

The challenge of drug-resistant tuberculosis

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- **CLINICAL ISSUES** After declining for decades, the incidence of tuberculosis is again increasing, and strains resistant to multiple drugs are appearing. The greatest increases in infection have been in blacks and Hispanics. The disease is most aggressive in patients infected with human immunodeficiency virus and in patients receiving immunosuppressive therapy; diagnosis may be difficult in these groups. Resistance to antituberculosis drugs is the result of inadequate regimens or of patients not complying with prescribed regimens.
- **RECOMMENDATIONS** The current epidemic can be stopped, but this will require a serious commitment by the public, the medical community, government, and industry. Physicians must prevent the spread of tuberculosis, detect people who are infected, treat infected people preventively with isoniazid, and, in people with active disease, rapidly establish the diagnosis and use adequate, directly supervised, four-drug regimens to treat it. Convenient combined preparations and programs to directly supervise the taking of medications are needed.

■ INDEX TERMS: TUBERCULOSIS; DRUG RESISTANCE, MICROBIAL; ANTITUBERCULAR AGENTS; COMMUNICABLE DISEASE CONTROL ■ CLEVE CLIN J MED 1994; 61:431-437

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THE FAMILIAR photographs of tuberculosis sanatoriums in the early days of this century show patients sitting outside on deck chairs in the winter, taking the "fresh air treatment." The 5-year survival rate for such patients was 50%. And nearly 100 years later, patients with multiple-drug-resistant tuberculosis without human immunodeficiency virus (HIV) infection have a 5-year survival rate of about 50%.¹

After decades of declining incidence, tuberculosis is staging a comeback in the United States. In many parts of the world it never went away. Fully one third of the world's population—1.7 billion people—are infected with *Mycobacterium tuberculosis*.^{2,3} Twenty million people have active tuberculosis, and 8 million more acquire the disease each year. Over 3 million people die of tuberculosis each year, making it the most common infectious cause of death in the world. More than 4 million people are infected with both *M tuberculosis* and HIV, according to the World Health Organization.

In 1953, when data collection began for tuberculosis, 84 new cases of tuberculosis per 100 000 population were reported in the United

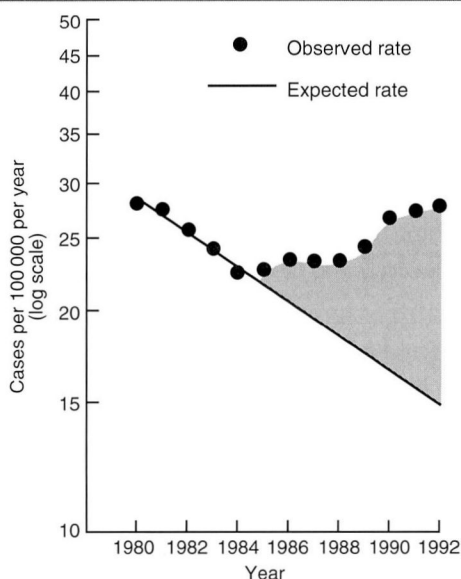


FIGURE. Expected and observed cases of tuberculosis in the United States, 1980 to 1992. Data from the Centers for Disease Control, reference 5.

States. The incidence declined by 5% to 6% per year until 1984, when 22 cases per 100 000 were reported; thereafter, it leveled off and began to rise again. Nearly 27 cases per 100 000 were reported in 1992 (Figure).⁴ Based on the historic decline of tuberculosis of about 5% per year, the Centers for Disease Control and Prevention (CDC) has calculated that there have been 52 000 “excess” cases of tuberculosis from 1984 through 1992.⁵ The biggest increase has been among blacks and Hispanics between ages 20 and 40. Of even more concern is an increase of the disease in children under age 5, again primarily among blacks and Hispanics, because cases of pediatric tuberculosis signify recent transmission of infection in the community.⁶ The incidence is also rising among non-Hispanic elderly whites.

WHY TUBERCULOSIS IS RETURNING

Although socioeconomic factors, eg, substance abuse, limited access to health care, poverty, substandard housing, and homelessness, have led to an excess number of cases, these are not the only reasons for the reburgeoning of tuberculosis in the United States. Also to blame are the HIV epidemic, a deterioration in the health care infrastructure, and increases in the number of foreign-born persons.

