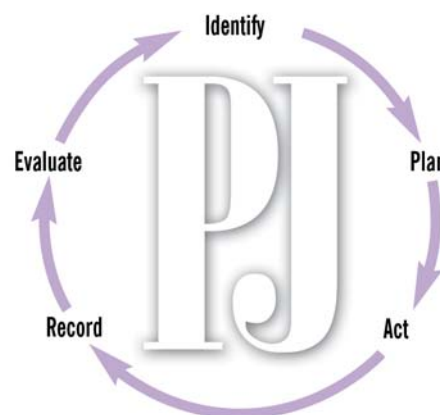


Tuberculosis chemotherapy in the UK

In this third article of our series on tuberculosis, **Anthony Grosso**, **Yogini Jani** and **June Minton** provide an overview of standard treatment



Identify knowledge gaps

1. How long does treatment for pulmonary tuberculosis usually last?
2. What advice could you give to patients with TB about their medicines?
3. How can you monitor for compliance with therapy?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states and their drug therapies" (see appendix 4 of "Plan and record").

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Pulmonary tuberculosis accounts for 80 per cent of TB cases

Chemotherapy for tuberculosis (TB) was established after the discovery of streptomycin in the 1940s. Before this, bed rest, good food, fresh air and sunshine in sanatoriums built on hillsides, with or without surgery (eg, thoracoplasty) was the only way to treat TB.

Sputum conversion (from culture positive to culture negative), clinical improvement (eg, no haemoptysis) and radiological improvement were achieved after two to three months of streptomycin therapy. However, resistance followed rapidly. The addition of aminosalicylic acid was shown to reduce the emergence of resistance to either drug.

It was the introduction of isoniazid that led to the development of successful primary chemotherapy regimens in the 1950s. When isoniazid was added, resistance was reduced,

implying that combination treatment was superior to monotherapy. However, to prevent the emergence of resistance, a "standard" regimen of streptomycin plus aminosalicylic acid and isoniazid had to be given for a minimum of 18 months. Aminosalicylic acid was sometimes substituted with ethambutol or thiacetazone depending on acceptability and availability.

In the 1960s, treatment in a domiciliary setting was found to be effective and not to expose close contacts to an additional risk of infection. Unfortunately, adverse reactions were common and poor compliance often led to treatment failure and multiple drug resistance. Therefore, fully supervised intermittent chemotherapy (to ensure drug ingestion) was introduced. Since the introduction of rifampicin in the 1970s and the reuse of pyrazinamide, short-course chemotherapy (typically lasting six months) has become the main treatment strategy for TB.

Modern therapy

TB is now treated in two phases — an initial phase using at least three drugs and a continuation phase using two drugs. The concurrent use of at least three drugs during the initial phase is designed to reduce the bacterial

population as rapidly as possible and to prevent the emergence of drug resistance.

The initial phase usually lasts two months, during which culture and sensitivity tests can be performed. If *Mycobacterium tuberculosis* has been cultured but sensitivity results are not available, initial phase treatment should continue until full sensitivity has been confirmed.

The aims of chemotherapy are:

- To cure patients, with minimal disruption to their lives
- To prevent death and disease progression
- To avoid relapse

Summary

- Tuberculosis is treated in two phases
- The initial phase, usually lasting two months consists of taking rifampicin, isoniazid and pyrazinamide
- The continuation phase usually lasts four months
- Compliance is essential for treatment success and to prevent drug resistance
- Directly observed therapy may be necessary to ensure compliance

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Patient education and counselling

Patient education is an important role for pharmacists and pharmacy staff, who can confirm and add to information that patients have already received. Written information, in addition to verbal counselling, should be provided with all TB regimens. It should be emphasised that TB can be cured but treatment can take many months and patients should take their medicines as prescribed, even if they feel better. The patient should be told what adverse effects to expect and when he or she needs to seek medical advice. Pictorial images and translated written information are useful for patients with poor English. Other important counselling points include:

- Standard treatment should be taken as a single daily dose, usually first thing in the morning. Ideally this should be about an hour before food to aid rifampicin and isoniazid absorption

