

Tuberculosis

— pharmacological management

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From pigeon dung to modern multidrug regimens, the treatment of tuberculosis has improved dramatically over the past few centuries, although resistance is still a problem. This article describes current drug therapies, their side effects and main interactions



Chest radiograph showing bilateral upper zone shadowing with some cavitation and fibrosis which is typical of pulmonary TB

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Early remedies used in the management of tuberculosis (TB) included a mixture of pigeon dung and weasel's blood prescribed by the medieval physician John of Gaddeston. Perhaps more palatable was cod liver oil, which became the most widely prescribed remedy for TB at the Brompton Hospital for Consumptives in London for several decades after its foundation in the mid 19th century.¹

The discovery of streptomycin in 1944 by Albert Schatz and Selman Waksman heralded a new era in TB treatment, albeit confounded by the rapid emergence of drug resistance. A second therapeutic revolution followed with the introduction of isoniazid in 1952 and rifampicin in 1967, providing the foundation of the modern multidrug regimens used today.

Mortality from untreated active pulmonary TB is approximately 50 per cent with infection resolving in a further 25 per cent of patients and the remainder developing chronic tuberculous disease.² However, if the correct combination of drugs is taken for the appropriate length of time, cure and completion rates in around 98 per cent of patients and relapse rates of zero to 3 per cent have been observed in clinical trials and routine clinic use.³

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A guideline from the National Institute for Health and Clinical Excellence setting out best practice guidance for the diagnosis, treatment, prevention and control of TB in the NHS in England and Wales is expected to be published this spring. The scope of the NICE guidelines will not include pregnant patients or those with co-morbidities such as HIV infection, renal disease or hepatic disease.

Current guidelines adopted worldwide for the management of TB include those of the British Thoracic Society, the American Thoracic Society, the World Health Organization and the International Union Against Tuberculosis and Lung Disease. There are slight differences in the recommendations and this article will present the recommendations of the BTS unless otherwise stated.

Antituberculous drugs

The tubercle bacillus differs from other common or typical bacterial pathogens by virtue of its unique cell wall. The mycobacterial cell wall is largely composed of mycolic acids — branching lipid molecules that are strongly hydrophobic and provide a waxy impermeable barrier around the cell. In addition to presenting a specific target for several antituberculous drugs, mycolic acids contribute to the intrinsic resistance of these organisms to many antibiotics.

Mycobacteria also produce beta-lactamase enzymes, making them intrinsically resistant

to beta-lactam antibiotics such as penicillins and cephalosporins. Variations in certain peptidoglycan cell wall biosynthetic enzymes may also contribute to beta-lactam antibiotic resistance in these organisms.⁴ Antimicrobials that disrupt bacterial protein synthesis, such as macrolides, aminoglycosides and rifampicin, and antimicrobials that inhibit bacterial DNA folding, such as quinolones, are effective against both typical bacteria and *Mycobacterium tuberculosis* (MTb).

Commonly used first-line antituberculous agents are isoniazid, rifampicin, pyrazinamide, and ethambutol. Isoniazid and rifampicin are bactericidal and particularly effective against metabolically active organisms that are growing rapidly and continuously. Rifampicin also has activity against bacilli that display periodic bursts of metabolic activity and is comparatively more active than isoniazid against bacteria which multiply inside macrophages or in closed caseous lesions where the environment is more anaerobic.

Pyrazinamide is also bactericidal and particularly active against mycobacteria in the acidic environment of acute inflammatory lesions during the initial phase of therapy, and inside macrophages. Intracellular bacteria are responsible for relapse of TB and pyrazinamide is a valuable agent for preventing this relapse.

Ethambutol is a bacteriostatic agent that is principally used as a supplementary drug to

limit resistance. It may be omitted in patients with a low risk of resistance to isoniazid.

Second-line drugs effective against MTb include: the aminoglycosides streptomycin and amikacin and the related drug capreomycin; the quinolones ciprofloxacin and ofloxacin; the macrolides clarithromycin and azithromycin; cycloserine; prothionamide; and rifabutin, which is structurally related to rifampicin.

