Azathioprine - paediatric & adolescent (non-transplant indications)

Shared Care Guideline

This guideline is relevant to the care of children and adolescents up to the age of 18 or until they transition to adult services.

Specialist details	Patient identifier
Name: _____	
Location: _____	
Tel: _____	**Date:** _____

Introduction

Unlicensed indications include: juvenile systemic lupus erythematosus, autoimmune conditions (usually when corticosteroid therapy alone has proved inadequate), vasculitis, severe ulcerative colitis, Crohn's disease, severe eczema.

Paediatric & adolescent dosage and administration

Indications	Dosing schedule
Juvenile systemic lupus erythematosus, vasculitis, auto-immune conditions usually when corticosteroid therapy alone has proved inadequate	Child 1 month - 18 years initially 1 mg/kg daily adjusted according to response to max 3 mg/kg daily (consider withdrawal if no improvement within 3 months)
Severe ulcerative colitis and Crohn's disease	Child 2 - 17 years initially 2 mg/kg once daily, then increased if necessary up to 2.5 mg/kg once daily
Severe eczema	1 – 3 mg/kg/day

Dosage may need to be reduced in patients with renal and/or mild to moderate hepatic impairment.

Available as: azathioprine 25mg, 50mg tablets
Where possible, tablets should be prescribed. In exceptional circumstances, an (unlicensed) oral solution may be required. Azathioprine **50mg/5ml** is the standard strength that must be used.

Hospital specialist responsibilities

- Assess if the patient is suitable for treatment with azathioprine.
- Agree shared care with patient's GP.
- Varicella Zoster immune status: if non-immune, consider immunisation prior to starting treatment.
- Advise GP on dose of azathioprine to be prescribed.
- Provide the patient/carer with relevant (preferably written) information on use, side effects and need for monitoring of medication.
- If the liquid formulation is used, provide training on safe handling, storage, spillage and waste disposal (provide a cytotoxic spill kit and cytotoxic sharps box if necessary).
- Undertake baseline tests as indicated in monitoring table.
- Check vaccination history as live vaccines cannot be given while on immunosuppressant treatment.
- Review results of safety monitoring and request additional tests as required.
- Monitor disease response to treatment and need to continue therapy.
- Continue to review the patient at agreed specified intervals, sending a written summary to the GP whenever the patient is reviewed.
- Provide any other advice or information for the GP if required.

Monitoring table		Hospital specialist	GP			Hospital specialist
Test	**Indication**	Pre-treatment baseline	Stage of treatment			At review
			First 2 months	3 - 4 months	After 4 months	
FBC LFTs ESR/CRP (Rheumatology & Gastroenterology only) U&Es, serum creatinine Amylase (Gastroenterology only)	Baseline assessment, disease activity scoring & dose adjustment	✓	Every 1 - 2 weeks (as advised by specialist)	Every month	Every 1 - 3 months (as advised by specialist)	As part of the review or as clinically indicated
Height & weight	Baseline assessment	✓	Not routinely required			If clinically indicated
TPMT	To assess suitability for treatment					
Urinalysis	To assess for renal disease (proteinuria) or infection					
Blood pressure Chest x-ray PFTs, TB screening if indicated	Baseline assessment, respiratory and TB screening	If clinically indicated				
Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding		✓	At every consultation			✓
If a further DMARD/JAK is added as combination therapy, or the dose is increased, the 'First 2 months' schedule should be reinstated. There may be clinical circumstances where the frequency of monitoring may vary and this should be specified by the initiating specialist						

GP responsibilities

- Prescribe azathioprine.
- Arrange and record ongoing monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered. Contact the specialist if treatment is stopped or further advice required.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Administer **inactivated** influenza vaccine annually unless otherwise advised by the initiating specialist. Note the live formulation (eg. Fluenz Tetra®) must not be used.
- Check patient has received pneumococcal vaccine according to BNF or Green Book schedule.
- Provide COVID 19 vaccination as appropriate as per local arrangements and Green Book.
- Post exposure prophylaxis (antivirals or VZIG if antivirals are contraindicated) should be considered in non-immune at risk patients if exposed to chickenpox or shingles. Contact the consultant virologists, Regional Virus Laboratory, Royal Group of Hospitals on 07889 086 946 for advice if exposure is suspected. For other queries eg. those concerning exposure, infection or any recommendations relating to healthy susceptible household contacts, consult the Green Book and/or take additional advice from Regional Virus Laboratory, Royal Group of Hospitals
- Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding at every consultation.