When a disease has public health import, the public becomes concerned, at least initially, and resources are allocated to fight it. However, after some progress has been made, public interest declines, and programs are eliminated prematurely. As a result, the incidence of the disease rises again, a phenomenon this author calls the “U-shaped curve of concern.”⁷ This has happened with tuberculosis and with other diseases such as syphilis.

Tuberculosis has been ignored by the medical community for years, probably because cases have occurred only in racial or ethnic minorities. But now we are seeing outbreaks in prisons, shelters for the homeless, residential care facilities for patients with acquired immunodeficiency syndrome (AIDS), nursing homes, and “crack houses.” These outbreaks have led to nosocomial transmission of tuberculosis with the additional problem of multiple-drug-resistant strains.

Resistance to multiple drugs

Resistance to both isoniazid and rifampin substantially increases the cost and duration of treatment, while decreasing the efficacy. Multiple-drug-resistant strains are not necessarily more contagious than sensitive strains, but they are much harder to control, both in the patient and in the patient’s contacts.

The factors thought to favor outbreaks of multiple-drug-resistant tuberculosis are inadequate patient management leading to development of drug-resistant organisms, convergence of immunocompromised people and people with infectious tuberculosis, and inadequate infection control practices in isolation facilities. These problems exist in hospitals, nursing homes, prisons, shelters for the homeless, detoxification centers, and other settings.

The CDC has reported over 300 cases resistant to oral combinations of first-line and second-line antituberculosis agents in facilities in Miami, New York City, New York State, and New Jersey between 1988 and 1992. These were largely but not exclusively associated with HIV infection. The mortality rate was higher than 80%, and most of these people died within 4 weeks of diagnosis. In surveys of all tuberculosis cases reported to the CDC during the first quarter of 1991, approximately 3% were resistant to both isoniazid and rifampin; in New York City, 19% were.

In another example, the East Orange Veterans Administration Hospital reported 51 cases of tuberculosis between January 1990 and May 1992. Nine-

teen were found to be resistant to one or more drugs for tuberculosis, and 13 were resistant to two or more drugs. All of the patients were infected with HIV and, hence, were immunocompromised. All were black, all were born in the United States, and all were intravenous drug users. Twelve were men and three were also homosexual. Nine had pulmonary tuberculosis, and four had disseminated tuberculosis. Eleven patients died a median of 33 days after their cultures were found to be positive. Several factors were thought to facilitate the transmission at that facility: the isolation ward lacked negative-pressure ventilation; the patients were allowed to walk without masks in the halls where the doors were open; and all of the patients with HIV infections were kept in one ward.

Nosocomial infections

The problem is not confined to resistant organisms in hospitals in New York City. Ten renal transplant recipients in a ward at the University of Pittsburgh acquired tuberculosis; five of these died.^{8,9} Fortunately, the organisms were sensitive to all the drugs that were tested, making infection control and containment potentially easier. However, this incident demonstrates the ease with which nosocomial infections can spread among an immunosuppressed inpatient population. Failure to adhere to standard infection control procedures—not failure of these procedures—appears to be responsible for most nosocomial spread.

The conditions are particularly ripe for outbreaks of tuberculosis in prisons, where there is a high prevalence of tuberculous infection, a high incidence of tuberculosis, and a high prevalence of HIV infection. The inmates are both crowded and mobile; the authorities move them from one facility to another to keep them from forming cliques.

Among the homeless, various studies have reported a 6.8% prevalence of active disease and a 51% prevalence of infection.¹⁰ In the setting of shelters for the homeless, establishing the diagnosis is paramount.

Failure to establish diagnosis often causes spread

The usual reasons for failure to establish the diagnosis are (1) the physician does not consider the diagnosis of tuberculosis; (2) an inadequate amount of specimen is collected; (3) the laboratory report does not reach the physician; (4) the case has an

atypical presentation; and (5) the patient refuses to be tested.

At one hospital, 11 patients infected with HIV died of tuberculosis before a diagnosis of tuberculosis was established; no tuberculin tests were done, acid-fast smears were done in only three patients, and bronchoscopy was done in only four patients. Probably most important, *Pneumocystis carinii* pneumonia was presumptively diagnosed in nine patients, after which their physicians stopped looking for another cause of their illness. Tuberculosis can coexist with *P carinii*, and in an HIV-infected person the manifestations of tuberculosis can vary widely and make recognition of the disease difficult. Incorrectly diagnosing tuberculosis as *P carinii* infection and treating it with aerosolized pentamidine could lead to a local epidemic as the patient continues to cough and spread aerosolized tubercle bacilli.

