AUDIT, RESEARCH AND GUIDELINE UPDATE

A UK-based resource to support the monitoring and safe use of anti-TB drugs and second-line treatment of multidrug-resistant TB

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ABSTRACT

Using the best available evidence and expert consensus, this document provides guidance for adverse effect monitoring in multidrug-resistant TB (MDR-TB). It includes recommendations for baseline tests, routine drug and toxicity monitoring guides as well as individual drug monographs for all drugs currently available in the UK to treat TB. These recommendations provide a structure through which healthcare professionals can better manage the complex drug regimens required for the treatment of MDR-TB; minimising the risk of adverse incidents and helping to improve patients' tolerance, compliance and treatment completion.

CLINICAL CONTEXT

Multidrug-resistant TB (MDR-TB) is caused by bacteria that do not respond to the two most powerful anti-TB drugs; isoniazid and rifampicin. MDR-TB is a growing concern; the WHO estimates that there were 450 000 new cases of MDR-TB in 2012 and global incidence almost doubled in that same year.[1] In the UK, MDR-TB cases have nearly tripled over the last decade and we continue to discover cases of XDR-TB[2]; defined as TB that is resistant to both isoniazid and rifampicin (MDR-TB) plus a fluoroquinolone and at least one of the injectable agents (amikacin, capreomycin, kanamycin).

The cost of treatment for MDR-TB is estimated to be 10 times that of fully sensitive TB.[3] Treatment regimens are complex and prolonged with a high risk of serious adverse drug reactions (ADRs). Treatment is associated with significant morbidity and mortality, threatening adherence[4] and increasing the risk of transmission of these difficult to treat strains of TB. The Global plan to Stop TB aims for successful treatment completion in 75% for all patients with MDR-TB; however, completion rates for MDR-TB in the UK were below this target at only 70.6% for the period between 2004 and 2007.[5]

We are not aware of any previous guidelines in the UK that have adequately advised clinicians on the baseline testing that should be performed and how to ensure that anti-TB drugs are used safely and effectively in patients treated for drug-resistant TB. We would like to introduce the first UK guidance for adverse-effect monitoring in MDR-TB.

TARGET AUDIENCE

The guidance is aimed at all healthcare workers in the field of TB and in particular those who work with MDR-TB. It is relevant not only to UK practitioners but those working with MDR-TB around the world. This guideline is to aid monitoring for adverse effects during the treatment of MDR-TB. It is not a treatment guide or a guide for monitoring the progress of treatment. Treatment of MDR-TB is complex and users of this guidance should ensure all aspects of treatment are in consultation with local experts and published guidance.

SCOPE OF THE GUIDANCE

The guidance consists of two main sections. The first, 'Baseline and generic tests for adverse effects monitoring in patients being treated for MDR-TB', provides advice on the frequency of monitoring that should occur *at minimum* in all patients on MDR-TB treatment (box 1).

The second section includes 'drug monographs' for all drugs currently used to treat MDR-TB, including amikacin, bedaquiline, capreomycin, clarithromycin, clofazamine, co-amoxiclav, cycloserine, ethambutol, imipenem-cilastatin, isoniazid, levofloxacin, linezolid, meropenem, moxifloxacin, ofloxacin, P-aminosalicylic acid, prothionamide, pyrazinamide, rifabutin, rifampicin, streptomycin and thioacetazone. Each monograph was based upon a standard layout as is shown in box 2.

METHODOLOGY

This document was written using the best available published evidence and, where this was limited, expert consensus. The guideline team consists of five health professionals with experience treating patients with TB and MDR-TB; a TB pharmacist, a TB consultant physician, two respiratory registrars and a TB nurse.

An initial review of published guidelines was undertaken, which allowed us to identify gaps in

Box 1 Baseline and routine monitoring recommendations

Baseline tests and ongoing monitoring recommendations for adverse effects monitoring

- Blood tests
- Audiology
- Visual acuity and colour discrimination testing
- ECG

Box 2 Standard layout of each 'drug monograph'

Individual drug monographs
- Dosage
- Preparations
- Drug level monitoring
- Adverse effects
- Adverse effect monitoring recommendations
- Interactions
- Contraindications and cautions
- Laboratory information

knowledge and to gain an overview of current practice. To produce the individual drug monographs, a two-step approach was taken. Tertiary reference sources, published reviews and international guidelines were analysed to provide the basis for individual drug monographs since these have collated data from robust clinical and pharmacokinetic studies. This was supported and enhanced by a literature review using Medline and hand searching of reference lists from published studies. The latter strategy was particularly important where there was a paucity of published data to support recommendations. One individual reviewed the abstracts from each search to identify potentially relevant studies. On occasion systematic reviews suggested a dosing range rather than specific doses, and in this situation, expert consensus was used to guide our dose recommendations. Where there was no clear evidence, current practice, our own experience and expert consensus were used.

Our multidisciplinary guideline development group held regular teleconferences and corresponded by email. When evidence was sparse, expert consensus was sought from the British Thoracic Society TB Special Advisory Group (SAG) and UK MDR-TB Advisory Service. When other specialty input was required, this was sought from experts in that field. Once the guideline was developed, it was submitted to the TB SAG for peer review. Feedback was reviewed by the committee and accepted or rejected based on supporting evidence and/or expert consensus.

ONLINE ACCESS AND FUTURE DEVELOPMENTS

This guidance is designed to be available as an online resource so that it can be updated when the need arises, such as when new drugs are launched or when new data that affect the use of existing anti-TB drugs become available. The guidance has been published online at http://www.tbdrugmonographs.co.uk and will be freely accessible to all.

In addition to this web version, software is being developed to facilitate the ease of use of the guidance. This application will enable the monitoring guidance to be customised for individual patients based on their specific drug regimen. This will also be made available through the website.

New literature will be reviewed annually and incorporated where relevant. Additionally, an open invitation for feedback is incorporated into the website and within the guidance document. Any feedback received will be discussed among the guideline team with any required changes incorporated into the relevant monographs.

AUDIT AND RESEARCH RECOMMENDATIONS

Audit of this guidance is suggested after it has been implemented in a centre for a reasonable period of time; we suggest 6–12 months. Results will be used to revise recommendations and assess impact on treatment outcomes, costs and patient experience.

CONCLUSIONS

We hope that by introducing a guideline to aid ADR monitoring in MDR-TB treatment we can improve treatment adherence, morbidity and mortality and reduce treatment costs.

Contributors JLP is responsible for the inception of this piece of work, wrote the paper and played a major role in writing the main guidance. TC did the main literature review and provided content for the main guidance. WMR provided expert advice and editorial assistance on the main document. NW provided advice and perspective in her role as an experience TB nurse. OMK provided expert advice and additional literature review for the main guidance and the paper. He coordinated and chaired the committee meetings throughout the development of the guidance. He is responsible for the content of the paper and the guidance and acts as guarantor for both.

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Competing interests JLP owns the web domain http://www.tbdrugmonographs.co.uk, but has no pecuniary interest in its use.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Feedback documents following consultation with the BTS multidrug-resistant special advisory group with our own responses to the feedback following a committee meeting are available. All meeting minutes are also available for review.

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A UK based resource to support the monitoring and safe use of anti-tuberculosis drugs and second line treatment of multidrug-resistant tuberculosis

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Abbreviations

BNF	British National Formulary
BPM	Beats per minute
BTS	British Thoracic Society
CNS	Central Nervous System
DOT	Directly Observed Therapy
ECG	Electrocardiogram
FBC	Full blood count
FDA	Food and Drug Administration (USA)
G6PD	Glucose-6-pyruvate dehydrogenase
HIV	Human Immunodeficiency Virus
IM	Intra-muscular
IV	Intra-venous
LFT	Liver function tests
MDR-TB	Multidrug-resistant tuberculosis
Mg	Magnesium
MHRA	Medicines and Healthcare Products Regulatory Agency
NSAIDs	Non-steroidal anti-inflammatory drugs
QT/ QTc	QT interval/ corrected QT interval
SPC	Summary of product characteristics
SST	Serum separating tube
TB	Tuberculosis
TFT	Thyroid function test
U&E	Urea & Electrolytes (including creatinine, urea, potassium and sodium)
UK	United Kingdom
WHO	World Health Organisation

Introduction

This guideline is to aid monitoring for adverse effects during the treatment of MDR-TB. It is not a treatment guide or a guide for monitoring the progress of treatment. For treatment guidance please refer to the WHO treatment guideline and the BTS MDR-TB Clinical Advisory Service. Treatment of MDR-TB should always be undertaken in consultation with local experts as well as published guidance.

Due to the complexity of treatment regimens and comorbidity associated with the disease itself, more frequent monitoring may be needed in individual patients and this should be guided by the clinician in charge of the patient's care. Our recommendations are predominantly based on consensus opinion from TB physicians, pharmacists, nursing staff and specialties including audiology and ophthalmology and drug advisory organisations including the FDA and BNF.

We also appreciate that most patients with MDR-TB are established on treatment whilst an in-patient and may require more frequent blood test monitoring during the initial phase of treatment. We have produced this document to provide advice on the frequency of monitoring which should occur, *at minimum*, in all patients on MDR-TB treatment.

Many side effects cannot easily be measured with routine testing. As such, it is important that all healthcare staff routinely assess patients for symptoms with reference to the potential adverse reactions listed for each drug.

All recommendations below should cover any combination of drugs. Where additional monitoring is required with a specific drug we have noted this and provided a source for further information in the form of individual drug monographs.

Therapeutic drug level monitoring advice is available in individual drug monographs.

Links

British Thoracic Society MDR-TB Clinical Advisory Service:
http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx
WHO guidance on the treatment of MDR-TB:
http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf

Contents

Baseline and generic tests for adverse effects monitoring in patients being treated for MDR-TB

BASELINE TESTS	
Blood Tests	Renal function and electrolytes (U&Es), liver function tests (LFTs), bone profile, magnesium (Mg), thyroid function tests (TFTs), uric acid
	Full blood count (FBC), clotting
	HIV, Hepatitis B, Hepatitis C
	G6PD deficiency screen
Other Tests	ECG
	Visual Acuity and Colour Vision
	Audiometry
	Nutritional Assessment

ONGOING MONITORING RECOMMENDATIONS	
FBC	Monthly until 6 months. Consider reducing frequency after 6 months if stable and no changes to medication. If using Linezolid please see individual drug monograph for FBC frequency recommendations.
Clotting	Baseline and repeat if indicated, particularly if deranged LFTs.
U&Es	All MDR patients should be on an aminoglycoside therefore: Month 1 = twice weekly Month 2 = weekly Month 3 onwards: fortnightly Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable. Consider increasing frequency of monitoring if evidence of renal impairment.
LFTs	Weekly for the first month or until regimen is established, whichever is longest. Then to continue monthly throughout treatment. Consider reducing frequency after 6 months if LFTs stable and no pre-existing liver disease or changes to medication.
Calcium	Monthly until 6 months. Consider reducing frequency after 6 months if stable and no changes to medication.
TFTs	Monthly if patient on prothionamide and PAS combination therapy. If on only prothionamide or PAS, check TFTs 3 monthly.
Magnesium	Monthly until 6 months. Consider reducing frequency after 6 months if stable and no changes to medication.
ECG (For patients prescribed macrolides, fluoroquinolones, clofazamine or bedaquiline)	Baseline, at 2 weeks, then 3 monthly (1 monthly if on bedaquiline) throughout treatment. Repeat if symptomatic or after the addition of any new medication which is known to prolong QT. Be particularly cautious when prescribing more than one drug which might prolong QTc such as ondansetron, anti-depressants, anti-psychotics etc. Refer to EP Cardiologist if QTc outside normal range.
Visual acuity & Colour Vision	6 monthly or more frequently if symptoms noted. Refer for formal assessment with ophthalmology if baseline abnormality or changes noted during treatment.
Audiometry (Aminoglycosides)	Monthly until completion of treatment and a final test 2 months after treatment completion.

