Diagnosis and Treatment of Active TB

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For tuberculosis (TB), as for many other infectious diseases, rapid and accurate diagnosis coupled with delivery of effective treatment are the central elements of medical and public health efforts to control the disease. Recent shifts in the nature of TB—notably, the increasing numbers of multidrug-resistant TB (MDR-TB) cases and the particular vulnerability to TB of individuals infected with the human immunodeficiency virus (HIV)---have heightened the need for improved methods of diagnosis and for shorter, simpler treatment regimens.

Diagnostic methods currently in use in many countries have remained unchanged for decades; the need for improved methods is acute, particularly in areas with a high prevalence of HIV. In the United States, newer diagnostic methods have been adopted in the past few years, but additional developments are needed to respond adequately to the recent rise in TB and MDR-TB. Deficiencies in the current diagnostic technology could seriously hamper efforts to control the spread of TB among HIV-infected populations in particular.

This chapter examines current needs and capabilities for diagnosis of active, infectious TB, along with the rationale and design of corresponding treatment regimens. The focus is primarily on pulmonary TB, rather than the various forms of extrapulmonary TB (TB in organs or tissues of the body other than the lung), because pulmonary TB is the predominant form and is the one responsible for transmission of the disease (see chapter 2). Details concerning the diagnosis and treatment of extrapulmona.ry TB can be found in several recent reviews (75,217,227). Treatment of noncontagious tuberculous infection, as distinct from active TB, and issues concerning skin testing for infection are discussed in chapter 4.

DIAGNOSIS OF TB AND RESISTANCE TO ANTI-TB DRUGS

Rapid, accurate diagnosis of TB allows for appropriate treatment to be initiated so that patients can be rendered noninfectious, cured of the disease, and prevented from relapsing at a later date. By causing delays in initiating appropriate treatment, diagnostic delays and errors can lead to the avoidable continuation and spread of TB. In many ways, current problems in diagnosis are no different from those of the past. It has long been recognized that the available methods are far from ideal, but their widespread acceptance suggests that they are adequate inmost uncomplicated cases. Increasingly, however, the inadequacies of the current methods have become magnified in the face of rising drug-resistance and the need to prevent rapid spread of the disease among patients in congregate settings and among HIV-infected populations. Patients with HIV who develop active TB may be at increased risk for rapid death from TB if effective treatment is not begun promptly (14,174).

At present, there is no single, definitive, quick test for active TB. By necessity, diagnosis is based on a combination of clinical acumen (aided by an assessment of the patient's risk for TB, medical history, and clinical signs) and laboratory and x-ray findings (70). Clinical symptoms of active TB include a persistent cough, hemoptysis (coughing up of blood), weight loss, fatigue, night sweats, and fever (8).

The tuberculin skin test is the standard method for screening asymptomatic individuals for tuberCU1OUS infection (and possibly disease) (see chapter 4). However, because of a high rate of false negative reactions (and some false positives) in both immunocompetent and immunocompromised individuals with TB, the skin test is considered inadequate for diagnosing active disease (8).

The classic initial laboratory method for presumptively diagnosing active TB is the sputum smear. Samples of the patient's sputum (phlegm) are placed on a slide, stained with a dye for acid-fast bacilli (AFB), and examined under a light or fluorescent microscope (7,70). The sputum smear test is quick and inexpensive, but is useful only when positive; negative smears cannot be used to rule out TB. The smear test does not distinguish tubercle bacilli from other types of (nontubetculous) mycobacteria, nocardia, or some legionella and nor does it indicate the bacilli's susceptibility to anti-TB drugs. However, when considered with other indicators, the smear test is used to make a presumptive diagnosis (276). When the test shows AFB, it also allows an estimation of the number of bacilli present and being excreted, an indicator of the patient's degree of infectiousness (7).

The major limitation of the sputum smear is its inadequate sensitivity due in part to technician-variability: only 50 to 80 percent of patients with pulmonary TB may have positive sputum smears (276). The detection rate among patients with advanced stages of HIV-related immunosupression maybe even lower (70,174,236). Samples of other respiratory secretions, biopsy body fluids, gastrics washings, bone marrow aspirates, and urine sediments for staining and smear examinaion would be needed to rule out false negative results (8). In addition, false positives are an increasing problem, due to the high prevalence of nontuberculous mycobacterial infections in HIV-infected individuals.

Chest x-rays are also used to detect active TB. Typical findings of TB in immunocompetent adults include infiltrates in the upper lung areas and cavitation. In TB patients with HIV, chest x-ray findings are likely to be atypical (with more middle and lower lung lobe involvement, no cavitation, and hilar or mediastinal lymphadenopathy); in general, the more advanced the immunosuppression, the more atypical the radiographic signs of TB (215,236,242). Because of this and the likelihood of false negative sputum smears, diagnosis of TB in patients with HIV involves even more uncertainties than in immunocompetent patients.

