Non-tuberculous mycobacterial (NTM) Pulmonary Infection Guidance

Initiation by Infectious Diseases / Respiratory Consultant Only

ALL PATIENTS MUST BE DISCUSSED AT COMPLEX PULMONARY INFECTION MDT

NHS Tayside

NOTES:

- This guidance covers prescribing for most common NTM pulmonary infections: *M. avium, M. malmoense, M. abscessus*. Other NTM species discussed at MDT with review of current national/international guidance.
- For guidance on treating TB see link here
- Therapeutic Drug Monitoring (TDM):
  - TDM samples should be taken Monday to Thursday (to allow for transport to specialist lab) and state time of last dose on request
  - TDM results – if out with range discuss with pharmacist for dose adjustment and when to recheck levels
- **NTM infections in HIV patients and NON pulmonary NTM infections are excluded from this guidance**
- Doses assume non pregnant adults with normal renal and hepatic function (unless otherwise stated)

BASELINE EVALUATION:

- Add to Complex Pulmonary Infection MDT for discussion
- Consider discontinuing any antibiotics that may impair NTM growth (macrolides, cotrimoxazole, tetracyclines, aminoglycosides, linezolid) 2 weeks before collecting samples for patients undergoing diagnostic evaluation
- Full medication history and interaction check prior to commencing treatment – ask Pharmacist for advice
- See medicine information on page 3 for baseline investigations/bloods

FOLLOW UP:

- Sputum samples sent every 4- 12 weeks during treatment and for 12 months after completing treatment
- Patient should be reviewed in clinic at 3 months then every 3 -6 months
- Monitoring and TDM – as per specific medicine guidance on page 3
- Ask primary care to add any medicines supplied via hospital pharmacy to patient medication records to reduce risk of interactions
- Discussion at Complex Pulmonary Infection MDT every 6 - 12 months to confirm continuation or duration
- Culture conversion definition: 3 consecutive negative sputum cultures over minimum 3 months or single negative on a CT-directed bronchial wash

Mycobacterium avium Complex

Non severe: AFB smear –ve resp tract samples, no radiological evidence of lung cavitation /severe infection, mild /moderate symptoms, no signs systemic illness

Severe: AFB smear +ve resp tract samples, radiological evidence of lung cavitation or severe infection, severe symptoms or signs systemic illness

TREATMENT:

Non Severe:
Rifampicin 600mg 3 x week (450mg if <50kg)
+ Ethambutol 25mg/kg 3 x week (rounded to nearest 100mg)
+ Azithromycin 500mg 3 x week (or clarithromycin 500mg bd 3 x week)

Severe:
Rifampicin 600mg daily (450mg if <50kg)
+ Ethambutol 15mg/kg daily (rounded to nearest 100mg)
+ Azithromycin 250mg daily (or clarithromycin 500mg bd)
+ consider addition of IV amikacin 15mg/kg od or nebulised amikacin 500mg bd for up to 3 months

Macrolide resistant:
Rifampicin 600mg daily (450mg if <50kg)
+ Ethambutol 15mg/kg daily (rounded to nearest 100mg)
+ Moxifloxacin 400mg od or Isoniazid 300mg daily/pyridoxine 10mg daily
+ Consider IV amikacin 15mg/kg od or nebulised amikacin 500mg bd for up to 3 months

Duration: Minimum of 12 months after first of three negative cultures

Dispensing: Initial 1-3 month supply can be dispensed by hospital, or primary care under specialist advice, then prescribing can be continued in primary care (except amikacin supply via hospital)

Mycobacterium malmoense

Non severe: AFB smear –ve resp tract samples, no radiological evidence of lung cavitation /severe infection, mild /moderate symptoms, no signs systemic illness
Severe: **AFB smear +ve resp tract samples, radiological evidence of lung cavitation or severe infection, severe symptoms or signs systemic illness**

TREATMENT:

Non severe:
Rifampicin 600mg daily (450mg if <50kg)
+ Ethambutol 15mg/kg daily (rounded to nearest 100mg)
+ Azithromycin 250mg daily (or clarithromycin 500mg bd)

Severe:
Rifampicin 600mg daily (450mg if <50kg)
+ Ethambutol 15mg/kg daily (rounded to nearest 100mg)
+ Azithromycin 250mg daily (or clarithromycin 500mg bd)
+ consider addition of IV amikacin 15mg/kg od
or nebulised amikacin 500mg bd for up to 3 months

