Clinical Review

Managing drug resistant tuberculosis

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> *Summary points*
>
> Drug resistant tuberculosis is becoming more common
>
> Traditional laboratory methods for detecting drug resistance are slow and not generally available outside specialist laboratories. Rapid molecular methods are increasingly used in well resourced settings, and simple, cheap alternatives are being developed for resource limited settings
>
> The evidence base to guide drug treatment of resistant tuberculosis is weak, and randomised controlled trials are needed
>
> A service advising on the management of multidrug resistant tuberculosis is available in the United Kingdom
>
> Priorities for prevention of drug resistant tuberculosis include prompt detection of cases, effective treatment of drug sensitive and drug resistant cases, and prevention of tuberculosis transmission

Antituberculosis drug resistance is increasing both in the United Kingdom and internationally.[1] [2] It has come to greater public attention with the emergence of extensively drug resistant tuberculosis (box 1) in South Africa, where an outbreak proved rapidly fatal among people with advanced HIV infection.[3] In this article we review recent global and UK trends in drug resistant tuberculosis and summarise its diagnosis, treatment, and control. Few data are available from randomised controlled trials to guide treatment of drug resistant tuberculosis, and none for multidrug resistant tuberculosis; this review is based primarily on data from observational epidemiological studies and on national and international guidelines.

Box 1 Definitions relating to tuberculosis and drug resistance

- *Drug resistant tuberculosis*—Tuberculosis that is resistant to any first line antituberculosis drug (see table 1⇓)

- *Multidrug resistant tuberculosis (MDR-TB)*—Tuberculosis that is resistant to at least isoniazid and rifampicin

- *Extensively drug resistant tuberculosis (XDR-TB)*—Tuberculosis that is resistant to at least isoniazid and rifampicin and also to a fluoroquinolone and a second line injectable agent (amikacin, capreomycin, or kanamycin)

- *Drug resistance in new tuberculosis cases (primary drug resistance)*—Drug resistant tuberculosis in a person with no history of tuberculosis treatment, implying they were infected with a resistant organism. This reflects person to person transmission of drug resistant tuberculosis

- *Drug resistance among previously treated cases ("acquired" drug resistance)*—Drug resistant tuberculosis in a person with a history of tuberculosis treatment. This reflects drug resistance acquired during tuberculosis treatment but may also reflect infection or reinfection with a resistant organism

WHO group	Category	Drug name
1	First line oral agents	Isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E)
2	Injectables	Streptomycin (S), kanamycin (Km),* amikacin (Am), capreomycin (Cm)
3	Fluoroquinolones	Moxifloxacin (Mfx), gatifloxacin (Gfx),* levofloxacin (Lfx), ofloxacin (Ofx), ciprofloxacin (Cfx)
4	Second line oral agents	Ethionamide (Eto),* prothionamide (Pto),* cycloserine (Cs), terizidone (Trd),* para-aminosalicylic acid (PAS),* thioacetazone (Th)*
5	Unclear efficacy (not recommended for routine use)	Clofazimine (Cfz), clarithromycin (Clr), amoxicillin-clavulanate (Amx/Clv), linezolid (Lzd)

The table is adapted from World Health Organization.[19]

*Not routinely available in the UK.

Table 1
Categories of antituberculosis drugs (abbreviations common in the literature on tuberculosis are in parentheses)

How did we get to where we are?

Writing in this journal 60 years ago, Bradford Hill reported that although two thirds of patients with advanced pulmonary tuberculosis improved with streptomycin monotherapy, within six months 35 of 41 patients had developed streptomycin resistance.[4] Combining streptomycin with isoniazid and para-aminosalicylic acid limited the evolution of resistance, but treatment for one to two years was needed and excellent clinical trial outcomes were difficult to reproduce in programmes with limited resources for supervised drug treatment.[5] Clinical trials from 1970 that used regimens containing rifampicin showed that treatment could safely be shortened to six months, and, as a result of these regimens combined with directly observed treatment, cure rates have reached 95% in the best clinical settings.[6] However, drug resistance may emerge if an effective course of multidrug treatment is not completed, whether this results from poor delivery by health systems or poor adherence by patients.[7]

