Shared Care Guideline

Azathioprine and 6-mercaptopurine for paediatric gastroenterology & hepatology patients

1. Executive Summary - Shared Care Responsibilities

Hospital specialist (CUH paediatric gastroenterology):

- Initiate treatment and monitor first 3 months of treatment. After 3 months/satisfactory investigation results for at least 4 weeks, CUH will prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Encourage patients and families to sign up for MyChart.
- At point of initiating treatment check for drug interactions and contraindications
- Undertake baseline bloods including differential FBC, U&Es, LFTs including GGT, TMPT phenotype, varicella status, EBV, ESR, CRP, Hep B and C.
- Organise bloods for the first 3 months of treatment.
- Review the first 3 months of bloods, if not undertaken at CUH request local team to email to paediatric IBD team at add-tr.paediatricibd@nhs.net.
- Counsel the patient/ carer on the potential benefits and side effects of treatment and provide the patient information leaflet. Patient will be explained the principles of shared care during the consultation.
- Send a letter to the GP/ general paediatrician requesting shared care for the patient. This letter will include initial dosing, TPMT status, contact details and a blood test timetable.
- Assess the patients regularly in clinic throughout treatment and update local teams.
- Monitoring active metabolites twice a year
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments. The GP does not need to take any action as the hospital specialist will contact the family and take action in these situations.
- To provide any advice to the local team/patient/carer when requested.

General practitioner:

- Transfer to primary care (GP) is normally after the patient has been treated for 3 months and with satisfactory investigation results for at least 4 weeks. CUH will prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.

- Agreement to shared care guideline by the GP/ general paediatrician. A letter can be signed and returned to CUH to note agreement (see appendix 2). If the GP refuses shared care, they must fill out the shared care refusal letter (see appendix 3) and return to CUH. If no letters are received from the GP, it will be assumed that shared care is agreed and the GP will take over care after 3 months/satisfactory investigation results for at least 4 weeks.
- Prescribe the drug treatment as described.
- Monitor disease progression, and drug effects as advised by the paediatric gastroenterology team.
- Monitor drug therapy as per section 11 below above.
- If advice is required, email blood test results to the paediatric gastroenterology team.
- Request advice from the paediatric gastroenterology team when necessary.
- Provision of pneumococcal type and annual influenza vaccination (not live version).

Patient or parent/carer:

- Watch IBDmate video on azathioprine before attending clinic appointment. We are unable to start thiopurine treatment until the videos have been watched.
- Sign up for MyChart.
- Report to the paediatric gastroenterology team or GP if they do not have a clear understanding of their treatment.
- Patients must take the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments.
- Must inform relevant healthcare professionals (GP/ practice nurse/ school nurse/ dentist/ community pharmacist/ complimentary therapist) that they are receiving thiopurine treatment.
- Report any adverse effects to the paediatric gastroenterology team or GP.

2. Scope

Prescribing and monitoring of thiopurine treatment of paediatric gastroenterology and hepatology patients by general practitioners and/or general paediatricians.

3. Aim

To provide Shared Care Guidance on the prescribing and monitoring of thiopurine therapy in paediatric gastroenterology and hepatology patients.

4. Introduction

Thiopurines (azathioprine and mercaptopurine) are immuno-modulatory agents used to induce and maintain remission in inflammatory bowel disease (IBD) and auto-immune hepatitis.

5. Abbreviations

ALT alanine transaminase

AST aspartate transaminase

GP general practitioner

IBD inflammatory bowel disease

TPMT thiopurine methyltransferase

VZV varicella zoster virus

CUH Cambridge University Hospitals NHS Foundation Trust

6. Dose and administration

- Azathioprine (CHILD 2-18 years): 2.5mg/kg once daily taken with or after food
- mercaptopurine (CHILD 2-18 years): 1-1.5mg/kg ONCE daily (initial max. 50mg; may be increased to 75mg once daily) taken with or after food.
- If a child requires a liquid formulation they will be commenced on mercaptopurine as it is a licensed oral suspension (used off-label to treat IBD). They should not be prescribed liquid azathioprine, as this is an unlicensed special formulation.
- Azathioprine and mercaptopurine are NOT therapeutically equivalent; therefore, children should not be switched between the medicines without specialist advice from the CUH team.
- Mercaptopurine tablets and oral suspension are NOT bioequivalent; therefore, children should not be switched between formulations without specialist advice from the CUH team.
- Azathioprine and mercaptopurine should not be crushed.
- Therapeutic effect is usually evident after several weeks up to 3-6 months.
- Patients with a low TPMT will be started on a lower dose than normal – usually half the dose. This will then be titrated according to response. See 'Cautions' section below.

