Tuberculosis: Illness, Treatment, Lifestyle

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Dedication

To the patients who inspired this project and instill it with meaning.
Acknowledgments

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Project Goals

Learning Objectives

After viewing the video program, *Tuberculosis: Illness, Treatment, Lifestyle*, and reading these related materials the participant will be able to identify the following:

1. Five symptoms of pulmonary tuberculosis.
2. Five extrapulmonary sites of tuberculous infection.
3. Five obstacles to effective treatment of tuberculosis.
4. The role of Directly Observed Therapy in the management of patients with tuberculosis.
5. The demographic characteristics of tuberculosis.

*Tuberculosis: Illness, Treatment, Lifestyle*, is part of a larger project designed to increase the awareness and knowledge base of a new generation of clinicians about tuberculosis. The larger project, entitled *Tuberculosis Education in an Academic Health System*, is funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. The project is developing a curriculum for tuberculosis education based in the University of Pennsylvania School of Medicine with integrated components throughout the University’s Health System and surrounding community. The objective is to educate medical and nursing students, clinicians, and other health care providers about tuberculosis in order to provide optimum care for patients.

The goals of the project will be achieved through the following specific aims:

1. The expansion of the currently existing medical school curriculum to contain modules in each required year devoted to tuberculosis.
2. The development of a program of ambulatory medical education in tuberculosis-based outpatient services of the Mycobacterial Diseases Program of the Lung Center.

3. Transfer of the Medical Center’s tuberculosis infection control curriculum into modular components specific to clinical occupations throughout the Health System and region.

4. Education of the Penn Medical Student Community Volunteer program for outreach in the adjacent West Philadelphia community and surrounding counties.

5. Development of curricular materials to support a comprehensive outreach. Continuing education symposia for primary care attending physicians at satellite sites throughout the regional health system.

Background and Significance

In recent decades, the declining incidence of pulmonary tuberculosis and the circulation of susceptible strains attracted little attention to the disease and created the impression that the elimination of tuberculosis was at hand. As better anti-tuberculous drugs were added to our armamentarium, the duration of therapy shortened and patients rarely succumbed to the disease in the United States. In the mid-1980s, decades-old trends were reversed and hospitals and other health care settings became common meeting grounds for Mycobacterium tuberculosis (M.Tb.) and immunocompromised hosts.¹ The extreme vulnerability of patients co-infected with HIV and M.Tb. has resulted in rapid
progression from infection to disease and death. Multi-drug resistant (MDR) strains of tuberculosis and high mortality rates among HIV infected persons has increased our awareness of the importance of appropriate management of tuberculosis.

Historically, tuberculosis has been a disease of poverty and overcrowding. The conditions favorable for disease transmission are prevalent in many communities outside of our inner cities. In 1994, two suburban counties in Southeastern Pennsylvania were among the highest caseloads for tuberculosis in the Commonwealth. This region is the most populous in the state and accounts for nearly half of Pennsylvania’s Tb cases. In recent years, Philadelphia and Delaware County have had case rates exceeding the national rate.

The Commonwealth of Pennsylvania and its health districts reported a decline in cases and case rates in 1994 for the first time in this decade. By 1998 substantial improvements in cases and case rates were realized in Southeastern Pennsylvania and in the Commonwealth as a whole. Despite this success, Philadelphia’s case rate of 12 cases/100,000 population in 1998 is approximately twice the rate for the U.S.A. as a whole. The trend in Tb cases for 1993-1998 is displayed in Graph 1 on page 12.

Southeastern Pennsylvania carries the seeds of future epidemics of tuberculosis. The regional population is comprised of subgroups at high risk for tuberculosis including African-Americans, Hispanics, Asian and Pacific Islanders as well a substantial prison population with increased risk (data from the PA Department of Health). A seasonal influx of migrant workers, émigrés from developing nations with high rates of tuberculosis and the largest caseload of HIV cases in the Commonwealth creates a large pool from which new cases may develop. The racial distribution of cases in Philadelphia for 1998 is displayed in Graph 2 on page 12.
Clinician Knowledge

A recent survey by the Centers for Disease Control and Prevention (CDC) (unpublished) revealed that most clinicians do not recognize the signs and symptoms of tuberculosis. Mahmoudi and Iseman in reviewing tuberculosis management found that errors occurred in 80% of the cases reviewed in their series. On average, four management errors occurred per case. Many of the errors committed resulted in ineffective therapy or failed to identify risk factors for non-compliance.

