UNF UNIVERSITY of NORTH FLORIDA

Florida Public Health Review

Volume 7 Article 6

April 2010

Tuberculosis Screening and Treatment of Latent Tuberculosis Infection among International College Students

Bhavna Bhardwaj

Eknath Naik

Beata Casanas

Michael D. Breglia

Michael Lauzardo

Tuberculosis Screening and Treatment of Latent Tuberculosis Infection among International College Students

Bhavna Bhardwaj, MD, MPH, Eknath Naik, MD, PhD, Beata Casanas, DO, FACP, Michael D. Breglia, MD, Michael Lauzardo, MD

ABSTRACT

Tuberculosis (TB) remains in the crosshairs of many public health policies worldwide that are taking aim at eradicating this potentially curable and preventable illness. Although tuberculosis (TB) incidence has been declining in the United States for over a decade, it still remains a serious public health concern. Currently, there is no public health policy that requires the screening of non-immigrant international university students visiting the United States. Given the rising numbers of visiting international students, this population has come under scrutiny as potential vectors of transmission of TB into the United States. Foreign-born persons from countries with consistently elevated TB prevalence rates constitute an important high risk group for both TB exposure and infection in this setting. Although some universities have their own public health protocols, not all universities have a policy of screening international, non-immigrant students for TB. To further investigate the situation, we reviewed the medical charts of international students visiting the University of Florida. Students who visited the health department for evaluation of TB skin tests from January1998 to February 2002 were studied. Of the students with a positive tuberculin test (skin test >10mm induration), 97.6% had normal chest radiographs. Only 31 students (10.8%) agreed to undergo treatment for latent TB infection (LTBI), of which only half completed a six to nine month course and 86.8% were lost to follow-up. To attempt complete eradication of TB from the United States, universities with at-risk populations should consider the implementation of strict guidelines and well defined policies for the screening, follow-up and treatment of active and latent TB in international students.

Florida Public Health Review, 2010; 7, 26-31.

Introduction

Tuberculosis (TB) is a common infectious disease worldwide primarily caused by a small non-motile aerobic bacillus, *Mycobacterium tuberculosis*. This infection, frequently manifested by pulmonary disease, has been studied for several hundred years and is well described in the medical literature. It has been estimated that one-third of the world's population is infected with TB. Many nations, including the United States, have public health policy focused on TB recognition, isolation, and management. However, from a global perspective, alarming rates of infection persist, with roughly one new infection every second (WHO, 2007). Distribution of disease burden throughout the world is not uniform and has much higher rates of infection in the developing world, especially in regions of Africa and Asia.

The Centers for Disease Control and Prevention (CDC, 1989) announced a goal of eliminating TB from the U.S. by the year 2010. Following a transient 20% increase in the incidence rate reported by the CDC for 1992 (CDC 1993), a decline in infection rate has generally been observed since 1993. The average annual percentage TB rate decreased from 7.3% per year during 1993-2000 to 3.8% per year during 2000-2008 (CDC, 2009a). However, cases of TB and drug resistant TB continue to be reported in every state. An estimated 10-15 million people in the United States are currently infected and lacking intervention. In addition, about 10% of this population will develop active TB at some point in their life. It has been recognized that an overwhelming majority of all TB cases reported occur in a relatively small number of states or regions. For instance, four states reported more than 500 cases each for 2008 including Florida, California, New York, and Texas. Combined, these four states accounted for approximately half of all TB cases in 2008. Additionally, there is a great discordance of infection rates among different racial groups in both foreign-born and those born in the United States. Immigration from countries where TB has a high prevalence rate is one of the major contributing factors of increased TB cases in the U.S. In 2008, the TB rate in foreign-born persons in the United States

was 10 times higher than rates observed for those born in the United States (CDC, 2009a). The CDC (1998) Work Group on Tuberculosis among Foreign-born thus concluded that TB elimination in the U.S. will need to increasingly depend on elimination of TB among the foreign-born.

The majority of foreign-born individuals are those that legally migrate to the U.S. and transiently reside in the country with their families. About 29.6% of all TB cases among foreign-born individuals occur during the first year, and more than half (55.5%) of the cases occur during their first five years after arrival in the United States. Subsequently, the risk declines.

