Published in final edited form as:

Pharmacotherapy. 2009 December ; 29(12): 1468–1481. doi:10.1592/phco.29.12.1468.

Treatment of Active Pulmonary Tuberculosis in Adults: Current Standards and Recent Advances:

Insights from the Society of Infectious Diseases Pharmacists

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Abstract

Tuberculosis is a global pandemic, with 9 million new cases of the disease and approximately 2 million deaths each year. More than 98% of patients treated for tuberculosis in the United States between 1993 and 2007 had drug-susceptible strains. The standard treatment regimen for drug-susceptible tuberculosis has not changed in decades and was developed on the basis of empiric observations of different treatment regimens. Only recently has the veracity of the scientific basis for standard therapy been examined. The backbone of therapy is still isoniazid, rifampin, and pyrazinamide, although fluoroquinolones are being investigated as a replacement for isoniazid. Recent population pharmacokinetic studies have demonstrated the importance of individualized dosing of isoniazid, pyrazinamide, and rifampin. Isoniazid serum clearance differs depending on the patient's number of *N*-acetyltransferase 2 gene *4 (*NAT2**4) alleles. Pyrazinamide serum clearance has been shown to increase with increases in body weight. Rifampin's volume of distribution, clearance, and absorption have wide between-patient and within-patient variability. Microbial pharmacokinetic-pharmacodynamic (PK-PD) indexes and targets to optimize microbial killing and minimize resistance have been identified for rifampin, isoniazid, pyrazinamide, and the fluoroquinolones. These PK-PD indexes suggest that different doses and dosing schedules than those currently recommended could optimize therapy and perhaps shorten duration of therapy. Efflux pump inhibition is also being investigated to enhance first-line antituberculosis drug therapy. Comorbid conditions such as diabetes mellitus and genetically determined iron overload syndromes have been associated with significantly worse patient outcomes. Therapy for these and other patient groups needs further improvement. These patient factors, the covariates for pharmacokinetic variability, and PK-PD factors suggest the need to individualize therapy for patients with tuberculosis in order to optimize outcomes and reduce the duration of therapy.

Keywords

tuberculosis; population pharmacokinetics; rifampin; isoniazid; pyrazinamide; fluoroquinolones; microbial pharmacodynamics; dose individualization; efflux pumps

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Tuberculosis is a global pandemic, with 9 million new cases of tuberculosis disease and approximately 2 million deaths each year.¹ Most (98.2%) patients treated for tuberculosis in the United States between 1993 and 2007 had drug-susceptible strains.² However, multidrug-resistant tuberculosis is a continuing concern for clinicians. Recently, a great deal of attention has been paid to extensively drug-resistant tuberculosis because of the limited treatment options.^{2–4} Extensively drug-resistant tuberculosis rates in the United States have decreased from 0.07% (18 extensively drug-resistant cases out of 25,107 tuberculosis cases) in 1993 to 0.02% (2 extensively drug-resistant cases out of 13,293 tuberculosis cases) in 2007.² Although foreign-born persons who live in the United States have an increased risk for developing tuberculosis (57% of all tuberculosis cases reported in 2006), this has not translated into a higher risk of extensively drug-resistant tuberculosis in the United States.² Therefore, we focus on the treatment of drug-susceptible tuberculosis, provide an overview of second-line agents, and discuss recent progress and future directions in the treatment of tuberculosis.

Treatment of Drug-Susceptible Tuberculosis

Scientific Basis for Current Therapeutic Regimens

Current drug regimens grew out of empiric observations and failure of early clinical strategies. Treating tuberculosis with streptomycin, isoniazid, or pyrazinamide monotherapy in the 1950s and 1960s led to an initial favorable response that was quickly abolished by the emergence of resistance.^{5–7} Use of combination therapy led to reduction in the emergence of drug resistance and became the standard for antituberculosis therapy.^{8–10} A related rationale has been a belief that in cavitary tuberculosis, there are thought to be three populations of *Mycobacterium tuberculosis*: bacilli in log-phase growth, slowly replicating bacilli under acidic conditions, and nonreplicating bacilli under hypoxic conditions.¹¹ Drugs such as rifampin, isoniazid, and pyrazinamide are thought to have selective action on each of these populations, making it necessary to use multiple-drug therapy to eradicate all bacilli. Isoniazid is thought to kill bacilli in log-phase growth, whereas pyrazinamide is thought to kill slowly replicating bacilli during the first 2 months of the initial phase of therapy. Rifampin is thought to slowly kill nonreplicating persistent bacilli during the 6 months of therapy, with isoniazid added to prevent resistance during the continuation phase. These very popular concepts were developed to explain observed therapeutic actions of drugs, but have yet to be stated as falsifiable hypotheses and interrogated with use of modern experimental techniques. Thus, their veracity is unknown. Nevertheless, they form the current “scientific” basis for explaining chemotherapy in guidelines for the treatment of tuberculosis by the American Thoracic Society (ATS)–Centers for Disease Control and Prevention (CDC)–Infectious Diseases Society of America (IDSA), the International Union Against Tuberculosis and Lung Diseases, and the World Health Organization.