DRUG MONOGRAPHS

AMIKACIN

Please note amikacin is not licensed for the treatment of tuberculosis in the UK.

DOSAGE

For intramuscular or intravenous administration only. (Intravenous route is preferred, as the volume of doses required would necessitate two IM injections each day.)

Amikacin is usually given once daily (although for pragmatic reasons there is experience giving it 5 days per week) for an initial period (usually at least two months). In clinical practice the frequency is usually then reduced to three times weekly.

Single-Dose Regimen (usually as an intravenous infusion, diluted in 100mL sodium chloride 0.9% or glucose 5% and infused over 30 to 60 minutes):
Adults: 15mg/kg daily (usual maximum 1g daily, but can be increased if necessary in large muscular adults). After initial period (usually at least two months): **15mg/kg three times per week**.
Age >59 years: 10mg/kg daily (maximum 750mg daily). After initial period: **10mg/kg three times per week**.

Renal failure: 12-15mg/kg TWO to THREE times a week. *Please discuss with a pharmacist.*

Obesity: It has been suggested that markedly obese patients should have an adjusted dose using ideal body weight plus 40% of the excess weight in markedly obese patients. The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.

- Male ideal body weight (kg) = 50 + (2.3 x height in cm above 152.4)/2.54
- Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above 152.4)/2.54

Adjust dose and/or frequency according to serum amikacin concentration (see below).

Children: 15-22.5mg/kg daily (usual maximum 1g daily). After initial period: **15-30mg/kg three times per week**.
Adjust dose and/or frequency according to serum amikacin concentration (see below).

PREPARATIONS

Parenteral: 100mg/2mL, 500mg/2mL injection.

DRUG LEVEL MONITORING

Indications for monitoring:

- Ensure therapeutic dose.
- Ensures that accumulation is not occurring in renal impairment.

Target Level: <5mg/L (*trough*)
25 – 35mg/L (*peak)*

Timing of sample:

- Pre dose.
- Take a level 90 – 120 minutes and 6 hours after the infusion ends. Then plot on semi-logarithmic paper and extrapolate back to time = 0 and use this as the peak level.

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

- Alternatively, taking a level 60mins after infusion ends may be appropriate as a measure of the peak level, but may underestimate the true peak level.

Frequency of Levels:

- Peak serum level in first week, repeat if poor response.
- Trough serum levels weekly for 4 weeks. This can reduce to fortnightly when stable.

Suggested Actions:

- **Trough level**: High – extend interval.
- **Peak level**: High – reduce dose; low – increase dose.

ADVERSE EFFECTS

COMMON:

Nephrotoxicity: Accumulation if renal impairment.
Ototoxicity: Irreversible vestibulo-cochlear nerve damage.

SERIOUS:

Endocrine: Hypocalcaemia, hypomagnesaemia, and hypokalaemia.
Neurological: Neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually dose-related and self-limiting).
Audiological: Ototoxicity - auditory > vestibular (higher with prolonged use and older age)
Renal: Nephrotoxicity (higher with prolonged use).

ADVERSE EFFECTS: MONITORING

Renal, **auditory** and **vestibular** monitoring is essential

Renal function: Month 1 = twice weekly.
Month 2 = weekly.
Month 3 to end of treatment = fortnightly.
Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable.
Consider increasing frequency of monitoring if evidence of renal impairment.

Loss of hearing usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances are also signs of **ototoxicity.**

Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies. If this occurs, Amikacin should be discontinued or dosing reduced in frequency to avoid further hearing loss, although the hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change. Of the current injectable agents, Capreomycin may be less ototoxic.

We recommend that patients have baseline audiometry and then monthly reviews until treatment with aminoglycoside ceases. A final audiometry review should be offered 2 months after the final dose.

Routine tests as per generic MDR-TB drug monitoring guidelines.

INTERACTIONS

Increased risk of **ototoxicity** if given with: loop diuretics
Increased risk of **hypocalcaemia** with bisphosphonates.

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

Increased risk of **nephrotoxicity** if given with: capreomycin, cephalosporins, ciclosporin, colistimethate sodium, tacrolimus.
NB: There is no clinical benefit in prescribing amikacin AND capreomycin or kanamycin or streptomycin.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To amikacin or other aminoglycosides.
Myasthenia Gravis: As amikacin may impair neuromuscular transmission.
Pregnancy: Risk of vestibular or auditory nerve damage to foetus if used in second or third trimester.

Cautions:
Obese: Use ideal weight for height to calculate dose and monitor serum amikacin levels closely.
Elderly: Nephrotoxicity and ototoxicity common in the elderly; monitor and reduce dose if necessary.
Renal Disease: Use with caution. Reduce the frequency of dosing and monitor serum concentrations.

LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider for contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
Sample Type: Serum.
Volume Required: 1-2mL (min 0.1mL).
Sample Container: Plain glass or plastic (non SST).
Container Type: Any.
Availability: NS.
Turnaround Time: Telephoned same day if received 9am-3pm Mon-Fri. Written confirmation report will be sent by 1st Class post.

BEDAQUILINE

There are limited data available on bedaquiline. Clinicians are advised to monitor patients closely to ensure the safe and effective use of this drug.

Patients should be advised that the following serious side effects can occur with bedaquiline: death, heart rhythm abnormalities, and/or hepatitis. In addition, patients should also be advised about other potential side effects: nausea, joint pain, headache, increased blood amylase, haemoptysis, chest pain, anorexia, and/or rash. Additional testing may be needed to monitor or reduce the likelihood of adverse effects.

DOSAGE

Adults (aged 18 to 64 years): 400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks. (Maximum duration = 6 months).
Children: not currently recommended in people aged less than 18 years.

Bedaquiline should be taken with food.
Patients should be advised to avoid alcohol whilst on bedaquiline.

PREPARATIONS

Oral: 100mg tablets.

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

- **Report all suspected adverse drug reactions to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme.**

COMMON:
Arthralgia
Chest pain
Gastrointestinal: Nausea.
Neurological: Headache.
Respiratory: Haemoptysis

SERIOUS:
Cardiovascular: QTc prolongation (more common in hypokalaemia, proarrhythmic conditions, in combination with other drugs that prolong the QT interval such as clofazimine, fluoroquinolones or macrolides).
Hepatic: Increases in LFTs.

ADVERSE EFFECTS: MONITORING

ECG: Baseline, 2 weeks then every month and after the addition of any new medication that is known to prolong QT.

- Discontinue bedaquiline and all other QT prolonging drugs if the patient develops:

  - Clinically significant ventricular arrhythmia
  - A QTc interval of > 500 ms (confirmed by repeat ECG)
- Monitor ECGs frequently to confirm that the QTc interval has returned to baseline.
- If syncope occurs, obtain an ECG to detect QT prolongation.

LFTs: at baseline, and repeated monthly.
U&Es, calcium & magnesium: at baseline and repeated monthly and if QT prolongation is detected.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTIONS

Anti-arrhythmics: Risk of prolonged QT interval (e.g. amiodarone, sotalol, procainamide, dysopyramide and quinidine).
Antiretrovirals: Limited data.
Antidepressants, Tricylic: Risk of prolonged QT interval**.**
Antipsychotics (thioridazine, haloperidol, chlorpromazine, trifluoperazine, percycline, prochlorperazine, fluphenazine, sertindole, and pimozide): Risk of prolonged QT interval**.**
Azole antifungals (e.g. ketoconazole, voriconazole, itraconazole, fluconazole): Increased exposure to bedaquiline. Avoid co-administration for more than 14 days.
Carbamazepine: Accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
Chloroquine & hydroxychloroquine: Risk of prolonged QT interval.
Clofazimine: Risk of prolonged QT interval.
CYP3A4 inducers: Accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
CYP3A4 inhibitors: Reduced metabolism resulting in increased serum concentrations of bedaquiline. Avoid prolonged co-administration for more than 14 days.
Fluoroquinolones: Risk of prolonged QT interval.
Macrolides: Risk of prolonged QT interval. Avoid co-administration for more than 14 days.
Phenytoin: accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
Rifampicin, Rifabutin & Rifapentine: accelerated metabolism of bedaquiline resulting in reduced effect. Avoid co-administration.
Statins: Avoid co-administration.

This information is not inclusive of all drug interactions. Please refer to the SPC or BNF for further information, or discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Pregnancy & breast feeding. Men should agree to use a highly effective method of birth control and not to donate sperm during treatment and for 3 months after receiving the last dose of TB treatment.
There are no adequate or well-controlled studies in pregnant women. It is not known whether bedaquiline or its metabolites are excreted in human milk.
Hypersensitivity: To bedaquiline**.**
Children aged <18 years: The safety and effectiveness has not been established in children.

Cautions:

Elderly patients ≥ 65 years: Lack of data in patients aged 65 and over to determine whether they respond differently from younger patients

Extrapulmonary TB (e.g. meningitis): There are no data on the use of bedaquiline in extra pulmonary TB and consequently it is not currently recommended for the treatment of this.

Cardiovascular: Due to the risk of QT prolongation with bedaquiline, ECGs should be monitored closely in patients:

- Taking other QT prolonging drugs (e.g fluoroquinolones, macrolides, clofazimine).
- with a history of Torsade de Pointes, congenital long QT syndrome, hypothyroidism and bradyarrhythmias, or uncompensated heart failure .
- With serum calcium, magnesium, or potassium levels below the lower limits of normal.

HIV/TB co-infection: limited or no information on the use of bedaquiline.

Alcohol or substance use: Limited or no information on alcohol or substance use in association with bedaquiline however, manufacturer recommends avoiding alcohol whilst taking bedaquiline.

Liver disease: Lack of data in severe liver disease. No dose adjustment required in mild to moderate hepatic impairment.

Renal disease: Use with caution in patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis.

LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider for contact details. Turnaround time is usually a few days to a week but this can be reduced by calling ahead and informing the laboratory in advance.

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

CAPREOMYCIN

DOSAGE

Capreomycin is usually given once daily for an initial period (usually at least two months), then the frequency may be reduced to three times weekly.