Definitive diagnosis of TB has traditionally been based on specific identification of the causative organism, *Mycobacterium tuberculosis,* isolated from sputum, body fluids, or tissue and cultured in the laboratory (8). Positive culture examination is considered to be far more sensitive and specific than sputum smears, but is also more expensive and time-consuming (123,276). Typically, conventional culture tests require 3 to 6 weeks to generate results because of the organism's slow growth rate. Culture methods provide confirmation of suspected TB cases, but, by necessity, empiric treatment is usually begun before such results are available.

Diagnosis of active TB in children poses additional difficulties, since sputum smear and culture tests often do not reveal the presence of tubercle bacilli (which may be present, though in smaller numbers than in an adult). It is also difficult to distinguish tuberculous infection from active TB in children. Various indirect means are usually used to establish a presumptive diagnosis of TB in a child, including epidemiologic information about the child's exposure to an adult with active TB, tuberculin skin test results, chest x-ray findings, and physical examination for symptoms consistent with TB even though the child may be asymptomatic (302). Conflation of active TB through culture examination is often more difficult in children because of the difficulty in collecting sputum samples and because of the even lower sensitivity of alternative fluids (such as gastric washings) for bacteriologic confirmation of TB (306).

In recent years, many laboratories responsible for processing TB specimens have incorporated more efficient methods for culture examination.
An automated, radiometric method (known by its trade name BACTEC ™), which detects growth of M. *tuberculosis in* a selective medium containing radiometric palmitic acid by measuring radioactive carbon dioxide given off by the bacteria, reduces the testing time to about 10 days (384). Gene probes specific for M. *tuberculosis* can also be used in conjunction with radiometric testing to shorten the time needed to identify tubercle bacilli. Another method, also producing faster definitive results, is based on detecting microcolonies of the organism grown on solid media and identifying them as M. ***tuberculosis*** by morphology (384).

Conventional methods for testing tubercle bacilli's drug susceptibility, using solid media and indirect testing, typically take 8 to 12 weeks to identify bacilli resistant to anti-TB drugs. The newer radiometric techniques, along with direct testing, which are also used to test for susceptibility to the five first-line drugs, take up to 3 weeks (133). Conventional drug susceptibility testing methods, taking several weeks longer, are used to test for resistance to other drugs and to confirm results of the radiometric studies (382).

Jacobs and colleagues recently reported a new laboratory method for rapid determination of drug-susceptibility (158). The technique is based on a light-producing reaction catalyzed by the firefly enzyme luciferase to distinguish drug-resistant and drug-sensitive tubercle bacilli, and can generate results in 2.3 days. It has not yet been adapted for clinical use.

TB diagnosis based on deoxyribonucleic (DNA) methods has recently been reported. At present, the most fully developed of these methods is one based on DNA amplification using the polymerase chain reaction (which allows the use of uncultured clinical specimens) followed by gene probes for DNA sequences specific for M. *tuberculosis* (44,281). Results can reportedly be obtained in 48 hours (89), although the testis not yet available for routine clinical use. An alternative to the use of radioactive isotopes in this method was recently reported (322). Other approaches, such as those based on immunoassay, are in developmental stages (70,122,188).

Delayed diagnosis was considered to be one of the main factors contributing to several of the recent nosocomial outbreaks of MDR-TB (discussed in chapters 3 and 4). Patients with TB who remained infectious for prolonged periods transmitted the disease to other patients and health care

workers (HCWS). There were several likely reasons for this, including HCWS' failure to suspect TB, unusual clinical features of TB in these patient populations, and the lengthy period of time required for laboratory identification, confirmation, and reporting of drug-susceptibility results (174). In addition, adequate infection control precautions were either not taken or not maintained, permitting infectious patients to remain in contact with patients and staff (see chapter 4). In congregate settings, such as hospitals, prisons, nursing homes, and other sites, there is a premium on rapid, accurate diagnosis to reduce the risk of active transmission.

The increasing prevalence of MDR-TB creates additional need for a rapid capability to identify the resistance pattern in each case so that the initial period of infectiousness can be shortened by administration of appropriate drugs for treatment. Recent Centers for Disease Control and Prevention (CDC) recommendations state that during the initial period when specific drug resistance information is not yet known, patients should generally be treated initially with four drugs (8,366). CDC lists patients more likely to have drug-resistant TB as those:

- from high-prevalence areas of the United States or foreign countries; and
- who have been in contact with other patients already infected with MDR-TB, have cavitary disease, or have been previously treated for TB (382).