Treatment Regimen and Duration

The ATS-CDC-IDSA tuberculosis treatment guidelines recommend that ideal body weight be used to dose antituberculosis drugs.¹² This recommendation is based on one case report and is somewhat concerning given that weight and/or height significantly affect the pharmacokinetics of first-line drugs (discussed below). The recommended initial phase for the treatment of tuberculosis consists of rifampin 10 mg/kg (maximum 600 mg), isoniazid 5 mg/kg (maximum 300 mg), pyrazinamide 15–30 mg/kg (maximum 2 g), and ethambutol 15–20 mg/kg (maximum 1.6 g) given daily for 8 weeks, followed by a continuation phase of isoniazid 15 mg/kg (maximum 900 mg) and rifampin 10 mg/kg (maximum 600 mg) administered 2–3 times/week for 18 weeks.¹² A recent article indicates that using twice-weekly or rifapentine-containing regimens in the continuation phase may be significantly associated with relapse.¹³ Alternatively, the continuation phase may be administered as daily doses of isoniazid 5 mg/kg and rifampin 10 mg/kg.

Daily (or thrice-weekly) therapy in the continuation phase is recommended for patients with the human immunodeficiency virus (HIV) who have CD4⁺ lymphocyte counts less than 100 cells/mm³ because of the increased risk of developing rifamycin resistance. In addition, therapy should be extended for an additional 12 weeks (total 9 mo) for patients with cavitary disease who have a positive culture at 2 months. Alternatively, a once-weekly regimen of isoniazid and rifapentine can be used in the continuation phase for 18 weeks in the treatment of HIV-negative patients who have no cavitary disease and have a negative sputum acid-fast bacilli (AFB) smear at 2 months. However, rifapentine should not be used to treat HIV-infected patients because of an increased risk of relapse and the development of rifamycin monoresistance. Ethambutol may be discontinued when susceptibility results indicate no drug resistance to isoniazid.

Recommended monitoring parameters for patients with tuberculosis can be found in Table 1. Second-line agents are used in cases of intolerance or some other contraindication to the first-line antituberculosis agents (rifampin, isoniazid, pyrazinamide, and ethambutol) and consist of cycloserine, ethionamide, *p*-aminosalicylic acid (PAS), capreomycin, and the aminoglycosides. Fluoroquinolones are recommended as second-line agents, but are being tested in multicenter trials as first-line agents. Several clinical trials (which can be found at www.clinicaltrials.gov) are testing the possibility of replacing isoniazid with moxifloxacin, in an attempt to reduce duration of therapy to 4 months. Thus, in this review, we discuss fluoroquinolones as possible first-line antituberculosis agents.

Special Populations

Extrapulmonary Tuberculosis—The same drugs are used to treat extrapulmonary tuberculosis as pulmonary tuberculosis. A 6–9-month treatment duration is recommended. Cases with meningeal involvement are recommended to receive 9–12 months of therapy.¹² Comparative data to support this longer duration for meningeal disease are lacking. Clinical response should be monitored closely in order to prolong therapy for patients who are slow to respond. Patients with pericarditis or meningitis should also receive corticosteroids.

Preexisting Liver Disease—A 6-month regimen of rifampin, ethambutol, and pyrazinamide can be used in patients whose aspartate aminotransferase (AST) levels are greater than 3 times the upper limit of normal before starting antituberculosis treatment.¹² Hepatotoxicity can still occur in patients receiving rifampin and pyrazinamide. A 9-month regimen of isoniazid and rifampin can be used as an alternate regimen. These patients should also receive ethambutol as a third drug until susceptibility results for rifampin and isoniazid are available. Patients with severe liver disease should not receive any or receive only one hepatotoxic drug. A regimen of rifampin plus ethambutol for 12 months is suggested by the guidelines, with a fluoroquinolone being used for the first 2 months of therapy. Alternatively, a regimen of streptomycin, ethambutol, a fluoroquinolone, and another second-line agent would contain no hepatotoxic drugs. These recommendations are based on expert opinion.

Pregnant or Lactating Women—All pregnant patients who have a moderate-to-high likelihood of tuberculosis should be treated with rifampin, isoniazid, pyrazinamide, and ethambutol for 2 months followed by rifampin and isoniazid for an additional 4 months.¹² The risk of tuberculosis to the fetus is much greater than teratogenicity from antituberculosis drugs. Patients who receive only rifampin, isoniazid, and ethambutol should be treated for 9 months. Streptomycin should not be used in pregnant patients as it is the only antituberculosis drug definitively associated with teratogenicity (congenital deafness). Fluoroquinolones and ethionamide should be used with caution due to potential teratogenic effects. Breastfeeding is considered to be safe while taking antituberculosis drugs. Drug concentrations in breast milk are insufficient to serve as tuberculosis treatment for the newborn. Supplementation with

pyridoxine 25 mg/day is recommended for all pregnant or lactating women receiving isoniazid, as pyridoxine content in most multivitamins is insufficient.

Fixed-Dose Formulations

Fixed-dose combination products have been recommended to help minimize the likelihood of inadvertent monotherapy, acquired drug resistance, and medication errors in patients receiving daily therapy.¹² The two combination products on the market are rifampin 300 mg–isoniazid 150 mg (Rifamate; sanofi-aventis, Bridgewater, NJ) and rifampin 120 mg–isoniazid 50 mg–pyrazinamide 300 mg (Rifater; sanofi-aventis). It is important to ensure that these products are not confused with Rifaidin (sanofi-aventis), a brand name of rifampin. If Rifamate is used as part of intermittent therapy, two additional 300-mg isoniazid tablets are required to provide appropriate doses of both drugs. Patients weighing more than 90 kg who receive Rifater require additional pyrazinamide. Rifater should not be used in patients with renal insufficiency because of the necessity to adjust the pyrazinamide dosage. Neither combination product should be used in patients with hepatic disease until a stable antituberculosis regimen for the individual patient is established.