Licensed for intramuscular administration only. There is experience of using capreomycin as an intravenous infusion. (Diluted in 100 mL of 0.9% Sodium Chloride or glucose 5% and administered over 30 to 60 minutes.)
Adults: **15mg/kg daily** (usual maximum 1g daily, but can be increased if necessary in large muscular adults). After initial period: **15mg/kg three times per week**.
Age >59 years: 10mg/kg daily (maximum 750mg daily). After initial period: **15mg/kg three times per week**.

Renal failure: 12-15mg/kg TWO to THREE times a week. *Please discuss with a pharmacist.*

Obesity: Use ideal body weight plus 40% of the excess weight in markedly obese patients. The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.

- Male ideal body weight (kg) = 50 + (2.3 x height in cm above 152.4)/2.54
- Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above 152.4)/2.54

Children: **15-30mg/kg daily** (usual maximum 1g daily). After initial period: **15-30mg/kg three times per week**.

PREPARATIONS

Parenteral: 1g powder for injection.

DRUG LEVEL MONITORING

Drug levels cannot currently be performed for capreomycin in the UK.

ADVERSE EFFECTS

COMMON:
Nephrotoxicity: Higher risk with prolonged use.
Ototoxicity: Auditory > vestibular (Maybe lower risk than with amikacin; higher risk with prolonged use and older age).
Drug-induced eosinophilia: Usually subsides with intermittent dosing.
SERIOUS:
Dermatological: Induration and local pain with IM injection.
Endocrine: Hypocalcaemia, hypomagnesaemia, and hypokalaemia.
Hepatic: Liver function test abnormalities when used with other anti-TB drugs.
Neurological: Neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually with rapid IV infusion).
Audiological: Ototoxicity - auditory > vestibular (Maybe less than with amikacin; higher with prolonged use and older age).
Renal: Nephrotoxicity (higher with prolonged use).

ADVERSE EFFECTS: MONITORING

Renal, **auditory** and **vestibular** monitoring is essential.

Renal function: Month 1 = twice weekly.
Month 2 = weekly.
Month 3 to end of treatment = fortnightly.
Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable.
Consider increasing frequency of monitoring if evidence of renal impairment.

Loss of hearing usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances are also signs of **ototoxicity.**

Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies. If this occurs, Capreomycin should be discontinued or dosing reduced in frequency to avoid further hearing loss, although the hearing loss that has occurred is likely to be permanent. Expert advice should be sought at this point to consider a regimen change.

We recommend that patients have baseline audiometry and then monthly reviews until treatment with aminoglycoside ceases. A final audiometry review should be offered 2 months after the final dose.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTIONS

Increased risk of **nephrotoxicity** if given with: aminoglycosides, colistimethate sodium.
Increased risk of **ototoxicity** if given with: aminoglycosides.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To capreomycin.
Pregnancy: Risk of vestibular or auditory nerve damage to infant if used in second or third trimester.

Cautions:
Renal Disease: Use with caution. Reduce the frequency of dosing and monitor serum concentrations.
Obese: Use ideal weight for height to calculate dose and monitor serum-aminoglycoside levels closely.
Elderly: Nephrotoxicity and ototoxicity common in the elderly; monitor and reduce dose if necessary.

LABORATORY INFORMATION

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Not currently available in the UK.

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

CLARITHROMYCIN

Please note clarithromycin is not licensed for the treatment of tuberculosis in the UK.
Clarithromycin is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

DOSAGE

For all patients over 12 years old:
By intravenous infusion:

- 500mg twice a day given through a large proximal vein.

By mouth:

- 500mg twice a day.

Paediatric doses: [NOTE: Limited data on evidence for dosing in TB. These doses are based on clarithromycin dosing for respiratory tract infections in the latest BNF for children 2012-2013.]
By intravenous infusion into large proximal vein

- Child 1 month–12 years: 7.5 – 15 mg/kg twice a day
- Child 12–18 years: 500 mg twice a day

By mouth:
Child 1 month – 12 years:

- body-weight under 8 kg: 7.5 mg/kg twice a day
- 8–11 kg: 62.5 mg twice a day
- 12–19 kg, 125 mg twice a day
- 20–29 kg, 187.5 mg twice a day
- 30–40 kg, 250 mg twice a day

Child 12 – 18 years: 500mg twice a day

PREPARATIONS

Oral: 250mg, 500mg tablets.
125mg/5mL, 250mg/5mL suspension.
Parenteral: 500mg powder for solution for injection

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Gastrointestinal: Abdominal pain (2%), diarrhoea (3-6%), nausea (3%), vomiting (6%) and taste perversion (3-19%).
Neurological: Headache (2%).
SERIOUS:
Cardiovascular: QTc prolongation (very rare)
Dermatological (rare): Anaphylaxis, leukocytoclastic vasculitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome.
Hepatic: Hepatomegaly, hepatic dysfunction & hepatic failure (rare).

Immunological: Anaphylaxis.
Infective: Clostridium difficile-associated diarrhoea and colitis.
Ototoxicity: Hearing loss and tinnitus reported in association with long-term use.

ADVERSE EFFECTS: MONITORING

ECG: Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
Audiometry: Baseline and repeat if symptomatic.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTIONS

Use with caution with antivirals:

- *Increased plasma concentrations* of: atazanavir, etravirine, nevirapine, telaprevir, tipranavir, and possibly maraviroc, rilpivirine.
- *Increased clarithromycin concentrations* with: atazanavir, ritonavir, telaprevir, tipranavir.
- *Reduced clarithromycin concentrations* with: atravirine, nevirapine.
- *Increased risk of ventricular arrhythmias* with saquinavir and telaprevir.

Increased plasma concentrations of:

- Antiepileptics: carbamazepine, phenytoin (monitor plasma concentrations).
- *Ciclosporin* (avoid clarithromycin, or monitor ciclosporin plasma concentrations).
- *Coumarins* e.g. warfarin (increased **anticoagulant** effect).
- *Ivabradine* (avoid use).
- *Linezolid* (consider drug level monitoring)
- *Rifabutin* (requires rifabutin dose reduction).
- *Sirolimus* (avoid clarithromycin, or monitor sirolimus plasma concentrations).
- *Statins* (avoid use).
- *Tacrolimus* (avoid clarithromycin, or monitor tacrolimus plasma concentrations).
- *Theophylline* (reduce theophylline dose and monitor plasma concentrations).
- *Ticagrelor* (avoid use).

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To macrolides.
Use of other drugs that may prolong the QT interval.
Renal & liver disease: Avoid in patients with both severe renal and liver disease.

Cautions:
Pregnancy & Breast-feeding.
Renal Disease: Use with caution. Reduce the dose.
Myasthenia Gravis: Macrolides may aggravate myasthenia gravis.
Cardiovascular Disease: Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesaemia,

bradycardia (<50 bpm), or when co-administered with other medicinal products associated with QT prolongation.

LABORATORY INFORMATION

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The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

CLOFAZIMINE

Please note clofazimine is not licensed for the treatment of tuberculosis in the UK.
Clofazimine is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

DOSAGE

Adults: Recommend 100mg to 200mg once daily (oral).
Doses of 200mg daily for two months, then 100mg daily have been used. (Doses up to 300mg once daily have been used in leprosy).
Children: Limited data, WHO recommendation is based on experience and expert opinion and suggests 3-5mg/kg/day.

Clofazimine should be taken with meals or with milk to maximise absorption and reduce gastrointestinal adverse effects.

PREPARATIONS

Oral: 100mg capsules (unlicensed medicine).

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Dermatological: Pink to brownish-black skin discoloration (resembling sun-tanning) within 1-4wks in 75-100% of patients. It gradually disappears within 6-12 months after stopping treatment. It is important to advise patients of this prior to commencing treatment.
Ichthyosis & dry skin (8-38%), pruritis (5%), rash (1-5%), photosensitivity reactions (wear protective clothing and sunscreens).
Gastrointestinal: (up to 50% of patients): Abdominal pain, nausea, vomiting, diarrhoea, weight loss.
SERIOUS:
Gastrointestinal: (<1%): bowel obstruction, GI haemorrhage.
Ophthalmic: Conjunctival pigmentation (38-57%), subjective dimness of vision (12.3%), and dry eyes, burning, and other ocular irritation (24.6%).
Psychiatric: Reactive depression due to skin discolouration.
Other: Splenic infarction, discolouration of body fluids.

ADVERSE EFFECTS: MONITORING

Risk of QT prolongation and ventricular tachyarrhythmias (thought to be torsades de pointes) has been highlighted in case reports.
ECG: Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

May *reduce the absorption rate of rifampicin*, but is unlikely to be clinically significant.
Isoniazid may increase plasma and urinary concentrations of clofazimine and decrease skin concentrations.
Increased risk of prolonged QTc with other drugs that prolong QTc including fluoroquinolones and bedquiline.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To clofazimine.
Hypersensitivity: To peanuts or soya, as clofazimine capsules contain soybean oil.

Cautions:
Pregnancy & Breast-feeding
Renal Disease: Use with caution. Dose reductions are not necessary.
Liver Disease: Use with caution. Metabolised by the liver, therefore may require dose adjustment in severe liver disease.

LABORATORY INFORMATION

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Not currently available in the UK.

CO-AMOXICLAV

Please note co-amoxiclav is not licensed for the treatment of tuberculosis in the UK.
Co-amoxiclav is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen. It is sometimes recommended in combination with meropenem for its clavulanate content. Co-amoxicalv inhibits the beta-lactamase which destroys meropenem activity. Clavulanate alone is not available for use in the UK.

DOSAGE

[NOTE: Limited data on evidence for dosing in TB. The adult doses are based on those used in the treatment of respiratory tract infections in the BNF no 65, March 2013. The paediatric doses are similarly based on dosing for respiratory tract infections in the latest BNF for children 2012-13].
For all patients over 12 years old:

By intravenous infusion over 3-4 minutes:

- *Patients over 12 years old:* 1.2g 8 hourly

- *Neonates:* 30mg/kg every 12 hours
- *Children 1 -3 months* 30mg/kg every 12 hours
- *3 months – 18 years* 30mg/kg every 8 hours

By mouth:

- *Patients over 12 years old:* 625mg, 8 hourly

- *Neonates:* 0.25 mL/kg of *125/31* suspension every 8 hours
- *Children 1 month- 1 year* : 0.25 mL/kg of*125/31* suspension every 8 hours
  Dose doubled in severe infection
- *1–6 years:* 5 mL of*125/31* suspension every 8 hours
  or 0.25 mL/kg of *125/31* suspension every 8 hours
  Dose doubled in severe infection
- *6–12 years*: 5 mL of *250/62* suspension every 8 hours
  Or 0.15 mL/kg of *250/62* suspension every 8 hours
  Dose doubled in severe infection

In renal failure dose reduction may be necessary. *Please discuss with a pharmacist.*

PREPARATIONS

Oral: 250/125mg (375mg), 500/125mg (625mg) tablets.
125/31mg, 250/62mg suspension.
Parenteral: 500/100mg, 1000/200mg Powder for solution for injection or infusion.