Inpatients with drug-susceptible TB or who are TB resistant to a single drug, the four-drug regimen should render him or her noninfectious within a short period and offer the eventual possibility of cure. The regimen may be inadequate, however, in patients with resistance to three or more of the drugs. These MDR-TB patients could remain infectious for prolonged periods, posing a risk of transmitting the disease to other patients, family, and institutional staff. In New York City, where the incidence of MDR-TB is the highest in the country, the prevalence of resistance to both INH and RIF may be as high as 19 percent, according to a recent survey (107). Delays in obtaining drug-susceptibility data create additional need for hospitals to implement infection control precautions and isolation procedures to protect other patients and staff. Treatment of patients with MDR-TB must rely on the more toxic and expensive second-line drugs (discussed later) or newer drugs with *in vitro* activity against tubercle bacilli.

TREATMENT OF ACTIVE TB

Fifty years ago, before antibiotics were available for use in treating TB, treatment involved mainly improved nutrition, extended bed rest (often in TB sanatoria or other specialized institutions) and on some forms of surgical intervention to remove part of the lung (127). Mortality rates averaged around 50 to 60 percent 5 years after completion of treatment (200).

The introduction of antibiotic drug treatment in the late 1940s and combined-drug regimens in the 1950s dramatically changed the outcome of TB treatment. Rather than spending long periods of time in sanatoria or hospitals, patients could be treated on an outpatient basis with oral drugs that quickly rendered them noninfectious. Hospitalization could be limited to patients who needed diagnostic evaluation, developed complications, or could not care for themselves (l). Surgical intervention became unnecessary in most cases. Generally, patients could be treated at home and could return to outside activities soon after treatment was initiated (178). Although it was not the case for the initial single antibiotic (streptomycin) regimen, the multidrug regimens have reduced mortality from TB to about 4 percent (236).

Since the 1940s, the theory and practice of antibiotic treatment for TB has undergone substantial change and refinement both in the combination of drugs used and in the overall duration of treatment. Streptomycin (SM) was the first antibi-

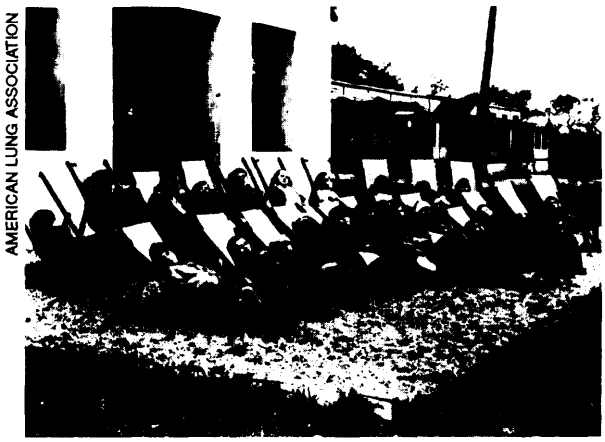
otic applied to TB, followed by isoniazid (INH), p-aminosalicylic acid (PAS), and ethambutol (EMB). The potential for effective treatment and cure of TB was quickly apparent, but the long duration of treatment required for cure (e.g., 18 to 24 months) suggested the need for better drugs. The subsequent availability and use in the 1960s and 1970s of two other drugs-rifampin (RIF) and lower doses of pyrazinamide (PZA)--permitted shorter regimens to be used.

During the past 20 years, no new drugs have replaced or supplemented the five main first-line drugs-INH, RIF, PZA, EMB, and SM. Numerous other drugs of lesser effectiveness and greater toxicity have also been available as second-line drugs. During this time, clinical research and practice have focused on determining the optimal use of the first-line drugs. These efforts have resulted in revised combinations and durations of treatment for enhancing effectiveness, reducing toxicity, improving compliance, and reducing costs. Current regimens call for more intensive use of these drugs over shorter periods of time—now 6 months, compared with the previous 18- to 24-month schedule of treatment. The 6-month period appears to be the irreducible minimum for the currently available drugs; further reductions in treatment time will depend on the development of new agents.

Clinical trials conducted internationally by the British Medical Research Council (BMRC) and the U.S. Public Health Service produced the evidence for these changes in practice. The first East African/BMRC study reported in 1977 demonstrated that treatment could be shortened from 18 to 9 months by using RIF along with INH and SM, while still producing cures in over 95 percent of patients (86). Subsequent BMRC studies conducted in Hong Kong, Africa, and Singapore helped to define alternative drug combinations, minimum durations of therapy, and frequency of drug administration. As of the early 1980s, these trials showed that a regimen of PZA added to the first 2 months of daily INH, RF, and SM therapy could elicit cures in 99 percent of patients, that 6 months was the minimum period of time necessary for such cure rates, and that intermittent therapy could be used without reducing effectiveness (154).