- Rifampicin will cause a harmless orange-red discoloration of urine and other bodily fluids, including sweat and tears
- Patients should be advised not to use soft contact lens because these can become permanently stained (hard and gas permeable lens are unaffected)
- Patients using the oral contraceptive pill should be advised to use non-hormonal methods of contraception for the duration of rifampicin treatment and for eight weeks afterwards
- Patients taking ethambutol should be told to report any changes in their vision to their doctor
- Patients should be told how to recognise signs of liver disease and advised to discontinue their treatment and seek immediate medical attention if these appear

- To prevent the emergence of acquired drug resistance
- To protect the community from infection

The regimens described below are based on the recommendations of the Joint Tuberculosis Committee of the British Thoracic Society and current practice at University College London Hospitals NHS Foundation Trust.

Initial phase The regimen of choice for the initial phase is the daily administration, at doses determined by the patient's weight, of the following four drugs:

- Rifampicin
- Isoniazid
- Pyrazinamide
- Ethambutol

Ethambutol is usually omitted if the risk of isoniazid resistance is low. Isoniazid resistance is considered likely if the patient has previously been treated for TB, if the patient is immunocompromised or if exposure to a resistant strain is known.

Streptomycin is now only used in the UK occasionally, for example, if isoniazid resistance has been confirmed (by sensitivity testing) before starting treatment. The occurrence of some adverse effects require discontinuation of some drugs but many side effects are harmless and transient.

Combination products Combination products are generally preferred because they aid compliance. Current practice at UCLH NHS Foundation Trust is to use a rifampicin and isoniazid combination product (eg, Rifinah or Rimactazid) and pyrazinamide for initial phase therapy. Pyrazinamide is no longer manufactured in the UK, so must be imported. A triple combination product (Rifater) is available but this contains ratios of drugs that differ (slightly) from those recommended by the British Thoracic Society.

Many consider the differences not to be clinically significant and the British National Formulary currently recommends Rifater as first line therapy. Pharmacists and consultants at UCLH NHS Foundation Trust are currently debating this issue.

Continuation phase After the initial phase, four months of rifampicin and isoniazid therapy (at doses determined by the patient's weight) is usually recommended. The regimen can be modified if resistance develops.

Supervised treatment regimens For short-course regimens to be effective, adherence is vital. Medication needs to be fully supervised ("directly observed therapy", DOT) in patients who cannot comply reliably with treatment. Intermittent regimens that allow for treatment to be given two or three times a week have been devised. These are particularly useful for patients who are homeless or who have chronic alcohol or drug misuse problems. In the developing world, intermittent regimens are also being used to reduce poor compliance. A number of trials have shown that short-course intermittent regimens are as effective as standard daily regimens.¹

Non-pulmonary tuberculosis There are few published comparative trials involving treatment of non-respiratory TB. Limited current data suggest that "respiratory regimens" are effective in non-respiratory disease, although treatment duration might need to be extended for some sites, such as lymph nodes and the meninges.

Rifampicin Rifampicin is bactericidal against a wide range of micro-organisms, including mycobacteria. It interferes with nucleic acid synthesis by inhibiting DNA-dependent RNA polymerase. Rifampicin is particularly useful because it has the ability to kill intracellular organisms. However, it is associated with several unwanted effects. The most

common include skin reactions (mostly flushing, with or without rash, but this is often transient), gastrointestinal disturbances (often within the first few weeks of treatment) and disturbances of hepatic function. Thrombocytopenia, associated with complement-fixing antibodies, is rare. Six toxicity syndromes have been recognised with rifampicin use: influenza-like symptoms, abdominal symptoms, respiratory symptoms, shock, renal failure and thrombocytopenic purpura.