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Dermatological: Rash & urticaria (3%).

Gastrointestinal: Nausea & vomiting (1-5%), diarrhoea (9%).
Infective: Candidiasis, particularly oral and vaginal (1%).
SERIOUS:
Dermatological: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis.
Hepatic: Hepatitis, cholestatic jaundice.
Immunological: Anaphylaxis.

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

No common serious drug interactions usually expected.
Anticoagulants: Case reports of increased INR in patients taking acenocoumarol or warfarin and prescribed a course of amoxicillin. Monitor INR.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To penicillins.
Liver Disease: Previous history of jaundice/hepatic impairment due to co-amoxiclav.

Cautions:
Pregnancy & Breast-feeding
Renal Disease: Use with caution. Reduce dose in severe renal impairment.
Liver Disease: Use with caution. Monitor liver function. Cholestatic jaundice may occur during or shortly after the use of co-amoxiclav. Risk is higher in patients aged >65 years and in men.

LABORATORY INFORMATION

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CYCLOSERINE

DOSAGE

Adults: Initially 250mg twice a day (oral), increased to 500mg twice a day depending on serum concentrations.
The usual target dose in adults is 10-20mg/kg/day once or twice per day. Maximum 1g per day.
Children: Target dose is 10-20mg/kg/day in two divided doses. Maximum 1g per day.

All patients must be prescribed pyridoxine whilst receiving cycloserine. The usual dose ranges from 50 to 100mg daily, up to 50mg per 250mg of cycloserine.

PREPARATIONS

Oral: 250mg capsules.

DRUG LEVEL MONITORING

Indications for monitoring:

- Ensure therapeutic dose.
- Ensure toxic levels are not reached.
- Renal impairment.

Target Level: 20 – 35mg/L (peak).
10 – 20mg/L

Timing of sample:

- Peak – 2 hours post dose.
  - Repeat at 6 hours if suspect delayed absorption**.**
- Trough levels – taken immediately prior to a dose.

Frequency of Levels:

- Serum levels after 4 days at target dose.
- Repeat fortnightly for one month and until stable.
- Repeat at least 6 monthly.
- Repeat if suspect malabsorption, treatment failure, or neuropsychiatric side effects (should be monitored monthly).
- *Patients with reduced renal function require more frequent monitoring, initially weekly until stable.*

Suggested Actions:

- **High Peak Level:** Reduce dose if level >35mg/L. If level is 35 to 50mg/L, consider reducing dose by 25% per day. If level >50mg/L, consider halving the dose. Recheck level after four days.
- **Low Peak Level**: Increase dose if level <15mg/L.
- **Trough levels:** Cyloserine absorption may be slow and consequently a 2-hour peak level may not capture the true Cmax. It is rare to see elevated peak levels in the absence of elevated trough levels, therefore a raised trough level may indicate potentially toxic 'true' peak levels. Consider serial peak serum level assays (e.g. at 2, 4 and 6 hours post dose), and dose reduction.

ADVERSE EFFECTS

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

COMMON:
Neurological: Confusion, disorientation, dizziness, somnolence (increased risk if peak serum level >35mg/L).
SERIOUS:
Cardiovascular: Sudden development of congestive heart failure (rarely reported at doses greater than 1 to 1.5g daily).
Dermatological: Rash and photosensitivity, Stevens-Johnson syndrome (rare).
Haematological: Vitamin B12 and/ or folic acid deficiency, megaloblastic anaemia or sideroblastic anaemia (rare).
Psychiatric: Depression, seizure, psychotic disturbances (increased risk if peak serum level >35mg/L).

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Alcohol: Increased risk of convulsions with cycloserine.
Isoniazid: Increased risk of CNS toxicity when given with cycloserine.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To cycloserine.
Neurological: Epilepsy, depression, severe anxiety, psychotic states.
Alcohol Dependence.
Renal Disease: Severe renal impairment.

Cautions:
Pregnancy & Breast-feeding
Neurological: Stop or reduce dose if symptoms of central nervous system toxicity such as convulsions, psychosis, somnolence, depression, confusion, hyper-reflexia, headache, tremor, vertigo, paresis or dysarthria.
Dermatological: Stop or reduce dose if allergic dermatitis develops.
Renal Disease: Use with caution. Reduce dose in severe renal impairment.

LABORATORY INFORMATION

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ETHAMBUTOL

DOSAGE

Adults: 15mg/kg once daily (oral); **or** for DOT supervised regimen: 30mg/kg three times per week. (*Round the dose up or down to the closest whole number of tablets*).

Note: Ethambutol should be dosed on lean body weight.
Male ideal body weight (kg) = 50 + (2.3 x height in cm above 152.4)/2.54
Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above 152.4)/2.54

Children (1 month to 18 years): 20mg/kg once daily (oral); **or** for DOT supervised regimen: 30mg/kg three times per week. (*Doses should be rounded down to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet*).

PREPARATIONS

Oral: 100mg, 400mg tablets
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).
Suspension (as a manufactured 'special' - unlicensed medicine).
An intravenous preparation may be available from specialist importers.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Renal impairment.
- Poor treatment response.

Target Level: 2 – 6mg/L *(Peak)*

Timing of sample:

- 2 hours post dose.
- Repeat at 6 hours if suspect delayed.

Frequency of Levels:

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Endocrine: Hyperuricaemia.
Gastrointestinal: Nausea, vomiting.
SERIOUS:
Ophthalmic: Optic Neuritis (1-6%; greatest risk at doses >25mg/kg/day, or >2 months treatment), red/green colour blindness.

ADVERSE EFFECTS: MONITORING

Opthalmic: Visual acuity and colour discrimination testing at baseline and 6 monthly, or more frequently if symptoms are reported.
Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Isoniazid: Possible increased risk of optic neuropathy caused by ethambutol.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:

Hypersensitivity: To ethambutol.
Ophthalmic: Optic neuritis and poor vision unless clinical judgement determines that it may be used.

Cautions:

Renal Disease: Reduce dose in severe renal impairment.
Young Children: Due to difficulty in testing eyesight and obtaining reports on symptomatic visual changes.
Elderly Patients: Due to the risks of ophthalmic adverse effects.

LABORATORY INFORMATION

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Sample Type: Serum.
Volume Required: 2 ml.
Sample Container: Plain (non SST).
Container Type: Any.
Availability: Office Hours.
Turnaround Time: 7 Days.

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IMIPENEM/CILASTATIN

Please note Imipenem is not licensed for the treatment of tuberculosis in the UK.
Imipenem is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

DOSAGE

[NOTE: Limited data on evidence for dosing in TB]
Adults (>50kg): 1g twice a day (intravenous).
Adults (<50kg): 15mg/kg twice a day (intravenous).
Children: 20-40mg/kg (max 2g) three times a day (intravenous).

In renal failure dose reduction may be necessary. *Please discuss with a pharmacist.*

PREPARATIONS

Parenteral: 500/500mg 250mg powder for solution for infusion.

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Dermatological: Rash & urticaria (3%), injection site pain.
Gastrointestinal: Nausea, vomiting, diarrhoea.
Haematologic: Thrombophlebitis (3%), eosinophillia (4%).
Hepatic: Transient mild increases in LFTs.
Renal: Transient increases in urea and/or serum creatinine concentrations (<2%).
SERIOUS:
Immunological: Anaphylaxis.
Infections: Clostridium difficile-associated diarrhoea and colitis.
Haematologic: Pancytopaenia, neutropaenia, leucopaenia, thrombocytopaenia, thrombocytosis (rare): agranulocytosis.
Neurological: Seizures.
Renal (rare): Acute renal failure, oliguria/anuria, polyuria, urine discoloration.

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Ganciclovir: Increased risk of convulsions.
Valproate: Reduced serum concentrations of valproate. Avoid concomitant use.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:

Hypersensitivity: Severe hypersensitivity to penicillins, carbapenems or cephalosporins.
Pregnancy.

Cautions:

TB Meningitis: Increased risk of seizures. Meropenem may be preferred.
CNS disease: Increased risk of seizures. Meropenem may be preferred.
Breast-feeding.
Renal impairment: Increased risk of seizures, reduce dose.
Liver disease: Monitor LFTs (risk of increase in transaminases, hepatic failure and fulminant hepatitis).

LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time for tests is usually a few days to a week but this can be reduced by calling ahead and informing the laboratory in advance.

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ISONIAZID

DOSAGE

Adults: 300mg once a day (oral or intravenous). Consider 5mg/kg once a day if low body weight (oral or intravenous); **or** for DOT supervised regimen: 15mg/kg three times a week (oral).

Children: 10mg/kg (max. 300mg) once a day (oral or intravenous); **or** for DOT supervised regimen: 15mg/kg (max. 900mg) three times a week (oral).
Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet.
Isoniazid should be taken 30-60 minutes before food, or 2 hours after food.

Low level isoniazid resistance:

Children: 15-20mg/kg once a day
Adults: Doses of 16-18mg/kg once a day have been used.

Pyridoxine can be used to reduce the risk of peripheral neuropathy in all patients taking isoniazid. In particular it should be prescribed for those most at-risk, such as patients with diabetes, alcohol abuse or malnutrition.

All patients prescribed high-dose isoniazid must also be prescribed pyridoxine as there is an increased risk of peripheral neuropathy.

PREPARATIONS

Oral: 100mg capsules.
Liquid (as a manufactured 'special' - unlicensed medicine).
Rifinah® 300/150 tablets (rifampicin 300mg, isoniazid 150mg).
Rifinah® 150/100 tablets (rifampicin 150mg, isoniazid 100mg).
Rifater tablets (rifampicin 120mg, isoniazid 50mg, pyrazinamide 300mg).
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).
Parenteral: 50mg/2mL ampoules.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: 3 – 5mg/mL *(Peak).*
Timing of sample:

- 2 hours post dose.
- Repeat at 6 hours if suspect delayed absorption**.**

Frequency of Levels:

- Drug levels need not be routinely measured.

Adherence Monitoring

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

INH strips can be used to measure adherence to isoniazid treatment.

- BBL Taxo INH Test Strips are absorbent paper strips that colour green, blue or purple in the presence of isonicotinic acid (a metabolite of isoniazid)
- BBL Taxo INH Test Control is an isoniazid-impregnated disc that will yield a positive result in the test procedure.

ADVERSE EFFECTS

COMMON:
Neurological: Peripheral Neuropathy.
Hepatic: Transient increases in LFTs.
SERIOUS:
Dermatological: Skin reactions e.g. urticaria (uncommon).
Haematologic: Agranulocytosis, megaloblastic anaemia, thrombocytopaenia.
Hepatic: Hepatotoxity (rare).
Immunological: Drug-induced lupus (rare).
Musculoskeletal: Arthralgia, rhabdomyolysis.
Neurological: Seizure, psychosis (rare).

