There is a new NEL-wide SCG for Azathioprine and Mercaptopurine for all indications which supersedes this document. Please refer to the new NEL-wide SCG for up to date information on use of Azathioprine, and continue to use this (existing) version for Mycophenolate.

BHR ICP & BHRUT NHS Trust

Shared Care Guidelines

North East London Clinical Commissioning Group

Access the NEL-wide Azathioprine and Mercaptopurine here:
https://primarycare.northeastlondon.icb.nhs.uk/home/meds/nel-wide-non-mental-health/

Azathioprine and Mycophenolate for patients with Neurological Indications in BHRUT

1. Background	Azathioprine and Mycophenolate Mofetil are immunosuppressant agents used in inflammatory neurological conditions. Their use is widely established in treating these conditions. However they require monitoring for liver damage and for bone marrow suppression. A particular issue with azathioprine is that it is metabolised by the enzyme thiopurine methyltransferase (TPMT). TPMT activity is a mandatory test performed prior to commencement of azathioprine. Approximately 11% of patients have intermediate TPMT activity and are at greater risk of adverse drug reactions on standard doses and 0.3% have no detectable TPMT activity and are at risk of suffering life-threatening complications even when treated with low doses of the drug. Mycophenolate mofetil was originally used to prevent transplant rejection. It has fewer bone marrow suppression side effects than azathioprine. It has known teratogenicity. There has been a safety alert over the possibility that men on the medication may on fertilisation confer teratogenicity so it is recommended that adequate contraception be used by men or their partners while taking the medication. All immunosuppressant drugs have potential side effects in increasing susceptibility to infection and activating latent infections. They may also increase the risk of developing cancer years later due to poor immunological surveillance. They should be prescribed balancing risk versus benefits and after counselling the patient on these risks and benefits. This guidance is to be accompanied by a patient information leaflet specific for these medications and by the general National (RMOC) Shared Care guideline documentation.
2. Indications **(Please state whether licensed or unlicensed)**	Autoimmune neurological conditions (all unlicenced): • Myasthenia gravis as first line steroid sparing agent. • CNS vasculitis and other CNS inflammatory conditions • Inflammatory myopathy or neuropathy • Neurosarcoidosis.
3. Locally agreed off-label use	Unlicenced

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4. Contraindications and cautions

Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.

Azathioprine Contraindications:

- Hypersensitivity to azathioprine or to any of the excipients
- Severe infections
- Severely impaired hepatic or bone-marrow function.
- Thiopurine methyltransferase (TPMT) deficiency
- Pancreatitis
- Concomitant use of any live vaccines especially BCG, smallpox, yellow fever
- Pregnancy- Treatment should not generally be initiated during pregnancy. Careful assessment of risk versus benefit.
- Lactation. (May use if potential benefit outweighs risk)

Azathioprine Cautions:

- Avoid sun exposure and protect skin with a sunscreen, which has a high protection SPF (SPF 30 or more) to protect against UVB, and the UVA circle logo and/or 4 or 5 UVA stars to protect against UVA.
- Thiopurine methyltransferase (TPMT) status
- Reduce dose in elderly, hepatic & renal impairment
- Increased risk of haematological toxicity with co-trimoxazole/trimethoprim
- Patients must avoid 'live' vaccines such as oral polio, MMR, BCG, nasal Flu vaccine and yellow fever (see COVID vaccine note below).
- Patients should avoid contact with people who have active chickenpox or shingles and should report any such contact urgently to their GP or specialist.
- Careful assessment of risk versus benefit should be carried out before use during pregnancy and breast-feeding.
- Any other interacting drugs (refer to the latest BNF Edition)
- Avoid prescribing allopurinol in patients on azathioprine due to a clinically significant interaction that can lead to increased toxicity. Concomitant prescription of allopurinol is occasionally used to increase azathioprine efficacy. In this situation 25% of the original dose of azathioprine must be given.

Mycophenolate Mofetil (MMF) Contraindications:

- Hypersensitivity to MMF or to any other excipients
- Severe infections
- Malignancy
- Severely impaired hepatic or bone-marrow function.
- Concomitant use of any live vaccines
- Pregnancy- Treatment should not generally be initiated during pregnancy.
- Lactation

Mycophenolate Mofetil (MMF) Cautions:

- Avoid sun exposure (see azathioprine)
- Women must not become pregnant or breast feed during MMF treatment and must use contraceptive measures during treatment and for 6 weeks after the last dose of MMF.
- Men to use barrier contraceptive methods during the treatment and for 90 days after the last dose.