Strategies for Treatment Interruptions

A common clinical dilemma in the treatment of drug-susceptible tuberculosis is treatment interruption. Treatment interruptions are most commonly due to noncompliance or toxic effects from drugs. Unfortunately, there are no data to guide clinicians in the management of patients who interrupt their treatment. Health departments have developed various strategies based on expert opinion. One example high-lighted in the ATS-CDC-IDSA guidelines is the approach used by the New York City Department of Health. The New York City Tuberculosis Control Clinical Policies and Protocols guidelines suggest that the clinician should first determine the duration of the treatment interruption.¹² In the initial phase of therapy, if the interruption was less than 14 days, they recommend that the patient's treatment should be continued. If the initial phase is not completed within 3 months, or treatment interruption was for more than 14 days, then the patient should restart therapy from the beginning.

For patients in the continuation phase, the guidelines recommend calculating the percentage of doses in the continuation phase that have been completed. If the patient completed at least 80% of therapy and had an initial AFB smear that was negative, then no additional treatment may be required. Completion of the continuation phase is still recommended for patients whose initial AFB smear was positive. For patients who completed less than 80% of the continuation phase and the treatment interruption was for less than 3 months, the patient can continue treatment and await results of the repeat culture. If the repeat culture is negative, therapy should be completed within 9 months of the original start date. The duration of therapy should restart from the new start date if not completed within 9 months of the original start date. If the repeat culture is positive, then the patient should restart a four-drug regimen while awaiting susceptibility results. For patients who have treatment interruptions of at least 3 months, four-drug therapy using directly observed therapy should be restarted from the beginning. Also, the patient's AFB smears and cultures should be rechecked. If the repeat culture is negative, treatment can be stopped after a total of 9 months of therapy.

Population Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Considerations for Dosing of First-Line Agents

Although use of pharmacokinetic-pharmacodynamic (PK-PD) dosing is not a new concept in infectious diseases, little information was available that defined the PK-PD index and target values of antituberculosis drugs until the past 5 years. Microbial PK-PD concepts relate to the

shape of the concentration-time profile that optimizes efficacy, as well as the particular antibiotic exposure that is associated with optimal kill of the pathogen. These concepts and their utility in treatment of many infectious diseases have been summarized recently.¹⁴ In general, antibiotics segregate into one of three patterns: those whose effect is best explained by the area under the concentration-time curve (AUC):minimum inhibitory concentration (MIC) ratio, those whose effect is best explained by peak concentration (C_{max}):MIC ratio, and those whose effect is best optimized by keeping the percentage of time that the concentration is above MIC ($T>MIC$) high. Drugs whose effect is linked to the C_{max} :MIC ratio should have doses combined together and administered as high intermittent doses. Drugs whose effect is linked to $T>MIC$ should have their doses divided into smaller doses that are administered more frequently, unless the antibiotic already has a long half-life. The effect of the shape of the concentration-time profile on toxicity will also help determine whether this is feasible in patients. The actual drug concentrations that drive the PK-PD indexes are subject to pharmacokinetic variability. To this end, compartmental population pharmacokinetics of rifampin, isoniazid, and pyrazinamide have been performed recently.

Rifampin

Recently, in a study of 261 adults with tuberculosis, an interpatient variability of 53% for serum clearance and 43% for volume of distribution was demonstrated, whereas interoccasional variability for serum clearance was 23% and mean transit time during absorption was 68%.¹⁵ Moreover, use of single-drug formulations compared with fixed-dose formulations increased the mean transit time by 104% and serum clearance by 24%. This is likely due to variability in oral bioavailability. This means that both the C_{max} and AUC of rifampin are highly variable among patients with tuberculosis and will be lower with non-fixed-dose formulations. Both animal and hollow fiber models have determined that the AUC:MIC ratio is the best predictor of microbial killing by rifampin.^{16, 17} Prevention of rifampin resistance was optimized by achieving a rifampin C_{max} :MIC ratio of 175 or greater.¹⁶ Increasing the dose of rifampin is the optimal method to achieve both of rifampin's PK-PD targets. This was recently demonstrated to be true for the rifamycin antibiotic, rifapentine, in a mouse model of tuberculosis.¹⁸ Another group also demonstrated that doubling the currently recommended dose of rifampin led to doubling of the rate of kill of bacilli in sputum in patients with tuberculosis during the first 2 days of therapy.¹⁹ Further investigation is needed as this study enrolled only 14 patients. The long-term efficacy and safety of higher rifampin doses are also unknown, as the patients were followed for only 2 weeks. Future studies of higher doses of rifampin, based on population pharmacokinetics, PK-PD, and toxicodynamics, are needed, as they have great potential to shorten the duration of antituberculosis therapy.

Isoniazid

A recent population pharmacokinetic analysis revealed that 88% of the variability in isoniazid serum clearance is driven by the number of *N*-acetyltransferase 2 gene *4 (*NAT2**4) alleles, with demographics, sex, and body weight accounting for very little variability.²⁰ Since AUC can be viewed as dose x bioavailability/serum clearance, this means that isoniazid AUC is mostly driven by patient genotype and the dose administered. In preclinical models of tuberculosis, isoniazid AUC:MIC ratio best correlated with microbial killing.^{21, 22} Clinical trial simulations strongly suggested that in certain ethnic groups where *NAT2**4 genotypes associated with a high serum clearance dominate, doses that are greater than the standard dose may be needed, especially if isoniazid MICs are also relatively high.²² Clinical confirmation of these findings is still needed in the context of multidrug therapy, as well as the utility of genotyping patients for purposes of optimizing isoniazid doses and minimizing toxicity.