A recently reported randomized, multicenter study conducted by CDC demonstrated the effectiveness of shorter combination regimens in U.S. patients with TB (62). The study compared the effectiveness and toxicity of a 6-month regimen with the "standard" 9-months regimen among 1,451 newly diagnosed adults patients with pulmonary TB. The study did not include immunocompromised patients such as those with metastatic cancer or with HIV. Patients receiving the 6-month regimen were further randomized to treatment consisting of individual antibiotics taken together and treatment with Rifater™, a single, combination capsule containing the same three antibiotics. The 9-month regimen consisted of INH and RIF given daily for 36 weeks; the 6-month regimen consisted of the same two drugs given daily for 24 weeks, plus a third drug, PZA, given daily for the first 8 weeks of therapy. Patients randomized to the Rifater™ regimen received all three drugs for the first 2 months, followed by INH and RIF (Rifamate™ combination tablets) during the remaining 4 months.

The study found the 6-month regimen of the three drugs produced better results than the standard two-drug, 9-month regimen. Among patients on the 6-month regimen, about 95 percent had negative sputum cultures by 16 weeks of therapy (compared with 90 percent of patients on the 9-month regimen). Patients taking Rifater™ had even higher conversion rates than patients on the original 6-month regimen. The two groups had similar rates of relapse (about 3 percent) by 96 weeks after treatment and similar rates of adverse drug reactions (about 7 percent), although the 6-month regimen was associated with a higher rate of nonhepatotoxic reactions (primarily gastrointestinal upset and joint pain). The efficacy of both regimens was very high—over 96 percent of the patients were cured. An important practical benefit to the shorter regimen



During the 1920s, before the discovery of drugs to treat tuberculosis, sanatoriums and other TB hospitals were the centerpiece of treatment that focused on keeping the patient hearty. Sanatoriums were phased out *during the 1950s and 1960s.*

was that a higher proportion of patients successfully completed therapy.

Rationale for Antimicrobial Treatment of TB

Theoretically, the ultimate goal of treatment is to rid the body of tubercle bacilli before irreversible physiologic damage occurs in the lung, but in practice, the specific goals are to render the patient noninfectious, prevent the emergence of drug-resistant disease, and to allow cure without subsequent relapse. Certain characteristics of tubercle bacilli and their sites of infection in the body are important in determining how this can be accomplished. In general, tubercle bacilli replicate slowly and can remain dormant in the body for many years. Under favorable physiologic conditions for bacilli, they double in number every 20 hours, but in unfavorable conditions, they divide much less frequently or remain dormant for prolonged periods. This characteristic accounts for the long periods of treatment necessary to eradicate all dividing bacilli in the body and for occasional relapses despite apparently effective treatment.

Current anti-TB drugs kill tubercle bacilli only during periods of replication and activity. Conditions are most favorable for the bacilli's active metabolism in the open cavities of the lung, where the largest bacterial population is likely to be in an adult with pulmonary TB. In immuncopetent hosts, bacilli in closed caseous lesions and in macrophages are relatively slow metabolizes and replicate only intermittently.

A theoretical model for characterizing different subpopulations of tubercle bacilli in the body and for explaining the differential action of the major antibacterial drugs has been proposed (192). These four subpopulations are distinguished according to growth rates and sites of infection in the body.

One group is the subpopulation of bacilli responsible for the infectiousness of TB. It is characterized by active metabolism, relatively rapid growth rates, and large numbers of bacilli, including drug-resistant ones. These bacilli are usually found in the wall of lung cavitary lesions, where conditions favorable for growth occur (high oxygen and low acidity), and in the sputum. Bacilli are also found in the sputum. They are particularly vulnerable to the bactericidal action of INH, which kills rapidly growing bacilli during the frost few days of treatment.

A second group of tubercle bacilli is characterized by slower or intermittent growth in acidic environments within cells (and possibly also outside of cells where there is an inflammatory response). There are probably fewer of these types of bacilli in the body, but they may persist despite short-term bactericidal treatment. They can also cause subsequent relapses later. PZA is believed to be most active in killing these bacilli.

A third group is believed to persist within cells and either remain dormant for long periods or undergo intermittent activity. These are thought to be treated most effectively with RIF. A fourth population of bacilli maybe largely dormant, not affected by any of the antibiotic drugs, existing within solid caseous lesions and probably inaccessible to host immune forces (216).

Tubercle bacilli can undergo mutation in genes that confers resistance to the effects of anti-TB

drugs. It is estimated that 1 in 100,000 to 1 in 100 million bacilli are initially resistant to any single drug used against TB. These few bacilli can, under certain conditions such as treatment with only one drug or erratic drug taking, become the predominant cell type in a bacterial population, creating single- or multidrug-resistant TB. Treatment with an adequate combination of drugs can prevent the emergence of a population dominated by drug-resistant bacilli (75).