7. Adverse Effects

Very common (≥ 1 in 10)

- Bone marrow suppression, leucopenia and therefore increased risk of infection (healthcare professional review is advised if temperature >38°C and not responding to paracetamol for 24 hours).
- Nausea, vomiting, anorexia and abdominal discomfort.

Common (≥ 1 in 100 and < 1 in 10)

- Thrombocytopenia.

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Anaemia.
- Pancreatitis.
- Cholestasis and degeneration of liver function tests (including hepatic necrosis).
- Hypersensitivity reactions (fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness.

Rare (≥ 1 in 10000 and < 1 in 1000)

- Neoplasms – significantly skin cancer and lymphoma.

- Alopecia.
- Photosensitivity.

8. Cautions

- The patient should be advised to report any signs of bone marrow suppression or hypersensitivity (ie infection, fever, chills, cough, unexplained bruising or bleeding, fatigue, hypotension, myalgia, dizziness) to their GP or general paediatrician or paediatric gastroenterology team.
- Prior to commencing thiopurine therapy the prescriber at CUH should check the patient's varicella zoster virus (VZV) immunity despite a positive history of previous exposure and document if the patient has any history of VZV.
- Patients who have no immunity should be vaccinated against varicella zoster prior to commencing thiopurine treatment if clinically appropriate.
- Patients with no immunity should be provided with a letter to act as emergency plan in the event of exposure – see section 11.
- Patients who have no history of exposure will be advised to avoid contact with individuals with chickenpox or herpes zoster. If the patient is exposed to VZV, this should be reported to the GP or hospital specialist and treatment commenced within 7 days.
- Cold sores should be reported to the GP as topical and/or oral antiviral therapy may be required.
- Patients may have an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) which will make them unusually sensitive to the myelosuppressive effect. Patients will have TPMT levels checked by the CUH prescriber prior to starting thiopurine treatment, with results included in clinic letters. Patients with a low TPMT level (<68mU/L) will start on half of the normal dose and titrated to tolerance. Treatment may be reconsidered in those who are deficient. Those with a high activity will metabolise the thiopurine more quickly and therefore the therapeutic effect and hepatotoxicity (due to the inactive metabolites) will be closely monitored.
- If a patient is noted by the specialist team at CUH to be hypermethylating and thioguanine nucleotides (TGNs) are sub-therapeutic, we recommend either adding 100mg allopurinol daily or dose splitting – e.g. giving 50 mg twice a day instead of 100 mg once daily. If necessary, this will be initiated by the specialist team only.
- Careful assessment of risk versus benefit should be carried out before use during pregnancy and breastfeeding. A discussion should be carried out between the patient and the hospital specialist team at the time of pregnancy.
- Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor (30-50) to minimise the risk of skin cancer and photosensitivity.

9. Contraindications

- Hypersensitivity to azathioprine, mercaptopurine (metabolite of azathioprine) or to any of the excipients.
- Severe infections.

- Severely impaired hepatic or bone-marrow function.
- Pancreatitis.
- Any live vaccine eg BCG, smallpox, yellow fever .
- Pregnancy unless the benefits outweigh the risks.

10. Interactions

- Allopurinol – decreased metabolism of thiopurines. The dose of azathioprine/ mercaptopurine must be reduced to a quarter of the original dose.
- Immunosuppressives (ciclosporin/tacrolimus) – increased risk of immunosuppression.
- ACE-inhibitors, co-trimoxazole/ trimethoprim, cimetidine or indomethacin – increased risk of myelosuppression.
- Warfarin – Anticoagulant effect of warfarin possibly reduced by thiopurines. Monitor INR.
- Aminosalicylic acid derivatives (olsalazine, mesalazine and sulphasalazine) – increased myelosuppressive effect of azathioprine.
- **Live** vaccines – increased risk of the generalised infection.

