Preventive Therapy for Tuberculosis (TB) in HIV-infected Persons

Boonmee Sathapatayavongs, MD, FRCP (UK)

Ramathibodi Hospital, Mahidol University

Prevention of Nosocomial Transmission of TB

Boonmee Sathapatayavongs, MD, FRCP (UK)

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Risk of Developing TB in HIV-infected Persons with (+) Tuberculin Skin Test*

5-8% per year or ≥ 30% in lifetime

* TST with 5-TU PPD by the Mantoux method, (+) = > 5 mm. induration

Mechanisms of Developing TB

- Reactivation of latent infection
- Rapid progression of primary infection
- Reinfection

Types of Preventive Intervention for TB Control

- Case-finding and treatment
- Preventive chemotherapy
- Use of BCG
- Environmental control

Preventive Therapy of TB

= Treatment of symptomless *M. tuberculosis* infections to prevent the development of active disease

Efficacy in non-HIV = 25-92% reduction of TB*

* Adv Tuberc Res 1969 ; 17 : 28-106.

Efficacy of Preventive Rx in HIV-person (RCT)

Study Site (no.)	Regimen	TB cases/100P-Y Treatment	Placebo	RR
Haiti (118)*	12 H	2.2	7.5	3.4 (1.1-10.6)
PPD (+)	12 H	1.7	10.0	5.8 (1.2-28.7)
PPD (-)	12 H	3.2	5.7	1.8 (0.4-9.2)
Zambia (647)**	6 H	2.1	5.3	
	(differences decrease with time after Rx stopped)			

* Lancet 1993;342:268,
** Wadhawan et al, 9th IC on AIDS. Berlin 1993

Efficacy of Preventive Rx in HIV-person (RCT)

Study Site	Regimen	TB cases/100P-Y Treatment	Placebo	RR
Uganda (2736)*				
PPD (+)	6H	1.08	3.41	0.33 (0.14-0.77)
	3HR	1.32	3.41	0.40 (0.18-0.86)
	3HRZ	1.73	3.41	0.51 (0.24-1.08)
Anergic	6H	2.53	3.06	0.83 (0.34-2.04)
Kenya (684) **	6H	4.29	3.86	0.92 (0.49-1.71)
PPD (+)	6H	5.59	8.03	0.60 (0.23-1.60)
PPD (-)	6H	3.28	2.73	1.23 (0.55-2.6)

* N Engl J Med 1997,337:801 ** AIDS 1997;11:875.

Efficacy of Preventive Rx in HIV person (Observational study)

- 52 PPD (+) IDU in New York*, regimen 12H
  compliant vs. noncompliant = 0 v.s. 9.7/100 P.Y

- 121 PPD (+) in Madrid, Spain**, regimen 9-12H
  treated v.s. non-treated = 1.6 v.s. 9.4/100 P.Y

* JAMA 1992;268:504 ** Anch Intern Med 1997;157:1729

In summary :

- INH prophylaxis is effective, at least short term, among PPD (+) HIV-person. 12-month course is preferable. In PPD (-) or anergic HIV-person, no effectiveness has been shown.

- Other multi-drug regimens of shorter duration (3HR, 3HRZ) are as effective as INH alone but more adverse effects in PPD (+) group.

- The higher the proportion of TB cases from reactivation the greater is the potential effectiveness of preventive Rx. If cases result from reinfection, the effectiveness of preventive Rx is likely to be short-lived.

From "study" to "practice"

Main concern : The possible emergence of drug resistance with increased use of INH monotherapy and inadequate system for active TB exclusion.

Consideration before implementing preventive Rx program

- Feasibility
- Sustainability
- Cost effectiveness
- Methods of delivery
- Monitoring for exclusion of active TB
- Safety
- Compliance

Upper room UVGI

- UV-C shert wavelength (~ 254 nm)
- Proper installation provide lethal dose to bacteria in upper air but safe at lower intensity in lower air (< 0.1 μ watt/cm^2)
- Need ceiling height of $\geq$ 8 ft. to ensure safety
- Relative humidity > 60% reduces efficacy
- Efficacy depends on air mixing in the room
- UV-C : no reports of oncogenesis, may produce burn, conjunctivitis.