Immigrants who intend to reside permanently in the U.S. are screened for TB before they enter the U.S.; screening may include tuberculin skin testing, chest radiograph and sputum examination for Acid Fast Bacilli (AFB) to detect active or latent tuberculosis infection (LTBI). The policy of screening for LTBI among permanent resident immigrants does not apply to certain populations including students and workers who enter the country for long-term stays without seeking permanent residence. Historically, only a small number of regions account for a majority of TB cases among foreign-born persons in the United States. In 2008, only four countries accounted for approximately half of foreign-born TB cases: Mexico, the Philippines, India, and Vietnam (CDC, 2009a). Because health screening is not required for students and workers coming to the U.S., implementing a screening program for the high risk individuals would require a detailed analysis of the TB risk for this population. Serious consideration should be given to mandating school and employment-based screening and treatment programs for these recent immigrants and their families.

Currently, there is very limited information regarding TB screening, treatment and compliance to follow-up among international students. A few exceptions are notable, such as a study at Kirkwood Community College in Iowa (Norton, 2000). At this community college, the college health services implemented a TB screening policy for all newly enrolled international students in an effort to minimize the occurrence of active TB on the campus community which has experienced a significant increase in their international student population. Of the 171 international students from seventy different countries enrolled, 59 (35%) of those screened for TB showed a positive skin test, and subsequently, 34 students initiated isoniazid therapy, but only 27 completed their treatment.

In addition, an earlier study conducted at the University of California, Los Angeles (UCLA) was performed secondary to concerns of TB infection in visiting international students. Tuberculin skin tests from nonimmigrant foreign students were required prior to registration of classes. Out of a total of 589 students tested, 339 were positive (57.6%) at the level of 5mm or greater (Quillan, Malotte, & Shlian, 1990). The study also observed compliance with isoniazid (INH) therapy which was recommended for all positive reactors who did not have any contraindications. This study and screening policy further illustrates this potential mechanism of transmission of visiting international students and the need for more stringent screening strategies.

Ironically, the statistics denoting a decrease in TB incidence have resulted in a decrease in funding available for prevention programs. Thus, appropriate allocation of dwindling resources is more imperative than ever. To determine the adequacy of a TB screening program, a protocol needs to be quantifiably defined and a database implemented to plan future interventions in the context of limited resources.

In a CDC survey of 796 colleges and universities (Hennessey, Schulte, Cook, Collins, Onorato, & Valway, 1998), a readily available tuberculin screening skin tests among students yielded a low prevalence of positive tests and a few TB cases. The authors concluded that to optimize the use of ever dwindling public health resources, tuberculin screening should focus only on students at high risk for infection.

Because no comprehensive analysis existed regarding TB screening and management of LTBI among international students at the University of Florida, we conducted a retrospective study in order to evaluate the circumstances prevailing at the University of Florida and construct a database for future reference.

Methods

The present study included international students attending the University of Florida between January 1998 and February 2002, who had been referred to Alachua County Public Health Department (ACPHD) for tuberculosis evaluation. TB Evaluation was based on medical history, physical examination, Mantoux (PPD) tuberculin test, chest radiograph, and bacteriologic or histologic examination. Medical history considered symptoms of disease, history of TB exposure, infection, history of previous TB management, demographic risk factors for TB, and medical conditions that increase the risk of TB disease. Of note, radiographic abnormalities are frequently noted in apical or posterior segments of upper lobe or superior segments of lower lobe in chest radiographs. However, these findings alone

cannot confirm a diagnosis. TB cultures were utilized to confirm diagnosis of TB.

Case Definitions

Case definitions were based on ones devised by the CDC (2009b). *Clinically active TB* cases included students with symptoms of productive, prolonged cough (duration of ≥3 weeks), chest pain, hemoptysis, fever, chills, night sweats, appetite, weight loss and easy fatigability and bacteriological, and/or radiographic evidence of current tuberculosis. Cases of *latent TB infection (LTBI)* included students with positive reaction to the tuberculin skin test (> 10 mm induration), and no clinical, bacteriological, or radiographic evidence of active tuberculosis. *Suspected TB cases* include those students who were classified when a diagnosis of tuberculosis was being considered, whether or not treatment had been started, until diagnostic procedures were completed.

The study consisted of retrospective data collection through patient medical chart review. In order to determine if a patient was a student at UF, we compiled from ACPHD records a list of name, sex, and date of birth, occupation (stating "UF student"), social security number, and country of origin. The list was used to cross reference records regarding chest radiograph reports, and any other follow-up investigations conducted such as sputum examination and culture; treatment offered, and compliance to treatment. To maintain patient confidentiality, all the identifiers were removed from the final data base used for analysis. Institutional Review Board (IRB) approval was obtained from the University of South Florida, and the local county health department.