Please note that the above list is NOT exhaustive.

Before the patient starts any new medicine, they have been advised to check with the GP/ prescriber.

Further information can be found in the Summary of Product Characteristics.

11. Monitoring Standards & Actions to take in the event of abnormal test results/ symptoms

Monitoring during therapy to be undertaken by CUH

Differential FBC, U&Es and LFTs including GGT, CRP

Weeks 1, 2, 3, 4, 6, 8, 12.

Monitoring during therapy to be undertaken by GP

Differential FBC, U&Es and LFTs including GGT, CRP

Every 3 months after week 12.

These results will be reviewed periodically by the paediatric gastroenterology team when emailed.

More frequent blood tests will be needed if:

- high dosages are used.
- renal function is impaired.
- hepatic function is mildly to moderately impaired.
- bone marrow function is mildly to moderately impaired.
- in patients with hypersplenism.

The paediatric gastroenterology team at CUH will provide advice on the tests needed and frequency.

Amylase and Lipase

If the patient complains of central abdominal pain/has clinical signs of pancreatitis, primary care should seek urgent advice from the paediatric gastroenterology team.

Action to take in the event of abnormal test results/ symptoms

Abnormal FBC results

Test	Action
White cell count < 2.5 x 10^9 /L	Stop azathioprine/ mercaptopurine and discuss with paediatric gastroenterology team immediately
Haemoglobin <100 g/L	Stop azathioprine/mercaptopurine and contact the paediatric gastroenterology team
Platelets <150 x 10^9	Stop azathioprine/mercaptopurine and contact the paediatric gastroenterology team
Neutrophils **a) < 1.0 x 10^9/L** **b) 1 – 1.5 x 10^9/L**	a) Stop Azathioprine/ mercaptopurine and contact the paediatric gastroenterology team. b) Re-check in one week and contact paediatric gastroenterology team for guidance to restart.
Lymphocytes < 0.5	Stop Azathioprine/ mercaptopurine and contact the paediatric gastroenterology team. Re-check in one week and contact paediatric gastroenterology team for guidance to restart.
MCV > 105 fl	Check B12, folic acid and thyroid stimulating hormone (TSH). Treat as appropriate and discuss with the paediatric gastroenterology team.

Abnormal LFT results

Test	Action
>2 fold rise in AST, ALT (from upper limit of reference range)	Repeat LFTs in 1 month.
>3 fold rise in AST, ALT (from upper limit of reference range)	Stop Azathioprine/ mercaptopurine and contact the paediatric gastroenterology team.

Abnormal symptoms

Symptom	Action
Severe or persistent infections, fever, chills and/ or persistent sore throat	Stop Azathioprine/mercaptopurine and check FBC. If FBC is **abnormal** contact the paediatric gastroenterology team. If FBC is **normal**, wait until infection resolved and restart at original dose.

Symptom	Action
Abnormal bruising or bleeding (bleeding that does not stop with applied pressure or bruising that is unexplained)	Stop Azathioprine/ mercaptopurine and contact the paediatric gastroenterology team.
Presence of cold sores	Treat with topical acyclovir as per BNF for children Treat with a course of oral aciclovir if not responding to topical in 2 days as per BNF for children
Varicella/Shingles	If the patient does not have immunity, prescribe Acyclovir attenuated dose 7 days after exposure for 7 days Contact the paediatric gastroenterology team with ANY concerns If the patient develops lesions – commence Oral Aciclovir immediately, advise family if no improvement in 24-48 hours admission to hospital for IV Acyclovir may be necessary.

12. Contact numbers for advice and support

Patients and their carers should be encourage to sign up to MyChart. MyChart is the electronic patient portal at Addenbrooke's and The Rosie hospitals which allows patients to securely access parts of their health record held within the hospitals' Epic electronic patient record system.