Combination therapy During replication of MTb, small numbers of naturally occurring drug-resistant mutants regularly emerge. The larger the bacteria population and the more active its replication, the more drug-resistant mutants will appear. If treated with a single agent, drug-resistant mutants become the predominant population. In an early clinical trial of isoniazid monotherapy for TB, resistant bacilli were found in 11 per cent of patients after one month, 52 per cent after two months and 71 per cent after three months.⁵ The likelihood of mutants being resistant to two antituberculous drugs is rare due to the unrelated nature of the resistance mechanisms. Resistance also develops rapidly (within six to eight weeks) if rifampicin or pyrazinamide are used alone. A fundamental principle in the therapy of active TB is that treatment with a single drug should never be attempted and a single drug should never be added to a failing regimen.

Duration of therapy

Because TB bacteria grow relatively slowly (generation time 15 to 20 hours as opposed to 20 minutes for *Escherichia coli*) and dormant bacteria divide only when threatened by antibiotic therapy, six-month treatment regimens are necessary to ensure all active and dormant organisms are killed.

Effective treatment durations have decreased — before the introduction of rifampicin treatment was given for approximately two years. The six-month treatment regimen currently

used as standard chemotherapy for TB has evolved following a series of clinical trials conducted throughout the world since the 1970s.

A common feature of most recommended therapy regimens is a two-phase treatment strategy. An initial intensive treatment phase is used to eradicate actively growing and semi-dormant bacilli. At least two bactericidal drugs are required in this phase — typically isoniazid and rifampicin are used. The addition of pyrazinamide to the intensive treatment phase allows the total duration of treatment to be shortened from nine months to six, but pyrazinamide provides no further benefit beyond the second month (providing the organism is fully sensitive). The second phase or continuation phase uses dual therapy with isoniazid and rifampicin to eliminate residual bacilli and reduce the risk of treatment failure or relapse. Ethambutol may be added in the initial intensive phase when there is a risk of drug resistance or the burden of organisms is high.

A Cochrane systematic review comparing randomised controlled trials of six months or longer with regimens of shorter duration reported significantly greater relapse rates with the shorter courses. Three-month regimens were associated with an odds ratio of 15.6 for relapse (95 per cent CI 5–49) compared with regimens of six months or longer. The odds ratio for risk of relapse after four-month courses was 3.64 (95 per cent CI 1.71–7.75) compared with six months or longer. In contrast, there was no significant difference in relapse rates between five and seven-month courses.⁶

Respiratory TB A six-month regimen of isoniazid plus rifampicin, supplemented in the first two months with pyrazinamide plus ethambutol is recommended for adults and children with active respiratory TB. The use of combination tablets such as Rifater and Rifinah reduces the risk of patients inadvertently receiving monotherapy for TB with the associated risks of resistance. Combination tablets may also aid compliance and some evidence suggests that incidence of side effects is lower with combination tablets than with individual drug formulations.⁷ One disadvantage of combination tablets however, is the lack of flexibility of dosing which precludes their use for intermittent treatment regimens.

Intermittent dosing Administration of therapy on an intermittent basis facilitates supervision of therapy and improves outcomes. Tubercle bacillus growth is inhibited by a post-antibiotic effect of several days *in vitro* and a series of clinical trials have demonstrated that intermittent dosing is as effective as daily dosing and no more toxic.⁸ Isoniazid is metabolised in the liver by acetylation and patients may display the fast-acetylator or slow-acetylator phenotype. Acetylator status is relevant clinically if

a once-weekly intermittent dosage regimen is used, when fast acetylation is associated with compromised efficacy.

Non-respiratory TB With the exception of TB meningitis, the six-month antituberculous regimen described above for respiratory TB is also recommended for non-respiratory TB, including lymph node disease, bone and joint TB, pericarditis and disseminated or miliary TB. The addition of steroids is recommended for large pleural effusions and for meningeal TB and pericarditis, and are likely to reduce morbidity and mortality in these cases.