<table>
<tr><td></td><td colspan="2">

- MMF may interact with other medication e.g. antacids, anti-epileptics, antibiotics (e.g. metronidazole, norfloxacin, rifampicin), antivirals (e.g. aciclovir) and some antipsychotics (e.g. Clozapine).
- Avoid live vaccines during MMF treatment (see COVID vaccine note below). If immunisation with a live vaccine required, MMF should be stopped 6 months before and until 2 weeks after the vaccination. Flu vaccines (not nasal Flu vaccine) and Pneumovax are safe and recommended.

Note re COVID vaccines:
According to both the Patient Group Direction for COVID-19 mRNA vaccine BNT162b2 (Pfizer/BioNTech) and the Patient Group Direction for COVID-19 Vaccine AstraZeneca, (ChAdOx1-S [recombinant]) there are **no** groups of potentially immunosuppressed patients that should be excluded from receiving the vaccine based on their treatment or disease alone. It is, however, noted that some immunosuppressed patients may have a suboptimal response to the vaccine and should therefore continue to avoid exposure unless they are advised otherwise by their doctor.

Please see SPC for comprehensive information.
</td></tr>
<tr><td>5. Initiation and ongoing dose regime

Note -
•The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
•All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician
•Termination of treatment will be the responsibility of the specialist.</td><td colspan="2">

<u>Maintenance dose of Azathioprine:</u>

High TPMT level (>150microU/L): Dose- 1mg to 3 mg/kg daily, start at half target dose for *first week* to minimise side effects

Normal TPMT level (68 – 150microU/L): Dose- 0.5mg to 1.5mg/kg daily

Deficient (<10microU/L) - Low 20 – 67microU/L) TPMT level: Avoid azathioprine

The initial maintenance dose must be prescribed by the initiating specialist.

<u>Maintenance dose of Mycophenolate mofetil:</u>

1-3g daily, given BD

<u>Conditions requiring dose adjustment:</u>

- Control of symptoms
- Avoidance of dose dependent marrow suppression
</td></tr>
<tr><td rowspan="4">6. Pharmaceutical aspects</td><td>Route of administration:</td><td>Oral</td></tr>
<tr><td>Formulation:</td><td>Azathioprine 50mg tablets
Mycophenolate mofetil 500mg tablets</td></tr>
<tr><td>Administration details:</td><td>Given twice daily</td></tr>
<tr><td>Other important information:</td><td>Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 g but avoid unnecessary switching because of pharmacokinetic differences.</td></tr>
</table>

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<table>
<tr><td>7. Significant medicine interactions

For a comprehensive list consult the BNF or Summary of Product Characteristics.
SPC</td><td colspan="2">The following list is not exhaustive; please see SPC for comprehensive information and recommended management.
Azathioprine and allopurinol (see above)
Azathioprine and co-trimoxazole/trimethoprim (see above)
Mycophenolate mofetil and antacids, antiepileptics, antibiotics (e.g. metronidazole, norfloxacin, rifampicin), antivirals (e.g. aciclovir) and some antipsychotics (e.g. Clozapine).</td></tr>
<tr><td>8. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist</td><td colspan="2">Baseline investigations:
FBC, U&Es, LFTs, TPMT phenotype (for azathioprine), Varicella Zoster serology

Initial monitoring by specialist:
FBC, LFT, U&E every week for four weeks, thereafter every 3 months or after any dose change (specialist to provide blood test forms to the patient for the first 3 months and thereafter if indicated.)</td></tr>
<tr><td rowspan="2">9. Ongoing monitoring requirements to be undertaken by primary care.