Pyrazinamide

Pyrazinamide population pharmacokinetics were recently evaluated in 227 patients with tuberculosis.²³ The results demonstrated that patients were either slow or fast absorbers. These investigators also found that serum clearance and volume of distribution were mostly dependent on weight. Pyrazinamide serum clearance increased by 0.545 L/hour⁻¹ for every 10-kg increase in weight over 48 kg. Similarly, pyrazinamide's volume of distribution increased by 4.3 L for every 10-kg weight increase above 48 kg. A recent hollow fiber PK-PD study demonstrated that pyrazinamide's sterilizing effect was best explained by the AUC:MIC ratio, whereas resistance suppression was linked to T>MIC.²⁴ Monte Carlo simulations revealed that doses higher than the currently recommended 2 g/day would have a better likelihood of achieving the AUC:MIC ratio associated with 90% of maximal effect. However, the safety of higher doses is unclear. Additional clinical studies should examine higher-dose pyrazinamide therapy, as well as dosing based on weight, so that different weight categories will receive different pyrazinamide doses (in mg/kg). These studies should compare clinical outcomes of weight-based doses with those of traditional maximum doses used in current regimens.

Fluoroquinolones

Most data regarding the PK-PD of second-line antituberculosis agents are for the fluoroquinolones. In a recent murine study, the PK-PD parameter associated with effect of all fluoroquinolones was the AUC:MIC ratio.²⁵ In the hollow fiber system, most of the bacterial population was resistant to ciprofloxacin by the end of the first week in spite of ciprofloxacin achieving excellent early bactericidal activity with recommended doses (AUC:MIC ratio of 80.4 µg•hr/ml).²⁶ Another hollow fiber study determined that moxifloxacin was able to suppress the development of resistance with a free-drug AUC from time zero to 24 hours (AUC₀₋₂₄):MIC ratio of 53 µg•hour/ml.²⁷ Clinical trial simulations using moxifloxacin 400 mg/day had a target attainment rate of only 59%. Simulations using a dose of 800 mg/day achieved a target attainment rate of 90% or greater. Another group recently confirmed this in a mouse tuberculosis study of continuous moxifloxacin dosing, which validated that keeping exposures at a free AUC:MIC ratio less than 53 at AUC:MIC ratio achieved by 400 mg/day led to resistance emergence in the mice while higher ratios suppressed for resistance emergence.²⁸ We caution that the safety of administering moxifloxacin 800 mg/day to humans has not been established, and this dosage is not yet recommended until studies of its safety are performed.

Limitations

A major limitation of applying these concepts is that each of these drugs was examined as monotherapy, which is not acceptable in current clinical practice. Since antimicrobial combinations can be antagonistic, additive, or synergistic, the pharmacodynamic targets for these agents will need to be defined in combination regimens in order to increase their clinical relevance. In addition, safety data for doses higher than the current maximum doses in the literature will be needed. In this regard, however, results of a recent study are interesting.¹³ The authors examined the probability of relapse with daily therapy in the continuation phase versus intermittent therapy in 32 cohorts, and demonstrated that the odds of relapse for daily initial phase plus a thrice-weekly continuation phase was 1.6, for daily initial phase plus a twice weekly or thrice weekly continuation phase was 2.8, for daily initial phase plus once-weekly continuation phase with rifapentine was 5.0, and for thrice-weekly initial phase plus once-weekly continuation phase with rifapentine was 7.1. The more intermittent the regimens, the higher the relapse. This harmonizes with microbial PK-PD findings even in combination therapy. Rifamycins, isoniazid, and pyrazinamide are AUC:MIC ratio driven, as discussed above. The more intermittent regimens do not fully compensate with a corresponding dose

increase, so that at the end of the week the total dose (and therefore AUC) of each drug is considerably less than that with daily therapy. As an example, based on the ATS-CDC-IDSA guidelines, rifampin is given as 600 mg/day with daily therapy (4200 mg/wk) or as 600 mg 3 times/week (1800 mg/wk), or 600 mg twice/week (1200 mg/week), or 600 mg once/week, so that the AUC decreases from daily therapy 2.3-fold with the thrice-weekly regimen, 3.5-fold with the twice-weekly regimen, and 7-fold with once-weekly rifampin.

Adverse Events and Drug Interactions of First-Line Agents

Hepatotoxicity

Table 2 describes the common adverse events associated with antituberculosis drugs. Among these, hepatotoxicity is a significant concern given that rifampin, isoniazid, and pyrazinamide all are associated with this adverse event. Drug-induced hepatotoxicity is defined as a serum AST level greater than 3 times the upper limit of normal with symptoms, or 5 times the upper limit of normal without symptoms.¹² The occurrence of isoniazid-induced hepatotoxicity increases with age, underlying liver disease, and heavy alcohol consumption. One meta-analysis found that 2.7% of patients receiving rifampin plus isoniazid developed clinical hepatotoxicity.²⁹ Pyrazinamide-associated hepatotoxicity is believed to be rare at a dose of 25 mg/kg/day or lower.^{30–33} Higher rates of hepatotoxicity (11–14%) were reported with pyrazinamide's initial use in the 1950s, when 40–70-mg/kg daily doses were used.^{34, 35}