Data Management and Analysis

A template was designed for transcribing the chart data. A codebook was prepared before designing and storing data in Excel database. All the data were was manually checked for any omissions and errors. The database possessed automatic edit checks and validations. Missing codes were pre-assigned before the data was entered into the data base. Once the data was entered, it was checked for missing data and frequency of variables. Initially, summary frequencies of all variables were obtained and then further analysis performed to detect any associations between outcome and exposure variables. Subsequently, multivariate analysis was used to assess confounding variables and interactions for statistical analysis. Epi Info 2000 V1.1 software from CDC was utilized.

Results

There were 288 tuberculin test positive international students who were referred to the health department for further evaluation. Table 1 describes the demographics profile of the study participants. The median age of the students was 29 years of age (range 19-49 years). There were 127 (44.1%) females and 161 (55.9%) males. Students came from 64 different countries, with highest numbers from Korean Republic (19.1%), and China (16%), (Table 1). Other countries constituting the top eight countries of origin were India (8%), Japan (6%), France (5%), Taiwan (4%), Turkey and Brazil (3% each). This accounted for 64% of PPD-positive international students evaluated. The majority of students in this study were in the U.S. for duration of < 1 year (74%), 265 students (92%) were in the U.S. for five years or less (Table 1). Status of prior Bacillius Calmette-Guèrin (BCG) vaccination was not available for majority of the students and this was not recorded.

The PPD skin testing was not done in two students. Both of these students had a previous history of active tuberculosis, and had received complete anti-tubercular treatment in the past. Only three students had a PPD skin test < 10mm. Of the students tested, 283 (98%) students had PPD skin test ≥ 10mm (positive test). The mean positive PPD reaction was 16.89mm (range10-50mm). Two hundred and thirty one (80.2%) students had a PPD reaction of <20mm (Table 2). Chest radiograph was done as a part of the evaluation process for TB in 286 (99%) students; most of these 281 (97.6%) were normal (Table 3). Three of the students (1%) had x-ray abnormalities indicative of pathology other than TB, while 2 (0.7%) showed abnormalities suggestive of TB lesion.

Only ten (3.4%) students complained of symptoms and six of these students complained of cough. One had symptoms like fatigue, fever, night sweats, and other non-specific symptoms. Seven of the ten students complaining of symptoms had been in the U.S. for <1 year.

Irrespective of any chest radiographic findings, students were offered treatment for LTBI. Unfortunately, 250 (86.8%) students were lost to follow-up, because they never again attended the TB clinic (Table 4). Thirty-one students (10.8%) were offered treatment and of these, only 15 students completed six to nine months of treatment. No significant correlation was seen between time in the U.S. and taking or not-taking treatment ($\chi^2 = 54.7672$, df = 63, p = 0.7605). However, it was noted that 28 of 31 students who underwent treatment were in the U.S. less than two years. Comparing compliance to treatment and country of origin, there was no significant correlation ($\chi^2 = 217.6222$, df=189; p = 0.0753).

Table 1. Demographic Variables Distribution of International Students with Positive PPD

Variables	Number of Students with positive PPD	Percent
Age (Years)		
19-23	36	12.5
24-28	107	37.2
29-33	94	32.6
34-38	34	11.8
39-43	10	3.5
44-50	7	2.4
Total	288	100
Sex		
Females	127	44.1
Males	161	55.9
Total	288	100
Nationality		
S. Korea	55	19.1
China	46	16.0
India	24	8.3
Japan	17	5.9
France	13	4.5
Taiwan	11	3.8
Turkey	9	3.1
Brazil	8	2.8
Others (56)	105	36.5
Total (64)	288	100
Time (Years) in US		
<1	213	74.0
1	12	4.2
2	18	6.3
3	8	2.7
4	5	1.7
5	9	3.1
>5	23	8.0
Total	288	100

We found no association between sex and reluctance to initiate treatment for LTBI (OR=1.10, 95% CI 0.52, 2.35) nor reason for not completing treatment (OR=1.14, 95%CI 0.43, 3.03).