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Carbamazepine: increased plasma concentration of carbamazepine. Increased risk of hepatoxicity.
Food: Reduced absorption. Take isoniazid 30-60 minutes before food, or 2 hours after food.
Food: Possible increased risk of headache, sweating, palpitations, flushing, hypotension when eating certain foods such as cheese, skipjack tuna or other tropical fish, or red wine. Usually, no dietary restrictions are required unless symptoms are experienced. This reaction is thought to be due to the high histamine or tyramine content of these foods and drink, resulting in an exaggerated histamine poisoning reaction due to inhibition of histamine metabolism by isoniazid, or the sympathomimetic action of tyramine due to inhibition of mono-amine oxidase by isoniazid.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To isoniazid.

Cautions:
Liver disease, alcohol abuse, hepatitis B co-infection: monitor LFTs closely.
Malnutrition, HIV co-infection, diabetes mellitus, and alcohol dependence: Increased risk of peripheral neuropathy; prescribe prophylactic pyridoxine.

LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies

depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
Sample Type: Plasma.
Volume Required: 2 ml.
Sample Container: Fluoride Oxalate.
Container Type: Any.
Availability: Office Hours.
Turnaround Time: 7 Days.

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

LEVOFLOXACIN

Please note levofloxacin is not licensed for the treatment of tuberculosis in the UK.

- Despite the lack of data establishing the safety and efficacy of fluoroquinolone use in children they continue to be used to treat MDR-TB in children of all ages in clinical practice. It is felt the benefit of treatment of MDR-TB outweighs the small potential risk of adverse reactions.
- If using a flouroquinolone we would recommend moxifloxacin as first choice agent followed by levofloxacin.

DOSAGE

Adults: 500mg to 1000mg once daily (oral or intravenous).
Children (>5 years): 10mg/kg once daily.
Children (<5 years): 7.5-10mg/kg once daily (limited experience).

Maximum dose: 750mg/ day

PREPARATIONS

Oral: 250mg, 500mg tablets.
Parenteral: 400mg/100mL solution for infusion.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: 8 – 12mg/L *(peak).*
0.5 – 2 mg/L *(trough).*

Timing of sample:

- 2 hours post oral dose (or 1 hour after the end of intravenous infusion).
- Repeat at 6 hours if suspect delayed absorption**.**
- Consider taking a trough level.

Frequency of Levels:

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Gastrointestinal: Nausea, vomiting, diarrhoea.
Other: Dizziness, headache.
Hepatic: Transient increases in LFTs.
SERIOUS:
Cardiovascular: QTc prolongation (rare; more common in hypokalaemia, and predisposing cardiac conditions).
Dermatological: Stevens-Johnson syndrome or toxic epidermal necrolysis (rare).
Metabolic: Hypoglycaemia (in patients on hypoglycaemic drugs, uncommon).
Haematologic: Eosinophilia, leucopaenia (uncommon), thrombocytopaenia, neutropaenia (rare).
Hepatic: Acute hepatitis (rare).

Immunological: Anaphylaxis, immune hypersensitivity (uncommon).
Musculoskeletal: Tendon inflammation and rupture (see contra-indications below).
Neurological: Seizures (caution in patients with CNS disorders).
Renal: Renal impairment (rare).

ADVERSE EFFECTS: MONITORING

ECG: Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
LFTs, U&Es and FBC should also be monitored sporadically throughout treatment. No specific frequency recommendations but generic monitoring guidelines should be frequent enough.
Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Amiodarone: Increased risk of ventricular arrhythmia.
Antacids: Reduced absorption of levofloxacin.
Anticoagulants: Possible enhanced effect of coumarins (e.g. warfarin) and phenindione.
Ciclosporin: Increased risk of nephropathy.
Iron: Reduced absorption of levofloxacin.
NSAIDS: Possible increased risk of convulsions.
Theophylline: Increased risk of convulsions. Reduce dose of theophylline and monitor levels.
Zinc: Reduced absorption of levofloxacin.
Drugs known to prolong the QT interval: use with caution in patients taking Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To levofloxacin or other quinolones.
Epilepsy/Seizure Activity: May induce convulsions in patients with or without history of convulsions, use with caution if epileptic or conditions predisposing seizures.
Tendon Damage: Rarely reported but damage or rupture may occur within 48 hours of treatment and several months after stopping treatment. Increased risk in patients with a history of tendon disorders related to quinolone use, aged over 60 years, concomitant use of corticosteroids. Cease all quinolone treatment if tendinitis suspected.
Pregnancy: Avoid in pregnancy, animal studies have shown quinolones cause arthropathy.
Breast Feeding: Avoid, present in milk in animal studies.
Children: Levofloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in TB with caution. Arthropathy has developed in weight-bearing joints in young animals.

Cautions:
May impair performance of skilled tasks such as driving
Long QT Syndrome: Can prolong QT interval. Use with caution in patients with risk factors for QT interval prolongations.
Myasthenia Gravis: Risk of exacerbation.
G6PD deficiency: Risk of haemolytic reactions when treated with quinolones.
Liver Disease: Monitor LFTs.
Renal Disease: Reduce dose in renal impairment.

Sunlight: Risk of photosensitivity reaction.
Serious bullous skin reactions: Risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.
Peripheral Neuropathy: Sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness.

LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
Sample Type: Serum.
Volume Required: Ideally 2ml (min 0.1mL).
Sample Container: Plain glass or plastic (non SST).
Container Type: Any.
Availability: NS.
Turnaround Time: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post
The sample must be heat-treated before dispatch if HIV positive.
Please telephone at least one day in advance of the sample.

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

LINEZOLID

Please note linezolid is not licensed for the treatment of tuberculosis in the UK.
Linezolid is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

DOSAGE

By mouth or intravenous infusion.
Adults, and adolescents: 600mg once a day (oral or intravenous).
Children (age 1 week – 12 years): Based on WHO recommendations: 10mg/kg twice a day, or once a day if age >10years.

PREPARATIONS

Oral: 600mg tablets.
100mg/5mL granules for oral suspension.
Parenteral: 600mg/300mL solution for infusion.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: 12-24 mg/L (*peak).*
Timing of sample:

- 2 hours post-oral dose or 1 hour post IV infusion.

Frequency of Levels:

- No need for regular monitoring.

ADVERSE EFFECTS

COMMON:
Gastrointestinal: Diarrhoea (4%), nausea (3%), vomiting.
Neurological: Headache (2%).
Infections: Candidiasis, particularly oral and vaginal (1%).
Hepatic: Transient increases in LFTs.
SERIOUS:
Metabolic: Lactic acidosis.
Dermatological: Urticaria, rash; (rare): Bullous disorders such as Stevens-Johnson syndrome & toxic epidermal necrolysis.
Haematologic: Myelosupression.
Neurological: Peripheral neuropathy, seizure, serotonin syndrome.
Ophthalmic: Optic neuropathy.

ADVERSE EFFECTS: MONITORING

FBC: Weekly for the 2 months. Consider reducing to monthly if stable thereafter.
VISUAL ACUITY & COLOUR DISCRIMINATION: Encourage patients to report any changes to their vision and refer to ophthalmology if any reported. Routine monitoring 6 monthly.

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Clarithromycin: increases linezolid serum levels with risk of toxicity (consider drug level monitoring).

Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, linezolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, $5HT_1$ agonists ('triptans'), tricyclic antidepressants, sympathomimetics, dopaminergics, buspirone, pethidine and possibly other opioid analgesics.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To linezolid.
Mono-amine oxidase inhibitors: Avoid concomitant use of other drugs that inhibit monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any such medicinal product.
Avoid in patients with: Uncontrolled hypertension, phaechromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia or acute confusional states.
Breast-feeding

Cautions:
Pregnancy
Avoid: Consumption of large amounts of tyramine rich foods.
Epilepsy/history of seizures: Increased risk of convulsions.
Renal impairment: No dose adjustment is required. However two primary metabolites may accumulate in severe renal impairment, but the clinical significance of this is unknown. Use with caution and monitor for adverse effects closely (see above).
Liver disease: No dose adjustment is required. However due to limited clinical data, use with caution and monitor for adverse effects closely (see above).
Peripheral and optic neuropathy: Patients should be advised to report symptoms of visual impairment.

LABORATORY INFORMATION

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Sample Type: Serum.
Volume Required: 2ml (min 0.1mL).
Sample Container: Plain plastic (non SST).
Container Type: Any.

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Availability: NS
Turnaround Time: Telephoned same day if received 9am-3pm Mon-Fri. Written confirmation report will be sent by 1st Class post.
The sample must be heat-treated before dispatch if HIV positive.
Please telephone at least one day in advance of the sample.

The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

MEROPENEM

Please note meropenem is not licensed for the treatment of tuberculosis in the UK.
Meropenem is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

DOSAGE

Adults:

- 1g three times a day (intravenous).
- NB. Should be used in combination with clavulanate in the form of a combination of co-amoxiclav 625mg (500 mg/125 mg) three times a day.

Children:

- Adult dose in weights over 50Kg.
- 1 month–12 years 10–20 mg/kg every 8 hours.

Maximum dose: 400mg/day

In renal failure dose reduction may be necessary. *Please discuss with a pharmacist.*

PREPARATIONS

Parenteral: 500mg, 1g powder for solution for injection or infusion.

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Dermatological: Rash, pruritis, injection site inflammation (2%).
Gastrointestinal: Abdominal pain, diarrhoea (3-7%), nausea & vomiting (3%).
Haematological: Thrombocythaemia.
Hepatic: Transient increases in LFTs.
Neurological: Headache (2-8%).
SERIOUS:
Dermatological: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Haematological: Eosinophilia, thrombocytopaenia, leucopaenia, neutropaenia.
Immunological: Anaphylaxis, angioedema.
Infective: Clostridium difficile-associated diarrhoea and colitis.
Neurological: Seizures.

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Valproate: Reduced serum concentrations of valproate. Avoid concomitant use.
Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To carbapenems.
Hypersensitivity: Severe hypersensitivity to penicillins or cephalosporins.
Pregnancy

Cautions:
Breast-feeding.
Liver disease: Monitor LFTs (hepatic dysfunction with cholestasis and cytolysis).

LABORATORY INFORMATION

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The information we have provided here is not exhaustive and is aimed as a practical tool for aid in the management of patients with MDR-TB. A list of references is included in a separate document however the majority of these recommendations are based on expert consensus. Feedback is welcomed. This is a drug monitoring guideline, for treatment guidance please refer to the WHO treatment guideline http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf and the BTS MDR-TB Clinical Advisory Service http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/mdrtb-clinical-advice-service.aspx.

MOXIFLOXACIN

Please note moxifloxacin is not licensed to treat tuberculosis in the UK.

- Despite the lack of data establishing the safety and efficacy of fluoroquinolone use in children they continue to be used to treat MDR-TB in children of all ages in clinical practice. It is felt the benefit of treatment of MDR-TB outweighs the small potential risk of adverse reactions.
- If using a flouroquinolone we would recommend moxifloxacin as first choice agent followed by levofloxacin.

DOSAGE

Adults: 400mg once a day (oral or intravenous).
Children: 7.5 – 10mg/kg once a day (oral).