Rifampicin use is also complicated by the fact that it is a potent inducer of hepatic enzymes. The metabolism of several drugs (eg, oestrogens, phenytoin, corticosteroids, sulphonylureas, methadone and anticoagulants) is, therefore, accelerated. Interactions with anti-retroviral drugs are complex and are best investigated in detail. An excellent web site to refer to is www.HIV-druginteractions.org

Isoniazid Isoniazid is highly active against rapidly dividing *M tuberculosis* but is considered to be only bacteriostatic against semi-dormant organisms and has less sterilising activity than both rifampicin and pyrazinamide. The mechanism of action of isoniazid has only become clearer over the past few years. Although it has been found to interfere with various bacterial cell functions, it is likely that isoniazid owes its activity against *M tuberculosis* to interference with mycolic acid synthesis. The effect is achieved by inhibition of a fatty acid desaturase after intracellular oxidation of isoniazid to an active compound.

Adverse effects are relatively uncommon at standard doses and are more frequent in people who are slow acetylators. Neurological side effects are the most common and include restlessness, insomnia, muscle twitching and difficulty in initiating micturition. More serious, but less frequently encountered, neurological side effects include optic neuritis, encephalopathy, anxiety, depression, paranoia and peripheral neuropathy. Other less common side effects include arthralgia, an influenza-like syndrome, hypersensitivity reactions, rashes, eosinophilia and haemolysis in patients with glucose-6-phosphate deficiency (more common in people of African, Asian or Mediterranean origin). Isoniazid can also exacerbate acute porphyria and induce anti-nuclear anti-bodies, although overt systemic lupus erythematosus is rare.

Pyridoxine Pyridoxine (vitamin B₆) is usually co-prescribed for patients at an increased risk of peripheral neuropathy (eg, patients with hepatic impairment, pregnant women, alcoholics, renal dialysis patients, HIV-positive patients, the malnourished and the elderly). Isoniazid may increase excretion of pyridoxine or act as a pyridoxine antagonist.

Pyridoxine antagonises isoniazid on a milligram for milligram basis. However, studies have shown that only 6mg/day of pyridoxine is needed to prevent peripheral neuropathy and 10mg/day is the recommended dose at UCLH NHS Trust. Due to the difficulty of procuring a UK licenced 10mg dosage form,

UCLH NHS Trust TB treatment guidelines advocate using 25mg (half a 50mg tablet) daily for supplementation to “high-risk” patients. Some centres advocate routine supplementation, up to a dose of 50mg each day.

Pyrazinamide Pyrazinamide is an important sterilising drug that is required for short-course regimens to be effective. However, the mechanism of action of pyrazinamide is poorly understood because of its unusual properties. What is known is that the principle metabolite, pyrazinoic acid, disrupts cell membrane energetics and inhibits membrane transport function in *M tuberculosis*.²

Pyrazinamide is usually well tolerated. Moderate elevations of serum transaminases occur early in treatment. Severe hepatotoxicity is relatively uncommon with standard doses, except in patients with pre-existing liver impairment. Pyrazinoic acid also inhibits renal excretion of uric acid, occasionally causing gout. An unrelated arthralgia, notably of the shoulders and unresponsive to analgesics, also can occur. Other side effects include anorexia, nausea, mild skin flushing and photosensitisation.

Ethambutol Ethambutol is a slow acting and, primarily, bacteriostatic anti-mycobacterial agent that inhibits arabinosyl transferases. These enzymes bring about the polymerisation of arabinose to form arabinan, a polysaccharide component of the core polymers of the mycobacterial cell wall.

The most important adverse effect of ethambutol is optic neuritis, which can be irreversible if treatment is not promptly discontinued. Patients should be counselled accordingly and this drug should, ideally, not be used in patients who are unable to notice or report visual changes (eg, young children).

Monitoring efficacy and compliance

In pulmonary tuberculosis, sputum examination and culture are sensitive markers of treatment success. Patients taking regimens containing rifampicin and isoniazid are considered non-infective within two to three weeks. If a patient is still culture-positive, drug resistance or non-compliance should be suspected, the latter being the most common cause. Chest radiography provides only limited information on treatment progress.

As already discussed, regimen compliance is essential for successful therapy. However, routine monitoring of adherence has proved difficult in clinical practice. A simple method to monitor compliance is to check the colour of a urine sample provided within four hours of when the dose was meant to be taken — rifampicin will colour the urine orange-red. Monthly tablet counts are another useful indicator. Plasma drug level monitoring can be considered for some patients, although this is not routine practice because of the cost and its invasive nature.