Meningeal TB Patients with active meningeal TB should receive a 12-month treatment regimen, with isoniazid and rifampicin being given for the full 12 months and pyrazinamide plus a fourth drug (usually ethambutol) for the first two months. There are no RCTs comparing duration of treatment for meningeal TB but the serious risk of disability and mortality that comes with this form of the disease must be taken into consideration. Isoniazid and pyrazinamide achieve best penetration of the cerebrospinal fluid, rifampicin penetrates less well and ethambutol and streptomycin penetrate only if the meninges are inflamed. Glucocorticoid treatment is also recommended for meningeal TB, supported by evidence from a trial indicating a reduced risk of death in adult patients who received dexamethasone (relative risk 0.69, 95 per cent CI 0.52–0.92). Use of a steroid also appeared to protect patients from adverse events, in particular hepatitis.⁹ Of the second-line antituberculous agents, prothionamide and rifabutin achieve good central nervous system penetration and the quinolones penetrate if the meninges are inflamed. Cycloserine also penetrates the CNS well but central side effects, including seizures, limit its use in meningeal TB. CNS penetration of the drugs used in TB therapy is summarised in Panel 1.

Pericardial TB In addition to the standard six-month regimen of antituberculous drugs, treatment with steroids should be considered for patients within pericardial TB. For adults, a glucocorticoid equivalent to prednisolone at a dose of 60mg per day, tailing off over two to three months is supported by clinical trial evidence.¹¹ For children a regimen of glucocorticoid equivalent to prednisolone 1mg/kg per day tailing off over two to three months should be considered.

Treatment of latent TB Isoniazid is typically used for the treatment of latent TB in selected patients and daily administration for six to 12 months is reported to be 60 to 90 per cent effective in reducing progression to active disease. Rifampicin with or without isoniazid may also be prescribed for four

Panel 1: CNS penetration of TB drugs¹⁰

Drug	CNS penetration
Isoniazid	Good (20–100%)
Rifampicin	Poor (10–20%)
Pyrazinamide	Good (75–100%)
Ethambutol	Poor (4–64%)*
Streptomycin, amikacin, capreomycin	Poor (<5%)
Ciprofloxacin, ofloxacin	Fair (50–90%)
Prothionamide	Good (100%)
Cycloserine	Good (50–100%)

*if meninges are inflamed

months. Shorter regimens with combinations of rifampicin and pyrazinamide for two to three months have proved as effective as 12 months of isoniazid therapy but are associated with an increased rate of hepatotoxicity and fatal hepatitis.⁸

— Adverse drug reactions

Adverse reactions are common with antituberculous drug regimens and can be expected in 10 per cent of patients treated for pulmonary TB, many requiring modification of therapy. Adverse reactions are significantly more common in patients receiving second-line therapy. Discontinuing first-line drugs is not a decision that should be taken lightly and it is preferable to manage less severe adverse effects with symptomatic therapy if possible. For all adult patients, baseline liver function tests, serum creatinine and platelet counts are required and, for patients starting ethambutol, testing of visual acuity and red-green colour differentiation should be conducted.

Gastrointestinal symptoms Gastrointestinal upset, including nausea, vomiting, abdominal pain and poor appetite can be caused by many antituberculous drugs, particularly pyrazinamide, and is common in the first few weeks of therapy. Liver function tests are recommended to exclude hepatotoxicity. The absorption of first-line antituberculous drugs is delayed or moderately decreased by administration with food. However, if patients experience nausea or epigastric discomfort, administration with food is preferable to dividing the dose or changing to a second-line agent since there is no clinically significant effect upon efficacy.

Non-gouty polyarthralgia Pyrazinamide causes polyarthralgia in up to 40 per cent of patients on daily therapy. However, symptoms usually respond to non-steroidal anti-inflammatory drugs and dosage adjustment or drug discontinuation is rarely required.

