REVIEW ARTICLE

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Treatment of Tuberculosis

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Tuberculosis, a scourge since prehistoric times, affects more than 9 million people and causes the death of 1.5 million people each year. Effective treatment has been available for 60 years, but such treatment takes at least 6 months, and resistance to the drugs, which is increasing throughout the world, threatens the effectiveness of treatment.[1] This review summarizes the theoretical principles of tuberculosis treatment, current therapeutic approaches, areas of uncertainty, and persistent challenges.

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Principles of Tuberculosis Treatment

A series of clinical trials conducted by the U.K. Medical Research Council and the U.S. Public Health Services between 1948 and 1986 showed that completion of a 6-month course of multidrug therapy could lead to a cure of drug-susceptible tuberculosis, with less than a 5 to 8% chance of relapse.[2,3] When relapse occurs, it usually happens within 12 months after the completion of therapy, indicating that the disease was incompletely treated.[4] These trials showed that use of rifampin with isoniazid allowed treatment to be shortened from 18 months to 9 months, and the addition of pyrazinamide for the initial 2 months allowed further shortening of treatment to 6 months. In four recent clinical trials, attempts to shorten treatment to 4 months by adding a fluoroquinolone were unsuccessful, with relapse rates of 13 to 20%.[5-8] Thus, standard treatment now consists of a 2-month induction phase with at least isoniazid, rifampin, and pyrazinamide, followed by a 4-month consolidation phase with at least isoniazid and rifampin.

During the first 2 months of effective therapy, viable bacteria in sputum samples from patients show a characteristic biphasic kill curve (Fig. 1A).[9] This indicates that there are at least two bacterial subpopulations that differ in their intrinsic drug susceptibility: one subpopulation is rapidly killed, and the other responds more slowly. The bacilli in this second and slowly replicating or nonreplicating subpopulation have been classified as persistent (Fig. 1B). Persistent bacteria are thought to be in a metabolic state that renders them less susceptible to killing by drugs because of either local variation in an environmental factor (e.g., oxygen abundance or pH) or generation of phenotypic variants under host immune pressure.[10] The effectiveness of combination therapy with antimycobacterial agents in contemporary short-course regimens has been theorized to be the result of the differential effectiveness of the individual agents against these discrete bacterial subpopulations.[11] This paradigm was most clearly enunciated by Mitchison, who identified some drugs as having "bactericidal" activity (i.e., the ability to kill rapidly multiplying bacteria) and others as having "sterilizing" activity (i.e., the ability to kill persistent, or nonreplicating, bacteria).[12]