PREPARATIONS

Oral: 400mg tablets.
Parenteral: 400mg/250mL solution for infusion.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: 2.5 – 4mg/L (*peak).*
Timing of sample:

- 2 hours post dose.
- Repeat at 6 hours if suspect delayed absorption.

Frequency of Levels:

- No need for regular monitoring.

ADVERSE EFFECTS

COMMON:
Cardiovascular: QTc prolongation (more common in hypokalaemia, proarrhythmic conditions, in combination with other drugs that prolong the QT interval such as ondansetron).
Gastrointestinal: Nausea, vomiting, diarrhoea.
Hepatic: Transient increases in LFTs.
Other: Dizziness, headache.
SERIOUS:
Cardiovascular: QTc prolongation (rare; more common in hypokalaemia, and predisposing cardiac conditions).
Dermatological: Stevens-Johnson syndrome or toxic epidermal necrolysis (rare).
Haematological: (Uncommon) agranulocytosis, aplastic anaemia, haemolytic anaemia, thrombocytopaenia.
Hepatic: Acute hepatitis (rare).
Immunological: Anaphylaxis, immune hypersensitivity (uncommon).
Metabolic: Hypoglycaemia (in patients on hypoglycaemic drugs, uncommon).
Musculoskeletal: Tendon inflammation and rupture (see contra-indications below).

Neurological: Seizures: (Caution in patients with CNS disorders).
Renal: Renal impairment (rare).
Respiratory: Extrinsic allergic alveolitis (rare).
Other: Serum sickness (rare).

ADVERSE EFFECTS: MONITORING

ECG: Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
LFTs, U&Es and FBC should be monitored sporadically throughout treatment. No specific frequency recommendations, please see generic monitoring guidelines for further information.
Blood glucose should be monitored regularly in patients with diabetes (risk of hypoglycaemia).
Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Antacids: Reduced absorption of moxifloxacin.
Anti-arrhythmics: Increased risk of ventricular arrhythmias with amiodarone or disopyramide.
Antidepressants: Increased risk of ventricular arrhythmias with tricyclics.
Antimalarials: Increased risk of ventricular arrhythmias with chloroquine, hydroxychloroquine, mefloquine, quinine.
Antipsychotics: Increased risk of ventricular arrhythmias with benperidol, droperidol, haloperidol, phenothiazines, pimozide and zuclopenthixol.
Antivirals: Increased risk of ventricular arrhythmias with saquinavir.
Beta-blockers: Increased risk of ventricular arrhythmias with sotalol.
Ciclosporin: Increased risk of nephropathy.
Erythromycin: Increased risk of ventricular arrhythmias when erythromycin given via intravenous route.
Iron: Reduced absorption of moxifloxacin.
NSAIDS: Possible increased risk of convulsions.
Pentamidine: Increased risk of ventricular arrhythmias.
Theophylline: Increased risk of convulsions. Reduce dose of theophylline and monitor levels.
Zinc: reduced absorption of moxifloxacin.
Drugs known to prolong the QT interval: use with caution in patients taking Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To moxifloxacin or other quinolones.
Tendon Damage: Rarely reported but damage or rupture may occur within 48 hours of treatment and several months after stopping treatment. Increased risk in patients with a history of tendon disorders related to quinolone use, aged over 60 years, concomitant use of corticosteroids. Cease all quinolone treatment if tendinitis suspected.
Pregnancy: Avoid in pregnancy, animal studies have shown quinolones cause arthropathy.
Breast Feeding: Avoid, present in milk in animal studies.
Children: Moxifloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in TB with caution. Arthropathy has developed in weight-bearing joints in young animals.

Cardiovascular: Due to the risk of QT prolongation with moxifloxacin, is should not be used in patients with congenital or documented acquired QT prolongation, clinically relevant bradycardia, clinically relevant heart failure with reduced left-ventricular ejection fraction, previous history of symptomatic arrhythmias, or electrolyte disturbances, particularly in uncorrected hypokalaemia.
Liver disease: Chronic liver disease; particularly Child Pugh severity score C and in those patients with transaminase levels 5 fold greater than the upper limit of normal. Consider using Levofloxacin as an alternative in these patients.
Concurrent use with other drugs that prolong the QT interval.

Cautions:
May impair performance of skilled tasks such as driving
Myasthenia Gravis: Risk of exacerbation.
G6PD deficiency: Risk of haemolytic reactions when treated with quinolones.
Sunlight: Risk of photosensitivity reaction.
Epilepsy/Seizure Activity: May induce convulsions in patients with or without history of convulsions, use with caution if epileptic or conditions predisposing seizures.
Liver Disease: Cases of fulminant hepatitis potentially leading to liver failure (including fatal cases) have been reported.
Serious bullous skin reactions: Risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.
Peripheral Neuropathy: Sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness.

LABORATORY INFORMATION

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Sample Type: Serum.
Volume Required: 2ml (min 0.1mL).
Sample Container: Plain glass or plastic (non SST).
Container Type: Any.
Availability: NS.
Turnaround Time: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.
Please telephone at least one day in advance of the sample.

OFLOXACIN

Please note ofloxacin is not licensed to treat tuberculosis in the UK.

- Despite the lack of data establishing the safety and efficacy of fluoroquinolone use in children they continue to be used to treat MDR-TB in children of all ages in clinical practice. It is felt the benefit of treatment of MDR-TB outweighs the small potential risk of adverse reactions.
- If using a flouroquinolone we would recommend moxifloxacin as first choice agent followed by levofloxacin.

DOSAGE

Adults: 400mg twice a day (oral or intravenous).
Children: 15-20 mg/kg (max. 400mg) once daily (oral).

PREPARATIONS

Oral: 200mg, 400mg tablets.
Parenteral: 200mg/100ml solution for infusion.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: Unknown.
Timing of sample:

- 2 hours post oral dose (or 1 hour after the end of intravenous infusion).
- Repeat at 6 hours if suspect delayed absorption**.**
- Consider taking a trough level.

Frequency of Levels:

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Gastrointestinal: Nausea, vomiting, diarrhoea.
Other: Dizziness, headache.
Hepatic: Transient increases in LFTs.
SERIOUS:
Cardiovascular: QTc prolongation (rare; more common in hypokalaemia, and predisposing cardiac conditions).
Dermatological: Stevens-Johnson syndrome or toxic epidermal necrolysis (rare).
Metabolic: Hypoglycaemia (in patients on hypoglycaemic drugs, uncommon).
Haematological: Eosinophilia, leucopaenia (uncommon), thrombocytopaenia, neutropaenia (rare).
Hepatic: Acute hepatitis (rare).
Immunological: Anaphylaxis, immune hypersensitivity (uncommon).
Musculoskeletal: Tendon inflammation and rupture (see contra-indications below).
Neurological: Seizures (caution in patients with CNS disorders).
Renal: Renal impairment (rare).

ADVERSE EFFECTS: MONITORING

ECG: Baseline, 2 weeks then every 3 months and after the addition of any new medication that is known to prolong QT.
LFTs, U&Es and FBC should also be monitored sporadically throughout treatment. No specific frequency recommendations but generic monitoring guidelines should be frequent enough.
Blood glucose should be monitored regularly in patients with diabetes (risk of hypoglycaemia).

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Antacids: Reduced absorption of ofloxacin.
Anticoagulants: Possible enhanced effect of coumarins (e.g. warfarin).
Ciclosporin: Increased risk of nephropathy.
Iron: Reduced absorption of ofloxacin.
NSAIDS: Possible increased risk of convulsions.
Theophylline: Increased risk of convulsions. Reduce dose of theophylline and monitor levels.
Zinc: Reduced absorption of ofloxacin.
Drugs known to prolong the QT interval: Use with caution in patients taking Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To levofloxacin or other quinolones.
Epilepsy/Seizure Activity: May induce convulsions in patients with or without history of convulsions, use with caution if epileptic or conditions predisposing seizures.
Tendon Damage: Rarely reported but damage or rupture may occur within 48 hours of treatment and several months after stopping treatment. Increased risk in patients with a history of tendon disorders related to quinolone use, aged over 60 years, concomitant use of corticosteroids. Cease all quinolone treatment if tendinitis suspected.
Pregnancy: Avoid in pregnancy, animal studies have shown quinolones cause arthropathy.
Breast Feeding: Avoid, present in milk in animal studies.
Children: Levofloxacin is contra-indicated in the UK for use in children or growing adolescents. Use in TB with caution. Arthropathy has developed in weight-bearing joints in young animals.
G6PD deficiency: Risk of haemolytic reactions when treated with quinolones.

Cautions:
May impair performance of skilled tasks such as driving.
Long QT Syndrome: Can prolong QT interval. Use with caution in patients with risk factors for QT interval prolongations.
Myasthenia Gravis: Risk of exacerbation.
Liver Disease: Monitor LFTs.
Renal Disease: Reduce dose in renal impairment.
Sunlight: Risk of photosensitivity reaction
Serious bullous skin reactions: Risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.

Peripheral Neuropathy: Sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness.

LABORATORY INFORMATION

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Sample Type: Serum.
Volume Required: 2ml (min 0.1mL).
Sample Container: Plain glass or plastic (non SST).
Container Type: Any.
Availability: NS.
Turnaround Time: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.
Please telephone at least one day in advance of the sample.

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P-AMINOSALICYLIC ACID (PAS / PASER®)

Please note p-aminosalicylic acid is not licensed in the UK.

DOSAGE

Adults: 150mg/kg/day in two to four divided doses (oral). Usual dose is 8-12g per day.
Children: 50mg/kg/day (max 12g) in 2-3 divided doses. However doses of 200-300mg/kg/day have been used.

The Paser® brand of p-aminosalicyclic acid should be prescribed, since these have an acid-resistant coating, preventing stomach gastric acid from degrading the drug to m-aminophenol, a known hepatotoxin. The enteric coating therefore prevents acid degradation of the drug in the stomach, and releases the drug in the small intestine where neutral pH causes fast dissolution of the enteric coating.

The granules of p-aminosalicyclic acid should be sprinkled on to an acidic food such as applesauce or yogurt, or mixed in acidic juices such as tomato, grape, grapefruit, cranberry, apple, or orange. The granules must not be chewed, and must not be mixed with neutral pH food or drink.

Take p-aminosalicyclic acid with food to reduce gastrointestinal adverse effects.

P-aminosalicyclic acid is only available in 4g sachets. In order to give part of a sachet, flatten out the packet, so that the granules are spread evenly in the packet. Cut the packet to the approximate dose required – i.e. cut into halves for 2g doses, and into quarters for 1g doses. Discard the remaining unused portions of the packet.

PREPARATIONS

Oral: 4g granules per sachet (unlicensed medicine).

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Gastrointestinal: Nausea, vomiting, diarrhoea, abdominal pain.
Immunological: Hypersensitivity reactions (5-10%) including rash & fever.
SERIOUS:
Metabolic: Hypothyroidism.
Haematological: Haemolytic anaemia (patients with G6PD deficiency), agranulocytosis, eosinophilia, leucopaenia, and thrombocytopaenia.
Hepatic: Acute hepatitis (rare).