Rifampin, isoniazid, and pyrazinamide should all be immediately discontinued in patients who develop drug-induced hepatotoxicity.¹² These agents should be replaced by a combination of at least two of the following agents: ethambutol; capreomycin or streptomycin, amikacin, or kanamycin; or a fluoroquinolone. When the patient's symptoms have markedly improved and the AST level has returned to lower than 2 times the upper limit of normal, first-line drugs should be restarted sequentially, with frequent monitoring of AST level, bilirubin level, and clinical symptoms. Rifampin should be reintroduced first. Isoniazid should then be added for patients whose AST level does not increase; pyrazinamide may be added in a similar fashion after a week of isoniazid therapy. Pyrazinamide should not be restarted in patients with severe hepatitis who tolerate rifampin and isoniazid being reintroduced. Pyrazinamide can be assumed to be the culprit responsible for hepatitis in these patients.

Rifamycins

Most drug interactions associated with anti-tuberculosis therapy arise from use of rifamycins. Rifampin is the most commonly used rifamycin and is a potent inducer of the cytochrome P450 (CYP) system. Drug interaction references (e.g., www.aidsinfo.nih.gov) should be consulted before rifamycins are used in all patients—with or without HIV infection—who are receiving other drugs for concomitant diseases. Rifabutin is a weaker inhibitor of the CYP system, which can be used to minimize these interactions, but dosage adjustments are still required when combined with efavirenz or protease inhibitors. Rifabutin is also a substrate of CYP3A4 and requires dosage adjustments when used concomitantly with CYP3A4 inhibitors. Rifapentine is administered once weekly and is a moderate inhibitor of CYP enzymes. Pruritus, with or without a rash, during rifampin therapy is generally self-limiting, and rifampin therapy should be continued. Only 0.07–0.3% of patients develop a true hypersensitivity reaction that requires discontinuation of rifampin.^{36–38} A major counseling point for patients taking rifampin is that orange discoloration of body fluids including sputum, sweat, and urine should be expected. These discolored fluids may permanently stain clothes as well as soft contact lenses.

Isoniazid

Isoniazid drug interactions are not as highly publicized because isoniazid only minimally inhibits CYP3A4. However, isoniazid is a potent inhibitor of the CYP2C9, CYP2C19, and

CYP2E1 isoenzymes.³⁹ Examples of drugs whose metabolism is inhibited by isoniazid therapy include phenytoin, carbamazepine, diazepam, and triazolam. When isoniazid is used as part of combination therapy for active pulmonary tuberculosis, the effects of rifampin's enzyme induction are generally more potent than isoniazid's inhibition of these enzymes.

In terms of adverse events, peripheral neuropathy is a dose-dependent adverse event with isoniazid therapy that occurs in less than 0.2% of patients, at dosages of 3–5 mg/kg/day.^{30, 36, 40} Patients at an increased risk for peripheral neuropathy include those with diabetes mellitus, HIV infection, renal failure, alcoholism, or malnutrition, as well as pregnant or lactating women, and they should receive concomitant pyridoxine 25 mg/day.⁴¹ Isoniazid produces asymptomatic elevations of aminotransferase levels in 10–20% of patients, which generally return to normal without isoniazid being discontinued.⁴² Development of antinuclear antibodies occurs in approximately 1 of 5 patients receiving isoniazid.⁴³ Isoniazid should be discontinued in the less than 1% who develop clinical lupus erythematosus. Diarrhea commonly occurs with the syrup formulation due to its sorbitol content.

Pyrazinamide

Nongouty polyarthralgias are common adverse events (40%) associated with pyrazinamide therapy, but they do not usually occur in the initial phase of treatment.¹² Aspirin or non-steroidal antiinflammatory drugs are generally effective in eliminating the pain associated with this adverse event. Only rarely do patients require dosage adjustment or discontinuation of pyrazinamide. Gout is rarely seen in patients taking pyrazinamide who do not have a previous history of acute gouty arthritis.⁴⁴ However, pyrazinamide should not be administered to patients with a history of acute gouty arthritis because of its ability to increase uric acid concentrations. Although routine measurement of serum uric acid concentrations is not recommended in patients with tuberculosis, this parameter may be used as a surrogate marker for pyrazinamide compliance if patient adherence is questionable.

Ethambutol

Retrotubular neuritis is the most serious adverse event associated with ethambutol therapy, but only minimal risk exists for patients receiving 15 mg/kg/day.^{45, 46} Doses of 30 mg/kg/day or more have been associated with toxicity in 18% of patients, which makes appropriate dosage adjustment of ethambutol in patients with renal insufficiency paramount. Serum drug concentrations should be obtained for patients with renal insufficiency to avoid toxicity. An initial examination documenting baseline visual acuity and red-green color discrimination is recommended for patients starting ethambutol. Monthly questioning by the clinician should occur to allow the patient to report any changes in one or both eyes. Follow-up testing is only required for patients reporting clinical symptoms, receiving 20 mg/kg/day or more of ethambutol, or receiving ethambutol for more than 2 months.¹²

Fluoroquinolones

Levofloxacin is the preferred fluoroquinolone in the ATS-CDC-IDSA guidelines because more long-term safety data were available for it when the guidelines were written (2003).¹² Moxifloxacin is the fluoroquinolone being evaluated for inclusion as part of the first-line regimen for tuberculosis due to its increased in vitro potency against *M. tuberculosis*. Fluoroquinolones should be administered at least 2 hours before or 2 hours after ingestion of drugs or food containing di- and trivalent cations.⁴⁷ Patients may be at higher risk for developing tendonitis or tendon rupture.