Transmission of *M.tuberculosis*

- Air borne transmission
- Infectious particles : droplet nuclei 1-5 μ,
  - small enough to remain air borne for long time and distribute widely
  - produced from coughing, singing, speaking, aerosolization of abscess material
  - AFB smear (+) source

Isolation rooms

- Single room
- Negative pressure
- 6-12 air exchange per hour
- Exhaust air to outside or recirculated by using HEPA filters
- Upper room UV GI as adjunct measure

High Efficiency Particle Air (HEPA) Filter

- Remove 99.93% of air-borne particles $\geq 0.3\ \mu$
- Problem of "flow limitation"

WHO recommendation on TB preventive Rx in HIV-infected persons*

INH (6-12 months duration) shoud be considered for HIV-infected people with positive PPD (> 5mm), when active TB has been excluded.

(However, the emphasis of TB control program still remains at curative Rx of cases of TB to interrupt the transmission)

*Wkly Epidemiol Rec 1993;68:361.

Principles of Control of TB Transmission

Source Control	Environmental Control	Recipient Control
• Early Dx. & Rx of case • Proper case isolation • Face mask to trap coughing material	• Air dilution (Ventilation) • Air filtration (HEPA) • UV germicidal irradiation (UVGI)	• Personal protective resp. device • HCW surviellance inc. PPD status • HCW education & training

Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Facilities, 1994

Executive Summary

This document updates and replaces all previously published guidelines for the prevention of *Mycobacterium tuberculosis* transmission in health-care facilities. The purpose of this revision is to emphasize the importance of a) the hierarchy of control measures, including administrative and engineering controls and personal respiratory protection; b) the use of risk assessments for developing a written tuberculosis (TB) control plan; c) early identification and management of persons who have TB; d) TB screening programs for health-care workers (HCWs); e) HCW training and education; and f) the evaluation of TB infection-control programs.

Transmission of *M. tuberculosis* is a recognized risk to patients and HCWs in health-care facilities. Transmission is most likely to occur from patients who have unrecognized pulmonary or laryngeal TB, are not on effective anti-TB therapy, and have not been placed in TB isolation. Several recent TB outbreaks in health-care facilities, including outbreaks of multidrug-resistant TB, have heightened concern about nosocomial transmission. Patients who have multidrug-resistant TB can remain infectious for prolonged periods, which increases the risk for nosocomial and/or occupational transmission of *M. tuberculosis*. Increases in the incidence of TB have been observed in some geographic areas; these increases are related partially to the high risk for TB among immunosuppressed persons, particularly those infected with human immunodeficiency virus (HIV). Transmission of *M. tuberculosis* to HIV-infected persons is of particular concern because these persons are at high risk for developing active TB if they become infected with the bacteria. Thus, health-care facilities should be particularly alert to the need for preventing transmission of *M. tuberculosis* in settings in which HIV-infected persons work or receive care.

Supervisory responsibility for the TB infection-control program should be assigned to a designated person or group of persons who should be given the authority to implement and enforce TB infection-control policies. An effective TB infection-control program requires early identification, isolation, and treatment of persons who have active TB. The primary emphasis of TB infection-control plans in health-care facilities should be achieving these three goals by the application of a hierarchy of control measures, including a) the use of administrative measures to reduce the risk for exposure to persons who have infectious TB, b) the use of engineering controls to prevent the spread and reduce the concentration of infectious droplet nuclei, and c) the use of personal respiratory protective equipment in areas where there is still a risk for exposure to *M. tuberculosis* (e.g., TB isolation rooms). Implementation of a TB infection control program requires risk assessment and development of a TB infection-control plan; early identification, treatment, and isolation of infectious TB patients; effective

engineering controls; an appropriate respiratory protection program; HCW TB training, education, counseling, and screening; and evaluation of the program's effectiveness.

Although completely eliminating the risk for transmission of *M. tuberculosis* in all health-care facilities may not be possible at the present time, adherence to these guidelines should reduce the risk to persons in these settings. Recently, nosocomial TB outbreaks have demonstrated the substantial morbidity and mortality among patients and HCWs that have been associated with incomplete implementation of CDC's *Guidelines for Preventing the Transmission of Tuberculosis in Health-Care Facilities, with Special Focus on HIV-Related Issues* published in 1990.* Follow-up investigations at some of these hospitals have documented that complete implementation of measures similar or identical to those in the *1990 TB Guidelines* significantly reduced or eliminated nosocomial transmission of *M. tuberculosis* to patients and/or HCWs.

PROBABLE ROLE OF ULTRAVIOLET IRRADIATION IN PREVENTING TRANSMISSION OF TUBERCULOSIS: A CASE STUDY

William W. Stead, MD; Carole Yeung, RN, CIC; Carolyn Hartnett, BSN, COHN

The problem of transmission of tuberculosis (TB) in healthcare facilities is a serious one, all the more so when compounded by organisms that are drug resistant. The purpose of this report is to describe our experience with prolonged hospital care of a patient with advanced multidrug-resistant cavitary pulmonary TB in a hospital with complete pre-exposure tuberculin skin-test data.