The problems identified in this case series are not unique. Brudney and Dobkin have reported an 89% non-compliance rate among a cohort of patients with active pulmonary tuberculosis discharged from one institution. Kopanoff, reporting on the characteristics of patients who had recurrent tuberculosis, found that 20% did not have chemotherapy prescribed for their initial episode and another 20% had inappropriate or inadequate therapy prescribed. Patients under the care of private physicians were more likely to complete therapy but were also more likely to receive inappropriate therapy than patients treated in other settings. These obstacles to effective management of tuberculosis must be addressed in order for health systems to appropriately treat a complex disease that is unfamiliar to many of its clinicians.

The means to control tuberculosis already exist. They include early recognition, isolation, curative chemotherapy, environmental control systems and personal protective equipment. The means to disseminate this information has not been addressed in a systematic way. This project will use the educational and clinical resources of an academic health system to close gaps in medical knowledge and impact on the management of tuberculosis in a region with higher endemic case rates than the national average.
Tuberculosis has been a threat to human health and survival for thousands of years. Mummified human remains show evidence of skeletal tuberculosis dating back five thousand years. As society evolved to urban living conditions during the Industrial Revolution, the disease reached epidemic proportions. Contagious persons in small dwellings with many susceptible individuals permitted near-universal exposure to tuberculosis among the population. The sanitorium movement in the latter part of the 19th Century began the era of tuberculosis control in which persons with active pulmonary Tb were removed from society until their disease was under control. This coincided with a period of intense investigation for medical cures culminating in the development and use of para-aminosalicylic acid (PAS) and streptomycin in the late 1940s.

Subsequently, the antituberculous armamentarium has grown, the duration of therapy has been shortened, and the sanatoria have all been closed. During the 1970s and 1980s, many patients
did not complete curative courses of therapy because of a lack of public health system supports to address their human and medical needs. The result was the reversal of the trend toward fewer cases every year and an increase in the incidence of multi-drug resistant tuberculosis (MDR-Tb). The recognition of this trend, the initiation of four drug initial therapy for Tb, and the creation of programs of Directly Observed Therapy (DOT) to insure compliance has led to a decline in cases and rates of Tb again.

The event most responsible for the re-emergence of tuberculosis in the United States in the 1980s was the occurrence the epidemic of HIV infection. With an estimated 25 million people latently infected with Mycobacterium tuberculosis in the U.S., immigration from areas of the world highly endemic for Tb and the persistence of poverty, drug and alcohol addiction, and the ongoing HIV epidemic, the goal of eliminating tuberculosis in this country remains a formidable challenge.

The Illness
Exposure to Disease

Tuberculosis is caused by the bacterium, Mycobacterium tuberculosis, which is spread person to person through the air. The risk of infection with Mycobacterium tuberculosis is dependent on the number of organisms that a patient with active disease coughs into the air and the length of time that a susceptible person is exposed to a case. Household contacts of persons with active disease are most likely to become infected because of their prolonged exposure. Only patients who are able to expel the contagious particles, known as infectious droplet nuclei, into the air are capable of spreading the disease. Extrapulmonary disease is not contagious unless droplet nuclei can be expelled from the site of infection.

Once an individual becomes infected there is a lifetime risk of approximately 10% of developing active disease. The greatest risk occurs in the first two years after infection. Impairment of immune function increases the risk of progression to active disease. Co-infection with HIV dramatically increases the risk of developing active disease. Anti-tuberculous therapy complicates the treatment of HIV. Rifampin, a key drug for Tb treatment, reduces the levels of the protease inhibitors (PI), important components of HIV therapy. In such cases, rifampin should be replaced with rifabutin and HIV therapy should be modified to use PIs with diminished interaction with rifabutin. Graph 3 on page 13 describes the HIV status of reported cases of Tb in Philadelphia in 1998.