Visual acuity should be tested using a Snellen chart before ethambutol administration.

Other side effects include peripheral neuritis, arthralgia, hyperuricaemia, rashes and, rarely, thrombocytopenia and jaundice.

Streptomycin Streptomycin is taken into cells by active transport where they bind to the 30S and, to some extent, the 50S ribosomal subunits, inhibiting protein synthesis and generating errors in the transcription of the genetic code.

Streptomycin has an adverse event profile similar to that of other aminoglycosides. Caution is needed in patients with impaired renal function and plasma concentrations should be monitored. Allergic reactions occur in about 5 per cent of treated patients, although the majority of reactions are often trivial and respond to anti-histamine therapy. Continuation of therapy is appropriate in many cases but this should be exercised with caution because occasional severe, and even fatal, exfoliative dermatitis reactions have been reported. Pain and irritation at the injection site is also relatively common and many patients also develop paraesthesia (a burning or prickling sensation) in and around the mouth.

Monitoring toxicity

Liver function should be investigated before starting rifampicin, isoniazid or pyrazinamide. Patients with pre-existing liver disease or alcohol dependence should have frequent liver function tests during the first few months of therapy. For patients with an apparently healthy liver, further checks are only deemed necessary if signs or symptoms of hepatic disease develop.

Mild hepatic reactions (eg, transaminitis) are common but no action is required. More modest elevations of liver enzymes are frequently seen in the first two months of therapy but these return to baseline so treatment is usually continued. Severe hepatitis, which is often associated with anorexia, nausea and vomiting, requires all treatment to be stopped temporarily, until hepatitis is resolved.

In seriously ill patients, treatment can be restarted with streptomycin and ethambutol. For others, treatment is cautiously reintroduced with isoniazid first, followed by rifampicin (because rifampicin is considered more likely to cause hepatitis than isoniazid). Liver function tests are performed daily for inpatients. Current practice at UCLH NHS Trust for pyrazinamide-induced severe hepatitis, once treatment has been successfully re-established with rifampicin and isoniazid, is not to reintroduce pyrazinamide but to switch to ethambutol (presuming it was not required in the initial phase). The total regimen is then continued for nine months from the date on which the three drugs were restarted. Specialist advice should be sought for rifampicin- or isoniazid-induced severe hepatitis.

Renal function should also be checked before therapy and dose adjustments made accordingly.

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. What treatments are recommended locally for TB? How do these compare to current UK guidelines?
2. Consider what pictorial images would be effective on TB leaflets for patients with poor English.
3. Find out where your local TB clinic is. Is any pharmaceutical input required?

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Chemoprophylaxis

Chemoprophylaxis can be required for patients who have evidence of latent TB infection (eg, positive Heaf test; see *PJ*, 4 September p318) and are receiving treatment with immunosuppressants such as cytotoxics or chronic systemic corticosteroids. Under these circumstances, six months of isoniazid therapy is often indicated. The Joint Tuberculosis Committee also recommends chemoprophylaxis for:

- Patients with documented recent tuberculin conversion (a positive tuberculin skin test result following a previous negative result), eg, where previous latent disease has been reactivated
- Some tuberculin-positive children identified in Bacillus Calmette-Guérin schools programmes
- Children under two years of age in close contact with smear-positive tuberculosis (including those previously vaccinated with BCG but now showing a positive Heaf test)
- Children under 16 years of age showing a positive Heaf test at a new immigration or contact screening

Chemoprophylaxis should also be considered in immigrant adults (aged 16–34 years) without a BCG scar but with a strongly positive Heaf test.

The final article in this series will look at the treatment of drug-resistant TB.

References

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2. Zhang Y, Wade MM, Scorpio A, Zhang H, Sun Z. Mode of action of pyrazinamide: disruption of Mycobacterium tuberculosis membrane transport and energetics by pyrazinoic acid. *Journal of Antimicrobial Chemotherapy* 2003;52: 790–5.