Despite the usefulness of this conceptual model, there are some important

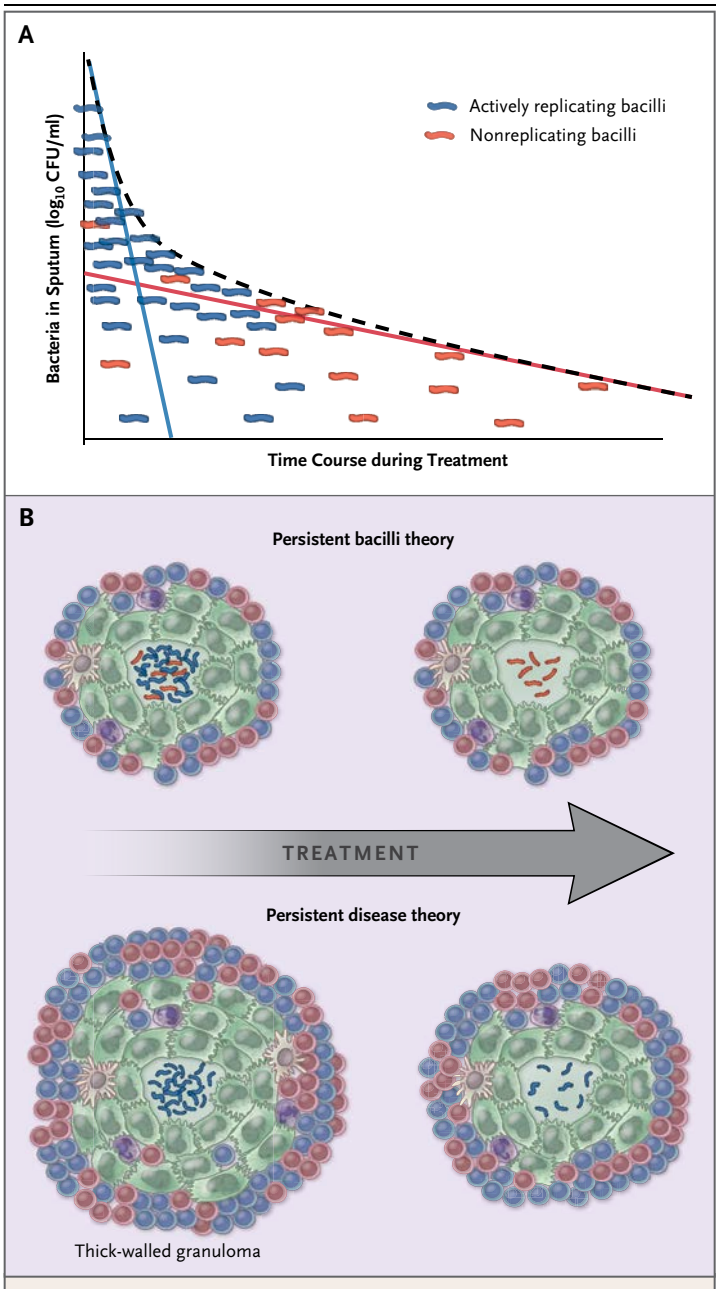

Figure 1. Biphasic Decline in Viable Bacteria during Treatment for Tuberculosis.
Panel A shows the time course of decline of viable *Mycobacterium tuberculosis* in a sputum sample from a patient being treated for tuberculosis. The number of bacteria declines at a rapid rate during the early phase of therapy (blue curve), with a less rapid rate of decline during the later phase (red curve). The biphasic pattern that is observed (black dashed curve) suggests that there are bacterial subpopulations that differ in their drug susceptibility. CFU denotes colony-forming units. Panel B shows two proposed explanations for this differential response: persistent bacilli and persistent disease. The first explanation is that bacteria in a replicating state (blue) are more susceptible to drugs than are bacteria in a nonreplicating state (red), which can persist despite drug treatment. The second explanation is that some bacilli are sequestered in thick-walled granulomas, where antibiotics are not able to reach them, resulting in persistent disease.

unexplained observations. After the first 2 months of combination drug therapy, most patients no longer have bacilli in their sputum that can be cultured, but many must still complete an additional 4 months of treatment to avoid relapse. The 6-month standard course of therapy for drug-susceptible disease is clearly longer than is necessary for some patients.[5-8] Unfortunately, it has proved extremely challenging to identify which patients can be successfully treated for a shorter time. A clinical trial of shorter treatment for patients without cavities on baseline chest films and with negative sputum cultures at 2 months was unsuccessful.[13] This highlights one of the central compromises we accept in standardized tuberculosis treatment: overtreatment of many cases to ensure cure of the overall population.

Recent studies suggest that in many patients, *Mycobacterium tuberculosis* bacteria are sequestered in compartments that are inaccessible to antibiotic action; this could explain the poor long-term treatment response in some patients despite clearance of bacteria from the sputum. The leading candidates for these sequestered compartments are the interior of granulomas, abscesses, and cavities.[14] Patients with extensive and long-standing disease frequently have substantial numbers of bacilli in such compartments (Fig. 1B and 2). Studies of tuberculosis in higher-vertebrate models (monkeys and rabbits) and in patients with tuberculosis have used a specialized imaging mass spectrometer that provides spatial information about how well tuberculosis drugs penetrate lesions. The degree of penetration varies among agents. For example, rifampin and pyrazinamide, the two drugs that have contributed most to our ability to shorten treatment, penetrate well into caseous foci. Moxifloxacin has heterogeneous distribution across the granuloma, concentrating in the cellular periphery and only minimally penetrating the caseous center[15-17]; this may partially explain the inability to shorten treatment in clinical trials of moxifloxacin-containing regimens. Thus, the lack of sterilization with moxifloxacin may be attributable to the characteristics of the disease or to the drug's inability to kill persistent bacteria, or to both. The ability of drugs to penetrate lesions may be important in determining the effect of specific drugs on treatment duration, especially for patients with long-standing disease and substantial tissue destruction in whom large numbers