Rash Cutaneous hypersensitivity of varying severity can be caused by all antituberculous drugs. Pruritis with or without rash may occur in as many as 6 per cent of patients taking rifampicin but true hypersensitivity is uncommon (0.07–0.3 per cent). Skin reactions requiring discontinuation of the drug are reported in 0.2–0.7 per cent of patients on ethambutol. If a rash is localised or presents as itching alone, it may be managed symptomatically with antihistamines without discontinuing TB therapy. Petechial rash may indicate thrombocytopenia in patients taking rifampicin (incidence <0.1 per cent) and, if confirmed on platelet count, rifampicin should be discontinued and restarted. A generalised erythematous rash warrants immediate discontinuation of all TB drugs, particularly if associated with fever

Panel 2: Counselling points for patients taking antituberculous drugs

Patients taking isoniazid, rifampicin, or pyrazinamide should be advised about how to recognise signs of liver disorder such as persistent nausea, vomiting, malaise or jaundice. If these symptoms develop, the patient should discontinue treatment and seek immediate medical attention. Cases of fatal hepatitis have been associated with continuing treatment despite symptoms of hepatotoxicity. Patients should be counselled to recognise signs of cutaneous hypersensitivity such as rash or hives and more serious skin reactions, and should be advised to avoid alcohol during therapy.

Patients on rifampicin should be advised to contact their doctor if they notice unusual bleeding or bruising. They should be told that their urine, saliva, sweat, tears and faeces may turn a red-orange colour, and that rifampicin may permanently stain soft contact lenses and reduce the effectiveness of oral contraceptives.

Patients taking isoniazid should be advised to contact their doctor if they notice any tingling, numbness or pain in their hands or feet, and patients taking pyrazinamide should contact their doctor if they notice any joint pain or swelling. Patients taking ethambutol should seek medical advice if they notice any changes in vision such as blurred vision or colour-blindness.

or mucous membrane involvement, due to the risk of Stevens-Johnson Syndrome. Three new antituberculous drugs should be prescribed until the rash has improved significantly and the first-line agents should be sequentially reintroduced by dose titration at intervals of two to three days to identify and eliminate the causative agent.

Drug fever Fever can persist for as long as two months after initiating TB therapy but recurrence of fever after several weeks of therapy despite evidence of microbiological and radiological improvement is suggestive of drug fever. Drug fever is characterised by a high temperature (above 39C) in a patient who otherwise looks and feels well. Patients should be investigated for superinfection or worsening of TB and, once these are excluded, all drugs should be suspended and reintroduced as described previously. Isoniazid-induced fever occurs in 1 per cent of patients and usually presents between weeks one and six of therapy.

Hepatotoxicity Asymptomatic elevations of LFT markers up to five times the upper limit of normal (ULN) occur in 10 to 20 per cent of patients receiving isoniazid, often returning to normal even with continued administration of the drug. Clinical hepatitis occurs in 1.6 per cent of patients taking isoniazid combined with other agents (not rifampicin), 1.1 per cent of patients taking rifampicin combined with other agents (not isoniazid) and 2.7 per cent of patients taking both isoniazid and rifampicin. Hepatotoxicity attributable to pyrazinamide occurs in around 1 per cent of recipients. The risk of hepatotoxicity increases with age, during the post-partum period and possibly also in patients with underlying hepatic disease or a history of heavy alcohol consumption.

Drug induced liver injury must be suspected if aspartate transaminase (AST) rises to greater than three times the upper limit of normal with symptoms or signs of clinical

hepatitis or if it increases to greater than five times ULN in the absence of symptoms. In addition to AST rises, there may be significant increases in bilirubin and alkaline phosphatase. If hepatitis occurs, treatment with isoniazid, rifampicin and pyrazinamide should be suspended, the patient should be tested for viral hepatitis and questioned regarding exposure to other hepatotoxins especially alcohol.

