DRUG THERAPY

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TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS

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THE era of modern, predictably effective tuberculosis chemotherapy began in 1952. Since then, strains of *Mycobacterium tuberculosis* have acquired resistance to various drugs, thus compromising both treatment and control programs. Most ominously, the rising prevalence of multidrug-resistant strains (defined here as *M. tuberculosis* resistant to isoniazid and rifampin, with or without resistance to other drugs) has resulted in many cases of marginally treatable, often fatal, disease. The care of patients with documented multidrug-resistant tuberculosis will be the focus of this report. I shall also examine briefly the origins, biologic mechanisms, and epidemiology of drug resistance, its impact on the outcome of therapy, and the implications of multidrug resistance for standard initial therapy regimens.

INADEQUATE TREATMENT PROGRAMS AND ACQUIRED DRUG RESISTANCE

Streptomycin was introduced for the management of tuberculosis 45 years ago. Soon thereafter, it became evident that streptomycin monotherapy frequently resulted in treatment failure that was associated with in vitro resistance to the drug.[1,2] Aminosalicylic acid and isoniazid were then combined with streptomycin, in a regimen that cured tuberculosis in nearly all patients. Treatment was highly successful because it was carried out in hospitals, where compliance could be assured, and therefore acquired drug resistance was uncommon. In the late 1960s, however, therapy was shifted to the outpatient setting, because patients with tuberculosis were not thought to be a public health hazard when receiving chemotherapy. Unfortunately, the shift to outpatient care reduced compliance and led to rising rates of treatment failure, relapse, and acquired drug resistance. The prevalence of drug-resistant organisms among patients with pulmonary tuberculosis in the United States has steadily increased from approximately 2 percent to 9 percent in the past three decades,[3-7] and similar increases have occurred in many other countries.[8]

Biologic Mechanisms of Resistance

Tubercle bacilli have spontaneous, predictable rates of chromosomally borne mutations that confer resistance to antimicrobial agents.[9] These mutations are unlinked; hence, resistance to a drug is generally not associated with resistance to an unrelated drug. The emergence of drug resistance represents the survival of random preexisting mutations, not a change caused by exposure to the medication.[9] That the mutations are not linked is the cardinal principle underlying modern chemotherapy of tuberculosis. For example, mutations causing resistance to isoniazid or rifampin occur in roughly 1 in 10^8 to 10^9 replications of bacteria.[9] The likelihood of spontaneous mutations causing resistance to both isoniazid and rifampin is the product of these probabilities, or 1 in 10^{16}. Patients with tuberculosis, even those with extensive cavitary disease, harbor far fewer mycobacteria than this, so the development of spontaneous, dual resistance is highly improbable.

This model breaks down when chemotherapy is inadequate, however. In the circumstances of monotherapy,[10] erratic drug ingestion, omission of one or more of the prescribed agents, suboptimal dosage, poor drug absorption, or an insufficient number of active agents in a regimen,[11] a susceptible strain of *M. tuberculosis* may become resistant to multiple drugs within a matter of months.

Current Epidemiology of Resistance

Recent patterns in the prevalence of drug resistance in selected areas of the United States are shown in Table 1. Resistance is not distributed uniformly but is more prevalent in large urban areas and coastal or border communities. Surveys in Los Angeles[12] and Texas[16] revealed that drug-resistant pulmonary tuberculosis occurred with about equal frequency in all ethnic groups, but another survey in Los Angeles found the rates of resistance were higher among Hispanics, Asians, and blacks than among whites.[13]

The most powerful predictor of the presence of multidrug-resistant organisms in all these studies was a history of treatment for tuberculosis. Inadequate therapy is the most common means by which resistant organisms are acquired, and patients who have previously undergone therapy should be presumed to harbor drug-resistant organisms until proved otherwise. In addition, patients with cavitary lesions have a high frequency of resistance,[2,12] presumably because they harbor greater numbers of mycobacteria.