In two-thirds of cases, tuberculosis will cause disease and symptoms in the lung. The distribution of Tb cases by form of disease is shown in graph 4 on page 13. Ten percent of the time, disease will occur in the lungs and in an extrapulmonary site concurrently. In 24% of cases disease is confined to extrapulmonary sites. The symptoms associated with pulmonary tuberculosis are listed on page 11. Extrapulmonary sites of infection are listed in Graph 5 on page 14.
**Demographics**

Tuberculosis today retains its historic characteristics of affecting the poor, immigrants, and those living in crowded conditions. Minority persons comprise about 50% of Philadelphia’s population but account for 90% of all cases of tuberculosis. Case rates in Philadelphia are highest among the Asian population followed by the African-American and Hispanic communities.

Twenty-five percent of the tuberculosis cases in Philadelphia occur in foreign-born persons. The largest proportion of tuberculosis imported into Philadelphia is from Asia. Nationwide, 40% of all Tb cases are imported from foreign countries. Graph 6 on page 14 describes the distribution of tuberculosis cases in Philadelphia country or origin.

**Contact Investigation**

Following the identification of an active case of pulmonary tuberculosis, contacts of the case must be tested and assessed for infection. Public health officials will identify close contacts and perform follow-up tuberculin skin tests (Mantoux 5 TU) as soon as possible after exposure and again 10-12 weeks following exposure. Recent contacts with a tuberculin reaction of 5 mm or greater should receive isoniazid prophylaxis to reduce the risk of developing active disease. *See Appendix 1: Tuberculin Skin Testing Table.*
Graphs

Graph 1
Reported Tuberculosis Cases

Graph 2
TB Incidence by Race
Philadelphia, 1998

Philadelphia Department of Public Health
Graph 3

HIV Status of Reported Cases
Philadelphia, 1998

- Unknown: 27%
- Negative: 21%
- Positive: 14%
- Refused: 3%
- Not Offered: 24%
- Test Done, Results Unknown: 11%

Philadelphia Department of Public Health

Graph 4

Reported Tuberculosis Cases by Form of Disease
Philadelphia, 1998

- Pulmonary: 66%
- Extrapulmonary: 24%
- Both: 10%

Philadelphia Department of Public Health
Graph 5
Extrapulmonary Cases by Site of Disease
Philadelphia, 1998

- All Others: 34%
- Pleural: 19%
- Lymphatic: 26%
- Bone and/or Joint: 12%
- Genitourinary: 9%

Graph 6
Foreign Born TB Cases by Country of Birth
Philadelphia, 1998

- All Others: 39%
- Vietnam: 16%
- India: 16%
- Puerto Rico: 11%
- Haiti: 4%
- Dominican Republic: 7%
- Cambodia: 7%
Virtually all patients with active pulmonary tuberculosis should be admitted to the hospital to initiate treatment. Initial therapy requires four anti-tuberculous medications: isoniazid, rifampin, pyrazinamide and either ethambutol or streptomycin.\textsuperscript{8,9} Admitting the patient to initiate therapy permits observation for side effects, education regarding the disease, and assessment of psychosocial issues which may impede therapy. Patients initiated on therapy as outpatients cannot be readily assessed for these problems. Patients with drug susceptible tuberculosis will begin to respond to treatment within two weeks of initiating therapy. A patient who has not sterilized his sputum after twelve weeks of therapy may have a resistant isolate requiring the addition of new medications. \textit{See Appendix 2: Drug Tables.}

Hospitalized patients must remain in airborne isolation as a precaution to prevent the spread of the infection to susceptible persons.\textsuperscript{4} The isolation room is ventilated in a way that draws air into the room from the corridor (negative pressure relative to
adjacent spaces) and exhausts the room air outside the building. The entire room air volume must be exchanged a minimum of six times per hour. At that rate, the room air is decontaminated in approximately one hour. Persons entering the isolation room must wear certified respirators which filter particles in the size range of the tubercle bacillus out of the room air.

**Experience of Isolation**

The experience of tuberculosis isolation for patients is a demeaning one. Patients describe feelings of embarrassment, seclusion, and shame at the thought of family members and friends having to wear a mask to visit them. Patients in airborne isolation are not permitted to move freely about the hospital because of the potential of spreading the disease to other patients.