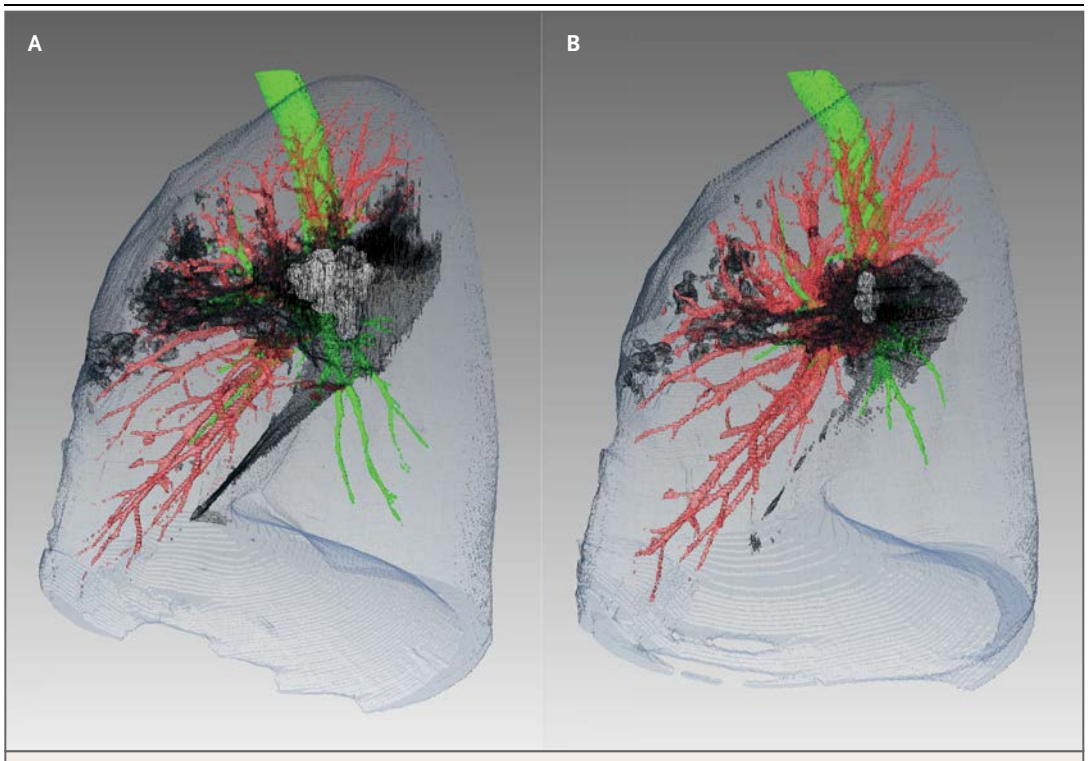

Figure 2. CT Scans of the Lung in a Patient with Pulmonary Tuberculosis.

CT scans with three-dimensional volumetric rendering were obtained before treatment (Panel A) and after 2 months of treatment (Panel B) and show slow resolution of a radiodense lesion (black) around the interior air (white) of a cavity. The airways are shown in green and the vasculature in red.

of caseating tissue foci, poor vascularization, or both may result in reduced drug delivery into tissues.

Another potential explanation for the poor clinical responses in some patients is inadequate serum antimycobacterial drug levels, since low serum levels further impede the ability of drugs to penetrate infectious foci. One cause of low serum levels can be inadequate absorption. Isoniazid, rifampin, and pyrazinamide levels are decreased when the drug is taken with food, whereas rifapentine absorption is increased with a high-fat meal; fluoroquinolone absorption is decreased by antacids.[18] In addition, transporter gene products can influence drug absorption; variations in rifampin absorption (and excretion) have been attributed to such gene products.[19] Genetically determined metabolic pathways can also influence serum drug levels. *N*-acetyltransferase is an enzyme that is involved in isoniazid clearance; human genetic variation in the gene encoding *N*-acetyltransferase (*NAT2*) can lead to underexposure (in "fast acetylators") or to an elevated risk of hepatotoxicity (in "slow acetylators")[20]; this slow-acetylator genotype is present in more than 50% of white persons. Poor clinical responses to tuberculosis therapy have been associated with decreased serum levels of both rifampin and pyrazinamide.[21,22]

Finally, it was recognized early in the course of clinical trials that multidrug chemotherapy was necessary to prevent the emergence of drug-resistant disease during tuberculosis treatment.[2] The concurrent administration of at least two and preferably three drugs markedly reduces the proportion of relapses attributable to the emergence of drug resistance. Since *M. tuberculosis* does not appear to acquire resistance mutations through transposition or conjugation, resistance has been attributed to random genetic mutation.[23] Random genetic variation is primarily due to errors introduced during DNA replication, and lineages of *M. tuberculosis* strains do not appear to vary substantially in the intrinsic fidelity of DNA polymerase.[24] However, the role of antibiotics in promoting *M. tuberculosis* mutation during treatment has not been extensively explored. Fluoroquinolones have been shown to increase

bacterial mutation in vitro,[25] and subtherapeutic levels of antimycobacterial agents have been associated with the emergence of drug resistance in vivo.[26] With the exception of drug-resistance mutations, *M. tuberculosis* genetic factors appear to have little bearing on the outcome of tuberculosis treatment. Although epidemiologic associations between *M. tuberculosis* families and a number of clinical outcomes have been observed, no specific bacterial genes or gene products mediating such events have been identified.[27-29]

CURRENT TREATMENT APPROACHES

Diagnosis of tuberculosis has undergone rapid evolution in the past decade. Although culture remains the standard for both diagnosis and drug-susceptibility testing, molecular DNA–based diagnostics have become widely available and permit both rapid diagnosis and preliminary assessment of drug susceptibility. These approaches facilitate prompt initiation of tuberculosis treatment regimens that can be expected to be effective for individual patients. Ideally, the initial isolate for each patient should be tested to rule out baseline drug resistance; if resources are limited, such testing should at least be performed for all patients who have a history of previous treatment or contact with a patient with a drug-resistant isolate.

