settings, attributable largely to the long duration of therapy.[13] Recently, the use of combination INH and rifapentine (RPT), given once weekly under directly observed therapy (DOT) for a three month duration as an alternative to the 9 month standard of care, has received favourable attention based on results from three randomized controlled trials.[14-16] This alternate shorter-term regimen, which is recommended for otherwise healthy patients ≥12 years, may be optimal for healthcare workers, and improve completion rates of LTBI treatment. Other options for treatment of LTBI include twice weekly INH for 6 or 9 months or rifampin daily for 4 months.

Our study has several limitations. This was a retrospective chart review and relevant data such as history of BCG vaccination was unavailable in some instances, despite our efforts to contact employees for additional information. Our small sample size did not permit adequate assessment of factors that predicted compliance because of lack of adequate power. The treatment duration for LTBI was prolonged to 9 months during the latter part of our study period, which may have adversely affected compliance further, although we took this into consideration in our study.

These limitations notwithstanding, our findings add to the existing body of literature that highlights the inadequate compliance with treatment of LTBI. Interventions to promote adherence to LTBI treatment in HCW such as close follow-up may lead to improvement in adherence rates.

Conclusion

Adherence of healthcare workers to treatment of LTBI remains poor despite evidence showing that treatment of LTBI decreases the risk of progression to active tuberculosis. Future studies should examine the underlying factors responsible for poor compliance. Close follow up of employees who start first line or alternative for treatment should be undertaken, especially given the possibility of drug-related side effects. In addition, regimens of shorter duration should be explored to facilitate completion of therapy.

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