Duration: Minimum of 12 months after first of three negative cultures

Dispensing: Initial 1-3 month supply can be dispensed by hospital, or primary care under specialist advice, then prescribing can be continued in primary care (except amikacin supply via hospital)

Mycobacterium abscessus

Regimen may differ from below depending on sensitivities e.g. IV/Neb amikacin would be substituted with an alternative antibiotics if the M. abscessus is resistant to amikacin

TREATMENT:

Macrolide sensitive or inducible resistance:

Induction Phase 1-3 months:
IV Amikacin 15mg/kg daily
+ IV Tigecycline 50mg bd (no loading dose required)
+ if tolerated IV Imipenem/Cilastatin 1g/1g bd (= Primaxin® 2 vials bd)
+ oral Azithromycin 250 - 500mg daily (or clarithromycin 500mg bd)

Continuation Phase:
Nebulised Amikacin 500mg bd
+ oral Azithromycin 250 - 500mg daily (or clarithromycin 500mg bd)
+ 1-3 from list below guided by susceptibility and patient tolerance:
  - oral clofazamine 100mg daily (unlicensed)
  - oral linezolid 600mg daily
  - oral minocycline 100mg bd
  - oral moxifloxacin 400mg daily
  - oral co-trimoxazole 960mg bd

Macrolide resistant:

Induction Phase 1-3 months:
IV Amikacin 15mg/kg daily
+ IV Tigecycline 50mg bd (no loading dose required)
+ if tolerated IV Imipenem/Cilastatin 1g/1g bd (= Primaxin® 2 vials bd)

Continuation Phase:
Nebulised Amikacin 500mg bd
+ 2-4 from list below guided by susceptibility and patient tolerance:
  - oral clofazamine 100mg daily (unlicensed)
  - oral linezolid 600mg daily
  - oral minocycline 100mg bd
  - oral moxifloxacin 400mg daily
  - oral co-trimoxazole 960mg bd

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DURATION: Depends on severity, treatment response and tolerance but usually 18 months to 2 years.

Dispensing: Usually always supplied via hospital pharmacy but primary care medication records should be updated to reduce risk of interactions with new medicines.

Medicine (Patient Info Leaflets here)	Route	Dose	Baseline Investigations	Monitoring	Adverse effects	Advice/Comments
Amikacin	IV (infusion over 30 minutes)	15mg/kg daily or 15-25mg/kg 3x week See link to guidance for dosing calculation and TDM advice	Aminoglycoside genetic testing (m.1555A>G) Audiometry Mg/Ca/UEs	Audiometry monthly until 2 months after stopping. UEs/Mg/Ca twice weekly during induction phase then reduce to weekly then fortnightly TDM: predose <2mg/L 1 hour post end of infusion 25-45mg/L (45-65mg/L for 3x week). Once in range and if renal function remains stable, check trough concentrations weekly for 4 weeks then fortnightly for 1 month then reduce to monthly if long term. Pre dose high → extend interval Post dose high → decrease dose	Nephrotoxicity Ototoxicity Auditory>vestibular Hypocalcaemia Hypomagnesaemia Hypokalaemia	Advise patient to report any tinnitus/vestibular disturbance/hearing loss
Amikacin (liposomal nebules Arikayce® - only by non formulary request)	Nebulised (using injection)	500mg bd		Consider TDM in patients with renal impairment to ensure no accumulation	Bronchospasm (give bronchodilator before dose), dysphonia, sore mouth/throat, toxicity	Supervised test dose required in CIU. Use Pari LC Plus with filter attachment nebuliser. Make each dose up to 4ml with 0.9% sodium chloride.
Azithromycin	oral	Depends on mycobacterium being treated – see above	ECG/LFTs/UEs/FBC	ECG at 2 weeks and after the addition of any new medicines known to prolong QT. 3-6 months routine bloods	GI upset, prolonged QT, arthralgia, ototoxicity, hepatotoxcity	Check drug interactions
Cefoxitin Avoid in severe penicillin allergy	IV infusion	200mg/kg/day in 3 divided doses (max 12g/day)	FBC/UEs/LFTs	Twice weekly for 2 weeks then reduce frequency	Fever, rash, hypotension, seizures, deranged LFTs, neutropenia (50% affected)	Alternative IV antibiotic only if other IV options not suitable. Not kept in stock.
Clarithromycin	oral	500mg bd	ECG/LFTs/UEs/FBC	ECG at 2 weeks and after the addition of any new medicines known to prolong QT. 3-6 months routine bloods	GI upset, prolonged QT, arthralgia, ototoxicity, metallic taste, hepatitis	Check drug interactions
Clofazamine (check for nut allergy, capsules contain soya)	oral	200mg od for 2 months then 100mg od	ECG/LFTs/UEs/FBC Patients of child bearing potential & male patients who have female partners must use effective birth control during treatment & until 4 months after completion	ECG at 2 weeks and after the addition of any new medicines known to prolong QT. 3-6 months routine bloods	Skin darkening within 1-4 weeks. Dry/itchy skin, prolonged QT, photosensitivity GI side effects, depression, visual changes and ocular irritation, hepatotoxicity	Take with food to increase absorption and reduce GI side effects. Advise patient re skin pigmentation and may take 12 months to reverse. Advise re suncream