In the past, most patients with multidrug-resistant organisms acquired the organisms through multiple, ineffectual courses of treatment with various drugs. Among such patients admitted to the National Jewish Center hospital from 1976 through 1983, the average duration of previous treatment was nine years.[11] Recently, however, a new phenomenon has emerged: transmission of multidrug-resistant strains of *M. tuberculosis* to contacts.[17-22] Epidemics have been described mainly among contacts with preexisting acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, but reactivity to the tuberculin skin test has developed in substantial numbers of HIV-negative health care

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Table 1. Selected Recent Reports of Resistance to Antituberculosis Drugs in the United States.

Source	Percent of Patients with Resistant Organisms	Comments
CDC National Survey, 1982–1986[7]	No prior treatment: 9 Prior treatment: 23	No differences according to age or race. Great majority show single-drug resistance.
Harbor General Hospital survey, Los Angeles, 1980–1984[12]	No prior treatment: 23 Prior treatment: 59	No differences according to age or race. Higher risk with cavitary disease. Multidrug resistance rare.
Los Angeles County Hospital survey, Los Angeles, 1984–1986[13]	No prior treatment: 6, 23 Prior treatment: 13, 42	The first number is the risk among white patients; the second the risk among Asian, black, and Hispanic patients. Multidrug resistance rare.
New York City, first quarter 1991*	No prior treatment: 23 Prior treatment: 44	Resistance to isoniazid and rifampin: 7% without prior treatment, 30% with prior treatment.
Preliminary results, national drug susceptibility survey, first quarter 1991[15]	Overall: 14 Cities with populations ≥250,000: 17	Overall, approximately 6% of isolates were multiply resistant. Among isolates from large cities (populations ≥250,000), 9% were resistant to two or more drugs.

*Data are from Frieden et al.[14]

workers and institutional personnel. Well-defined, large-scale epidemics of multidrug-resistant tuberculosis have also been described among HIV-negative groups.[23-25] My colleagues and I have treated nine HIV-negative patients who acquired multidrug-resistant tuberculosis from source patients. Among them were three nurses and three physicians who were exposed in the course of their work (unpublished data). Hence, we may expect a late wave of cases among immunocompetent persons who are exposed and infected during outbreaks of multidrug-resistant tuberculosis.

Effects of Drug Resistance on Treatment Outcome

HIV-Negative Patients

The best data on the influence of drug-resistant *M. tuberculosis* on treatment outcome come from trials conducted in East Africa, Hong Kong, and Singapore.[26] For patients treated for six months or longer, the presence of drug-resistant organisms at the start of therapy was associated with an 83-fold greater risk (11.6 percent vs. 0.15 percent) of treatment failure, defined as the failure of treatment to produce negative cultures. There was also a twofold (11 percent vs. 5 percent) greater risk of relapse, defined as recurrence of disease after treatment was stopped. Infections with organisms resistant to single drugs such as isoniazid or streptomycin could be treated successfully with four-drug regimens featuring the extended use of rifampin. The success rate was much lower among patients with organisms resistant to rifampin and isoniazid: 8 of 11 patients (73 percent) with isoniazid- and rifampin-resistant bacilli did not respond to treatment or relapsed.

From 1976 to 1983 at National Jewish Center hospital, 171 HIV-negative patients were found to have extensive pulmonary tuberculosis resistant to isoniazid and rifampin as well as various other drugs; the average strain was resistant to 5.8 drugs.[11] The usual duration of the hospital stay was seven months, and the patients received an average of 5.7 drugs. After discharge, nearly all patients returned to their home communities to complete therapy under close supervision. Oral medications were given for an average of 24 months after the organisms could no longer be detected in the sputum. This approach yielded a disappointing 65 percent initial rate of sputum conversion and, because of subsequent relapses, a long-term rate of only 56 percent.