Following discharge from the hospital, patients are permitted to return home. Any subsequent exposure among household personnel will be no more severe than that which occurred prior to admission. As an outpatient, it may be difficult to remember to take the medications. The likelihood that a patient will not be adherent to therapy is difficult to predict. For that reason, all patients should be referred for treatment follow-up on a Directly Observed Therapy (DOT) basis. Directly Observed Therapy is administered by the Health Department and consists of the patient self-administering their medications in the presence of an observer. Such programs have greatly enhanced the compliance with treatment of Mycobacterium tuberculosis infections.

Directly Observed Therapy became necessary in this country when it was observed that a significant proportion of patients failed to complete a curative course of therapy. In a seminal paper reported from the Harlem Hospital it was learned that 89% of patients failed to complete therapy. Predicting compliance with a complicated medical regimen can be difficult. Therefore, all patients with tuberculosis should be considered
candidates for DOT. Some individuals, despite hospitalization and DOT, are unable to remain adherent to therapy. In such cases it may be necessary to obtain a court order to remand the patient for examination and treatment.

Departments of Health in most jurisdictions possess the statutory authority to detain, examine, and isolate patients known or suspected to have tuberculosis. Patients may be held against their will under order from a court to insure their compliance with medical therapy. Such orders are reserved for those individuals who have demonstrated lack of awareness, indifference, or inability to comply with their anti-tuberculous regimen.10

The Lifestyle

A variety of factors may interfere with a patient’s ability to complete treatment. Some of these factors are listed in the table on page 18. If these issues are not addressed as a part of the treatment plan, they may impede effective therapy and lead to the development of drug resistance.
The social element of tuberculosis has always been an important determinant of who gets the disease and who is able to be cured. The lower socio-economic status often associated with immigrants and members of minority populations in a society confers higher risk of acquiring infection and disease. The crowded living conditions associated with congregate settings such as prisons, homeless shelters, and refugee camps provide opportunities for transmission among susceptible persons with chronic diseases and malnutrition. Cultural obstacles and language barriers further impede the ability to treat some populations.

Alcoholism and illicit drug use often result in organ failure or immune suppression that increase the risk of tuberculous disease after infection and impair the ability to complete therapy. HIV infection dramatically increases the risk of developing active disease and is associated with greater risk of death if not diagnosed and treated rapidly. The newest and most effective class of antiretroviral drugs, the protease inhibitors, are susceptible to drug-drug interactions from rifampin which may render the protease inhibitors ineffective. In any single patient multiple obstacles to therapy may be present and any one may result in the failure to effectively treat the patient. Each obstacle to treatment must be effectively addressed if a cure is to be achieved.
Conclusion

The goal of the United States Public Health Service is to eliminate tuberculosis in this country by 2010. That goal was thrown off track during the 1980s and 1990s by the resurgence of cases in areas of high prevalence for HIV infection. One-third of the tuberculosis cases in the United States are imported from other countries. Now that the numbers of cases and case rates are falling again, the challenge will be to stay the course in this country and then to find diagnostic tools and therapies that can be inexpensively applied to the enormous reservoir of tuberculous disease that exists in the impoverished countries of the developing world.

References

   Centers for Disease Control and Prevention...Jeffrey P. Koplan, M.D., M.P.H. Director

   Describes risks to HIV infected persons of infection with M.Tb.


*Detailed document setting the standard for preventive measures in health care facilities for Tb control.*


*Review of the National Jewish experience related to common errors made by physicians in the management of tuberculosis leading to the emergence of multi-drug resistance.*


*Seminal article describing the proportion of patients failing to complete therapy at one hospital. Raised awareness of need for DOT.*


*An assessment of factors resulting in recurrent disease.*


*Recommendations and rationale for initial therapy in the era of MDR-TB.*


*The bible of therapeutic standards for tuberculosis in the U.S.A. based on American Thoracic Society recommendations. Updated periodically.*


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**Photography Credits**

1. cover photo: Eagleville Hospital, Eagleville, PA

2. page 8: Alumni Association of Philadelphia General Hospital School of Nursing

3. page 9: Visiting Nurse Society of Philadelphia

4. page 15: ibid.