An interactive graphic is available at NEJM.org

The standard treatment regimen for presumably drug-susceptible tuberculosis includes an induction phase consisting of rifampin, isoniazid, and pyrazinamide, to which ethambutol is added as protection against unrecognized resistance to one of the three core drugs. Once susceptibility to isoniazid, rifampin, and pyrazinamide has been confirmed, ethambutol can be discontinued. In young children, this drug is frequently omitted if the source of transmission is known to have drug-susceptible tuberculosis, because recognizing the toxic effects of ethambutol is challenging in children. The induction phase is followed by a consolidation phase consisting of rifampin and isoniazid for an additional 4 months of treatment.

The standard 6-month treatment regimen for drug-susceptible tuberculosis is an exceptionally long course of treatment as compared with the duration of treatment of other bacterial infectious diseases.[30,31] The prolonged regimen poses two major challenges to success: managing drug toxicity and ensuring that patients adhere to the full course of treatment. Drug toxicity is substantial; a review of retrospective studies using similar definitions estimates that 3 to 13% of patients have hepatotoxic effects.[32] A recent prospective cohort study of patients with drug-susceptible disease who received standard tuberculosis therapy documented a 15% incidence of adverse drug reactions resulting in interruption or discontinuation of one or more of the drugs.[33] Of these adverse reactions, 7.7% resulted in hospitalization, disability, or death. A wide variety of reactions were reported; the most common were hepatotoxic effects, gastrointestinal disorders, allergic reactions, and arthralgias.

Overall, 16 to 49% of patients do not complete the regimen.[34] Reasons for failure to complete treatment are varied and include adverse drug reactions, cost of treatment, stigma, and the patient's belief that cure has been achieved when symptoms have resolved and bacteria can no longer be recovered from the sputum.[35] Treatment support and direct-observation programs are useful in improving adherence but have not entirely overcome these factors.

There is less evidence to support recommendations for treatment of drug-resistant disease than there is to support treatment recommendations for drug-susceptible disease. Drugs with proven or potential efficacy against *M. tuberculosis* that can be considered for treatment of drug-resistant disease are shown in Table 1, and in Table S1 in the Supplementary Appendix and in the interactive graphic, both available with the full text of this article at NEJM.org. In the case of resistance to isoniazid (or unacceptable toxic effects associated with isoniazid) in the absence of rifampin resistance, a standard 6-month regimen in which isoniazid is replaced by a later-generation fluoroquinolone (levofloxacin or moxifloxacin) is likely to lead to a similar treatment outcome, and a 6-month regimen containing rifampin, moxifloxacin, pyrazinamide, and ethambutol for 2 months, followed by rifapentine and moxifloxacin for 4 months, was recently shown to be effective.[8]

Multidrug-resistant (MDR) tuberculosis, defined as disease caused by *M. tuberculosis* that is resistant to both rifampin and isoniazid (and frequently other drugs), is complicated, and treatment should always be guided by an experienced physician.[36] Whenever possible, the initial treat-

Table 1. Tuberculosis Drugs, Recommended Dosages, and Common Adverse Events.*

Drug	Route	Dose in Adults	Comments
Rifamycins			
Rifampin	Oral, IV	10 mg/kg daily (higher doses may be more effective)	A higher dose (13 mg/kg IV in the first 2 wk) improves treatment outcome in TB meningitis (low CSF penetration); monitor for hepatotoxicity; dose adjustments may be necessary in patients receiving interacting drugs (e.g., ART)
Alternative rifamycins			
Rifabutin	Oral	5 mg/kg daily (doses up to 450 mg daily sometimes used)	Less likely than rifampin to interact with antiretroviral agents and may be useful in patients with HIV infection; monitor for hepatotoxicity; dose adjustments may be necessary in patients receiving interacting drugs (e.g., ART)
Rifapentine	Oral	Not recommended in the U.S. for induction phase; consolidation phase: 600–1200 mg once weekly	Has a very long half-life and can be administered weekly in the consolidation phase; monitor for hepatotoxicity; dose adjustments may be necessary in patients receiving interacting drugs (e.g., ART)
Isoniazid and later-generation fluoroquinolones			
Isoniazid	Oral, IV	5 mg/kg daily (higher dose recommended for MDR-TB)	MDR-TB: in the absence of a *katG* S315T mutation, *inhA* promoter mutations (8A/C, 15T, 16G) confer low-level isoniazid resistance (MIC, <1 mg/liter), and a dose of 16–20 mg/kg should be considered; monitor for hepatotoxicity; give with pyridoxine
Levofloxacin	Oral, IV	10–15 mg/kg daily	May potentiate QTc-interval prolongation when given with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval
Moxifloxacin	Oral, IV	400 mg daily	May potentiate QTc-interval prolongation when given with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval; concurrent use with bedaquiline or delamanid not recommended
New drugs with documented efficacy			
Bedaquiline	Oral	400 mg daily for 2 wk, followed by 200 mg 3 times/wk for 22 wk (take with food)	Approved by the FDA and EMA as part of an appropriate combination regimen for MDR-TB when an effective treatment regimen is unavailable because of resistance to or unacceptable adverse effects of other medications; may potentiate QTc-interval prolongation when used with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval; concurrent use with delamanid or moxifloxacin not recommended
Delamanid	Oral	100 mg twice a day for 24 wk	Approved by the EMA for use as part of an appropriate combination regimen for MDR-TB when an effective treatment regimen is unavailable because of resistance to or unacceptable adverse effects of other medications; may potentiate QTc-interval prolongation when used with other drugs; close monitoring recommended when used with other drugs that prolong the QTc interval; concurrent use with bedaquiline or moxifloxacin not recommended
Injectable agents with sufficient efficacy data			
Amikacin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	Recommended duration of therapy for MDR-TB is 8 mo; IV administration recommended if possible, since IM injections can be painful; monitor renal function, electrolytes, and hearing; hearing loss can be substantial before becoming clinically apparent