If symptoms or signs of hepatitis occur during treatment of active TB and treatment cannot be interrupted, drugs such as ethambutol, streptomycin and ofloxacin, which do not cause hepatotoxicity, may be substituted temporarily. The BTS guidelines suggest a reintroduction regimen for the first-line agents.

Peripheral neuropathy Peripheral neuropathy is a dose-related side effect of isoniazid and is uncommon at conventional doses (incidence <0.2 per cent). The mechanism involves inhibition of pyridoxine (vitamin B₆) activity resulting in decreased production of several neurotransmitters including dopamine, norepinephrine, serotonin and GABA. Peripheral neuropathy can be prevented by small doses of pyridoxine, such as 10mg to 25mg per day, but higher doses should be avoided due to the risk of interfering with the antibacterial activity of isoniazid. The BTS advises adding 10mg daily pyridoxine only for those at increased risk of neuropathy — patients with malnutrition or chronic renal failure, diabetes, alcoholism and those who are HIV positive. If peripheral neuropathy develops, it can be successfully treated with pyridoxine doses of 100mg to 200mg daily, without interrupting isoniazid administration.

Flu-like syndrome Flu-like syndrome caused by rifampicin can occur in up to 0.7 per cent of patients receiving intermittent therapy but is less common in patients on daily therapy.

Optic neuritis Ethambutol causes dose-related retrobulbar neuritis, presenting as decreased visual acuity or red-green colour blindness, but the risk is minimal at doses of 15mg/kg daily. The incidence increases at higher doses of 30mg/kg daily (affecting 18 per cent of patients) and in renal impairment.

— Special patient groups

Patients with chest infection/empyema

Of the first-line antituberculous drugs, only rifampicin has a broad spectrum of activity against common chest pathogens. However, concurrent pneumonia, or empyema will require treatment with standard anti-bacterial regimens in addition to TB therapy. Conversely, the use of macrolides and quinolones in the treatment of concurrent bacterial pneumonia may mask the symptoms of TB and appropriate microbiological investigations should be carried out to exclude TB in susceptible patients.

Pregnancy and post-natal TB

Untreated TB is considered to present a greater hazard to pregnant women and their fetuses than risks posed by the treatment and TB in pregnancy, managed with effective antituberculous therapy, should not affect the outcome of the pregnancy. The British Thoracic Society and the WHO recommend that standard treatment be given to pregnant women. However, the safety of pyrazinamide in pregnancy is unconfirmed. In the US, pregnant women with active TB are treated for nine months because pyrazinamide is not included in the first two months of therapy. Ethambutol and

isoniazid are safe to use in pregnancy but patients prescribed isoniazid are at increased risk of peripheral neuropathy and should be prescribed pyridoxine at the higher dose of 25mg per day. Rifampicin has been associated with a teratogenic risk but no adverse fetal events have yet been proven.

Streptomycin is the only antituberculous drug documented to have harmful effects on the fetus. Streptomycin (and other aminoglycosides) are associated with a risk of eighth cranial nerve damage and fetal ototoxicity and should be avoided throughout pregnancy. The BTS also recommends avoidance of prothionamide due to potential teratogenicity.

HIV-positive patients Treatment of TB in HIV-positive patients is essentially the same as for HIV-negative TB patients and standard daily or three times weekly regimens for standard durations appear to be effective. Several antiretroviral drugs (most protease inhibitors and non-nucleoside reverse transcriptase inhibitors except efavirenz) should not be used with rifampicin due to induction of hepatic microsomal enzymes. Rifabutin has less of an effect on liver enzymes and may be used in place of rifampicin but dose adjustments to rifabutin and anti-retrovirals may be required. Immune reconstitution may result in a temporary exacerbation of symptoms or signs of TB and requires expert evaluation and management.