Withhold azathioprine and contact specialist if:

- WCC < 3.5 x 10^9/L
- Neutrophils < 1.6 x 10^9/L
- **Unexplained** eosinophilia > 0.5 x 10^9/L
- Platelets < 120 x 10^9/L
- MCV > 105fL, (check B12 & folate & TFT)
- AST/ALT > 3 times the upper limit of normal (for results between 2 - 3 x ULN, continue azathioprine, repeat bloods and seek specialist advice). Minor elevations of AST/ALT are common
- If renal impairment develops (not always appropriate to stop but may need dose adjustment)
- Unexplained fall in serum albumin
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough.

Normal reference range may vary slightly between labs.
Please note an unusual fall or rise or a consistent downward or upward trend in any value should prompt review of the patient and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Adverse effects, precautions and contraindications

General signs of malaise such as dizziness, diarrhoea, rash, myalgia and arthralgia occur infrequently. If severe or persistent refer to initiating specialist.
Renal impairment. Caution is advised regarding adequacy of renal function if azathioprine is to be used concomitantly with NSAIDs, ACE inhibitors or angiotensin II antagonists.
Infection. Immunosuppressants can increase susceptibility to infection. It is advisable not to commence or continue treatment with azathioprine when patients have a confirmed or established local or systemic infection. It is advisable to recommence once the infection has been treated. Precise period of discontinuation depends on the nature and severity of infection and the activity of the underlying disease.
Nausea can occur initially but can be reduced by taking the tablets after food.
Blood disorders: leucopenia, anaemia and thrombocytopenia. GPs should be alert to any oral ulceration, sore throat, unexplained rash or abnormal bruising/bleeding.
Pancreatitis has been reported in a small percentage of patients.
Pregnancy / contraception. Where applicable for sexually active patients, women of childbearing potential and men receiving azathioprine should be advised to use effective contraception. Patients discovered or planning to become pregnant should be referred to the initiating specialist at the earliest opportunity without discontinuing azathioprine.
Breastfeeding. Women being treated with azathioprine should seek specialist advice.
Cancer risk. Patients receiving long-term immunosuppressive drugs are at increased risk of developing a malignancy. The most frequently occurring types are lymphoma and skin malignancy. The avoidance of excessive exposure to the sun, and the use of high factor sunscreen and protective clothing are advised. Adherence to population screening programmes is particularly important in this population.
Live vaccines. Consult the Green Book and take additional advice from initiating specialist if required.
Contraindications include:

- Hypersensitivity to mercaptopurine
- Severe hepatic impairment
- TPMT deficiency - avoid if deficient or reduce dose if low levels.

Common drug interactions

Allopurinol prolongs activity of azathioprine increasing risk of severe myelosuppression. If it must be given concomitantly, it is essential that only a quarter of the usual dose of azathioprine is given.
Aminosalicylates (eg. sulfasalazine) contribute to bone marrow toxicity and increased monitoring may be required. A lower dose of azathioprine may be required.
Concomitant use of **ACE inhibitors** are predicted to increase risk of anaemia/leucopenia. Increased monitoring may be required.
JAK inhibitors may enhance the immunosuppressive effects of azathioprine. Concomitant use of filgotinib should be avoided; baricitinib should be used cautiously in combination.
Febuxostat: avoid concomitant use.
Ribavarin: increases risk of myelosuppression.
Trimethoprim and co-trimoxazole: there is a risk of haematological abnormalities.
Warfarin effect may be reduced requiring an increased dose of warfarin.

Communication

For any queries relating to this patient's treatment with azathioprine, please contact the specialist named at the top of this document.

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