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Table 1. (Continued.)

Drug	Route	Dose in Adults	Comments
Capreomycin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	Recommended duration of therapy for MDR-TB is 8 mo; IV administration recommended if possible, since IM injections can be painful; electrolyte abnormalities can be severe and life-threatening and should be monitored carefully; also monitor electrolytes and hearing; hearing loss can be substantial before becoming clinically apparent
Kanamycin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	Recommended duration of therapy for MDR-TB is 8 mo; IV administration recommended if possible, since IM injections can be painful; monitor renal function, electrolytes, and hearing; hearing loss can be substantial before becoming clinically apparent
Streptomycin	IM, IV	15 mg/kg daily 5–7 days/wk; a dose of 15 mg/kg 3 days/wk can be used after culture conversion (maximum daily dose, 1 g)	IV administration recommended if possible, since IM injections can be painful; monitor renal function, electrolytes, and hearing; hearing loss can be substantial before becoming clinically apparent; many MDR-TB strains are resistant to streptomycin
Oral drugs with sufficient efficacy data†			
Ethambutol	Oral, IV	15–25 mg/kg daily	Companion drug in the WHO first-line regimen but with less sterilizing activity than rifampin and isoniazid; may induce visual disturbance that can be rapid in onset and can begin with loss of red–green discrimination; monitor visual acuity
Linezolid	Oral, IV	600 mg daily	Severe adverse events are common with long-term therapy; close monitoring of blood count and awareness of peripheral neuropathy is mandatory; give with pyridoxine
Aminosalicylic acid	Oral, IV	Oral: 4 g 3 times/day; intravenous: 12 g daily	Often not tolerated in combination with protionamide or ethionamide; IV dosing (available in Europe) by central venous catheter only
Protionamide or ethionamide	Oral	15–20 mg/kg (usually 750 mg as a single daily dose or in 2–3 divided doses)	Often not tolerated in combination with aminosalicylic acid; monitor liver and thyroid function; give with pyridoxine
Terizidone or cycloserine	Oral	10–15 mg/kg (usually 750 mg as a single daily dose or in 2–3 divided doses)	Terizidone, the fusion product of two molecules of cycloserine and one molecule of terephthalaldehyde, is less toxic than cycloserine; monitor mental status; give with pyridoxine
Pyrazinamide	Oral	Daily dosing (preferred): 25–35 mg/kg daily (maximum dose, 2000 mg); intermittent dosing: up to 50 mg/kg daily 3 days/wk	Companion drug in induction phase of the WHO first-line regimen; if hepatotoxicity develops, reexposure is not suggested if reexposure to isoniazid and rifampin is tolerated; if not part of a standard regimen in the induction phase, treatment should be prolonged; monitor for hepatotoxicity
Companion drugs with limited efficacy data			
Amoxicillin–clavulanate	Oral, IV	Amoxicillin component: 40 mg/kg 2 or 3 times/day (maximum dose, 3000 mg/day)	Administer with meropenem if clavulanic acid is not available as a single drug

Clarithromycin	Oral	500 mg twice a day	Monitor QTc interval
Clofazimine	Oral	100–200 mg daily	In cases of severe skin discoloration, reduce dose to 5 times/wk; monitor QTc interval
Imipenem–cilastatin	IV	Imipenem component: 1000 mg 2 or 3 times/day	Long-term IV access recommended; administer with clavulanic acid (available as amoxicillin–clavulanate) at a dose of 125 mg 2 or 3 times/day; very limited data on use for MDR-TB
Meropenem	IV	1000 mg 2 or 3 times/day	Long-term IV access recommended; administer 1000–2000 mg 2 or 3 times/day with clavulanic acid (available as amoxicillin–clavulanate)
Amithiozone	Oral	150 mg daily	Cross-resistance with protionamide, ethionamide, and isoniazid; contraindicated in patients with HIV infection; give with pyridoxine