MyChart that enables patients to:

- check-in for appointments
- message the paediatric gastroenterology specialist team
- download recent visit records
- securely share MyChart information electronically with clinicians outside of Addenbrooke's & The Rosie i.e. your GP, community care staff, clinicians at other hospitals (via 'Share Everywhere' within MyChart)

MyChart is designed to improve communication between the patient and their clinical teams, and enables patients to be more involved and informed about their care by having access to their information.

To sign-up to MyChart patients and their carers can either:

Complete the online registration form

or speak with a clinic receptionist about MyChart sign-up during their next appointment.

Cambridge University Hospitals NHS Foundation Trust

Specialist	Post	Telephone
Mary Brennan Anna Folan	Paediatric IBD Clinical Nurse Specialists	01223 274757
Emma Wilkinson	Paediatric Pharmacist	01223 254417
Dr Robert Heuschkel	Consultant Paediatric Gastroenterologist	Secretary - 01223 274827
Dr Franco Torrente	Consultant Paediatric Gastroenterologist	Secretary - 01223 274827
Paediatric IBD helpline/ Email		01223 274757 add-tr.paediatricibd@nhs.net
Out of hours	Paediatric registrar on call via switchboard	01223 245151 – request paediatric on call registrar is contacted

13. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service Equality and Diversity statement.

14. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

Ratification process	Details
Authored by:	Cambridge University Hospitals NHS Foundation Trust
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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics for azathioprine and mercaptopurine.

Appendix 1

Key information given to patients prior to commencing thiopurine:

Most common side effects:

- Slightly increased risk of infection hence blood tests are important to ensure white cell count is not too low.
- Feeling sick and/or being sick, to reduce the risk of this side effect please give the patient the thiopurine in the evening (before bed) with a snack – please avoid dairy products.

Important information:

- Factor 30-50 sunscreen is advised to be worn from end of March to end of October. End of October to March SPF 15 is encouraged.
- Live vaccines must not be given – please see letter re: vaccinations. We encourage children on thiopurines to be vaccinated in line with the National Vaccination Programme. In addition to this we encourage that the patient has the Pneumococcal and annual flu vaccine (information in the Shared care guideline for healthcare professionals).
- If the patient has a temperature of 38 or above and not responding to paracetamol or continues for more than 24 hours, their carer should seek advice from a healthcare professional.
- If the patient experiences central abdominal pain or is vomiting – we have advised a review by a healthcare professional is sought as checking amylase and lipase is important to exclude pancreatitis.
- Before the patient is started on a thiopurine their chicken pox antibodies will be checked by CUH and the results communicated to the GP. If they DO NOT have immunity and are in direct contact with chicken pox or shingles, they should be prescribed an attenuated dose of aciclovir within 7 days of exposure as per the BNF for children. The GP can contact the duty virologist at CUH for further advice (Addenbrooke's via contact centre – 01223 245151).
- Blood tests must be taken according to the timetable. The patient's carers have been advised that should blood tests should not be missed but if they are please get them done as soon as possible.
- Transfer to primary care (GP) is normally after the patient has been treated for 3 months and with satisfactory investigation results for at least 4 weeks. CUH will prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- If the blood tests are not being undertaken at CUH please give the family a copy to bring to the patient's appointment.

Information provided:

- IBDmate video on azathioprine (patient only)
- Shared care guideline for healthcare professionals

Support/ advice:

- For parents and carers: Contact paediatric IBD help line on 01223 274757 or email add-tr.paediatricibd@nhs.net – This is not an emergency contact out of hours (after 16:00 – 08:00, not covered over weekend or bank holidays).
- For healthcare professionals: Pease contact the contact centre on 01223 245151 and ask to contact the paediatric registrar on call. The specialist paediatric IBD nurses mobile number: 07907573481 for use between 8am and 4pm, not covered over weekend or bank holidays.