Patients with liver disease The WHO recommends avoiding pyrazinamide in patients with known chronic liver disease. A

regimen without rifampicin may be used in decompensated liver disease. A suitable regimen for patients with fulminant liver disease is the combination of ethambutol, streptomycin and a fluoroquinolone. Baseline and regular monitoring of liver function is recommended for patients with known chronic liver disease.

Patients with renal disease Isoniazid, rifampicin and pyrazinamide are eliminated primarily by biliary excretion or are metabolised to non-toxic compounds and can be given in standard doses in renal impairment. In severe renal disease, pyridoxine should be given with isoniazid to prevent peripheral neuropathy and some experts recommend a dose reduction to 200mg daily of isoniazid. Ethambutol and streptomycin require dose reduction in renal disease and serum concentrations should be monitored.

— Promoting adherence

Strategies used to monitor and promote adherence to TB therapy include urine drug assays, examination of urine colour, tablet counts, controlled dosage systems, tablet diaries and signed care contracts. Hyperuricaemia can be used as an indicator of compliance with pyrazinamide. Incentives may be offered to encourage clinic attendance such as reimbursement of travel expenses, food and even money. Evidence suggests that reminder letters and health education counselling are also effective methods of encouraging adherence.

From a pharmacy perspective, adherence can be improved by providing TB medicines in a liquid form for children and those with difficulty swallowing. Information about the medicines should be available in languages spoken by the ethnic groups at increased risk of TB (see p73) and the importance of adherence to medication regimens should be emphasised during patient counselling. Advice that should be given to patients on antituberculous therapy is outlined in Panel 2 (p83). Multi-lingual information sheets are available from the Health Protection Agency website (www.hpa.org.uk). Providing information about how patients can get help with paying for their prescriptions is also likely to facilitate adherence. Many TB patients are exempt from prescription charges or receive free TB medication from hospitals.

DOT therapy The WHO has advocated universal directly observed therapy (DOT) with the aim of increasing treatment completion rates to over 85 per cent, at which point modelling predicts a decline in case numbers.¹² This strategy has proven somewhat controversial in light of experience in the US and the UK where treatment completion rates of 90 per cent have been achieved using mainly self-administered therapy and selective DOT.¹³

Important drug interactions

There are relatively few interactions that appreciably affect the concentrations of the first-line antituberculous drugs. It is more common for the antituberculous agents to cause clinically relevant changes in the concentrations of other drugs. This is especially true of rifampicin, which is a potent inducer of hepatic microsomal enzymes and reduces concentrations of drugs which are substrates of a wide range of cytochrome P450 isoenzymes, sometimes to subtherapeutic levels and treatment failure.

Classes of drugs which are affected to a clinically significant degree include: anti-retrovirals, anti-fungals, macrolide antibiotics, hormone therapy (including oral contraceptives and levothyroxine), narcotics (including methadone), anticoagulants, anticonvulsants, immunosuppressants (ciclosporin, prednisolone), cardiovascular drugs (calcium channel antagonists, beta blockers, digoxin), sulphonylureas and theophylline. Such interactions can be managed in clinical practice by titrating the dose of the affected drug to its response or to serum levels where possible. Doses of methadone may need to be increased by up to 50 per cent.

Isoniazid is a relatively potent inhibitor of a number of cytochrome P450 isoenzymes (2C9, 2C19 and 2E1) but not CYP3A, thus limiting its spectrum of interactions. Examples of clinically important interactions with isoniazid include: phenytoin, carbamazepine, valproate, warfarin and theophylline. In many cases, rifampicin and isoniazid have opposite effects on the metabolism of these drugs and the clinical relevance is difficult to predict.

Rifampicin does not affect isoniazid serum levels when used concurrently and protects isoniazid from increased renal clearance associated with concurrent prednisolone use.

Isoniazid is water soluble and its bioavailability is reduced by food and antacids, but not acid-suppressing drugs. Absorption of quinolones is markedly decreased by co-administration with medicines containing divalent cations, such as antacids, and administration should be separated by two hours.