Patients with HIV Infection or AIDS

The recent epidemics of multidrug-resistant pulmonary tuberculosis reported by the Centers for Disease Control and Prevention (CDC) have offered fragmentary but very discouraging data on the outcome of therapy in patients with HIV infection or AIDS.[17] Most of the epidemic strains were resistant to isoniazid and rifampin, but the pattern of resistance varied among the outbreaks. A large proportion of the isolates also were resistant to streptomycin and ethambutol, and some were resistant to ethionamide or kanamycin. Despite aggressive multidrug treatment, 72 to 89 percent of more than 200 patients were dead in 4 to 19 weeks, with 38 to 70 percent of the deaths caused by tuberculosis.

Detailed reports on two of these hospital outbreaks provide additional insight into the results of therapy. A group of 18 patients in New York City had a history of in-hospital exposure, most were homosexual, and all had longstanding AIDS.[18] All the initial isolates in this outbreak were resistant to isoniazid and streptomycin, and 12 were also resistant to rifampin and ethambutol. Among the patients who received two drugs other than isoniazid, streptomycin, rifampin, or ethambutol within 2 weeks of diagnosis, 6 of 17 survived 20 weeks, as compared with 2 of 11 patients treated less aggressively ($P = 0.01$). A group of 62 patients in Florida[20] had risk factors including homosexuality, AIDS, previous hospitalization on an HIV ward, and intravenous or inhalation therapy with pentamidine. More of these patients had concomitant pulmonary and extrapulmonary disease than did HIV-negative patients with tuberculosis at the same hospital. Of 25 HIV-positive patients who received two or more antituberculosis medications to which there was in vitro susceptibility, only 2 had three consecutive negative sputum cultures.[27] The median survival time for AIDS patients with multidrug-resistant tuberculosis in this outbreak was 1.5 months, as compared with 14.8 months for HIV-infected patients without AIDS. Because the extent of drug resistance

was not recognized at the time of these two outbreaks, therapy was less aggressive than is recommended now. However, even the patients who received several drugs with in vitro activity had poor responses to therapy, and bacteriologic conversions were very rare. Similarly, another report describes a group of 19 patients with HIV infection or AIDS and multidrug-resistant tuberculosis; 16 died despite the administration of a four-drug regimen for a mean of seven weeks.[28]

These admittedly limited data show a dismal outcome for immunodeficient patients with advanced infection, who undoubtedly have large numbers of bacilli despite treatment with multiple drugs. One should not conclude, however, that multidrug-resistant tuberculosis in patients with AIDS is incurable. Very few of the patients in these epidemics were treated with four drugs with in vitro activity, the regimen now recommended for treatment of HIV-negative patients with multidrug-resistant tuberculosis (see below).

Implications of Multidrug Resistance for Initial Therapy

Since 1986, the American Thoracic Society and the CDC have recommended that patients with tuberculosis be treated with a three-drug regimen: isoniazid, rifampin, and pyrazinamide (pyrazinamide is given for two months, and the other drugs for six months).[29] This regimen was recommended on the premise that the great majority of patients would have drug-susceptible disease. Because the prevalence of drug resistance is rising, however, this recommendation is inadequate.[30] Patients in communities in which there is even a small risk (>2 percent) of single-drug resistance should be treated with isoniazid, rifampin, pyrazinamide, and ethambutol until the results of drug susceptibility testing are available. In certain areas of a city such as New York, where many patients with tuberculosis are infected with strains resistant to two or more agents, at least five drugs are needed to protect against additional acquired resistance.[14] For patients with HIV infection or AIDS in these areas, a six-drug regimen based on local patterns of resistance may be indicated until the resistance pattern of the patient's organisms is known.

In many cities and states in the United States, the results of drug susceptibility tests are not available for two to four months, although the tests can be done far more rapidly.[31] For example, nearly all sputum specimens that contain many organisms (smear-positive) can be tested adequately in two weeks (Heifets L: personal communication); three to five weeks are required for smear-negative specimens. Obtaining the results of susceptibility tests rapidly allows treatment to be modified in a timely manner to protect against further acquired drug resistance and to diminish the potential toxicity of empirical five- or six-drug regimens. In addition, the timely collection of cumulative data on the prevalence of drug resistance within communities is crucial for guiding local choices for initial therapy.