Discussion

The University of Florida (UF) ranks 23rd among universities with international students, with 3039 international students (6.7% enrollment) enrolled in 2000 (*Gainesville Sun*, May 22, 2002). South Korea, India and China are the leading countries of origin among UF international students. In 2001, there were

Table 2. PPD Skin Test Positivity Among International Students

PPD (millimeters)	Frequency	Percent
0 – 10	19	6.6
11 -20	231	80.2
21-30	32	11.1
31-40	2	0.7
41-50	4	1.4
Total	288	100

Mean PPD: 16.89 mm (SD: 5.88 ±0.35)
Median: 15 mm

Table 3. Results of Chest X-ray of International Students

Chest X-ray	Frequency	Percent
Normal	281	97.6
Non-TB	3	1
abnormality	2	0.7
Suggestive of TB	2	0.7
Not Done	288	100
Total		

3915 foreign citizens on the UF campus, of which 2737 were students, and 1178 were researchers and teachers (*Gainesville Sun*, July 23, 2002). At any given time, there are approximately 1000 international students enrolled in degree-seeking programs, and 250 in non-degree-seeking programs (Personal communication, UF Admissions Office). Approximately 70% of the international students in 2001 were from the ten countries listed. Over a four-year period (1998-2002) only 288 students were evaluated, an average of approximately 72 students per year. The number of students evaluated appears to have declined to 37 in 2001 after a peak of 95 in 2000. It is safe to assume that there are about 1500-2000 new international students attending UF every year, so it is indeed worrisome that <5% of the high risk students are evaluated for LTBI and active TB every year.

Another significant statistic derived from this study is that alarming numbers of students with positive PPD decline treatment or are permanently lost to follow-up despite strong recommendations for treatment. We observed that 250 of the 288 students (86.8%) were lost to follow-up, 3 refused treatment, and 4 had medical contraindications to treatment (Table 4). Therefore, about 90% of the students overall did not receive treatment for LTBI. Our data also indicated that of the 31 students that underwent treatment, only 15 completed it. In summary, only 15 of 288 students benefited from treatment offered for LTBI. The data for 273 students with a positive PPD test was inextricably lost within the University data network. It is worth emphasizing that for more than three decades, treatment of LTBI has been an essential component of TB control in the U.S. (CDC, 1995). It should be noted that since this study was completed there have been substantial changes made in the screening program at the University of Florida and at the county health department to improve adherence to therapy and decrease the loss to follow up. There are plans to review the impact of the new policies.

Studies indicate that chest radiographs are a cost effective tool for screening students from high prevalence countries, but has low yield if it is applied to students from low prevalence countries (Schwartzman & Menzies, 2000). The cost-effectiveness of any of the screening methods currently used is significantly augmented by adherence to a chemo-prophylactic regimen used for LTBI. In LTBI cases, the chest radiograph is usually normal, although it may show abnormalities that truly differ from those found in patients with active TB and can be distinguished as such (CDC, 2000). Our studies indicate that 281 of 288 (97.6%) students had no chest x-ray abnormality.

A variety of reasons germane to a student's reluctance to be evaluated and treated for LTBI may be invoked. BCG vaccine is currently used in many parts of the world where TB is highly prevalent. This likely provides a false sense of security, since the immunity conferred by BCG generally wanes with time and does not protect against pulmonary TB. In this context, it is worth noting that BCG immunity can be augmented by tuberculin testing in vaccinated persons (Sepulveda, Ferrer, Latrach, & Sorensen, 1990). It was revealed during student chart reviews that many of them held the opinion that there was no need for treatment because a positive skin test was normally expected after BCG vaccination. Further analysis to determine if such a belief was related to nation of origin was inconsequential. Therefore it appears to be a global belief. In 2005 FDA approved use of a newer test called "QuantiFERON TB-Gold" (QFT-G) test, which could be used in patients with BCG vaccination as previous vaccination does not interfere with its interpretation. However, it is believed that reactions ≥ 20mm is not likely caused by BCG (McKay, Kraut, Murdzak, & Yassi, 1999).

The concept of being administered drugs to treat a well documented latent infection that is not causing active health problems is unfamiliar to most international students. Therefore, enhancement of educational efforts is considered essential (Morisky, Malotte, Choi, Davidson, Rigler, Sugland, et al, 1990). Unfortunately and ironically, those people who are PPD positive (indicative of LTBI and at risk of TB disease in the future) are especially at risk to expose other members of society. A six- to nine-month regimen of isoniazid (INH) is the recommended treatment. This is both highly efficacious and relatively safe, especially when implemented with regular monitoring. It is worth noting that a short course of Rifampin (RIF) alone may be a valid alternative.

Other described barriers to treatment are culturally-derived health beliefs that are alien to Western medical approaches. These include language barriers, cultural differences, and lack of education of TB, affordability, and availability of treatment. In summary, the role of the public health policy is critical in making an effort to educate, screen, and treat the public, particularly those with higher risk of disease. In addition, cross-cultural sensitivity should be facilitated within the university system.