Recent trends in antituberculosis drug resistance

Global prevalence of drug resistant tuberculosis

The World Health Organization's 2008 report on antituberculosis drug resistance gives cause for concern.[2] Globally, by 2006, the estimated proportion of multidrug resistant tuberculosis was 2.9% and 15.3% for new and previously treated tuberculosis cases respectively. Global averages conceal major variation by region (fig 1)⇓: the population weighted mean of multidrug resistant tuberculosis among all tuberculosis cases was 0% in some western European countries, whereas in the former Soviet Union almost half of all cases were resistant to one drug and 20% had multidrug resistance; of those with multidrug resistance, up to 20% were extensively drug resistant.[2] In some provinces of China, over a third of new tuberculosis cases are resistant to one or more drugs.[2] Among an estimated 0.5 million cases of multidrug resistant tuberculosis globally in 2006, 23 353 were notified (half of these in the European Union); treatment meeting the standards established in the WHO guidelines was known to have started in only just over 2000 cases.[8] Few African countries report resistance data: in Rwanda and Tanzania, there is little resistance to second line antituberculosis drugs among multidrug resistant cases, consistent with little use of these drugs.[2] South Africa has a considerable burden of multidrug resistant tuberculosis.[2]

Fig 1 Prevalence of multidrug resistance among new cases of tuberculosis globally, 1994-2007. Adapted from World Heath Organization[2]

Drug resistant tuberculosis in the United Kingdom

In 2006, 7.7% of all tuberculosis cases in England, Wales, and Northern Ireland had some degree of drug resistance (6.9% had resistance to isoniazid and 0.9% had multidrug resistance).[9] Two cases of extensively drug resistant tuberculosis have been reported, one in 2003 and another in March 2008, in a man from Somalia treated in Glasgow. The proportion of tuberculosis with multidrug resistance has increased a little in recent years; the prevalence of isoniazid resistance has increased more and is highest in London (9.3%), Northern Ireland (7.7%), and the East Midlands (7.1%). The increase in isoniazid resistance is attributed partly to tuberculosis among migrants who acquire the disease outside the UK and partly to an outbreak of over 300 cases of isoniazid resistant tuberculosis centred in north London that was associated with homelessness, drug use, and imprisonment.[9] This outbreak illustrates that tuberculosis transmission can be maintained among high risk groups in the UK, contrasting with evidence from strain typing that most tuberculosis in the UK is acquired outside the country.[10] [11] If the strain in the north London outbreak had been more extensively resistant, the consequences for public

health would have been much more serious.

Emergence of extensively drug resistant tuberculosis

The term extensively drug resistant tuberculosis was introduced in 2005 and came to wider attention in 2006 when results of a survey in rural South Africa showed that 53 of 221 patients with multidrug resistant tuberculosis had extensive drug resistance, which was strongly associated with HIV infection and very high mortality, despite antiretroviral therapy.[3] Extensively drug resistant tuberculosis has now been reported from 45 countries,[2] though this almost certainly underestimates its true extent as many countries have no laboratory facilities to detect resistance to second line drugs. The outbreak in South Africa is particularly alarming because, unlike in many other settings, most patients with extensively drug resistant tuberculosis had no history of tuberculosis treatment, implying person to person transmission of extensively drug resistant tuberculosis, and because of evidence of transmission in healthcare settings.

How should drug resistant tuberculosis be diagnosed?

For the past 120 years the rapid diagnosis of tuberculosis has depended on the search for acid fast bacilli (after Ziehl-Neelsen staining) in clinical specimens. Diagnosing drug resistant tuberculosis is much harder because it generally requires pure cultures of *Mycobacterium tuberculosis*. Conventional testing of drug susceptibility for rapidly growing bacteria gives results within 24 hours, but these techniques do not work well for *M tuberculosis*, which takes 24 hours to replicate and about a month to produce visible growth on solid media. Consequently, detecting drug resistant *M tuberculosis* by growth on culture media incorporating antituberculosis drugs takes six to eight weeks, requires special laboratory facilities, and is largely unavailable in resource limited settings, where tuberculosis is common (see table 2⇓ for alternative tests that resolve or minimise these drawbacks).