5. page 17: Starr Centre Association of Philadelphia
### Appendix 1

#### Table on Treatment of Positive Tuberculin (PPD) Reactions

<table>
<thead>
<tr>
<th>Treatment recommended regardless of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reaction ≥ 5 mm</td>
</tr>
<tr>
<td>HIV infection (known or suspected)</td>
</tr>
<tr>
<td>close contacts of a case of infectious Tb case</td>
</tr>
<tr>
<td>chest x-ray film suggestive of previous Tb without adequate prior treatment</td>
</tr>
<tr>
<td>- Reaction ≥ 10 mm</td>
</tr>
<tr>
<td>underlying medical condition: HIV, substance abuse, M. Tb infection within two years (conversion), diabetes mellitus, silicosis, prolonged corticosteroid therapy, malignancy, end-stage renal disease, intestinal bypass, gastrectomy, chronic malabsorption, body weight 10% or more below ideal.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment recommended under age 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reaction ≥ 10 mm</td>
</tr>
<tr>
<td>Foreign born persons from highly endemic areas (Asia, Latin America)</td>
</tr>
<tr>
<td>Medically under-served populations</td>
</tr>
<tr>
<td>Residents and staff of long term care facilities</td>
</tr>
<tr>
<td>Children &lt; 4 years of age</td>
</tr>
<tr>
<td>Health care workers</td>
</tr>
<tr>
<td>- Reaction ≥ 15 mm</td>
</tr>
<tr>
<td>Persons &lt; age 35 with no known risk for Tb</td>
</tr>
</tbody>
</table>

Prophylaxis not recommended for persons > age 35 without increased risk for Tb as outlined above.
### Regimen Options for the Preferred Initial Treatment of Children and Adults *

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administer daily isoniazid, rifampin, and pyrazinamide for 8 wk followed by 16 wk of isoniazid and rifampin daily or 2-3 times/wk.** In areas where the isoniazid resistance rate is not documented to less than 4%, ethambutol or streptomycin should be added to the initial regimen until susceptibility to isoniazid and rifampin is demonstrated. Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.</td>
<td>Administer daily isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol for 2 wk followed by 2 times/wk** administration of the same drugs for 6 wk (by DOT), and subsequently, with 2 times/wk administration of isoniazid and rifampin for 16 wk (by DOT). Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.</td>
<td>Treat by DOT, 3 times/wk** with isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin for 6 mo.^ Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 mo.</td>
</tr>
</tbody>
</table>

* Adapted from MMWR Vol. 42/no. RR-7.

** All regimens administered 2 times/wk or 3 times/wk should be monitored by directly observed therapy (DOT) for the duration of therapy.

^ The strongest evidence from clinical trials is the effectiveness of all four drugs administered for the full 6 mo. There is weaker evidence that streptomycin can be discontinued after 4 mo if the isolate is susceptible to all drugs. The evidence for stopping pyrazinamide before the end of 6 mo is equivocal for the 3 times/wk regimen, and there is no evidence on the effectiveness of this regimen with ethambutol for less than the full 6 mo.
### Dosage Recommendation for the Initial Treatment of Tuberculosis in Children* and Adults

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Daily Dose</th>
<th>Twice-Weekly Dose</th>
<th>Thrice-Weekly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>5</td>
<td>20-40</td>
</tr>
<tr>
<td>Rifampin</td>
<td>mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>10</td>
<td>10-20</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>mg/kg</td>
<td>Max 600 mg</td>
<td>Max 600 mg</td>
</tr>
<tr>
<td></td>
<td>15-30</td>
<td>15-30</td>
<td>50-70</td>
</tr>
<tr>
<td></td>
<td>Max 2 g</td>
<td>Max 2 g</td>
<td>Max 4 g</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>mg/kg^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max 1.0 g</td>
<td>Max 1.0 g</td>
<td>Max 1.5 g</td>
</tr>
</tbody>
</table>

* Children < 12 yr of age.

^ Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (< 8 yr of age). However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or susceptibility is likely.