* An expanded table that includes doses in children and adverse events is in the Supplementary Appendix, available at NEJM.org. ART denotes antiretroviral therapy, CSF cerebrospinal fluid, EMA European Medicines Agency, FDA Food and Drug Administration, HIV human immunodeficiency virus, IM intramuscular, IV intravenous, MDR-TB multidrug-resistant tuberculosis, MIC minimal inhibitory concentration, QTc corrected QT, and WHO World Health Organization.
† Some drugs in the oral drugs category may have injectable formulations but are almost always given orally for tuberculosis treatment.

ment regimen should be individually tailored according to the results of drug-susceptibility testing of the *M. tuberculosis* isolate from the patient, with testing performed either by culture or with the use of DNA-based methods. In the absence of this information, empirical regimens can be used, but as soon as the results of drug-susceptibility testing become available, the treatment regimen should be adjusted.[37]

On the basis of a large retrospective meta-analysis, the World Health Organization (WHO) recommends that the initial regimen for the treatment of MDR tuberculosis include four drugs to which the patient's isolate is susceptible (plus pyrazinamide, for which susceptibility results are not usually available) in the induction phase, which should last 6 to 8 months.[38] Several observational studies have suggested that an induction phase with more drugs to which the patient's isolate is susceptible is associated with improved outcomes.[39-41] The need to use more drugs probably reflects the poorer antimycobacterial activity of these drugs as compared with isoniazid, rifampin, and pyrazinamide. In addition, these drugs are substantially more toxic than those used to treat drug-susceptible tuberculosis (Table 1, Table S1 in the Supplementary Appendix, and the interactive graphic). The appropriate duration of treatment for MDR tuberculosis also remains to be defined. The WHO recommends a minimum of 20 months (including the induction phase), but this recommendation is based on a database that included few patients treated for shorter periods. An observational cohort study of a highly intensive 9-month regimen of seven drugs for the treatment of MDR tuberculosis in Bangladesh showed a high proportion of successful outcomes, and the regimen is currently undergoing evaluation in a prospective, randomized, multicenter clinical trial.[41,42] This "Bangladesh regimen" and similar regimens have been used for the treatment of selected patients for 9 to 12 months, with cure rates of 85 to 89% and few relapses,[40,41] but until the results of the randomized trial are available, it is not clear whether these outcomes can be generalized.

Patients with human immunodeficiency (HIV) infection who have either drug-susceptible or drug-resistant tuberculosis should receive antiretroviral therapy (ART) while they are receiving treatment for tuberculosis. If they are not already

receiving ART when tuberculosis is diagnosed, ART should be initiated within 2 weeks after starting antituberculosis treatment for persons with a CD4+ T-cell count of less than or equal to 50 per cubic millimeter and within 8 weeks for persons with a count above 50 per cubic millimeter.[43,44] Interactions between tuberculosis drugs and antiretroviral drugs are common and may require dose adjustment or substitution of another agent.[45] Patients receiving ART and tuberculosis treatment are at high risk for the immune reconstitution inflammatory syndrome (IRIS), a sudden systemic inflammation and cytokine storm syndrome resulting from activation of the recovering CD4+ T cells, often from an unrecognized opportunistic infection; such patients should be observed carefully for this condition.[46]

AREAS OF UNCERTAINTY

There are conflicting opinions about many aspects of tuberculosis treatment, largely because of the paucity of strong evidence. Treatment guidelines have been prepared by the WHO, the International Union against Tuberculosis and Lung Disease (the Union), and a number of countries, and these various guidelines reflect this diversity (see Table S2 in the Supplementary Appendix).[30,47-59] In this section, we address some of the areas in which general consensus is lacking.

TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS

All the guidelines recommend use of the same regimen for the treatment of drug-susceptible tuberculosis, but with some variation in duration. The Indian guidelines,[57] for example, recommend continuation of ethambutol for the full 6-month course. Although overall treatment for 6 months is standard and the WHO does not recommend extension of treatment for any patients,[30] prolongation is recommended in various circumstances by a number of the guidelines. For example, U.S. guidelines suggest that persons with a cavity on the baseline chest film and a positive sputum culture at 2 months should receive an additional 3 months of consolidation therapy[53]; German guidelines[54] suggest extending therapy in the case of persistent bacteria in a smear or extensive disease, and Canadian guidelines[50] recommend extending treatment if cultures remain positive or cavities persist. Most guidelines also support intermittent dosing, either twice or three times weekly, during the consolidation phase of treatment for drug-susceptible tuberculosis, and some recommend once-weekly administration of rifapentine and isoniazid in the consolidation phase for selected patients. However, U.S. guidelines recommend daily administration in the consolidation phase for HIV-infected patients because of concern that twice-weekly dosing may lead to the emergence of resistance against rifampin.