CASE PRESENTATION

The patient, a 59-year-old white man with ankylosing spondylitis, was admitted to our hospital on January 2, 1992, with a diagnosis of cavitary pulmonary TB. In June 1990, he had been treated in another state with isoniazid (INH) and rifampin for 11 months with apparent recovery, despite irregular compliance. However, in the fall of 1991, he again developed a productive cough, for which the same drugs were given. When he failed to improve, he moved to Arkansas to be near a sister.

At the time of admission, the patient complained of a persistent productive cough and weight loss. The chest radiograph showed bilateral involvement with a thick-walled cavity in the right upper lobe measuring 60 × 110 mm. Sputum smears were 4+ positive for acid-fast bacilli (AFB).

Chemotherapy was instituted with rifampin, isoniazid (Rifamate), and pyrazinamide. By January 21, the patient had shown little improvement, the cough persisted, and the sputum smears remained strongly positive for AFB. A laboratory in the state from which he had come reported the organism to be *Mycobacterium tuberculosis*, resistant to rifampin and isoniazid but susceptible to ethambutol and streptomycin.

At this point, the drug regimen was changed to ethambutol (25 mg/kg/day), pyrazinamide (25 to 30 mg/kg/day) and streptomycin (1 gm/day). However, the 4+ positive sputum smears suggested a very large bacterial load that probably could not be controlled without resection of the thick-walled cavity.[1] After 10 days of this chemotherapy regimen, the right upper lobe was resected.

The operating room was one used for cardiac surgery and was particularly well ventilated (48 air changes per hour), supplemented by sterilization of upper air by ultraviolet germicidal irradiation (UVGI). The operating surgeon described the operation as the most difficult in his long career. A small empyema sac was entered inadvertently, and there was an audible escape of air and pus under pressure.

The lobectomy succeeded in converting the sputum smears to negative, with only one culture showing a few colonies of *M tuberculosis*. Following surgery, the patient was admitted to the surgical intensive care unit, which had ventilation of 22 air changes per hour supplemented by UVGI. The use of surgical masks was optional. Fiberoptic bronchoscopy was necessary on nine occasions to remove copious bronchial secretions. The patient's pulmonary reserve never was adequate to permit extubation, and he died on the 84th day. Pathologic examination of the right upper lobe confirmed the presence of a thick-walled cavity with abundant tubercle bacilli and a bronchopleural fistula with a localized empyema.

HOSPITAL CONTROL MEASURES FOR TB IN 1992

Since 1974, the hospital had been under contract with the Arkansas Department of Health for care of TB patients, providing recommended measures to contain TB and annual reporting of relevant data. Isolation rooms were provided with ventilation of 15 air changes per hour, supplemented by sterilization of the upper air by UVGI. Ventilation air (20% outside, 80% recirculated) was all HEPA filtered before enter-

From the Tuberculosis Control Program (Dr. Stead), Arkansas Department of Health, University of Arkansas College of Medicine, and the Baptist Medical Center (Ms. Yeung and Ms. Hartnett), Little Rock, Arkansas.

Address reprint requests to William W. Stead, MD, Director, Tuberculosis Program, Arkansas Department of Health, Mail Slot 45, 4815 W Markham St, Little Rock, AR 72205-3867.

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ing the room. Exhaust was to the outside, away from air intakes. The use of masks was not required.

In 1992, 15 other patients with TB were admitted. Of approximately 600 new employees that year, 36 (6%) were purified protein derivative (PPD) positive. Of 3,500 continuing employees, approximately 350 (10%) were known to be PPD positive. Of the remaining 3,150 PPD-negative employees, 15 (0.7%), none involved with our patient, showed PPD conversion during the year and were treated prophylactically with isoniazid. No employee developed TB. The case rate for Arkansas that year was 10.7 per 100,000.

RESULTS OF EPIDEMIOLOGIC INVESTIGATION

A total of 159 employees were identified as having contact with our patient over the 84-day period, most with daily contact during the first 30 days when sputum smears were consistently positive. Fifteen (9.4%) of the 159 were known already to be PPD positive (reaction $\geq$10 mm) and were followed clinically, in accordance with our long-standing policy.[2] Seven employees had relocated before postexposure testing and could not be located.