ADVERSE EFFECTS: MONITORING

TFTs: 3 monthly (if being given in combination with prothionamide, increase to monthly)
Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Antacids: Fast dissolution of acid-resistant coating, resulting in early release of p-aminosalicyclic acid into the stomach. However as the stomach gastric acid will have been neutralised, degradation of p-aminosalicyclic acid to m-aminophenol will not occur. No dose adjustments required, however administration of p-aminosalicyclic acid in acidic food or drinks is not required.
Digoxin: Possible decrease in digoxin absorption. Monitor digoxin serum concentrations.
Prothionamide: increased risk of hypothyroidism, possible increased risk of hepatoxicity.
Rifamycins: reduced absorption of rifamycins. Give 8-12 hours apart.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To p-aminosalicylic acid, or to aspirin.
Renal Disease: Manufacturer advises to avoid in severe renal failure, as an inactive metabolite is renally excreted. May worsen acidosis and/or crystalluria in severe renal failure.

Cautions:
Pregnancy: Use in pregnancy has not been studied/
Breast-feeding: P-aminosalicylic acid is secreted into breast milk at 1/70th of the maternal plasma concentration.

LABORATORY INFORMATION

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PROTHIONAMIDE

Please note prothionamide is not licensed in the UK.
Prothionamide is a thioamide, and is considered to be interchangeable with ethionamide (currently not available in the UK).

DOSAGE

Adult & paediatric doses are the same per kg.
Adults: 7.5-10mg/kg (max 500mg) twice a day (oral). Usual dose is 500 to 750mg (max. 1000mg) per day.
Children: 7.5-10mg/kg (max 500mg) once or twice a day (oral). Usual dose is 500 to 750mg (max. 1000mg) per day.
WHO advise a once daily dosing regimen if tolerated (to maximise peak levels), but twice daily regimens may be required if unable to tolerate.

Prothionamide should be taken with or after meals to reduce gastrointestinal adverse effects. Most patients also require gradual dose escalation, i.e. for adults: initially 250mg once a day, increasing by 250mg every 3 to 5 days.

All patients must be prescribed pyridoxine whilst receiving prothionamide. The usual adult dose ranges from 50 to 100mg daily, up to 50mg per 250mg of prothionamide.

PREPARATIONS

Oral: 250mg tablets (unlicensed medicine).

DRUG LEVEL MONITORING

- Not required.

ADVERSE EFFECTS

COMMON:
Hepatic: Transient increases in LFTs.
Gastrointestinal: Nausea, vomiting, diarrhoea, anorexia, excessive salivation, metallic taste, stomatitis, and abdominal pain.
SERIOUS:
Hepatic: Acute hepatitis (rare).
Neurological (maybe increased in combination with cycloserine): Dizziness, encephalopathy, peripheral neuropathy.
Ophthalmic: Optic Neuritis (rare).
Psychiatric: Psychotic disturbances, depression.
Metabolic: Gynaecomastia, hypoglycaemia, hypothyroidism.

ADVERSE EFFECTS: MONITORING

TFTs: 3 monthly (if being given in combination with PAS increase to monthly).
Blood glucose should be monitored regularly in patients with diabetes (risk of hypoglycaemia).
Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Cycloserine: possible increased risk of neurotoxicity.
Isoniazid: increased serum concentrations.
P-aminosalicylic acid: increased risk of hypothyroidism, possible increased risk of hepatoxicity.
Rifampicin: increased risk of hepatoxicity.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To ethionamide or prothbionamide.
Severe Liver Disease: Due to risk of further hepatotoxicity.
Pregnancy.
Porphyria.

Cautions:
Renal Disease: Reduce dose in severe renal impairment.
Breast-feeding.

LABORATORY INFORMATION

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PYRAZINAMIDE

DOSAGE

Adults (<50kg): 1.5g once a day (oral); **or** for DOT supervised regimen: 2g three times a week (oral).
Adults (50kg+): 2g once a day (oral); **or** for DOT supervised regimen: 2.5g three times a week (oral).
Children: 35mg/kg (max. 1.5g if <50kg; 2g if 50kg+) once a day (oral); **or** for DOT supervised regimen: 50mg/kg (max. 2g if <50kg; 2.5g of 50kg+) three times a week (oral). (*Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet*)
Pyrazinamide may be taken with or without food.

PREPARATIONS

Oral: 500mg tablets.
Liquid (as a manufactured 'special' - unlicensed medicine).
Rifater tablets (rifampicin 120mg, isoniazid 50mg, pyrazinamide 300mg).
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: 20 – 40mg/L*(Peak).*
Timing of sample:

- 2 hours post dose.
- Repeat at 6 hours if suspect delayed**.**

Frequency of Levels:

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Hyperuricaemia.
Arthralgia.
Gastrointestinal: Anorexia, nausea, vomiting.
Hepatic: Transient increases in LFTs.
Dermatological: Rash.
SERIOUS:
Haematological: Sideroblastic anaemia (rare), thrombocytopaenia (rare).
Hepatotoxity.

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Probenecid: Pyrazinamide antagonises the effect of probenecid.

Sulfinpyrazone: Pyrazinamide antagonises the effect of sulfinpyrazone.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To pyrazinamide.
Cautions:
Gout.
Liver Disease.

LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.
Sample Type: Serum.
Volume Required: 2 ml.
Sample Container: Plain (non SST).
Container Type: Any.
Availability: Office Hours.
Turnaround Time: 7 Days.

RIFABUTIN

DOSAGE

Adult: 5mg/kg once a day (oral). Usual dose is 300mg, although doses of up to 450mg are sometimes used.
Children: 5mg/kg once a day (limited data).

PREPARATIONS

Oral: 150mg capsules.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: 0.3 – 0.9mg/L *(Peak)*
Timing of sample:

- 3 hours post dose.
- Repeat at 7 hours if suspect delayed**.**

Frequency of Levels:

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Reddish discolouration of urine, sweat, sputum, tears.
Haematological: Neutropaenia.
Gastrointestinal: Anorexia, nausea, vomiting, heartburn.
Hepatic: Transient increases in LFTs.
Opthalmic: Uveitis.
Dermatological: Rash.
SERIOUS:
Haematological: Anaemia, neutropaenia, thrombocytopaenia.

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Anti-arrhythmics: Accelerated metabolism of disopyramide.
Anticoagulants: Accelerated metabolism of coumarins (e.g. warfarin).
Anti-diabetics: Accelerated metabolism of tolbutamide and sulfonylureas (reduced effect).
Antiepileptics: Reduced plasma concentration of carbamazepine and phenytoin.
Antifungals: increased serum concentration of rifabutin with fluconazole, posaconazole, and voriconazole, and possibly itraconazole. Reduced serum concentrations of itraconazole, posaconazole and voriconazole. If benefit outweighs the risk, monitor antifungal serum

concentrations (increase dose of voriconazole); and monitor for rifabutin adverse effects such as leukopaenia and uveitis.
Antipsychotics: Possible reduced plasma concentration of aripiprazole.
Antivirals: *Please seek advice from an HIV physician before considering starting rifampicin in patients on anti-retrovirals due to the frequency of drug interactions:* Increased serum concentration of rifabutin when given with: amprenavir, Fosamprenavir/ritonavir, Lopinavir/ritonavir, Ritonavir, and Tipranavir/ritonavir. Reduce dose of rifabutin. Consider alternative protease inhibitor to ritonavir.
Atovaquone: Reduced plasma concentrations of both rifabutin and atovaquone.
Contraceptives: Accelerated metabolism of oestrogens and progestogens (reduced contraceptive effect).
Corticosteroids: Possible accelerated metabolism of corticosteroids (reduced effect).
Hormone Replacement Therapy (HRT): Rifampicin would be expected to reduce the efficacy of HRT
Macrolides: Increased risk of neutropaenia with azithromycin; increased plasma concentration of rifabutin when taken with clarithromycin and possibly erythromycin (reduce dose of rifabutin).
P-aminosalicylic acid: Reduced absorption of rifamycins. Give 8-12 hours apart.
Sirolimus: Reduced in plasma concentration of sirolimus.
Tacrolimus: Reduced in plasma concentration of tacrolimus.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To rifabutin or other rifamycins.
Pregnancy.
Breast-feeding.
Cautions:
Liver Disease: Use cautiously and monitor LFTs.
Renal Disease: Reduce dose in severe renal impairment.

LABORATORY INFORMATION

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Sample Type: Serum.
Volume Required: 2 ml.
Sample Container: Plain (non SST).
Container Type: Any.
Availability: Office Hours.
Turnaround Time: 7 Days.

RIFAMPICIN

DOSAGE

Adults (<50kg): 450mg once a day (oral or intravenous); **or** for DOT supervised regimen: 600mg three times a week (oral).
Adults (50kg+): 600mg once a day (oral or intravenous); **or** for DOT supervised regimen: 900mg three times a week (oral).
Children: 15mg/kg (max. 450mg if <50kg; 600mg if 50kg+) once a day (oral or intravenous); **or** for DOT supervised regimen: 15mg/kg (max. 900mg) three times a week (oral). (*Doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of capsule*).

Rifampicin should be taken 30-60 minutes before food, or 2 hours after food.

PREPARATIONS

Oral: 150mg, 300mg capsules.
100mg/5mL syrup.
Rifinah® 300/150 tablets (rifampicin 300mg, isoniazid 150mg).
Rifinah® 150/100 tablets (rifampicin 150mg, isoniazid 100mg).
Rifater tablets (rifampicin 120mg, isoniazid 50mg, pyrazinamide 300mg).
Voractiv® tablets (rifampicin 150mg, isoniazid 75mg, pyrazinamide 400mg, ethambutol 275mg).
Parenteral: 600mg powder for reconstitution.

DRUG LEVEL MONITORING

Indications for monitoring:

- Known or suspected malabsorption.
- Poor treatment response.

Target Level: 8 – 24mg/L *(Peak).*
Timing of sample:

- 2 hours post dose.
- Repeat at 6 hours if suspect delayed.

Frequency of Levels:

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Reddish discolouration of urine, sweat, sputum, tears.
Gastrointestinal: Anorexia, nausea, vomiting, heartburn.
Hepatic: Transient increases in LFTs.
Flu-like syndrome.
SERIOUS:
Haematological: Agranulocytosis (rare), Haemolytic anaemia (rare, usually intermittent therapy), Thrombocytopaenia (rare, usually high-dose / intermittent therapy).
Hepatic: Hepatotoxicity (rare).

Renal: Nephrotoxicity (rare).