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

Recommendations for the treatment of tuberculosis that is resistant only to isoniazid are varied but similar. All guidelines recommend a regimen consisting of a rifamycin, ethambutol, and pyrazinamide, with or without a fluoroquinolone, for 6 to 12 months. Rifampin resistance is rare in the absence of isoniazid resistance, but a 9-month regimen of isoniazid, pyrazinamide, and streptomycin has been shown to be effective[60]; however, it can be difficult for patients to complete 9 months of treatment with an injectable agent. Eighteen-month regimens comprising isoniazid, pyrazinamide, and ethambutol, with or without a fluoroquinolone, are also recommended, on the basis of clinical experience. The WHO and some countries[47] recommend a regimen for MDR tuberculosis even in cases of mono-resistant (i.e., rifampin-resistant) tuberculosis, because on the basis of testing with GeneXpert (Cepheid), many cases of tuberculosis are rifampin-resistant and companion susceptibilities are not known. If the isolate is susceptible to isoniazid and pyrazinamide, a shorter and less toxic regimen can be used. For MDR tuberculosis, all the national guidelines surveyed recommend regimens that are individualized on the basis of the results of drug-susceptibility testing. The WHO[47] and the Union[52] recommend the use of empirical regimens (based on prevailing national drug-susceptibility profiles) when susceptibility testing is not available.

TREATMENT OF TUBERCULOUS MENINGITIS

Most guidelines recommend prolonging therapy to 9 to 12 months and adding glucocorticoid therapy for patients with tuberculous meningitis. There is less agreement about the need to

ensure adequate drug delivery at the site of infection by either increasing the dose of rifampin or including in the regimen agents that have better penetration into cerebrospinal fluid.[61]

TREATMENT MONITORING

All guidelines recommend consideration of directly observed therapy but allow for flexibility in the application of this strategy. This is consistent with the lack of clinical trial data supporting the use of directly observed therapy and the lack of standardized methods for implementation.[62] Recommended follow-up schedules for assessment of the treatment response and monitoring for drug toxicity vary, but most guidelines recommend at least a follow-up visit at 2 months and a visit at or near the end of treatment to assess the clinical and microbiologic response.

PERSISTENT CHALLENGES

IDENTIFICATION OF PATIENTS REQUIRING PROLONGED TREATMENT

Clinical or laboratory algorithms that could predict which patients will have a response to a shorter course of treatment and which patients require a longer course would allow more appropriate targeting of resources and in many cases would reduce drug toxicity and lessen the effect of nonadherence to the regimen. Although clinical factors are inadequate for predicting responses in individual patients, new molecular techniques have identified some promising potential biomarkers.[63]

USE OF PHARMACOKINETIC DATA TO IMPROVE REGIMEN COMPOSITION

We need to better understand not only where drugs penetrate but also the dosing strategies that will achieve desired drug levels in tissues. It is clear that current dosing of rifampin and levofloxacin is suboptimal, and studies are in progress to identify doses that achieve the maximal clinical effect with an acceptable rate of adverse events.[64-66] A clearer understanding of the penetration into lung cavities and the overall pharmacokinetic profile of new drugs and second-line agents will facilitate more rational design of treatment regimens. Drug monitoring could potentially increase the ability to tailor regimens to individual patients so that the best ratio of therapeutic to toxic effects is achieved for each drug in the regimen.[67] In resource-limited settings, the traditional approach of "one size fits all" may still be necessary, but with better information and new tools, individualization of drug combinations, doses, and duration of treatment could revolutionize the field.

MORE RAPID AND ACCURATE ASSESSMENT OF DRUG RESISTANCE

Rapid progress is being made in molecular diagnostics for drug resistance. With improved accuracy and wider availability of molecular drug-susceptibility testing, the current 6-to-8-week delay in implementing the appropriate treatment regimen for patients with drug resistance could be shrunk to 24 hours.[68,69] This would substantially decrease the time spent on the administration of inadequate regimens.

DEVELOPMENT OF NEW ANTIMYCOBACTERIAL AGENTS

Several new classes of antimycobacterial drugs have been developed in the past 15 years[70] (Fig. 3). Two of these agents, the diarylquinoline bedaquiline and the nitroimidazooxazole delamanid, have received accelerated regulatory approval and are currently being confirmed in phase 3 clinical trials.[42,71] We hope that such agents will lead to shorter and more effective regimens for the treatment of MDR tuberculosis and will allow clinicians to avoid the use of injectable agents, which have unacceptably high rates of ototoxicity and renal toxicity. At the present time, the role of the new agents in the treatment of drug-susceptible tuberculosis appears to be limited. Other new drug classes (benzothiazinones and imidazopyridines) show promise in preclinical studies but have not yet progressed to clinical trials.[72,73] Resources to support such translational research are urgently needed.