In areas with a high incidence of tuberculosis, any immunocompromised patient with a new pulmonary infiltrate or signs and symptoms consistent with tuberculosis should be considered to have tuberculosis until proven otherwise.

HIV AND TUBERCULOSIS

People infected with HIV are particularly vulnerable to multiple-drug-resistant tuberculosis. The prevalence of tuberculosis in certain HIV-infected groups is high, and tuberculosis is the only HIV-related infection transmitted from person to person regardless of whether the exposed person is infected with HIV. However, high cure rates are attainable if tuberculosis is diagnosed and adequately treated, and preventive therapy can be effective in persons with HIV infection.¹¹

In the United States, about 10 million people are infected with *M tuberculosis*, and between 1 million and 1.5 million people are infected with HIV. The people infected with both are at very high risk for developing active tuberculosis (approximately 10% per year).¹² The overlap between the two populations differs according to geographic location. In rural or western areas in the United States there is very little overlap, and very little HIV-related tuberculosis. In inner-city areas there is more overlap and, therefore, more HIV-related tuberculosis. In East Africa, Haiti, and Southeast Asia, there is a huge tuberculosis-infected population, a huge HIV-infected population, a huge amount of overlap, and a huge prevalence of HIV-related tuberculosis.

WHAT SHOULD BE DONE?

This epidemic can be stopped, although it would have been easier to stop it 5 or 10 years ago. The national strategic plan for the elimination of tuberculosis published in 1989¹³ established the goal of eliminating tuberculosis by the year 2010 with an interim target case rate of 3.5 per 100 000 population by the year 2000. In 1988, when the plan was written, there were 22 500 cases and the case rate was 9.1 per 100 000.¹³ In 1992 there were almost 27 000 cases and the case rate was 10.6 per 100 000.⁴ Obviously, the trend is going in the wrong direction.

The strategic plan suggested that physicians and public health officials use the existing prevention and control methods more effectively in high-risk populations. The plan also called for developing and evaluating new technologies to prevent, diagnose, and treat tuberculosis, and for rapidly transferring these new technologies into clinical and public health practice. These new technologies, such as new diagnostic tests, drugs, and devices, will take time to develop and assess. In the meantime, there is no reason not to proceed with the drugs and tests already available.

The CDC's public health strategy for preventing and controlling tuberculosis is, first, to identify and treat people with active disease, cure their illness, and prevent further transmission, and, second, to identify and treat infected people to prevent future development of the disease.

The CDC has also issued guidelines for preventing the transmission of tuberculosis in health care settings¹⁴ which call for the following: (1) prevention of the generation of infectious airborne particles (droplet nuclei) by early identification and treatment of persons with tuberculosis infection and active tuberculosis; (2) prevention of the spread of infectious droplet nuclei into the general air circulation by applying source-control methods; (3) reduction of the number of infectious droplet nuclei in air contaminated with them; and (4) surveillance of health care facility personnel for tuberculosis and tuberculous infection.

TREATING TUBERCULOSIS PROPERLY

There are four populations of mycobacteria, each with a different rate of growth. The continuously growing organisms must be treated with bactericidal drugs. Organisms whose growth is inhibited by the

acidic milieu live in macrophages and are best treated with pyrazinamide. Slowly growing organisms that have spurts of metabolism are best treated with rifampin. Finally, dormant organisms, because they are not growing, are immune to treatment until they have spurts of metabolism.

Antibiotics must be used in combination to treat all of these organisms. Hence, there are two phases of therapy. The bactericidal phase—the initial intensive chemotherapy—is directed toward the rapid destruction of most of the large multiplying populations of tubercle bacilli. The sterilizing phase, the period of maintenance chemotherapy, is directed at eliminating most of the dormant bacilli; the destruction of these bacilli occurs during the intermittent spurts of metabolic activity. The drugs in current use are very specific: isoniazid and rifampin provide the best bactericidal effect, while rifampin and pyrazinamide provide the best sterilizing effect.

To prevent resistant organisms from emerging, ethambutol or streptomycin should also be added. Therefore, for the first 2 months of treatment, all people with tuberculosis need isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. This is followed by 4 months of isoniazid plus rifampin if the organism is susceptible to both of these drugs. If the organism is resistant to either of these, the other drugs can be continued.