Combined Formulations

Since the development of drug resistance in a patient with tuberculosis is most often the result of treatment with too few drugs, some physicians recommend the use of multiple drugs combined in a single capsule. A combination of isoniazid and rifampin is now available in the United States. A combination of isoniazid, rifampin, and pyrazinamide is available but not yet approved by the Food and Drug Administration (FDA). Such formulations are intended primarily for patients who administer their medications themselves, but there are no studies demonstrating that these formulations prevent acquired drug resistance. In fact, in one study from Singapore, a combined formulation of isoniazid, rifampin, and pyrazinamide was less effective than the same drugs given separately.[32] A combined formulation of the recently recommended standard four-drug oral regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) is not yet available in either Europe or North America.[30]

Treatment of Patients with Proved Multidrug-Resistant Tuberculosis

Initiation of drug therapy in patients with proved multidrug-resistant tuberculosis requires assessment of the history of treatment as well as meticulous laboratory studies to characterize the susceptibility of the specific strain. Studies of patients with multidrug-resistant tuberculosis treated at National Jewish Hospital from 1976 through 1983 clearly indicate that previous therapy with a drug for more than a month was associated with diminished efficacy of that drug regardless of in vitro tests indicating susceptibility.[11] These results place a great premium on obtaining records of therapy.

There are no proved in vitro criteria for predicting the susceptibility of *M. tuberculosis* to drugs used previously or new drugs. For isoniazid and streptomycin, large-scale tuberculosis-treatment studies identified reduced clinical efficacy with various levels of in vitro resistance, so-called critical concentrations.[2,33] Such data are unavailable for other agents, so that one must use indirect methods to estimate potential efficacy. A system that assigns to the minimal inhibitory concentration such descriptors as susceptible, moderately susceptible, moderately resistant, and resistant has been developed (Table 2).[34] These descriptors are based on comparisons of the achievable serum concentrations and the minimal inhibitory concentrations for a particular drug. Although they are analogous to other models of antimicrobial therapy, these descriptors must be regarded as tentative because of some unique aspects of mycobacterial infections.

Initiation of Retreatment

A tuberculosis retreatment regimen should always include at least four but possibly as many as six or seven drugs. The number of drugs used varies de-

Table 2. Susceptibility Criteria and Side Effects of Antituberculosis Medications.*

Drug	Susceptible	Moderately Susceptible	Moderately Resistant	Resistant	Side Effects†
	minimal inhibitory concentration (μg/ml)				
Isoniazid	≤0.1	0.2–1.0	2.0	≥4	Hepatitis, neuritis, lupus erythematosus syndrome, drowsiness, mood changes
Rifampin	≤0.5	1.0–4.0	8.0	≥16	Drug interactions, hepatitis, thrombopenia, abdominal distress, diarrhea
Pyrazinamide	≤100	300	900	>900	Hepatitis, rash, arthralgia or arthritis, hyperuricemia, abdominal distress
Ethambutol	≤2.0	4.0	8.0	≥16	Optic neuritis, abdominal distress
Streptomycin	≤2.0	4.0	8.0	≥16	Hearing loss, ataxia, nystagmus, azotemia, proteinuria, eosinophilia, serum electrolyte abnormalities
Amikacin	≤2.0	4.0	8.0	≥16	
Kanamycin	≤2.0	4.0	8.0	≥16	
Capreomycin	≤2.0	4.0	8.0	≥16	
Ofloxacin	≤2.0	4.0	8.0	≥16	Abdominal distress, headache, anxiety, tremulousness, thrush
Ciprofloxacin	≤2.0	4.0	8.0	≥16	Abdominal distress, headache, anxiety, tremulousness, thrush, drug interactions
Ethionamide	≤1.25	2.5	5.0	≤10	Abdominal distress, dysgeusia, diarrhea, hepatitis, arthralgia
Aminosalicylic acid		Not known			Abdominal distress, nausea, bloating, diarrhea, rash, edema
Cycloserine	NA	NA	NA	NA	Mood and cognitive deterioration, psychosis, seizures

*The susceptibility categories are from Heifets.[34] NA denotes not applicable.