DEVELOPMENT OF TREATMENT REGIMENS FOR PEDIATRIC TUBERCULOSIS

Our knowledge of how to diagnose and treat tuberculosis in children is inadequate. The pathophysiological manifestations of tuberculosis in young children differ from those in adults, as do immune responses; absorption, metabolism, and excretion of drugs; and sensitivity to drug toxic-

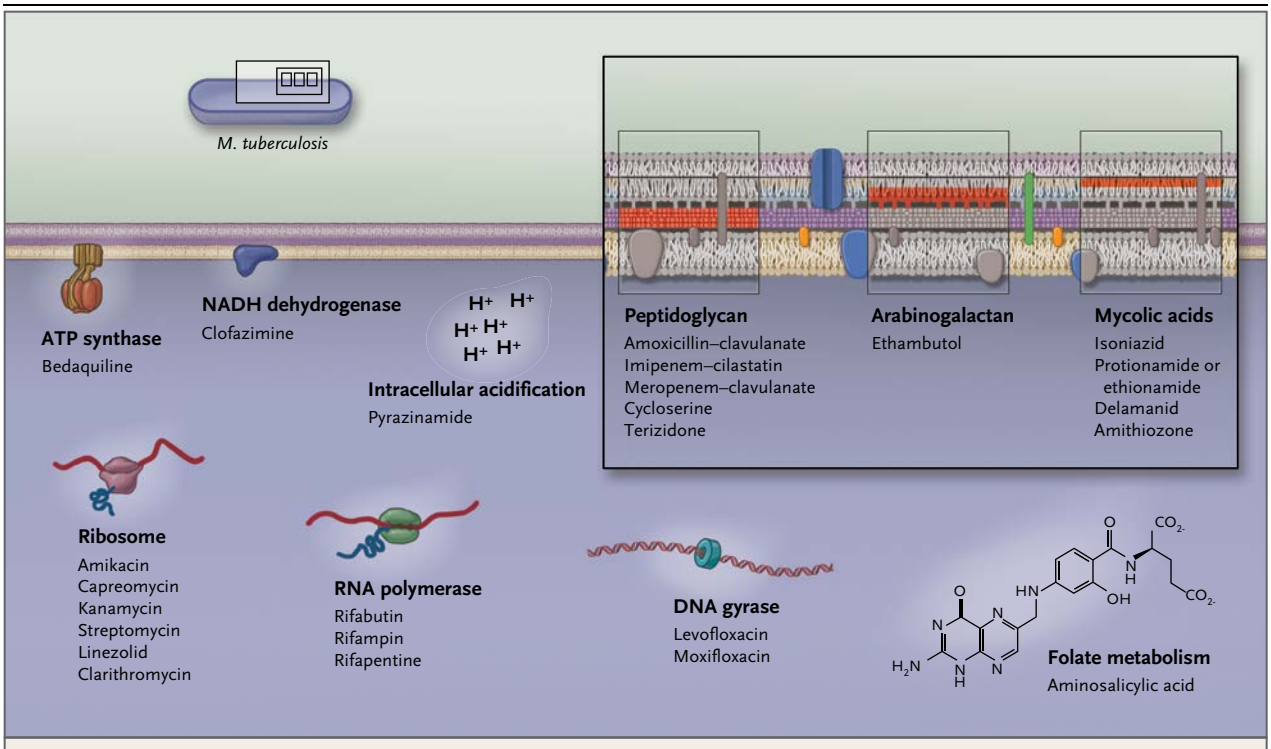

Figure 3. Sites and Mechanisms of Action of Antimycobacterial Agents.

Shown are the known targets of various agents that have been used clinically in tuberculosis treatment. Many antituberculosis agents target the *M. tuberculosis* cell envelope. The box is a high-resolution representation showing the agents that act on each of the three component polymers of the macromolecular outer cell envelope. Drugs such as aminosalicylic acid act like antimetabolites; they are incorporated into folate metabolism as substrates and inhibit downstream folate-dependent processes. The mode of action of pyrazinamide remains enigmatic, and the drug appears to act at least partially by acidifying the cytoplasm of the cell.

ity. All these factors combine to make generalization from adult to pediatric treatment a highly speculative undertaking. Efforts to define the most effective treatment approaches, including individualization of regimens, doses, and treatment duration, must be extended to this important group of patients.

FUTURE PROSPECTS FOR TUBERCULOSIS TREATMENT

Treatment of tuberculosis began in the mid-1950s with the first curative combination regimens of isoniazid, streptomycin, and aminosalicylic acid, administered for up to 2 years. The development of new drugs, first pyrazinamide and then rifampin, followed by a series of clinical trials, led to the current 6-month regimen. A resurgence of interest in tuberculosis drugs, stimulated by the Declaration of Cape Town in 2000, has given rise to the hope that less toxic, radically shorter regimens of curative treatment can be found. This will require developing a better understanding of effective ways to use the drugs that we have and moving a number of promising new compounds from the bench to clinical studies. The pharmaceutical drug development model translates poorly to the development of tuberculosis drugs, so the burden has fallen on foundations and publicly funded trial networks. Fortunately, the response has been robust, and many new studies are being planned or are under way. The next decade in the treatment of tuberculosis should be an exciting one.

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