Second-Line Agents

Second-line antituberculosis therapies are used when patients are intolerant to first-line drugs or cannot take first-line drugs (for whatever reason). They also form the standard for the treatment of multidrug-resistant tuberculosis. Unfortunately, there have been no recent population pharmacokinetic studies for these agents or PK-PD studies that have focused on their role as antituberculosis agents. Since they are less familiar to clinicians, we provide a brief summary of the basic aspects of these drugs. Table 2 lists their routes of administration, adjustment for renal insufficiency, and their potential for toxicity.

Capreomycin, Amikacin, Kanamycin, and Streptomycin

Dosing recommendations for capreomycin, streptomycin, kanamycin, and amikacin are the same. These agents are administered 5–7 days each week at a dose of 15 mg/kg/day (maximum 1 g/day) for the first 2–4 months of therapy in patients with normal renal function.⁴⁸ A decreased dose of 10 mg/kg/day (maximum 750 mg/day) is recommended for patients aged 60 years or older.^{49, 50} The use of concomitant nephrotoxic and ototoxic drugs (e.g., diuretics) should be avoided with these agents, given the baseline risk of these adverse effects. Baseline monitoring for patients receiving any of these agents should include an audiogram, vestibular testing, and Romberg testing.¹² Clinicians should ask patients if they have had any auditory or vestibular symptoms during each month of therapy. Follow-up audiograms or vestibular testing are required for patients reporting symptoms of ototoxicity. Serum creatinine concentration should be assessed at baseline and each month. A recent study demonstrated a nephroprotective effect of preadministering *N*-acetylcysteine in mice treated with amikacin.⁵¹ However, this strategy has not been examined in humans.

Capreomycin is a polypeptide antibiotic that is commonly mistaken for an aminoglycoside because of similar nomenclature, dosing, and adverse events. Patients who are elderly or have renal insufficiency are at an increased risk for developing ototoxicity.⁵²

Streptomycin was used as a first-line agent for the treatment of tuberculosis until it was replaced by ethambutol as the fourth drug in the first-line regimen. Both vestibular toxicity and hearing disturbances can occur with streptomycin. Risk factors for ototoxicity include increased age and large single or cumulative doses (especially > 100–120 g).⁵³ Nephrotoxicity is thought to occur less with streptomycin compared with capreomycin, amikacin, and kanamycin.⁵⁴ Streptomycin-associated nephrotoxicity requiring discontinuation has been reported in approximately 2% of patients.⁵⁵

Cross-resistance between amikacin and kanamycin is common in *M. tuberculosis* isolates.⁵⁶ Both agents generally retain susceptibility to streptomycin-resistant isolates. Amikacin has been the preferred agent due to easier availability, and more facilities are able to determine amikacin drug concentrations. Vestibular toxicity is thought to be less frequent in patients receiving amikacin or kanamycin compared with those receiving streptomycin.^{57, 58}

Cycloserine

Cycloserine is used as an alternative agent for patients who develop hepatotoxicity while receiving antituberculosis drugs or have unstable liver disease before treatment. Its main use is as a treatment option for patients with multidrug-resistant tuberculosis and patients with meningeal disease. It is dosed at 10–15 mg/kg in two divided doses each day (maximum 1 g/day). Seizures are more likely with higher doses of cycloserine (16% with 500 mg twice/day) than with lower doses (3% with 500 mg/day).⁵⁹ Pyridoxine 100–200 mg/day can be given as prophylaxis or treatment for cycloserine's neurotoxic effects.⁶⁰ Patients should have neuropsychiatric status assessed at baseline and each month (more frequently for patients with

symptoms). Serum drug concentrations can also be used for monitoring, targeting a dose that produces a $C_{\max}$ of 20–35 mg/ml.¹² Serum drug concentrations should be monitored to avoid toxicity in patients with renal failure.

Ethionamide

Ethionamide is administered at a dose of 15–20 mg/kg/day (maximum 1 g/day) once or twice/day. Ethionamide use is most commonly limited by gastrointestinal intolerance, which generally limits the maximum tolerated dose to 500–750 mg/day.¹² Taking ethionamide at bedtime or with food may improve tolerance. Hypothyroidism is an important adverse event; therefore, thyroid-stimulating hormone levels should be measured at baseline and monthly while patients are receiving therapy. Hepatotoxicity can also occur with ethionamide; therefore, baseline liver function tests should be obtained. Patients with abnormal baseline liver function tests or pre-existing liver disease should have liver function tests monitored each month of ethionamide therapy.

p-Aminosalicylic Acid

p-Aminosalicylic acid is available in the United States only as granules and is administered as 4 g 2–3 times/day. Patients with severe renal insufficiency should not receive PAS because of accumulation of the acetyl-PAS, which has renal elimination.^{61, 62} Another concern in renal failure is that salicylates may exacerbate uremia-induced platelet dysfunction. When there are no other alternatives available, PAS can be used in patients with renal failure, but with extreme caution. *p*-Aminosalicylic acid itself is not significantly removed by hemodialysis, but, fortunately, acetyl-PAS is significantly dialyzed; thus, the recommendation is that patients undergoing hemodialysis be treated with the same doses as those without renal failure.⁶³ Gastrointestinal intolerance is the most frequent adverse effect associated with PAS, occurring in 11% of patients.⁶⁴ Use of the granular formulation and lower doses (8 g/day) have been reported to decrease the occurrence of these symptoms. Malabsorptive syndrome has been reported with PAS, characterized by steatorrhea and the requirement of folic acid supplementation.⁶⁵ Liver and thyroid function tests should be performed at baseline and reevaluated every 3 months for patients receiving PAS.¹²