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTONS

Analgesics: Accelerated metabolism of opiates, resulting in reduced effect (e.g. alfentanyl, codeine, fentanyl, methadone, morphine and possibly oxycodone).
Antacids: Reduced absorption of rifampicin.
Anti-arrhythmics: Accelerated metabolism of disopyramide.
Antibacterials: Reduced plasma concentrations of chloramphenicol, clarithromycin, dapsone, doxycycline, linezolid, trimethoprim.
Anticoagulants: Reduced plasma concentration of apixaban, dabigatran and rivaroxaban; accelerated metabolism of coumarins (e.g. warfarin).
Anti-diabetics: Accelerated metabolism of tolbutamide and sulfonylureas (reduced effect); reduced effect of linagliptan, netaglinide and repaglinide.
Antiepileptics: Reduced plasma concentration of lamotrigine and phenytoin; phenobarbital possibly reduces plasma concentration of rifampicin.
Antifungals: Accelerated metabolism of ketoconazole, fluconazole, itraconazole, posaconazole, terbinafine and voriconazole (reduced plasma concentrations; avoid concomitant use of rifampicin with itraconazole or voriconazole). Rifampicin initially increases then decreases caspofungin levels (consider increasing caspofungin dose).
Antimalarials: Reduced plasma concentration of mefloquine (avoid use) and quinine.
Antipsychotics: Accelerated metabolism of haloperidol and possibly aripiprazole and clozapine.
Antivirals: Reduced plasma concentration of atazanavir, darunavir, fosamprenavir, lopinavir, nelfinavir, nevirapine, rilpivirine, saquinavir and telaprevir (avoid concomitant use), and possibly abacavir, boceprevir, ritonavir, and tipranavir. Rifampicin also reduces plasma concentration of efavirenz (increase dose of efavirenz), maraviroc and raltegravir (consider increasing doses). Accelerated metabolism of indinavir (avoid concomitant use).
Atovaquone: Reduced plasma concentrations of atovaquone; increased plasma concentration of rifampicin (avoid concomitant use).
Bosentan: Reduced plasma concentration of bosentan (avoid concomitant use).
Calcium-channel blockers: Accelerated metabolism of diltiazem, nifedipine, nimodipine and verapamil (significant reduction in plasma concentrations), and possibly isradipine and nicardipine.
Ciclosporin: Accelerated metabolism of ciclosporin (reduced plasma concentration.
Contraceptives: Accelerated metabolism of oestrogens and progestogens (reduced contraceptive effect). Avoid use of combined hormonal contraception (oral, patch or vaginal ring), progestogen-only contraception (pill and implant). Suitable alternatives include barrier methods, copper-bearing intrauterine system, or progestogen-only injectable (depot medroxyprogesterone acetate, norethisterone enantate, or levonorgestrel-releasing intrauterine system, which can be continued at the usual dose and dosing/replacement interval of 12 weeks, 8 weeks and 5 years, respectively).
Corticosteroids: Accelerated metabolism of corticosteroids (reduced effect).
Diuretics: Reduced plasma concentration of eplerenone (avoid concomitant use).
Hormone Replacement Therapy (HRT): Rifampicin would be expected to reduce the efficacy of HRT.
Mycophenolate: Reduced plasma concentration of active metabolite of mycophenolate.
P-aminosalicylic acid: Reduced absorption of rifamycins. Give 8-12 hours apart.
Ranolazine: Reduced plasma concentration of ranolazine (avoid concomitant use).
Sirolimus: Reduced in plasma concentration of sirolimus.

Tacrolimus: Reduced in plasma concentration of tacrolimus.
Tadalafil: Reduced plasma concentration of tadalafil (avoid concomitant use).
Theophylline: Accelerated metabolism of theophylline (reduced plasma concentration).
Ticagrelor: Reduced plasma concentration of ticagrelor.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: To rifampicin or other rifamycins.
Liver Disease: Avoid if jaundiced.
Drug Interactions: Avoid concomitant use with saquinavir or ritonavir.
Cautions:
Liver Disease: Use cautiously and monitor LFTs; hyperbilirubinaemia may occur early in treatment in some patients due to competition between rifampicin and bilirubin for hepatic excretion.

LABORATORY INFORMATION

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Sample Type: Serum.
Volume Required: Please note that rifampicin binds to glass and plastics and therefore there may be a significant loss of drug if a small volume of serum is dispatched in a relatively large container. Please try and fill the container to 2/3 -3/4 its capacity).
Sample Container: Plain glass or plastic (non SST).
Container Type: Any.
Availability: Office Hours.
Turnaround Time: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.
Please telephone at least one day in advance of the sample.

STREPTOMYCIN

Please note streptomycin is not licensed in the UK.
Streptomycin is not usually recommended for the treatment of MDRTB, as half of UK cases are resistant to streptomycin.

PREPARATIONS

Parenteral: 1g powder for reconstitution for injection (unlicensed medicine).

DOSAGE

For intramuscular administration only. There is experience of using streptomycin as an intravenous infusion, but the prescriber should ensure the streptomycin preparation used is suitable for intravenous administration.
Streptomycin is usually given once daily for an initial period (usually at least two months), then the frequency may be reduced to three times weekly.

Adults: **15mg/kg daily** (usual maximum 1g daily, but can be increased if necessary in large muscular adults). After initial period: **15mg/kg three times per week**.
Age >59 years: **10mg/kg daily** (maximum 750mg daily). After initial period: **15mg/kg three times per week**.

Renal failure: 12-15mg/kg TWO to THREE times a week. *Please discuss with a pharmacist.*

Obesity: Use ideal body weight plus 40% of the excess weight in markedly obese patients. The adjusted dose is due to the decreased distribution of extracellular fluids in adipose tissues.

- Male ideal body weight (kg) = 50 + (2.3 x height in cm above 152.4)/2.54
- Female ideal body weight (kg) = 45.5 + (2.3 x height in cm above 152.4)/2.54

Adjust dose and/or frequency according to serum streptomycin concentration (see below).

Children: **15mg/kg daily** (usual maximum 1g daily). After initial period: **15mg/kg three times per week**.
Adjust dose and/or frequency according to serum streptomycin concentration (see below).

DRUG LEVEL MONITORING

Indications for monitoring:

- Ensure therapeutic dose
- Ensure renal clearance, especially in at risk patients (e.g. renal impairment, elderly)

Target Level: <5mg/L (*trough*)
25 – 35mg/L (*peak)*

Timing of sample:

- Pre dose
- 60mins after infusion ends

Frequency of Levels:

- Peak serum level in first week, repeat if poor response.
- Trough serum levels weekly for 4 weeks, fortnightly for 4 weeks, then monthly if stable

ADVERSE EFFECTS

COMMON:
Nephrotoxicity: Accumulation if renal impairment.
Ototoxicity: Irreversible vestibulocochlear nerve damage.
Hypersensitivity skin reactions: Rashes, urticaria, erythroderma.
Drug-induced eosinophillia (Usually subsides with intermittent dosing).
SERIOUS:
Endocrine: Hypocalcaemia, hypomagnesaemia, and hypokalaemia
Immunological: Anaphylaxis (uncommon).
Neurological: Neuromuscular blockade and respiratory paralysis (more common in neuromuscular disease; usually dose-related and self-limiting).
Audiological: Ototoxicity - auditory > vestibular (higher with prolonged use and older age).
Renal: Nephrotoxicity (higher with prolonged use).

ADVERSE EFFECTS: MONITORING

Renal, **auditory** and **vestibular** monitoring is essential

Renal function: Month 1 = twice weekly
Month 2 = weekly
Month 3: End of treatment with an aminoglycoside = 2 weekly
Consider reducing to monthly after cessation of treatment with aminoglycoside, if renal function remains stable.
Consider increasing frequency of monitoring if evidence of renal impairment.

Loss of hearing usually occurs first and is detected by regular audiometric testing. Vertigo, loss of balance and auditory disturbances are also signs of **ototoxicity.** *Ototoxicity on audiogram is defined as a 20 dB loss from baseline at any one test frequency or a 10 dB loss at any two adjacent test frequencies.*

We recommend that patients have baseline audiometry and then monthly reviews until treatment with aminoglycoside ceases. A final audiometry review should be offered 2 months after the final dose.
Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTIONS

Increased risk of **nephrotoxicity** if given with: capreomycin, cephalosporins, ciclosporin, colistimethate sodium, tacrolimus
Increased risk of **ototoxicity** if given with: loop diuretics
Increased risk of **hypocalcaemia** with bisphosphonates.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
Hypersensitivity: to streptomycin or other aminoglycosides
Myasthenia Gravis: as aminoglycosides may impair neuromuscular transmission
Pregnancy: Risk of vestibular or auditory nerve damage to infant if used in second or third trimester

Cautions:
Obese: Use ideal weight for height to calculate dose and monitor serum streptomycin levels closely
Elderly: Nephrotoxicity and ototoxicity common in the elderly; monitor and reduce dose if necessary
Renal Disease: Use with caution. Reduce the frequency of dosing and monitor serum concentrations.

LABORATORY INFORMATION

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Sample Type: Serum.
Volume Required: 2ml (min 0.1mL).
Sample Container: Plain glass or plastic (non SST).
Container Type: Any.
Availability: Office Hours.
Turnaround Time: Telephoned same day if received 9am-3pm Mon-Fri *if* advanced warning given. Written confirmation report will be sent by 1st Class post.

The sample must be heat-treated before dispatch if HIV positive.

THIOACETAZONE

Please note thioacetazone is not licensed for the treatment of tuberculosis in the UK.
Thioacetazone is not usually recommended for the treatment of MDRTB. When it is used, it should be counted as half a drug in a treatment regimen.

DOSAGE

Adults: 150mg once daily.
Children: No information.

PREPARATIONS

Not currently available in the UK.

DRUG LEVEL MONITORING

- Drug levels need not be routinely measured.

ADVERSE EFFECTS

COMMON:
Dermatological: Rash (3%).
Gastrointestinal: Nausea, vomiting, diarrhoea, anorexia & dyspepsia.
Neurological: Giddiness (10%).
SERIOUS:
Haematological: Neutropaenia, anaemia, thrombocytopaenia; rarely: haemolytic anaemia, agranulocytosis, aplastic anaemia.
Hepatic: Hepatotoxicity with jaundice and acute hepatic failure.
Neurological: Dizziness, peripheral neuropathy, cerebral oedema (rare).

ADVERSE EFFECTS: MONITORING

Routine tests as per generic MDR-TB treatment monitoring guidelines.

INTERACTIONS

Streptomycin: Possible increased ototoxicty.

This information is not inclusive of all drug interactions. Please discuss with a pharmacist.

CONTRA-INDICATIONS & CAUTIONS

Contraindications:
HIV co-infection: Causes fatal skin rashes.
Prothionamide resistance: Risk of cross-resistance

NB: Thioacetazone is poorly tolerated by people of Asian or European origin. It is surprisingly well tolerated in East African countries and in South America. Consequently Thioacetazone is not routinely used by any of the TB programs we know in Cambodia, Lao PDR, Vietnam and China. Even in people of African or South American ethnicity, its use should be avoided in patients with HIV co-infection.

LABORATORY INFORMATION

Please find up to date information at www.assayfinder.com regarding individual providers of drug level monitoring tests. Click on the provider to discover contact details. Turnaround time varies depending on the test and whether it is run locally or sent to an external lab. By contacting laboratories in advance, turnaround time can significantly be reduced.

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