Current Treatment Regimens

Combinations of antibiotic drugs with overlapping functions are used in current treatment regimens to attack the various distinct groups of tubercle bacilli in the body (75). Anti-TB drugs are generally classified as bactericidal (producing rapid killing of bacilli) or sterilizing (killing the last surviving, slowly metabolizing bacilli over the long term). The major bactericidal drug is INH, which is capable of producing a rapid decrease in the number of living bacilli in the sputum at the beginning of treatment and rapidly reducing the bacillary load in the patient. RIF and PZA are the most potent sterilizing drugs. Their use allowed the overall duration of treatment to be reduced to 6 months while minimizing relapse rates after initially successful therapy (1 10,192). INH and RIF (and to a lesser extent EMB and SM) are considered the most effective drugs in preventing the emergence of drug-resistant bacilli.

Corresponding to the different roles of these drugs, current regimens consist of two phases of treatment: an initial intensive bactericidal phase intended to eliminate quickly the bulk of tubercle bacilli from most body sites, followed by a longer-term sterilizing phase intended to eliminate the remaining bacilli. The initial regimen involves the daily use of four drugs (INH, RIF, PZA and EMB or SM). The total duration of treatment is 6 months, although several variations of this regimen (in terms of types of drugs and frequency of administration) are also used (366). In general, the various combinations of the four-drug regimens yield cure rates of 98 percent or more and relapse rates of less than 3 percent (8).

These drugs are not without side effects, the most serious of which is hepatitis (inflammation of the liver) (380). Usually associated with INH, but also with RIF and PZA, drug-related hepatitis is more frequent among older patients, those with preexisting liver disease, and those who abuse alcohol (these are also risk factors for hepatitis unrelated to INH, PZA, and RIF) (1 14). Other common adverse reactions include: hypersensitivity reactions, along with gastrointestinal distress (caused by RIF), hyperuricemia (caused by PZA), vertigo or hearing loss and nephrotoxicity (caused by SM), and optic neuritis (caused by EMB). However, the more serious and more frequent adverse effects are generally associated with use of the second-line drugs (178).

The patient's improvement with treatment is measured first by clinical improvement such as loss of fever, reduction in coughing, increased appetite, and weight gain. Reduction in numbers of tubercle bacilli in the patient's sputum also indicates improvement. Failure of sputum culture conversion or reappearance of viable bacilli in the sputum following initial clearing may signal treatment failure. Subsequent signs of treatment failure include a worsening of clinical status and progression of disease as detected on chest radiography. Patients are usually monitored on a monthly basis for adverse effects and treatment response (178). Within 2 to 3 months of treatment, about 90 percent of patients with uncomplicated, pulmonary TB would have negative sputum cultures. Patients with drug-resistant TB may show persistently positive sputum cultures. The treatment of TB in children follows the same principles as in adults, although diagnosing and monitoring progress with treatment is more complex and necessitates the use of various indirect indices (303).

Treatment of TB in Individuals with AIDS

Current recommendations for treatment of TB in patients with AIDS specify the same combination of antibiotics as for immunocompetent TB patients (344,366,378).

In general, TB is treatable in individuals with HIV. Although experience is limited, reports to date suggest that HIV-infected patients, even those with advanced stages of immunodeficiency, can undergo rapid elimination of tubercle bacilli from the sputum, clinical improvement, and low rates of relapse following standard anti-TB treatment (232,290,321). Most documented cases of treatment failure in patients with HIV have been linked to incomplete treatment or poor absorption of anti-TB drugs (117,290).

Nevertheless, several added complexities in treating TB in patients with HIV exist. Coexisting infections and other AIDS-associated disorders require treatments that may interact with the antibiotics used to treat TB. High rates of toxicities and drug reactions, especially to RIP, have been noted in TB patients with AIDS (103,212,290). Many of the adverse reactions were considered serious enough to drop RIP from the regimen, making a cure of TB in these cases much more difficult. For a variety of reasons, toxicities from anti-TB drugs may be more difficult to interpret in patients with AIDS and TB (230).

Another complicating factor is that various types of disseminated or extrapulmonary TB appear to be more common among patients with HIV (100,230). Some of these (particularly central nervous system TB) may pose more immediate risks and are more difficult to diagnose and treat (212).

Completion of treatment, a critical factor in treatment of all TB patients, may be even more critical to successful outcomes in patients with HIV. At the same time, some subgroups of patients such as intravenous drug users with HIV may be at higher risk for treatment failure. Chapter 6 examines this issue in greater detail.