Medicine Patient Info Leaflets here)	Route	Dose	Baseline Investigations	Monitoring	Adverse effects	Advice/Comments
Co-trimoxazole	oral	960mg bd	FBC/UEs/LFTs	Routine bloods intermittently through treatment	Rash, GI upset, hyperkalaemia, anaemia, leukopenia, thrombocytopenia	
Ethambutol	oral	15mg/kg rounded to nearest 100mg	Visual acuity/colour vision	Routine bloods intermittently through treatment	Optic neuritis, red/green colour blindness	Patient should be advised to report any visual changes.
Imipenem/ cilastatin (not kept routinely in stock)	IV infusion	1g/1g bd	FBC/UEs/LFTs	Routine bloods intermittently through treatment	Hepatitis, GI upset, seizures, blood dyscrasias	Primaxin contains imipenem/cilastatin (renal dehydropeptidase inhibitor) 500mg/500mg per vial. Co-prescribe antiemetics. Significant interaction with valproate
Isoniazid (ideally before breakfast)	oral	300mg od	FBC/UEs/LFTs	Routine bloods intermittently through treatment	Peripheral neuropathy, hepatitis. Food interactions	Always co-prescribe pyridoxine 10mg od.
Linezolid	oral	600mg od	Lactate FBC/UEs/LFTs Visual acuity/colour vision	Consider TDM (peak 12-24mg/L) if co-prescribed with macrolide or to reduce dose in toxicity. FBC/lactate weekly for 2 months then consider reducing frequency.	Lactic acidosis, myelosuppression, peripheral neuropathy, serotonin syndrome, optic neuropathy	Patients should report any visual changes or symptoms of peripheral neuropathy. Check interactions.
Meropenem	IV bolus	1-2g tds	FBC/UEs/LFTs	Routine bloods intermittently through treatment	Rash, GI upset, deranged LFTs	As an alternative if IV imipenem not available or not suitable. Significant interaction with valproate
Minocycline	oral	100mg bd	FBC/UEs/LFTs	Routine bloods intermittently through treatment	Photosensitivity, rash, GI upset, oesophageal ulceration, skin discolouration	Advise re sunscreen. Take with plenty water during meals while sitting upright. Check interactions.
Moxifloxacin	oral	400mg od	ECG/LFTs/UEs/FBC	ECG at 2 weeks and after the addition of any new medicines known to prolong QT.	Prolonged QT. See local guidance for other adverse effects	Advise patient re adverse reactions and to report.
Rifampicin (ideally before breakfast)	oral	≥50kg 600mg od <50kg 450mg od	FBC/LFTs/UEs	LFTs at 2 weeks then intermittently through treatment	Leucopaenia, flu like symptoms, neutropenia, hepatitis, rash, renal failure	Check interactions. Warn patient re orange/red discolouration of body fluids
Rifabutin	oral	150-600mg od Depends on interacting medicines	FBC/LFTs	LFTs at 2 weeks then intermittently through treatment	Leucopaenia, anterior uveitis, flu like symptoms, neutropenia, hepatitis, rash	CYP450 induction less than rifampicin. Warn re orange/red discolouration
Tigecycline	IV	50mg bd (no loading dose required)	Amylase/clotting FBC/LFTs	Amylase/clotting/FBC/LFTs twice weekly initially then reduce frequency	GI side effects, deranged clotting, elevated LFTs, pancreatitis, hypoglycaemia	Co-prescribe antiemetics. Slow rate of infusion to reduce nausea and consider reducing to once daily