Future Directions

Efflux Pump Inhibitors

Mycobacterium tuberculosis is one of many bacterial pathogens that use efflux pumps to expel potentially harmful substances from its cytoplasm.⁶⁶ Two important examples demonstrate the potential importance of efflux pumps. Isoniazid efflux is through a pump encoded by a three-gene *M. tuberculosis* operon, *iniABC*.⁶⁷ In a recent PK-PD study, the traditional belief that isoniazid's activity against *M. tuberculosis* is due to the depletion of the population in log-phase growth was examined, and it was demonstrated instead that isoniazid's activity actually ceases due to the development of a resistant population in an in vitro model.⁶⁸ Resistance to isoniazid was due to single-point mutations in the catalase-peroxidase gene, *katG*, and to reserpine-inhibitable efflux pumps. A second important example concerns streptomycin. Recently, clinical isolates from Brazilian patients who exhibited streptomycin resistance were examined and demonstrated that efflux pumps were associated with the streptomycin resistance and could be inhibited by the calcium channel blocker verapamil.⁶⁹ The interactions of efflux pumps and chromosomal mutations are being examined by us and others. Of importance, the presence of efflux pumps opens up a new avenue to enhance antituberculosis therapy, which is through inhibition of efflux pumps.

Effect of Comorbid Conditions on Therapeutic Outcomes

The metabolic syndrome, which includes type 2 diabetes mellitus and central obesity, affects 1 in 4 Americans. This means that many patients with tuberculosis in the United States will have either diabetes or obesity or both. A recent meta-analysis demonstrated that patients with diabetes were 3 times as likely as those without to develop tuberculosis.⁷⁰ Patients with tuberculosis and diabetes are more likely to have increased body weight compared with those presenting with tuberculosis alone.⁷¹ In terms of therapy, patients with tuberculosis and diabetes were approximately 8 times more likely to be culture positive after 6 months of standard therapy compared with others.⁷¹ One group observed increased innate and type 1 cytokine responses in patients with tuberculosis and poorly controlled type 2 diabetes compared with patients with tuberculosis alone.⁷² Another group reported a significant association between rifampin AUC values and plasma glucose concentrations.⁷³ Although this finding requires confirmation, the need for strict control of diabetes in patients with tuberculosis will likely only grow in importance in the future.

Another important observation was recently made in patients with iron overload syndromes, which affects up to 10% of male patients in southern Africa as well as substantial numbers of patients in the United States.⁷⁴ In southern Africa, for example, genes associated with iron overload syndromes are autosomal dominant, with allelic frequencies of 0.03–0.05, whereas in the United States the syndrome is associated with mutations in the *SLC40A1* gene, which codes for ferroportin 1.^{74, 75} Male patients exhibiting pathologic iron overload were observed to be more likely to die than those without iron overload even when standard antituberculosis treatment is administered.⁷⁶ It has since been shown that if mice with tuberculosis are iron overloaded, the antimycobacterial effects of some standard antituberculosis drugs are either reduced or abolished.⁷⁷

The Coming Era of Individualized Dosing

The pharmacokinetic variability of antituberculosis drugs that is driven by weight, sex, and genetic traits are pointing the way toward individualized dosing. Poorer responses to antituberculosis therapy in patients with diabetes or iron overload syndromes provide a powerful rationale for individualized dosing regimens. Maximizing efficacy and minimizing toxicity of pyrazinamide will likely benefit from dosing that is individualized to each patient's weight. For isoniazid, the greater toxicity with some acetylation states (*NAT2*4* genotype) and the relationship between gene dose and serum clearance (AUC:MIC ratio) offer a straightforward example of how dosing can be adjusted for different patient genotypes. The role of weight in drug exposures of rifampin that are achieved in patients, as well as the possible gene-driven drug interactions, means that individualized dosing will play a major role in rifampin dosing in the future. For example, a recent study in volunteers examined the effects of rifampin and multidrug resistance gene polymorphism on concentrations of concomitantly administered moxifloxacin and demonstrated that rifampin reduced the moxifloxacin AUC_{0–24} by 27% through rifampin's induction of the sulfate conjugation of moxifloxacin.⁷⁸ This is important given that ongoing studies are examining the possibility of using pyrazinamide, rifampin, and moxifloxacin in a 4-month antituberculosis regimen.⁷⁹ The skills that pharmacists already possess in terms of understanding pharmacogenomics and pharmacokinetic variability means that they will play an increasing and central role in moving patient care toward individualized dosing for antituberculosis drugs.

Conclusion

Tuberculosis remains a significant worldwide public health issue. Although the first-line treatment of drug-susceptible tuberculosis has not changed in decades, advances in the field are being made including the definition of PK-PD indexes and targets for antituberculosis

drugs. Goals of future tuberculosis research should focus on shortening the duration of therapy and minimizing the potential of developing resistance during therapy.

Acknowledgments

Dr. Hall was supported by a grant from the National Center for Research Resources (NCRR [http://www.ncrr.nih.gov/]; grant KL2RR024983), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research (http://nihroadmap.nih.gov/clinicalresearch/overviewtranslational.asp). Drs. Leff and Gumbo were supported by an NIH–National Institute of General Medical Sciences New Innovator Award and a grant (R01AI07949) from the NIH–National Institute of Allergy and Infectious Diseases.