Finally, although patients with AIDS usually respond to TB therapy, the optimal duration of therapy to prevent relapse following treatment in these patients is uncertain (212,230). Initial recommendations for longer courses of treatment were based on case reports of several patients found to have progressive disease despite adequate treatment (319) and on prior difficulties with the treatment of other opportunistic infections. Recent reports of successful outcomes with 6-month regimens (290,321) cast doubt on the necessity of prolonged treatment, but clinical trials with long-term followup will be needed to determine the efficacy of short-course treatment in larger groups of HIV patients. In the meantime, HIV-infected patients treated for TB probably need frequent followup, including regular mycobacterial examinations, for life (230).

Treatment of Multidrug=Resistant TB

When SM was introduced in the late 1940s as the first chemotherapeutic agent against TB, it was administered singly. The first group of patients treated with SM responded well initially, but in a short time, relapsed with large numbers of SM-resistant tubercle bacilli. SM had effectively killed the susceptible bacilli but not the resistant ones, which had been present in small numbers from the outset by random mutation.

It was soon recognized that the use of a single antimicrobial drug in treating TB would lead predictably to the development of resistant disease, and that multiple drugs to which the bacilli were susceptible would be necessary to prevent the development of drug resistance. The use of combination chemotherapy to treat TB has been standard practice since the early 1950s, initially with INH, SM, and PAS, next with INH, SM, and EMB, then INH and RIF, and now with four drugs until a patient's drug susceptibility test results are known (287,366,382).

Given the current prevalence of MDR-TB in the United States, such a four-drug regimen is estimated to be adequate for over 95 percent of

TB patients (25). The remaining 4 to 5 percent are resistant to 2 or more drugs in the current recommended regimens. Cases of resistance of up to seven drugs have been documented in recent outbreaks of MDR-TB in several New York City hospitals and prisons (382). In addition, patients with bacilli resistant to as many as 11 drugs have recently been reported (1 18).

Failure to complete a full course of appropriate treatment is a major cause of MDR-TB. Patients on combination-drug therapy who stop taking all medications at the same time may ultimately relapse, but with bacilli showing the same-drug susceptibility pattern as before. The recurrent disease in such cases would be treatable with the same combination of drugs. In contrast, patients who take their medications erratically or who stop taking only one or two of the drugs while continuing the others may relapse with TB resistant to one or several of the medications (267). In these cases, treatment of recurrent disease requires a different combination of drugs. The success of further treatment depends, in part, on the effectiveness of the remaining drugs that can be used. Patients who remain inadequately treated may also be capable of transmitting MDR-TB to others.

Data derived from a number of clinical trials conducted overseas by the BMRC suggest that patients with bacilli resistant to either INH or SM can be treated effectively with regimens initially containing four drugs (resulting in 94 to 97 percent cure rates in 6-month regimens), since the other 3 drugs would be usable (194). Resistance to RIF, however, poses a greater risk of treatment failure (194). Successful outcome of treatment is even less likely if there is resistance to both INH and RIF, the two most active anti-TB drugs currently available. High treatment failure rates and overall mortality among HIV-infected individuals with MDR-TB have recently been reported (100,1 18).

Drug regimens for MDR-TB are determined on a case-by-case basis, beginning with information derived from the patient's medical history (e.g., prior drugs taken for TB) and drug-susceptibility testing. Cases resistant to two or more of the frost-line drugs would be treated with a combination of remaining first-line drugs, second-line drugs (capreomycin, kanamycin, ehtionamide, cycloserine, and p-aminosalicylic acid and amikacin), often for 18 to 24 months or longer after conversion of sputum cultures.

Individuals with active, drug-susceptible TB, like this one at Bellevue Hospital in New York City, *are often hospitalized during the initial period of their treatment while they are still infectious. Patients with drug-resistant TB may require longer hospitalizations.*

A number of other drugs have been less extensively studied for anti-TB activity, and are not yet approved (because of insufficient data on efficacy) for the treatment of TB-clofazimine, quinolones (sparfloxacin and ofloxacin) (153). Reliable data to judge the effectiveness of these second-line drugs are lacking, but anecdotal experience suggests that they are much less effective and much more likely to lead to serious toxic effects (287). Adjunctive surgery to remove tissue (usually in the lung) heavily infected with tubercle bacilli is sometimes used as a treatment of last resort in patients with localized lung disease for whom drug treatment is inadequate (1 16). In general, treatment of MDR-TB requires more complex interventions, longer hospitalization and more extensive laboratory monitoring.