Sharing of care depends on communication between the specialist, GP and the patient or their parent/ carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/ healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Appendix 2:

Shared Care Agreement Letter (Primary Care Prescriber to Specialist)

Primary Care Prescriber Response

Dear *[insert Doctor's name]*
Patient *[insert Patient's name]*
NHS Number *[insert NHS Number]*
Identifier *[insert patient's date of birth and/oraddress]*

Thank you for your request for me to accept prescribing responsibility for this patient under a shared care agreement and to provide the following treatment

Medicine	Route	Dose & frequency

I can confirm that I am willing to take on this responsibility from *[insert date]* and will complete the monitoring as set out in the shared care protocol for this medicine/condition.

Primary Care Prescriber signature: _____ Date: _____

Primary Care Prescriber address/practice stamp

Appendix 3:

Shared Care Refusal Letter (Primary Care Prescriber to Specialist)

Re:

Patient	*[insert Patient's name]*
NHS Number	*[insert NHS Number]*
Identifier	*[insert patient's date of birth and/oraddress]*

Thank you for your request for me to accept prescribing responsibility for this patient.

In the interest of patient safety NHS *[insert ICB name]***,** in conjunction with local acute trusts have classified *[insert medicine name]*as a Shared Care drug, and requires a number of conditions to be met before transfer can be made to primary care.

I regret to inform you that in this instance I am unable to take on responsibility due to the following:

		Tick which apply
1.	**The prescriber does not feel clinically confident in managing this individual patient's condition, and there is a sound clinical basis for refusing to accept shared care** As the patients primary care prescriber I do not feel clinically confident to manage this patient's condition because *[insert reason]*. I have consulted with other primary care prescribers in my practice who support my decision. This is not an issue which would be resolved through adequate and appropriate training of prescribers within my practice. **I have discussed my decision with the patient and request that prescribing for this individual remain with you as the specialist, due to the sound clinical basis given above.**	

		Tick which apply
2.	**The medicine or condition does not fall within the criteria defining suitability for inclusion in a shared care arrangement** As the medicine requested to be prescribed is not included on the national list of shared care drugs as identified by RMOC or is not a locally agreed shared care medicine I am unable to accept clinical responsibility for prescribing this medication at this time. **Until this medicine is identified either nationally or locally as requiring shared care the responsibility for providing this patient with their medication remains with you**	
3.	**A minimum duration of supply by the initiating clinician** As the patient has not had the minimum supply of medication to be provided by the initiating specialist I am unable to take clinical responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. ***Until the patient has had the appropriate length of supply the responsibility for providing the patient with their medication remains with you.***	
4.	**Initiation and optimisation by the initiating specialist** As the patient has not been optimised on this medication I am unable to take clinical responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. ***Until the patient is optimised on this medication the responsibility for providing the patient with their medication remains with you.***	

		Tick which apply
5.	**Shared Care Protocol not received** As legal responsibility for clinical care lies with the clinician who signs the prescription, I need to ensure that I am in possession of sufficient clinical information for me to be confident to prescribe this treatment for my patient and it is clear where each of our responsibilities lie to ensure the patient is safely managed**.** For this reason I am unable to take clinical responsibility for prescribing this medication at this time, therefore would you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. ***Until I receive the appropriate SCP, responsibility for providing the patient with their medication remains with you.***	
6.	**Other (Primary Care Prescriber to complete if there are other reasons why shared care cannot be accepted)**	

I would be willing to consider prescribing for this patient once the above criteria have been met for this treatment.

NHS England 'Responsibility for prescribing between Primary & Secondary/Tertiary care' guidance (2018) states that "when decisions are made to transfer clinical and prescribing responsibility for a patient between care settings, it is of the utmost importance that the GP feels clinically competent to prescribe the necessary medicines. It is therefore essential that a transfer involving medicines with which GPs would not normally be familiar should not take place without full local agreement, and the dissemination of sufficient, up-to-date information to individual GPs." In this case we would also see the term GP being interchangeable with the term Primary Care Prescriber.

Please do not hesitate to contact me if you wish to discuss any aspect of my letter in more detail and I hope to receive more information regarding this shared care agreement as soon as possible

Yours sincerely

Primary Care Prescriber signature: _____
Date: _____
Primary Care Prescriber address/practice stamp