Assay	Used directly on clinical specimens?	Time from receipt of clinical specimen to a result	Advantages and disadvantages
Phenotypic methods			
Conventional susceptibility testing using solid media	No— requires pure culture	>6 weeks	The traditional method, but slow, technically laborious, and requires special laboratory safety facilities
Automated susceptibility testing using liquid media	Possible— but most laboratories use pure culture	2-4 weeks (1-2 weeks if used on clinical specimens)	Fast, reliable, and safe, but requires expensive equipment. Rarely used outside reference laboratories in the developed world; may become cost effective where multidrug resistance is common
Microscopic observational drug susceptibility (MODS) assay	Yes	1 week	Fast, inexpensive, and safe. Requires an inverted microscope. Not yet evaluated in the developed world

Colorimetric methods	Possible— but most studies have used pure cultures	4-6 weeks (7-10 days if used on clinical specimens)	Bacterial growth in the presence of drug is detected by a colour change—uncertain value until performance on clinical specimens has been clarified
Genotypic methods			
Commercial assays for detecting rifampicin resistance	Yes	2 days	Fast, safe, and reliable, but expensive and results require confirmation with conventional methods
DNA sequencing	Yes— requires amplification product or DNA from pure cultures	2 days	Optimal method for detecting mutations but unavailable outside reference and research laboratories. Expensive and technically demanding
Real time polymerase chain reaction	Yes	1 day	May enhance speed and sensitivity when used on clinical specimens but yet to be evaluated in routine clinical practice
Microarrays	Possible— requires amplification product or DNA from pure cultures	2 days	Expensive research technique capable of detecting a large number of mutations throughout the bacterial genome. Has been used experimentally to detect bacteria resistant to rifampicin and isoniazid in clinical specimens

Table 2

Comparison of methods available for detecting drug resistant *Mycobacterium tuberculosis*

Molecular methods, which detect the bacterial genetic mutations responsible for producing phenotypic drug resistance, are increasingly available in industrialised countries. The UK's Mycobacterial Reference Unit uses a commercial assay (INNO-LiPA Rif TB assay, Innogenetics, Belgium) to identify rapidly *M tuberculosis* and the mutations responsible for rifampicin resistance. Compared with conventional phenotypic susceptibility tests, sensitivity and specificity were 85.2% and 88.2% respectively when used on clinical specimens, and 98.7% and 100% respectively on bacterial cultures.[12] In the UK, more than 80% of rifampicin resistant isolates are also resistant to isoniazid, making rifampicin resistance a useful surrogate marker for multidrug resistance.[13]

Much work has been done in recent years to develop susceptibility tests appropriate for resource limited settings. The microscopic observation drug susceptibility (MODS) assay is based on the unique microscopic appearance of *M tuberculosis* growing in liquid media.[14] Resistance is detected by observing growth in the presence of antituberculosis drugs; it gives results within seven days and can detect 99% of multidrug resistant bacteria when compared with conventional techniques.[14]

Table 2⇑ reviews tests for detecting drug resistant *M tuberculosis.*

How is drug resistant tuberculosis treated?

The problems surrounding treatment of drug resistant tuberculosis today are similar to those facing Bradford Hill in 1948: we have no randomised controlled trial evidence specifically relating to treatment; second line drugs are weak and toxic; and many patients have advanced disease requiring prolonged treatment. The management of multidrug resistant tuberculosis may be complicated by concurrent HIV infection, lack of facilities for resistance testing and for isolation of patients, and intermittent access to second line drugs, all of which contributed to the recent emergence of extensively drug resistant tuberculosis in South Africa.[15]

Presumptive treatment of drug-resistant tuberculosis

It is difficult to predict which patients will have drug resistance without performing susceptibility testing. In the UK, monoresistance to isoniazid is the most common form of drug resistance among individuals with no history of treatment for tuberculosis.[9] The main concern in such cases is that if adherence is suboptimal, patients risk acquiring resistance to other drugs. No controlled trials have specifically researched treatment of isoniazid monoresistant tuberculosis; guidelines are based on expert opinion. UK and American guidelines differ, recommending 10-12 months and 6-9 months of treatment respectively, depending on extent of disease and how much treatment has already been taken by the time monoresistance is detected.[16 17]

UK guidelines on risk factors for multidrug resistant disease are summarised in box 2. When multidrug resistant tuberculosis is strongly suspected—for example, if a patient fails a second course of treatment—it may be necessary to start treatment before susceptibility results become available, taking into account antituberculosis drug resistance patterns in the setting where infection was most likely to have been acquired and the patient's own treatment history. Empirical treatment includes at least three drugs likely to be effective. The regimen can be modified as soon as susceptibility results become available.[18] We believe that fluoroquinolones should not be given as presumptive broad spectrum antibiotic treatment to patients with possible tuberculosis as this may hinder the diagnosis of tuberculosis and risks promoting the development of tuberculosis strains that are resistant to fluoroquinolones.

