CLINICAL STATEMENT
November 2016

British Thoracic Society

THE MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS (MDRTB)

CONTEXT

The World Health Organization (WHO) has recently updated its guidance on the management of MDRTB (June 2016). Worldwide, there were an estimated 480,000 cases of MDRTB in 2014, the highest rates being in those from Eastern Europe and the Central Asian republics. In the same year, there were 52 notified cases in England (1.4% of all TB); treatment was completed within 24 months in just 54% cases. The management of MDRTB is more complex and associated with more adverse effects than standard treatment. Prior to effective chemotherapy, about a third of patients with tuberculosis remained alive but with a persistently positive sputum smear, i.e. they remained infectious. Failure to control MDRTB will have significant risks to public health.

Shorter regimens are preferred by patients and are cheaper. Preliminary evidence indicates that a 9-12 month regimen has a better cure rate than the 20 month course recommended in the WHO 2011 guidelines. However, given the differing patterns of drug resistance within the UK, careful selection and monitoring of appropriate patients for the shorter regimen is required. However, given the differing patterns of drug resistance within the UK, careful selection and monitoring of outcomes of appropriate patients for the shorter regimen is required.

SCOPE

This statement is aimed at those involved in the management of MDRTB who work in conjunction with local TB networks and with advice from the BTS MDRTB Clinical Advice Service: http://forums.brit-thoracic.org.uk/

THE WHO 2016 GUIDANCE IN THE CONTEXT OF THE UNITED KINGDOM

WHO recommends testing for rifampicin resistance on primary specimens at the time of diagnosis. In England, those with rifampicin resistance are likely to have MDRTB (46/54 in 2015)[1]. Currently, only those suspected of having MDRTB (previous TB treatment, from a high incidence area such as Eastern Europe and those with contact with an index case of MDRTB) have a test for *rpoB* mutations on the submitted specimen.

The "9-month Bangladesh" regimen was first reported in 2010[2]. The most effective regimen consisted of gatifloxacin, clofazimine, ethambutol and pyrazinamide for the entire course, supplemented by kanamycin, prothionamide and high dose isoniazid (900 mg daily) for the first 4 months or until sputum smear conversion, whichever was the longer period. Approximately half showed sputum smear conversion within 4 months and most by 7 months of the intensive initial phase of treatment. Cure rates were 90% (87.8 – 92.4%), which compares well with an estimated 78% (71.2 – 84%) for the 20-month standard regimen.

The WHO guidance indicates that the shorter 9-12 month MDR TB regimen can be used if:

a) No previous treatment with second-line drugs for > 1 month
b) Resistance to fluoroquinolones and second-line injectable agents has been excluded (or is unlikely)[3]

Relapses were common in those with resistance to fluoroquinolones or kanamycin[2]. Therefore, early testing of TB cultures for resistance to ethambutol, pyrazinamide, fluoroquinolones and injectable antibiotics by using rapid molecular tests is required for those starting the shortened regimen. The evidence does not yet include the effect of *inhA* mutations (susceptible to high dose isoniazid but resistant to prothionamide) and *katG* mutations (susceptible to prothionamide but resistant to high dose isoniazid) on treatment outcome or time to smear conversion. Resistance to fluoroquinolones is associated with *gyrA* mutations predominantly[4].

As with rifampicin[5], there is an almost two log difference in peak drug concentrations of moxifloxacin among different individuals[6]. A dose of 800 mg daily ensures that those with a lower peak drug level will still be above the mean inhibitory concentration for most strains of *Mycobacterium tuberculosis*. WHO advises a dose of 800mg daily when weight > 50kg and 600mg daily when weight 30-50 kg. Monitoring patients during treatment of MDRTB is important[7]. Follow-up includes measures of a response to treatment (sputum smear, chest x-ray and general health, especially weight), indices affected by many of the drugs, such as liver and renal function and more specific measures for individual drugs (TB monographs: http://www.tbdrugmonographs.co.uk). QTc prolongation has been reported for both clofazimine and moxifloxacin, but has been of the order of 6 ms[8].

The WHO 2016 guidelines comment that surgery is acceptable in the management of MDRTB. However, reviewing the evidence presented suggests that only those with minimal disease had a better outcome (as would have been expected *a priori*); the indications for surgery were not reported.

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GENERAL ADVICE FOR MDRTB

- The management of MDR/XDR (extensively drug resistant) TB cases should be led by a designated MDRTB centre
- All patients with suspected or proven MDRTB should be discussed within the TB network and advice sought from the BTS website for the UK MDRTB Clinical Advice Service (http://forums.brit-thoracic.org.uk/)
- Monitor the sputum smear in the intensive phase (weekly)
- Monitor for adverse effects as per the TB Drug Monograph (http://www.tbmonographs.co.uk) (e.g. pre and post dose ECGs)
- Useful forms can also be downloaded from within the TBNET consensus paper[7]
- Report adverse effects, treatment outcome and relapse over the subsequent 5 years
- Surgery should not be routine in the management of MDRTB, but governed by clinical indications (e.g. large cavities and bronchopleural fistulae)
- Clarithromycin (and other macrolides) should no longer be considered as one of the second line drugs for the treatment of MDRTB

SPECIFIC ADVICE FOR USING THE SHORT-COURSE REGIMEN FOR MDRTB

- Confirmation of tuberculosis and *rpoB* mutations should be sought on all patients with a positive sputum smear
- A positive test for *rpoB* mutations should be immediately followed by PCR testing for other first line and second-line drugs
- A positive test for *rpoB* mutations requires that cultures for second line drug sensitivity testing are set up at the same time as for first line drugs
- The regimen should NOT be used if there is evidence of resistance to fluoroquinolones or second line injectable agents especially and the use of the regimen is also not advised if there is resistance to pyrazinamide or ethambutol
- Gatifloxacin is not currently available: moxifloxacin or high dose levofloxacin (750-1000 mg daily) may be used instead.
- Kanamycin is not readily available within the UK; amikacin or capreomycin may be used as substitutes as they have the same locus of action
- The shorter MDRTB regimen is not advised in pregnancy
- Those with drug intolerance to the regimen should have an Individualised regimen
- The shorter MDR regime is not routinely recommended for extra-pulmonary TB but should be discussed with the UK MDRTB Clinical Advice Service (http://forums.brit-thoracic.org.uk/) as some types of limited disease may be appropriate

Statement of declarations of interest: Declarations of interest were completed in line with BTS Policy and are available from the BTS Office on request. (https://www.brit-thoracic.org.uk/about-bts/governance/)

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Useful Links: BTS MDRTB Clinical Advice Service
http://forums.brit-thoracic.org.uk/

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