Beginning in 1990, widespread shortages of certain anti-TB drugs occurred in the United States (224,352). A number of contributing factors have been identified, including various problems within the generic drug industry, the reliance on sole suppliers of a bulk drug (often outside the United States), single U.S. manufacturers of the finished drug product, a low demand for anti-TB drugs overall, and low profit margins for drug companies manufacturing these drugs (189). In April 1992, CDC began to make PAS and SM available through an investigational new drug agreement with the Food and Drug Administration (FDA). FDA has worked with U.S. manufacturers to reestablish production and supplies of the affected drugs. As discussed in chapter 7, the FDA has also begun offering a variety of incentives to pharmaceutical companies to develop new anti-TB drugs, such as granting orphan drug status, conducting expedited review of applications, offering accelerated approval with the development of surrogate markers (interim outcomes), and accepting foreign clinical data (225).

New Approaches to Treatment

The rising prevalence of MDR-TB and the complexities of treating TB in patients with HIV have heightened the need for new anti-TB drugs, shorter regimens, and better methods of drug delivery.

Combination tablets containing three of the frost-line drugs such as Rifater™, containing INH, RIF, and PZA, have been developed (192), but are not commercially available in the United States. In 1993, a new drug application to permit marketing of Rifater™ in the United States was submitted to the FDA (119). Rifamate™, a combination tablet containing INH and RIF, is FDA-approved and available; 40 percent of RIF prescribed in the United States is currently given as Rifamate™ (119). Some data are available on the effectiveness of combination preparations compared with the use of the same drugs given separately. In two BMRC studies, conflicting results were obtained in clinical trials, but in the recent study reported by Combs and colleagues, Rifater™ was found to be effective, although it was associated with a higher rate of adverse effects (62). Incorporation of these combined preparations into TB treatment, however, could possibly increase the overall success rate and help prevent the development of MDR-TB resulting from erratic drug taking or inadequate prescribing. One disadvantage of the combined preparations is that the regimen cannot be selectively modified to reduce adverse effects of component drugs without switching to individual drugs or discontinuing therapy altogether.

Intermittent therapy of equivalent effectiveness (twice or thrice weekly instead of daily administration) in the sterilizing phase of treatment improves chances for supervision of outpatient therapy, for reducing overall costs of treatment, and lowering drug toxicities (61). Further experimentation with even less frequent administration may depend on the use of drugs with longer duration of effect in the body (such as rifamycins). In this context, rifamycins are currently being studied in clinical trials in China (192). An optimal anti-TB agent would be bactericidal for all populations of bacilli within a very short period of time, orally administered or injectable in a single dose, and free of toxicities. Other drugs being investigated for this purpose include fluroquinolones, rifamycin derivatives, and phenazines (127).

Alternative methods of drug delivery have been discussed but are not yet ready for clinical evaluation. Some of these include implantable devices containing drugs for slow release into the bloodstream (similar in design to the Norplant™ device for contraception), and the use of liposomes as carriers for drugs directly to specific sites in the body. Immunotherapeutic approaches are also under investigation.

Table 5-l—Trends in Drug Costs for Treating Tuberculosis in a 165 lb (75 kg) Patient, 1986-92: An Uncomplicated Case Versus a Case Resistant to INH and RIF[a]

Uncomplicated case:

Drug	Daily dose	Duration	1986 cost	1990 cost	1992 cost
Isonizaid	300 mg	180 days	$ 5.04	$ 6.50	$ 8.50
Rifampin	600 mg	180 days	106.20	159.30	165.30
Pyrazinamide	25 mg/kg	60 days	98.00	160.00	179.20
			$209.24	$325.80	$353.00

Average annual percentage increase in cost, 1986-92: 9.10/0

A case resistant to *INH* ***and*** *RIF:*

Drug	Daily dose	Duration	1986 cost	1990 cost	1992 cost
Pyrazinamide	25 mglkg	540 days	$ 882.00	$1,440.00	$1,613.00
Ethambutol	15 mgikg	540 days	690,00	1,246.00	1,610.00
Streptomycin	15 mg/kg	120 days	138.00	192.00	206.00
Ethionamide	20 mglkg	540 days	890.00	1,458.00	1,691.00
Ciprofloxacin	1500 mg	540 days	**NA**	**3,000.00**	**3,600.00**
			$2,600.00	**$7,338.00**	**$8720.00'**

Average annual percentage increase in cost, 1986-92 (without Ciprofloxacin): 12.OYO

- Add ofloxacin=$4,080 .00
- Add amikacin=$27,648 .00
- Add clofazimine=$71 .00

KEY: NA - not available; mg - milligram; kg - kilogram (of patient body weight).
a Treatment costs based on median prices given in table 5-2. Costs are for an entire recommended treatment cycle. Estimates include drug costs only.

SOURCE: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, 1993.