If the patient is infected with HIV, treatment must be continued for an additional 3 months. If the probability of multiple drug resistance is high, another drug must be added. Fixed-dose combinations should always be used, when available, to improve patient compliance.

Standards of care for tuberculosis have been defined by the American Thoracic Society, the CDC, and the American College of Chest Physicians.^{15–18} However, in a study of patients with pulmonary tuberculosis admitted to the National Jewish Center for Immunology and Respiratory Medicine, therapeutic errors were made in 28 of 35 patients.¹⁹

PREVENTING RESISTANCE

Many cases of multiple drug resistance are not the fault of patient noncompliance but of an inadequate regimen. Mutations spontaneously occur in any population of tubercle bacilli, producing organisms resistant to certain drugs. If there are about 100 million organisms in an average tuberculous lesion, and isoniazid kills 999 999 of every million, the 100

that survive of the original 100 million will pass on their resistance to future generations with every cell division. The cells divide every 20 hours, and every antituberculosis drug has its own spontaneous mutation rate.

Fortunately, the likelihood of an organism mutating to be resistant to two antibiotics at the same time is the product of the probabilities of mutating to become resistant to each of them; with isoniazid plus rifampin, the odds are one in 10^{14} —and there are only 10^8 organisms in the lesion. This is the rationale behind giving multiple antibiotics. Of course, if the organism is already resistant to one of these agents, it will rapidly become resistant to the other one as well.

Unfortunately, except for isoniazid, the drugs used to control tuberculosis are moderately expensive. The cost of medications must be considered in plans for public health control, but cost can never be the main or governing factor.

COMBINED PREPARATIONS

Compliance can be enhanced by using combination preparations, which are one of the best-kept secrets in medicine. A combination of rifampin, isoniazid, and pyrazinamide is available in Europe, where it is sold by Marion Merrell Dow under the name of Rifater. It has been studied in about 20 institutions in the United States. Patients find it acceptable, and prescribing is simple and subject to less error than prescribing all three pills separately.²⁰ This product has recently been licensed in the United States.

A preparation of isoniazid and rifampin available in the United States, Rifamate (Marion Merrell Dow), is not widely used, although it should be. Moulding (personal communication) recently found that only 20% of the rifampin in the United States is sold in the form of Rifamate.

If the option is available, fixed combinations should always be used, and Rifater should be standard therapy. Remove the option to prescribe a single drug without the others and the opportunity for resistant organisms to develop is almost eliminated.

DIRECT OBSERVATION OF MEDICATION-TAKING

If tuberculosis is to be eradicated, patients must take all their medications all the time, and the only way to be absolutely sure they do this is to watch

them do it. Twelve years ago, our group successfully used directly observed therapy in 21 patients who had been manifestly noncompliant.²¹ Sputum cultures became negative in 20 of the 21 patients within 6 months; one patient had a relapse. We suggested that directly observed drug therapy be used in all patients suspected of noncompliance.

A statement of the Advisory Council for the Elimination of Tuberculosis recommended that directly observed therapy be considered in all patients.⁴ Iseman²² has also advocated directly observed therapy for all patients.

In an editorial, Annas²³ disagreed, saying there is “insufficient justification for requiring this annoying and inconvenient method of treatment for patients who are virtually certain to take their antituberculosis medications.” This author disagrees,²⁴ because there is no way to predict who these people are. There is no correlation of age, race, sex, or socioeconomic status with compliance with a medical regimen.^{25,26} Left to their own devices, people in general do not take their medications precisely as directed. A visit to the emergency department of any hospital will confirm this.

Therapy need not be observed by a paid health worker who goes out into the community or workplace. The patient's spouse or fellow worker can be engaged to make sure he takes his medicine. If resistance is to be avoided and tuberculosis eliminated, one cannot simply assume people will take their medicine as prescribed.