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Table 1**Recommended Monitoring for Patients Receiving First-Line Therapy for Tuberculosis¹²**

Evaluation	Frequency of Monitoring
Testing for HIV	Before starting tuberculosis treatment
CD4 ⁺ lymphocyte count	Baseline and every 1–3 mo for HIV-positive patients
Hepatitis B and C serologies	Baseline for patients at risk (e.g., injection drug use, patients born in Asia or Africa, HIV-infected patients)
AST, ALT, bilirubin, and alkaline phosphatase concentrations	Baseline and when symptoms occur; monthly follow-up only necessary if baseline values are abnormal or patient is at increased risk for hepatotoxicity
Serum creatinine concentration	Baseline; follow-up only necessary if baseline values are abnormal
Platelet count	Baseline; follow-up only necessary if baseline values are abnormal
Visual acuity and red-green color discrimination	Baseline; every month for patients receiving ethambutol for more than 2 mo or ethambutol doses greater than 20 mg/kg/day
Clinical questions regarding visual acuity	Every month (only for patients actively receiving ethambutol)
Drug concentration measurements	Phenytoin or carbamazepine concentrations should be measured as needed for patients receiving these agents

HIV = human immunodeficiency virus; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 2Select Characteristics of Drugs Used to Treat Tuberculosis¹²

	Dosage Adjustment for Creatinine Clearance < 30 ml/minute or Hemodialysis ^a			
Drug (route of administration)	Hemodialysis ^a		Potentially Hepatotoxic	Adverse Events
First-line drugs				
Rifampin (p.o., i.v.)	No change		Yes (2.7% with isoniazid)	Cutaneous reactions (6%); gastrointestinal reactions (variable); flu-like syndrome (0.4–0.7%, only seen with intermittent dosing); immunologic reactions including thrombocytopenia, hemolytic anemia, acute renal failure, and thrombocytopenic purpura (< 0.1%); orange discoloration of bodily fluids (sputum, urine, sweat, tears)
Isoniazid (p.o., i.v., i.m.)	No change		Yes (0.1–0.15% when given alone)	Peripheral neuropathy (< 0.2%), CNS disturbances (% unknown), hypersensitivity (rare), monoamine poisoning (rare), lupus-like syndrome (20% antinuclear antibody positive, < 1% develop lupus erythematosus), diarrhea (due to sorbitol in the syrup formulation)
Pyrazinamide (p.o.)	25–35 mg/kg/dose 3 times/wk		Yes (1% when given alone)	Gastrointestinal symptoms (common), nongouty polyarthralgia (up to 40%), asymptomatic hyperuricemia (expected), acute gout (rare), rash, (self-limiting), dermatitis
Ethambutol (p.o.)	15–25 mg/kg/dose 3 times/wk		No	Retrotubular neuritis (minimal risk at 15-mg/kg dose), peripheral neuritis (rare), cutaneous reactions (0.2–0.7%)
Levofloxacin (p.o., i.v.)	750 mg/dose 3 times/wk		No	Gastrointestinal symptoms (0.5–1.8%), CNS effects (0.5%), cutaneous reactions (0.2–0.4%), tendonitis or tendon rupture
Second-line drugs				
Cycloserine (p.o.)	500 mg/dose 3 times/wk		No	CNS effects (seizures 16% with 500 mg b.i.d., only 3% with 500 mg q.d.; pyridoxine 100–200 mg q.d. given as prophylaxis or treatment)
Ethionamide (p.o.)	No change		Yes, 2%	Gastrointestinal symptoms including metallic taste and vomiting that is often severe (symptoms may decrease by taking at bedtime or with food), neurotoxicity (1–2%), endocrine effects including gynecomastia, alopecia, hypothyroidism, impotence, and increased

Drug (route of administration)	Dosage Adjustment for Creatinine Clearance < 30 ml/minute or Hemodialysis ^a		Potentially Hepatotoxic	Adverse Events
<i>p</i> -Aminosalicylic acid (p.o.) ^b	No change		Yes, 0.5% (0.3% when given alone)	difficulty in management of diabetes mellitus Gastrointestinal distress (most common), malabsorption syndrome, hypothyroidism (common), coagulopathy
Streptomycin (i.v., i.m.)	12–15 mg/kg/dose 2–3 times/wk		No	Ototoxicity, neurotoxicity, nephrotoxicity (may be less nephrotoxic than amikacin and kanamycin)
Capreomycin (i.v., i.m.)	12–15 mg/kg/dose 2–3 times/wk		No	Nephrotoxicity (20–25% require discontinuation), ototoxicity
Kanamycin (i.v., i.m.)	12–15 mg/kg/dose 2–3 times/wk		No	Ototoxicity (less vestibular toxicity than streptomycin), nephrotoxicity
Amikacin (i.v., i.m.)	12–15 mg/kg/dose 2–3 times/wk		No	Ototoxicity (less vestibular toxicity than streptomycin), nephrotoxicity

CNS = central nervous system.

^a All patients receiving hemodialysis should have their antituberculosis drugs administered after dialysis to facilitate directly observed therapy and to avoid premature removal of any drugs by hemodialysis (e.g., pyrazinamide, cycloserine).

^b Only oral granules of *p*-aminosalicylic acid are available in the United States; other dosage forms (oral tablets, intravenous) are not available.