*Box 2 Risk factors for multidrug resistant tuberculosis**

Global risk factors

- History of treatment for tuberculosis

- Known recent contact with a person with drug resistant tuberculosis

- HIV infection

Additional risk factors in United Kingdom

- Age 25-44 years

- Born outside the UK (especially in a country with high prevalence of multidrug resistant tuberculosis—fig 1⇑)

- Male sex

- Residence in London

- *Adapted from National Institute for Health and Clinical Excellence[16]

Principles of treatment informed by drug susceptibility tests

The WHO guidelines for managing multidrug resistant tuberculosis[19] are based on expert opinion and a review of retrospective cohort data. Individualised treatment regimens aim for a minimum of four drugs with documented in vitro sensitivity, given daily under direct observation for at least 18 months after culture conversion, and 24 months for extensive disease. The WHO guidelines recommend that regimens include:

- All first line drugs to which the organism is still sensitive

- A fluoroquinolone whenever possible

- A daily injectable agent until sputum has been culture negative for six continuous months

- Other second line agents to make the total number of drugs to which the isolate is susceptible up to four or five (table 1⇑).

A role for surgery with localised disease remains for patients with good cardiopulmonary reserve and a low bacillary load.

In resource limited settings, most cases can be managed in the community with experienced workers using various incentives along with daily directly observed treatment. Over 30 such programmes have been established worldwide, with cure rates ranging from 48% to 77%.[20] [21]

In the UK, patients with multidrug resistant tuberculosis are increasingly managed in specialist centres. Clinicians can email a recently formed service (MDRTBservice@ctc.nhs.uk) that provides advice on management from a group of UK specialists. Randomised controlled trials are needed to inform evidence based treatment of multidrug resistant tuberculosis.
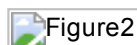
How can we prevent drug resistant tuberculosis?

The principles of tuberculosis control are equally relevant to the prevention of drug resistant tuberculosis: these include prompt case detection, provision of curative treatment, and prevention of transmission. The WHO's "Stop TB" strategy[22] is built around the successful DOTS (directly observed treatment short course) strategy, comprising political commitment, quality assured bacteriology for case detection, standardised treatment, an effective drug supply, and monitoring and evaluation. The DOTS strategy includes supervision and support of treatment, although there is little evidence that directly observed treatment alone improves cure rates.[23] Nevertheless, ineffective drug treatment is a strong risk factor for acquired drug resistance,[7] and proper administration of antituberculosis drugs is critical to reduce this risk. An enhanced DOTS programme, DOTS-plus, has been developed for managing multidrug resistant tuberculosis in resource limited settings,[19] and this programme recommends additional investment in facilities for culture and drug susceptibility testing for detection of drug resistant tuberculosis, and provision of appropriate second line antituberculosis drugs.

As most drug resistance arises from suboptimal treatment of active disease, prevention of active disease indirectly prevents drug resistance. In countries with greater resources and where reactivation of latent infection is an important source of new cases, such as the United States, treatment of latent
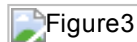
infection and of recent contacts of infectious cases is given high priority.[24] Such approaches have long been considered impractical in resource limited settings with a high prevalence of latent infection and high incidence of active disease, although this view has been challenged with respect to household contact tracing[25] and for HIV infected individuals.[26]

The emergence of extensively drug resistant tuberculosis highlights the importance of preventing transmission of drug resistant tuberculosis in healthcare facilities.[3] Preventive measures are needed when patients are at high risk of multidrug resistant tuberculosis and/or have acid fast bacilli in their sputum. In the UK these patients should be managed in close consultation with those responsible for hospital and community infection control (fig 2⇓). Prevention of transmission in healthcare settings is difficult in places where resources are limited with no isolation facilities; one approach is to manage cases with similar resistance profiles in segregated groups. However, simple, low cost interventions, such as opening windows, can reduce transmission of tuberculosis.[27]