†A partial listing; for more information see the *Physicians' Desk Reference* or the package insert provided with each medication.

pending on the extent of disease and the potency of the available agents. Therapy should be initiated in the hospital to permit observation of toxicity and intolerance and to allow a change of regimen before strongly aversive conditioning makes the patient psychologically as well as physically intolerant of the medications. At the National Jewish Center for Immunology and Respiratory Medicine, we usually initiate treatment with small doses of each drug and increase to the planned dose over 3 to 10 days. Drug dosages as well as optimal timing of administration should be determined for each patient in order to achieve maximal serum concentrations in the target range with minimal side effects (Table 3). Determination of peak and trough serum concentrations is used to optimize therapy since the bioavailability and clearance of most antituberculosis drugs are not predictable. In particular, care should be taken to document that absorption of antituberculosis medications is adequate in patients with AIDS, because they commonly have malabsorption of these drugs.[35]

These measures may seem tedious and time-consuming, but they offer the most effective way to institute retreatment. This approach is justified because of the implications of retreatment failure not only for the patient with a life-threatening disease but also for the public, in terms of the financial and social costs of extended, repeated hospitalization and the transmission of potentially incurable tuberculosis.[25]

Some strategies for treating patients with proved multidrug resistance are shown in Table 4. Their efficacy depends on the careful performance of laboratory studies to confirm the resistance pattern of a new isolate. A careful history of previous drug administration also is very important.

The treatment of patients in whom tuberculosis is known to be caused by drug-resistant organisms is straightforward as compared with that of patients for whom no current susceptibility results are available. When treatment fails or a relapse occurs, the original regimen should be continued or resumed until new susceptibility data are obtained. However, important variables must be investigated. Was drug susceptibility determined initially? If so, and the appropriate drugs were used, the unsuccessful outcome was probably caused by noncompliance. If not, resistance to the initial drug may have contributed to the unfavorable result. Was therapy self-administered or directly observed? If the former, noncompliance is probably the dominant factor. If the latter, there may be unrecognized drug resistance or malabsorption. Does immunosuppression or another factor make the patient vulnerable to tuberculosis? If the original regimen was unsuccessful in a patient with AIDS, for example, the retreatment regimen might include new drugs. How long will it take to obtain new susceptibility results? If the results will be available in two weeks, one might continue the prior medications. If the results will not be available for two

Table 3. Dosages and Pharmacokinetics of Antituberculosis Medications.

Drug	Usual Adult Daily Dosage*	Peak Serum Concentration	Usual MIC (Range)†
		μg/ml	*μg/ml*
First-line oral drugs			
Isoniazid	300 mg	3–5	0.01–0.25
Rifampin	600 mg	8–20	0.06–0.25
Pyrazinamide	30 mg/kg	20–60	6.2–50
Ethambutol	15–25 mg/kg	3–5	0.5–2.0
Injectable drugs			
Streptomycin	15 mg/kg	35–45	0.25–2.0
Amikacin	15 mg/kg	35–45	0.5–1.0
Kanamycin	15 mg/kg	35–45	1.5–3.0
Capreomycin	15 mg/kg	35–45	1.25–2.5
Second-line oral drugs			
Ofloxacin	400 mg b.i.d.	8–10	0.25–2.0
Ciprofloxacin	750 mg b.i.d.	3–5	0.25–2.0
Ethionamide	250 mg b.i.d. or t.i.d.	1–5	0.3–1.2
Aminosalicylic acid	3 g q.i.d.	40–70	Not known
Cycloserine	250 mg b.i.d. or t.i.d.	20–35	Not known

*B.i.d. denotes twice a day, t.i.d. three times a day, and q.i.d. four times a day.

†Data are from Heifets.[34] MIC denotes minimal inhibitory concentration.

Table 4. Potential Regimens for Patients with Tuberculosis with Various Patterns of Drug Resistance.