See section 10 for further guidance on management of adverse effects/ responding to monitoring results.</td><td>Monitoring</td><td>Frequency</td></tr>
<tr><td>(Only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to the GP):
FBC, LFT, U&E</td><td>Every 3 months</td></tr>
<tr><td rowspan="9">10. Adverse effects and managements

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme
www.mhra.gov.uk/yellowcard</td><td>Result</td><td>Action for GP</td></tr>
<tr><td>Neutrophils < 1.5 x 10^9/L</td><td>STOP Azathioprine & Mycophenolate Mofetil, contact specialist hospital clinician</td></tr>
<tr><td>AST/ALT > 4 fold rise (from upper normal limit)</td><td>STOP Azathioprine & Mycophenolate Mofetil, contact specialist hospital clinician</td></tr>
<tr><td>Neutrophils < 2.0 x 10^9/L</td><td>Discuss with specialist hospital clinician</td></tr>
<tr><td>Lymphocytes < 0.5 x 10^9/L</td><td>Discuss with specialist hospital clinician</td></tr>
<tr><td>Platelets < 150 x 10^9/L</td><td>Discuss with specialist hospital clinician</td></tr>
<tr><td>AST/ALT > 2 fold rise (from upper normal limit)</td><td>Discuss with specialist hospital clinician</td></tr>
<tr><td>GFR 20-50ml (Mild) renal impairment
GFR 10-20ml/min- (Moderate) renal impairment
GRF <10ml/min (Severe) renal impairment</td><td>Discuss with specialist hospital clinician</td></tr>
<tr><td>MCV > 105 fl</td><td>Check B12, TFT and Folate. GP to start supplementation if low</td></tr>
<tr><td>11. Advice to patients and carers
The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice,</td><td colspan="2">The patient should be advised to report any of the following signs or symptoms to their GP without delay:
Jaundice
Hypersensitivity reactions (malaise, dizziness, vomiting, diarrhoea, fever, rigors, rash, interstitial nephritis)</td></tr>
</table>

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including patient information leaflets on individual medicines.	• Abdominal pain suggestive of pancreatitis (rare adverse effect of azathioprine) • Cough, breathlessness suggestive of pneumonitis (rare adverse effect of azathioprine) • Nausea • Alopecia • Rash, abnormal bruising or bleeding • Severe or persistent sore throat, infection, fever, rigors, oral ulceration • Exposure to Varicella (If patient is non-immune and in contact with varicella or shingles, they will require Varicella Zoster immunoglobulin within the first 10 days of exposure. Please contact Consultant Microbiologist for advice. Supplies of this can be obtained from the Health Protection Agency (HPA) (contact details are available from the HPA website http://www.hpa.org.uk)
12. Pregnancy, paternal exposure and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.	**Pregnancy:** Not recommended. Careful assessment of risk versus benefit. **Breastfeeding:** Not recommended
13. Specialist contact information	Provided in letter to individual GP Emergency contact in office hours with on call Neurology Specialist registrar via switchboard. Emergency contact out of office hours with on call Neurology Consultant via switchboard.
14. Additional information	Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed.
15. References	• BNF 72. September 2016- March 2017 • Mims online • www.medicines.org.uk • Renal drug handbook, 3rd Edition, Ashley C & Currie A, 2009 • Pharmacological approaches to CNS vasculitis: where are we at now? Pagnoux C. Expert Rev ClinPharacol 2016;9:109-16. • Myasthenia Gravis: Association of British Neurologists' Management Guidelines, Sussman et al. Pract Neurol 2015;15:199-206. • Mycophenolate mofetil in primary CNS vasculitis. Salvarani et al., Semin Arthritis Rheum 2015;45:55-59. • An update on the management of chronic inflammatory demyelinating polyneuropathy. Gorson, KC. Ther Adv Neurol Dosord 2012;5:359-373. • Treatment of neurosarcoidosis; A comparative study of methotrexate and mycophenolate mofetil. Bitoun S et al., Neurology 2016; 87:2517-2521. • Treatment of inflammatory myopathy: emerging therapies and therapeutic targets. Moghadam-Kia S et al., 2015. Expert Rev Clin Immunol. 11:1265-1275. • Neurosarcoidosis: a clinical approach to diagnosis and management. Ibitoye RTet al., 2017. J Neurol 264:1023-1028.

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16. To be read in conjunction with the following documents	• RMOC Shared Care Guidance • NHSE/NHSCC guidance – items which should not be routinely prescribed in primary care: guidance for CCGs • NHSE policy- Responsibility for prescribing between Primary & Secondary/Tertiary Care
17. Local arrangements for referral Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.	Specialist to send a letter to the GP requesting shared care for the patient. GP to refer to specialist if adverse event or condition change. GP can contact specialist via the neurology referral team, DECT number 6836 (Switchboard number 01708 435 000) between 9am – 5pm). The neurology pharmacist can also be contacted via DECT phone number 6809 (Switchboard number 01708 435 000) between 9am – 5pm).