The Cost of Drugs for Tuberculosis Treatment

The purchase of anti-TB drugs varies by jurisdiction and can be done by State or local health departments, or by other organizations. The drugs' prices can vary depending on manufacturer, the quantities purchased, and other terms of the sale (190), In addition, not all States use all the same drugs or dose forms. In response to price concerns over anti-TB drugs, CDC recently completed a survey of 14 jurisdictions (13 States and Baltimore City) to gather data on the last prices they paid for their pharmaceuticals in 1986, 1990, and 1992. Tables 5-1 and 5-2 present CDC'S results. Table 5-1 gives estimates prepared by CDC of the costs of two possible drug regimens for a 165-pound (75-kg) adult: one for uncomplicated TB, the other a TB case resistant to INH and RIF. Table 5-2 presents data on increases in individual dosage forms of most first-line and second-line anti-tuberculosis drugs.[1] Although prices paid by State and local health departments vary and the precise number of drugs required for treatment is different for each patient, these estimates still give a sense of the resources needed for drugs to treat a TB patient as well as

[1] Some dosage forms were purchased by only a small subset of States. According tCDC, its discussions with some State and local authorities revealed that part of the increase in prices is due to the growing unwillingness of manufacturers to enter into contracts with public health authorities to supply drugs over time at a set, discounted price. Some of the range in prices is also due to the fact that some municipalities purchase in bulk under contract, while others lack the volume to do so (190).

Table 5-2—Trends in Tuberculosis Drug Prices: Results of U.S. Centers for Disease Control and Prevention Survey

Drug	Drug form and package size	1992 number States ordering	1992 price range	1992 median price	1990 median price	1986 median price	Percent increase 1990-92
Isoniazid	100 mg 100/bottle	14	$1.00-3.00	$1.75	$1.25	$ .85	40%40
Isoniazid	300 mg30/bottle	13	1.07-2.71	1,41	1.09	.84	29
Isoniazid	300 mg 100/bottte	5	1.64-3.65	2.41	2.33	1,36	3
Isoniazid	Syrup 1 pint bottle	14	6.25-12.86	9.55	7.72	8.29	24
Rifampin and Isoniazid	Combo pack30 day	11	27.36-31.89	31.40	27.36	19.60	15
Rifarnpin	150 mg 30/bottie	13	33.30-40.00	33.45	29.60	18.20	13
Rifampin	300 mg 60/bottle	14	26.10-59.04	27.25	26.55	17.70	3
Pyrazinamide	500 mg 100/bottle	6	65.49-75.12	71.70	60.97	38.42	18
Pyrazinamide	500 mg 500/bottle	9	280.00-359.28	326.63	292.63	188.62	12
Ethambutol	100 mg 100/bottle	10	19.73-30.25	29.18	24.05	16.37	21
Ethambutol	400 mg 100/bottle	7	97.66-103.75	101.57	78.87	53.82	29
Ethambutol	400 mg 1000/bottie	7	730.00-925.54	889.94	718.67	500.13	24
Streptomycin	1 gm vial	2	1.75-1.84	1.79	1.67	1.32	7
Streptomycin	2.5 gm vial	1	1.84	1.84	N/A	N/A	N/A
Streptomycin	5.0 gm vial	2	4.95-6.95	5.95	4.96	3.25	20
Paraamino salicydicacid	500 mg 500/bottle	3	34.46-49.00	41.86	33.70	14.80	24
Ethionamide	250 mg 100/bottle	12	56.97-118.24	103.88	89.51	52.87	16
Capreomycin	1 gm 10 ml	9	16.25-21.07	18.80	14,84	11.95	27
Kanamycin	1 gm 3 ml	6	.75-22 .60	.98	.75	1.40	31
Cycloserine	250 mg 40/bottle	10	89.99-115.50	108.85	86.10	34.78	26
Ciprofloxacin	250 mg 100/bottle	1	175.50	175.50	N/A	N/A	N/A
Ciprofloxacin	500 mng 100/bottle	8	108.13-236.85	225.27	94.12	75.00	133
Ciprofloxacin	750 mg 100/bottte	9	117.30-350,11	195.57	180.89	N/A	8
Clofazimine	50 mg 100/bottle	2	5.40-9.60	7.50	N\A	N/A	N/A
Clofazimine	100 mg lOO/bottle	3	5.10-18.50	11.80	17.06	14.29	N/A
Ofloxacin	400 mg 50/bottle	4	15.88-154.15	136.25	N/A	N/A	N/A
Amikacin	1 gm	1	51.02	51.02	31.20	31.21	64
Pyridoxine	25 mg 100/bottle	2	.59-1 .00	.80	N/A	N/A	N/A
Pyridoxine	50 mg 100/bottle	3	.84-1 .70	.95	.85	.67	12

KEY: gm = gram; mg - milligram; N/A- not applicable.

SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Services, Centers for Disease Control and Prevention, 1993.

the upward trend in their prices (190). The costs of the regimen for uncomplicated TB described in table 5-1 rose an average over 9 percent per year between 1986 and 1992, a rate significantly higher than inflation during these years.