Resistance	Suggested Regimen	Duration of Therapy	Comments
Isoniazid, streptomycin, and pyrazinamide	Rifampin Pyrazinamide Ethambutol Amikacin*	6 to 9 mo	Anticipate 100% response rate and less than 5% relapse rate[36]
Isoniazid and ethambutol (± streptomycin)	Rifampin Pyrazinamide Ofloxacin or ciprofloxacin Amikacin*	6 to 12 mo	Efficacy should be comparable to above regimen
Isoniazid and rifampin (± streptomycin)	Pyrazinamide Ethambutol Ofloxacin or ciprofloxacin Amikacin*	18 to 24 mo	Consider surgery
Isoniazid, rifampin, and ethambutol (± streptomycin)	Pyrazinamide Ofloxacin or ciprofloxacin Amikacin* Plus 2†	24 mo after conversion	Consider surgery
Isoniazid, rifampin, and pyrazinamide (± streptomycin)	Ethambutol Ofloxacin or ciprofloxacin Amikacin* Plus 2†	24 mo after conversion	Consider surgery
Isoniazid, rifampin, pyrazinamide, and ethambutol (± streptomycin)	Ofloxacin or ciprofloxacin Amikacin* Plus 3†	24 mo after conversion	Surgery, if possible

*If there is resistance to amikacin, kanamycin, and streptomycin, capreomycin is a good alternative. Injectable agents are usually continued for four to six months if toxicity does not intervene. All the injectable drugs are given daily (or twice or thrice weekly) and may be administered intravenously or intramuscularly.

†Potential agents from which to choose: ethionamide, cycloserine, or aminosalicylic acid. Others that are potentially useful but of unproved utility include clofazimine and amoxicillin–clavulanate. Clarithromycin, azithromycin, and rifabutin are unlikely to be active (see text).

to four months, however, it might be prudent to add several new drugs to prevent the development of further drug resistance and to prevent the spread of tuberculosis.

Drugs Used in Retreatment Regimens

Ofloxacin and ciprofloxacin are fluoroquinolone antimicrobial drugs that are proving useful in retreatment regimens. Ofloxacin has shown excellent activity in studies in animals[37] and has clinical efficacy when used for retreatment.[37-39] The minimal inhibitory concentrations of both ofloxacin and ciprofloxacin are low for strains of *M. tuberculosis* not previously exposed to these drugs.[40-42] At our center we have used ofloxacin or ciprofloxacin extensively for eight years and have noted remarkably good tolerance and little toxicity despite long-term, high-dose administration. Although the specific usefulness of these two drugs has never been studied, they are preferable to the other oral retreatment medications with regard to both antimycobacterial activity and safety. Resistance to fluoroquinolone drugs has developed when the drugs were used in inadequate regimens.

Aminosalicylic acid and ethionamide are second-line drugs. Treatment with either must be initiated slowly and the dosage increased cautiously. Few patients tolerate their simultaneous administration. Of all antituberculosis drugs, ethionamide is the most poorly tolerated. Gastrointestinal distress is almost universal and typically quite severe; other side effects include diarrhea and a bitter metallic taste that causes profound anorexia. Because few patients can tolerate the doses of ethionamide needed to obtain therapeutic serum concentrations, it should be used only when there are no alternatives.

Cycloserine is well tolerated in terms of gastrointestinal side effects, but it has substantial potential central nervous system toxicity. High serum concentrations may precipitate focal or grand mal seizures as well as psychotic or suicidal ideation. Some patients have dysthymia or impaired cognition in spite of appropriate serum concentrations. The serum concentrations should be measured regularly; peak concentrations two hours after a dose should be 25 to 35 μg per milliliter. Pyridoxine (50 to 100 mg daily) is given with cycloserine in the hope of preventing neurologic toxicity, but its value has not been proved.