PREVENTIVE THERAPY

The other way to halt the tuberculosis epidemic is to treat the people who are infected to keep them from developing the active disease. Preventive therapy substantially decreases the risk of latent asymptomatic infection progressing to clinical disease and prevents the recurrence of past disease.²⁷ Only people with active tuberculosis can spread it to other people, and only people with active tuberculosis can take their drugs improperly and acquire resistance. Preventive therapy reduces an infected person's risk of developing active tuberculosis. It consists of 6 to 12 months of daily isoniazid, during which the patients must be monitored for compliance and for symptoms of toxicity. Preventive therapy should *never* be given unless active disease has been completely and reasonably excluded, since this will only breed more resistant strains. CDC

TABLE
CRITERIA FOR DETERMINING NEED FOR PREVENTIVE THERAPY
FOR PERSONS WITH POSITIVE TUBERCULIN REACTIONS

Category	Age < 35	Age ≥ 35
With risk factor*	Treat if ≥ 10 mm, or if ≥ 5 mm and patient has recent contact, is infected with human immunodeficiency virus (HIV), or has radiographic evidence of old tuberculosis	Treat if ≥ 10 mm, or if ≥ 5 mm and patient has recent contact, is HIV-infected, or has radiographic evidence of old tuberculosis
No risk factor, high-incidence group†	Treat if ≥ 10 mm	Do not treat
No risk factor, low-incidence group	Treat if ≥ 15 mm‡	Do not treat

*Risk factors include human immunodeficiency virus (HIV) infection, recent contact with infectious person, recent skin-test conversion, abnormal chest radiograph, intravenous drug abuse, and certain medical risk factors

†High-incidence groups include foreign-born persons, medically underserved low-income populations, and residents of long-term care facilities

‡Lower or higher cutpoints may be used for identifying positive reactions, depending upon the relative prevalence of *Mycobacterium tuberculosis* infection and nonspecific cross-reactivity in the population

From the Centers for Disease Control, reference 27

guidelines on who should undergo preventive therapy are given in the *Table*.

Unfortunately, doctors as a rule do not prescribe preventive therapy. CDC data from 1984 indicate that preventive therapy abruptly declined in 1981 (CDC, unpublished data). In that year, Taylor et al²⁸ reported a decision analysis indicating that in young asymptomatic men the risks associated with isoniazid therapy outweighed its benefits and caused an average loss of life of 3 days. Unbeknownst to Taylor et al, the AIDS epidemic was starting in 1980 and would change any estimation of benefit and risk. An accompanying editorial by Comstock,²⁹ a universally acclaimed tuberculosis epidemiologist, said the data that went into the decision analysis were fatally flawed. Preventive therapy was also defended in an editorial by Snider,³⁰ and several other experienced clinicians. Apparently, however, physicians gave the one early article more credence than the several countering editorials.

Further, the original analysis concerned young men with asymptomatic infections. Certain groups are at greater risk of developing active tuberculosis after being infected with the bacillus: people with AIDS have 170 times the risk, people with HIV infection have 113 times the risk, other immunocompromising conditions impart 16 times the risk, and recent tuberculosis infection imparts 15 times

the risk (CDC, unpublished data). Unfortunately, the memory of the original article continues to prevent physicians from providing preventive therapy to people who need it.

Although isoniazid produces some toxic effects, it remains an extraordinarily safe and effective drug. If properly taken, severe isoniazid toxicity can almost always be prevented.

INFECTION CONTROL

Careful infection control is also essential in preventing the spread of tuberculosis. In pa-

tients with HIV infection, any undiagnosed pulmonary disease may well be tuberculosis. This should be considered when performing diagnostic procedures such as sputum induction or bronchoscopy, which can generate an aerosol, as well as therapeutic procedures such as pentamidine inhalation or bronchodilator treatments.

Groups at risk of acquiring infection include people in close contact with patients with infectious tuberculosis; people with other medical risk factors; people from countries where the prevalence of tuberculosis is high; people from medically underserved, low-income populations, especially blacks, Hispanics, and native Americans; alcoholics; injecting drug abusers; and residents of long-term care facilities such as prisons and nursing homes.³¹

SUMMARY

Tuberculosis can and must be controlled, but action is required soon on several fronts. First, the nation must adequately fund public health programs. These programs must provide for testing of large numbers of people and for workers who will directly observe patients when they take their medication. People with infections should be treated with isoniazid, and people with active disease should undergo treatment starting with four drugs.

Second, doctors and nurses must again learn to be vigilant for the presence of this disease, and hospitals, nursing homes, prisons, and shelters for the homeless must examine their infection control procedures to prevent its spread. Third, researchers must develop new diagnostic tests that are faster and more reliable than those available today, pharma-

ceutical companies must develop new antituberculosis medications, and the US Food and Drug Administration should evaluate and approve these new tests and drugs with all due speed. Only a serious commitment on the part of the public, the medical community, government, and industry will reverse the present trend.

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