DOT should be considered for individuals with active TB who are at risk of non-adherence to their treatment regimen including homeless people and patients with a history of non-adherence.

DOT may not be as efficacious as daily therapy and one trial reported a significantly higher proportion of culture negative patients after two months of daily therapy (85 per cent) compared with patients who received three times weekly DOT (77 per cent).¹⁴ Converting to a twice-weekly regimen in the continuation phase however, has been found to be equivalent to continuing on a daily regimen for bacterial failures or death during therapy.¹⁵

— Multidrug-resistant TB

Multidrug-resistant TB (MDR-TB) is defined as resistance to isoniazid and rifampicin. Treatment of MDR-TB requires prolonged courses, sometimes lasting two years, and patients with MDR-TB are infectious for a longer period, posing a significant threat to public health.

Resistance to one of the first-line drugs is currently 7.2 per cent in England, Wales and Northern Ireland and 1.3 per cent of tested clinical strains are resistant to both isoniazid and rifampicin (MDR-TB). Resistance to rifampicin is used as a reliable marker of MDR-TB because 95 per cent of rifampicin-resistant cases are also resistant to isoniazid. Rifampicin resistance can be detected relatively rapidly using polymerase chain reaction-based techniques to identify mutations in the *rpoB* gene, however this test is expensive and is usually only indicated in cases of suspected MDR-TB. Reasons to suspect MDR-TB include the following:

- Prior TB treatment
- Patients from countries with high MDR-TB prevalence (WHO "hotspots" include Latvia, Estonia, Russia, China, Argentina, Dominican Republic, and Ivory Coast)
- Local prevalence of isoniazid resistance greater than 4 per cent
- HIV-positive patients
- History of exposure to MDR-TB in hospital, prison or community settings with high prevalence

Treatment is complex and time-consuming and should be carried out under the direct supervision of experienced doctors. Patients should be treated in hospitals with appropriate isolation facilities and close liaison with the Health Protection Agency and regional centres for mycobacteriology is essential. Most authorities recommend starting treatment with five or more drugs to which the organism is or is likely to be susceptible, for three to six months. Following confirmation of *in vitro* sensitivity testing, treatment should continue with at least three

drugs for a further 15 to 18 months. A regimen recently used at Chelsea and Westminster Hospital, London, included azithromycin, amikacin, moxifloxacin, ethambutol and prothionamide.

The cost of treating MDR-TB has been estimated in the US at \$250,000 compared with \$20,000 for treating fully sensitive TB.

— Future treatment strategies

There are three areas of unmet medical need in the treatment of TB:

- Shortening or simplifying the treatment of TB caused by drug-susceptible organisms (for example, weekly administration)
- Improving the treatment of MDR-TB
- Providing more effective and efficient treatment of latent TB

Rifapentine, a rifamycin, is used extensively in the US and in some cases a once-weekly regimen with isoniazid can be effective in the continuation phase of pulmonary TB. There is also considerable interest in the newer quinolones levofloxacin, gatifloxacin and particularly moxifloxacin, with clinical trial data indicating that fluoroquinolones have the potential to shorten treatment course lengths significantly.⁸

Interestingly, mycobacterial resistance to penicillins can be overcome *in vitro* with the beta-lactamase inhibitors clavulanate or sulbactam¹⁶ and amoxicillin-clavulanate has been used clinically as a second line agent for multi-drug resistant TB.¹⁷

Finally, linezolid, an oxazolidinone antibiotic licensed for treatment of Gram-positive infections, has been found to have potent *in vitro* activity against MTb but animal and human studies are still to be published.

— Conclusion

Management of TB continues to present a significant challenge to health care professionals and therapeutic strategies continue to evolve with the introduction of new drugs and new treatment regimens. Pharmacists have an important role to play in tailoring therapy for individual patients to help ensure the optimal balance of benefit and risk for the patient. Pharmacists can also contribute to promoting concordance by communicating clearly and honestly with patients about their treatment and achieving a legitimate therapeutic partnership.

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