Injectable medications in addition to streptomycin include amikacin, kanamycin, and capreomycin. Amikacin and kanamycin are structurally quite similar, and there usually is cross-resistance between them; however, cross-resistance between them and streptomycin is rare. Capreomycin belongs to a different category of antibiotics than the former two agents, and there is no cross-resistance between it and amikacin, kanamycin, or streptomycin. Amikacin and kanamycin are administered intramuscularly, but they may be given intravenously through a central-venous-access device or a peripherally inserted central catheter.

Other oral medications that have been used for retreatment in patients with multidrug-resistant tuberculosis include amithiozone, clofazimine, amoxicillin–clavulanate, the new macrolide antibiotics (clarithromycin and azithromycin), and newer rifamycin antibiotics. Amithiozone, used in the developing nations because of its low price, has modest tuberculostatic activity; it is used mostly because it limits the development of resistance to isoniazid. It is not approved by the FDA. The side effects of amithiozone, though relatively uncommon, include erythema multiforme (Stevens–Johnson syndrome), especially in patients with HIV infection.[43] Clofazimine is an anti-leprosy drug that has in vitro activity against *M. tuberculosis*, but its clinical efficacy has not been established. One report suggests the potential efficacy of amoxicillin–clavulanate,[44] but the minimal inhibitory concentrations for most strains of *M. tuberculosis* are very high (Heifets L: personal communication). On the basis of the activity of clarithromycin and azithromycin against *M. avium*, there has been considerable interest in their potential activity against *M. tuberculosis*. The minimal inhibitory concentrations, however, are very high in relation to the maximal achievable serum concentrations (Heifets L: personal communication). The value of rifamycins other than rifampin for use in rifampin-resistant tuberculosis is unproved. We used rifabutin extensively at our center in the late 1980s but found high levels of cross-resist-

ance between it and rifampin, and its clinical benefit was minimal (unpublished data). The results of a trial of rifabutin in Hong Kong also were disappointing.[39]

Monitoring Retreatment

Sputum specimens should be obtained for semiquantitative smear and culture weekly during the initial phase of therapy in order to determine the base-line mycobacterial burden. Improvement in the results of bacteriologic tests of sputum is the main marker of response, but decreased fever, cough, sputum, and weight loss are important indirect markers of success. Improvement on the chest radiograph may lag behind other changes.

The optimal duration of retreatment has not been clearly identified; the periods recommended in Table 4 are general projections and subject to individual variation. At the National Jewish Center we usually administer drugs requiring parenteral administration for four to six months if toxicity does not intervene. Patients infected with organisms that are resistant to all or most of the first-line drugs are treated with oral medications for 24 months after the sputum culture becomes negative. This duration of treatment is based on the impression, not rigorously documented, that discontinuation of treatment before this time increases the risk of reactivation. As my colleagues and I noted in a recent review,[11] among 65 percent of patients who initially responded to therapy with sustained negative sputum cultures, approximately 20 percent had reactivation after discontinuation of therapy.

Experience with large numbers of patients with multidrug-resistant tuberculosis indicates that if chemotherapy is to achieve sputum conversion, it will do so within four months in most patients. If sputum conversion does not occur or the patient relapses, further acquired resistance to the agents being used will appear. Hence, if chemotherapy is not successful, the potential benefits of resectional surgery should be considered.

The Role of Resectional Surgery

In view of the adverse consequences of treatment failure, we have become more aggressive in using resectional surgery as an adjunct to medical treatment at our center, beginning with patients with localized disease and good cardiorespiratory reserve.[36] Historical comparisons indicate that surgery probably has an important role in curing patients with severe disease. As of September 1991, my colleagues and I had performed resectional surgery on 57 patients with multidrug-resistant tuberculosis.[45] One patient died after surgery of noncardiogenic pulmonary edema, and seven patients had major surgical complications, including bronchial disruption with bronchopleural fistulas in one patient. After surgery, six patients had oxygen dependency, respiratory insufficiency with hypercapnia, or both. Overall, however, the clinical and bacteriologic responses have been gratifying: 49 of 50 long-term survivors have had consistently negative results on sputum smears and cultures. Because most of these patients had active infection despite long periods of retreatment, few seemed likely to benefit from further medical therapy.