Fig 2 Summary of UK guidelines for preventing the transmission of drug resistant tuberculosis[16]

Successful control of drug resistant tuberculosis globally will depend on strengthening tuberculosis control programmes, wider access to rapid mycobacterial culture and sensitivity testing, and provision of effective treatment for drug resistant disease. The cost of effective control programmes may seem high, but the cost of ineffective control will surely be much higher. ⇓

Fig 3 Chest radiograph showing cavitating disease in patient with multidrug resistant tuberculosis

Sources and selection criteria

We searched PubMed for recent articles using the search terms "tuberculosis" and "resistance"; we also used World Health Organization reports, national and international guidelines, and personal archives. We selected articles for inclusion based on relevance to the purpose of the review.

Additional educational resources

For healthcare professionals

- Maartens G, Wilkinson R. Tuberculosis. *Lancet* 2007;370:2030-43. (A recent comprehensive review of tuberculosis)

- Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tuberc Lung Dis* 2006;10:829-37. (A good review of multidrug resistant tuberculosis)

- whqlibdoc.who.int/publications/2006/9241546956_eng.pdf. (WHO guidelines on the programmatic management of drug resistant tuberculosis)

- www.who.int/tb/publications/2008/drs_report4_26feb08.pdf. (The latest WHO report on anti-tuberculosis drug resistance)

- www.nice.org.uk/CG033. (Guidelines for England and Wales on tuberculosis from the National Institute for Health and Clinical Excellence)

- www.who.int/tb/publications/global_report/en/index.html. (The latest WHO report on tuberculosis control)

For patients

- TB Alert (www.tbalert.org/resources/clinical.php)—British charity publishing several leaflets for patients

- Patient UK (www.patient.co.uk/showdoc/23069042/)—Information about tuberculosis for patients

- NHS (www.immunisation.nhs.uk/Library/Publications/Translations/Translations)—Information sheets about tuberculosis in multiple languages (tuberculosis is listed last)

A case history

A 35 year old London born man presented to his general practitioner with several months of weight loss and a productive cough. He was treated with amoxicillin. He next returned two months later with worsening symptoms. His chest radiograph showed extensive cavitatory disease, and his sputum was smear positive for acid fast bacilli. He was started on Rifinah (combined isoniazid and rifampicin) and pyrazinamide and referred to the local tuberculosis service.

The patient failed to attend his first two appointments at the tuberculosis clinic. He had a history of substance misuse and several convictions for theft. Six weeks later he collected another month's prescription of antituberculosis treatment from his general practitioner but again missed his appointment at the tuberculosis clinic. By this time his initial sputum sample had grown isoniazid resistant *Mycobacterium tuberculosis* and the public health department was notified.

The patient was next seen five months later, after returning from a trip to the Caribbean. He said he had been taking antituberculosis medication while away, but his sputum was again smear positive. An HIV test was negative. After a brief stay in hospital he agreed to have directly observed treatment, and ethambutol was added in view of the isoniazid resistance. Unfortunately he didn't get on with his case worker and often missed appointments for directly observed treatment.

Eight months later he was admitted to another hospital, emaciated and unwell. His sputum grew *M tuberculosis* which was now resistant to isoniazid, rifampicin and ethambutol.

What could have been done to prevent this situation from developing?

- Consider tuberculosis, and arrange chest radiograph and sputum microscopy earlier

- Start with an antituberculous regimen of four drugs, and notify public health authorities at this point

- Consider the risk of drug resistant tuberculosis at the start of treatment

- Arrange better support for treatment adherence from the start of treatment

- Avoid adding a single drug to a failing regimen (add a minimum of two drugs known to be active)

- Encourage better communication between the healthcare services involved, particularly concerning the missed clinic appointments

Tips for non-specialists

- Consider drug resistant tuberculosis in individuals at higher risk

- If drug resistant tuberculosis is suspected, discuss rapid testing for resistance with the local microbiology laboratory and consider the need for additional infection control measures

- Refer patients with drug resistant tuberculosis to specialist centres

Notes

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Footnotes

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