Although prevalence is comparatively low in the United States and there is an overall decline in incidence, TB remains a global health concern. Continued vigilance against the disease is of utmost importance because TB remains disproportionately widespread in many regions and populations of the world. Preventive measures are especially required in the universities of the United States due to large population of students and faculty visiting from high risk regions where TB still reigns as the leading cause of mortality among infectious diseases. Public health policy must be adopted to improve efforts of eradicating this infectious disease in the United States. In summary, strategies should include a more aggressive TB screening program for non-immigrant visiting students, international student education concerning vaccination, diagnosis, and treatment, and adequate follow-up and treatment protocols. In addition, these policies must be adequately supported with appropriate funding which must be accordingly distributed.

References

Centers for Disease Control and Prevention. (1989). A strategic plan for the elimination of

tuberculosis from the United States. *Morbidity and Mortality Weekly Report*, *38* (Suppl No.S-3).

Centers for Disease Control and Prevention. (1993). Tuberculosis morbidity-United States, 1992. *Morbidity and Mortality Weekly Report*, *42*(36), 696-704.

Centers for Disease Control and Prevention. (1995). Essential components of tuberculosis prevention council for the elimination of tuberculosis. *Morbidity and Mortality Weekly Report*, *44* (No. RR-11), 1-16.

Centers for Disease Control and Prevention. (1998). Recommendations for prevention and control of tuberculosis among foreign-born persons. Report of the working group on tuberculosis among foreign-born persons. *Morbidity and Mortality Weekly Report*, *47*/No. RR-16.

Centers for Disease Control and Prevention. (2009a). Trends in tuberculosis—United States, 2008. *Journal of the American Medical Association, 301*(18), 1869-1871.

Centers for Disease Control and Prevention. (2009b). *Core Curriculum on Tuberculosis: What the Clinician Should Know*. Retrieved March 25, 2010 from: http://www.cdc.gov/tb/education/corecurr/

Centers for Disease Control and Prevention. (2000). Targeted tuberculin testing and treatment of latent tuberculosis infection. *Morbidity and Mortality Weekly Report*, *49*(RR06) 1-54.

Gainesville Sun. Opendoors.com. 2000 enrollment. May 22, 2002.

Gainesville Sun. July 23, 2002.

Hennessey, K.A., Schulte, J.M., Cook, L., Collins, M., Onorato, I.M., & Valway, S.E. (1998). Tuberculin skin test screening practices among US colleges and universities. *Journal of the American Medical Association, 280*(23), 2008-2012.

McKay, A., Kraut. A., Murdzak, C., & Yassi, A. (1999). Determinants of tuberculin reactivity among health care workers: Interpretation of positivity following BCG vaccination. *Canadian Journal of Infectious Disease*, *10*, 134-139.

Morisky, D.E., Malotte, C.K., Choi, P., Davidson, P., Rigler, S., Sugland, B., et al. (1998). A patient program to improve adherence rates with antituberculosis drug regimens. *Health Education Quarterly*, *17*, 253-267.

Norton, D. (2000).Tuberculosis screening for international students. *Journal of American College Health*, *48*(4), 187-189.

Quillan, S., Malotte, K., & Shlian, D. (1990). Evaluation of a tuberculosis screening and prophylaxis program for international students. *Journal of American College Health*, *38*, 165-170.

Schwartzman, K., & Menzies, D. (2000). Tuberculosis screening of immigrants to low-prevalence countries. *American Journal of Respiratory and Critical Care Medicine*, *161*, 780-789.

Sepulveda, R.L., Ferrer, X., Latrach, C., & Sorensen, R.U. (1990). The influence of Calmette-Guerin Bacillus immunization rates on the booster effect of tuberculosis testing in healthy young adults. *American Review of Respiratory Disease*, *142*, 24-28.

World Health Organization. (2007) Tuberculosis. Retrieved December 31, 2009 from: http://who.int/mediacentre/factsheets/fs10+4/en/index.html

Bhavna Bhardwaj (bhardwaj@ehs.ufl.edu) is with the Department of Environmental Health and Safety, University of Florida, Gainesville, FL. Eknath Naik (enaik@health.usf.edu), Beata Casanas (bcasanas@health.usf.edu), and Michael D. Breglia (mbreglia@health.usf.edu) are with the Department of Internal Medicine, University of South Florida College of Medicine, Tampa, FL. Michael Lauzardo (lauzam@medicine.ufl.edu) is Deputy Tuberculosis Controller with the Florida Department of Health, Alachua County Health Department in Gainesville, FL. This paper was submitted to the *FPHR* on December 31, 2009, revised and resubmitted, and accepted for publication on March 25, 2010.