Prevention of Tuberculosis in the Contacts of Patients with Multidrug-Resistant Tuberculosis

Patients with advanced multidrug-resistant tuberculosis are typically treated initially in the hospital, where the risk of transmission of tuberculous infection to health care workers and other patients is substantial.[46,47] Because infection with drug-resistant *M. tuberculosis* is especially hazardous, special precautions should be taken to minimize the risk.[48] Theoretically, this could be accomplished by proper ventilation, but studies of a recent tuberculosis outbreak in an office building indicated that there are practical limits to this method.[49] Widespread use of ultraviolet germicidal irradiation devices is both theoretically and practically the best means to curtail tuberculosis transmission[50,51]; the value of masks, respirators, and filtration devices is unproved and highly problematic. One nosocomial epidemic appeared to be curtailed by an aggressive program of rigorous isolation policies, negative-pressure ventilation of patients' rooms, filtration of major air conduits, use of submicron molded masks, and the use of ultraviolet fixtures in areas where negative-pressure ventilation could not be achieved.[52]

Isoniazid is the only medication proved efficacious and recommended for the prevention of tuberculosis.[29,53,54] On the basis of various in vitro studies and studies in animals, rifampin is believed to have equal or greater efficacy,[55] but for contacts thought to be infected with tubercle bacilli resistant to both these agents, there is no good choice for preventive chemotherapy. A recent Delphi-technique survey resulted in modest support for pyrazinamide and ofloxacin or ciprofloxacin as chemoprophylaxis for high-risk contacts of patients with multidrug-resistant tuberculosis.[56] The CDC has developed a complex but thoughtful set of recommendations for the care of persons exposed to multidrug-resistant tuberculosis.[57] The document helps clinicians estimate the likelihood of new tuberculosis infection and of drug-resistant infection, and the probability that the newly infected person will have active tuberculosis — vital elements in decision making about preventive therapy. For contacts deemed likely to be newly infected with multidrug-resistant tuberculosis and at high risk for active disease, treatment with ethambutol and pyrazinamide or, alternatively, ofloxacin or ciprofloxacin and pyrazinamide is suggested.

Given the lack of attractive drugs for preventive treatment, there is renewed interest in the use of the bacille Calmette–Guérin (BCG) vaccine for health professionals or others at high risk of exposure to tuberculosis, including multidrug-resistant strains.[58] BCG vaccine has not been clearly shown to be effec-

tive in adults, however. Its strongest protective effects are in infants and children[59]; two recent studies that included adults failed to show protection.[60,61] Hence, I am reluctant to use this vaccine of unproved efficacy, which would confound the results of tuberculin skin-test surveillance and create a potentially false sense of security among those who work in facilities where patients with tuberculosis are treated. In addition, vaccination with BCG — an attenuated but living strain of *M. bovis* — poses a potential risk of disseminated disease or progressive local infection among immunocompromised recipients.

Summary

The frequency of infections with *M. tuberculosis* resistant to antituberculous drugs is increasing in the United States and globally. This increase is a major threat to tuberculosis treatment and control programs. To prevent this situation from worsening, initial treatment programs that entail directly observed therapy supported by effective inducements or enforcements must be used.[62-64] Retreatment of patients who have multidrug-resistant tuberculosis should be carried out in programs with comprehensive microbiologic, pharmacokinetic, psychosocial, and nutritional support systems. Regimens of multiple drugs, which generally are poorly tolerated and more toxic than traditional regimens, must be administered for 18 to 36 months. Resectional surgery may be required for substantial numbers of patients. For patients with AIDS who acquire tuberculosis caused by multiply-resistant strains, the disease may prove lethal before effective therapy can be implemented. Ultraviolet irradiation systems should be used to protect health care personnel and other patients in high-risk environments. Enhanced federal, state, and local programs for prevention and control are urgently needed, and research to identify new medications and systems for their delivery is essential.

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