Of the 137 PPD-negative employees, 136 have remained nonreactive. One 35-year-old man showed a reaction of 15 mm on annual testing at another hospital, where he worked full time as a radiology technician. His exposure to our patient was by taking portable chest radiographs for 2 weeks following surgery, when the patient's bacteriology was negative. None of the 152 employees we could follow has developed TB in almost 4 years. We have heard nothing from the seven employees whom we could not trace.

DISCUSSION

TB generally is not a highly infectious disease. Israel studied five consecutive classes of nursing students at Philadelphia General Hospital in the 1930s.[3] He found that 366 (57%) of 637 were PPD positive on enrollment. After entry, 133 (48%) of 277 nonreactors converted to positive within 4 months, and 100% before graduation. Clinical TB developed in 34 (12.3%) of these. At the other extreme, Ehrenkranz and Kicklighter reported 21 (35%) of 60 PPD-negative employees converted to positive on the ward where a patient with unsuspected tuberculous pneumonia spent only 57 hours.[4] Two (10%) of the converters developed TB even before they could be given prophylactic therapy.

Catanzaro reported PPD conversion of 10 (77%) of 13 PPD-negative staff during fiberoptic bronchoscopy of a patient not suspected to have TB.[5] He calculated that, to do this, the patient had to excrete 249 infectious units per hour to achieve a concentration of one infectious unit per 69 cu ft of air.

In another episode, a similar exposure of hospital personnel occurred with PPD conversion of 36 (63%) of 60 PPD negatives, 5 (8.5%) of whom developed TB before preventive therapy could be given.[6] Templeton et al found that five of five PPD-negative employees became infected during autopsy on a man with undiagnosed miliary TB.[7] Two of the five (40%) developed positive sputum cultures for *M tuberculosis* with a restriction fragment-length polymorphism (RFLP) fingerprint identical to that of organisms isolated from autopsy material. Calculation indicated one infectious unit per 3.5 ft^3 of room air.

Based on these experiences, one might expect a patient remaining in hospital with positive sputum smears for a month to infect 10% to 30% of those caring for him or her. Of those, clinical TB would develop in at least 10% to 20%, if they were not given effective preventive chemotherapy.[2-7] However, we found only one converter not likely related to this case, and no one has developed TB.

For a brief time in the 1960s, it was believed that INH-resistant tubercle bacilli were much less virulent for humans than INH-susceptible ones. The experience of the last few years has shown the error of this notion.[8,9] We have no doubt the bacilli in this case would have spread infection had they not been killed in the air or removed by ventilation.

EXPERIENCE WITH UPPER AIR STERILIZATION

In the 1960s, Riley et al showed that UVGI of wavelength 254 nm was highly effective in killing tubercle bacilli suspended in air.[10] Drs. Riley and Nardell have reviewed the theory and experience with UVGI in two landmark papers.[11,12] Riley et al showed that UVGI can provide the equivalent of 17 air changes per hour.[13]

A decade of experience at the Milwaukee County Hospital in the 1960s to 1970s has been described briefly elsewhere.[14] We relied solely on UVGI to protect personnel of a 40-bed TB ward in a building of 1920s vintage with no mechanical ventilation. Retesting of all medical and nursing students after they had spent 6-week tours on the TB ward revealed no PPD conversions. In newer parts of the hospital, which had neither UVGI nor known TB patients, there always were several PPD conversions each year, presumably from patients with unrecognized TB.

New guidelines for protection of healthcare workers from TB have been issued by the Centers for Disease Control and Prevention.[15] They are discussed and critiqued in a recent paper by Menzies,[16] who

questions the almost exclusive emphasis on ventilation and respirators to control spread of TB in hospitals.

Perhaps one factor in the National Institute for Occupational Safety and Health's almost complete reliance on ventilation and respirators to protect hospital personnel is their vast experience with removing dust from air where the number of particles is in millions of particles per cu ft. A safe concentration of dust in the pottery industry (35% silica) is 10 million particles per cu ft.[17] This is at least seven orders of magnitude greater concentration than ever would occur with infectious particles of TB.

Ventilation can maintain such a safe level of dust, but it is a very different matter to clear the air of infectious particles of TB when inhalation of a single particle can cause infection. Indeed, Kantor et al demonstrated transmission of TB during an autopsy, despite a measured ventilation of 11 air changes per hour.[18] While air replacement is the only way to clear dust or fumes from the air, infectious particles of TB are readily killed with UVGI.[19,20]

It seems apparent that there is much yet to be learned about the best and most cost-effective way to protect healthcare workers from TB. We suggest that the experience reported here constitutes an urgent call for intensive study of upper air disinfection with germicidal UV irradiation in this effort.

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