

Guideline for the Management of Azathioprine Therapy in Children with Gastroenterological Conditions

A Clinical Guideline

For Use in:	Jenny Lind Children's Department
By:	Medical and Nursing Staff
For:	Children (0-16) who are on Azathioprine or being considered for Azathioprine treatment
Division responsible for document:	Paediatrics
Key words:	Azathioprine, Immunomodulator agent, Immunosuppression, 6-mercaptopurine
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Assessed and approved by the:	Clinical Guidelines Assessment Panel (CGAP) If approved by committee or Governance Lead Chair's Action; tick here <input checked="" type="checkbox"/>
Date of approval:	17/03/2022
Ratified by or reported as approved to (if applicable):	Clinical Safety and Effectiveness Sub-board
To be reviewed before: This document remains current after this date but will be under review	17/03/2025
To be reviewed by:	Dr Mary-Anne Morris/Dr Graham Briars
Reference and / or Trust Docs ID No:	CA5056 id 8271
Version No:	5
Compliance links: (is there any NICE related to guidance)	None

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Version and Document Control:

Version Number	Date of Update	Change Description	Author
5	17/03/2022	Minor changes following review. Agreed at Paed Gastroenterology team. Updating of section E -Monitoring of metabolites, with input from Rosalind Howe.	Dr Mary-Anne Morris Dr G Briars

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Objective/s

To ensure safe prescribing of azathioprine and effective monitoring of possible side effects in children who are prescribed azathioprine as an Immunomodulator Drug for gastroenterological conditions.

Rationale

A significant number of children with Inflammatory Bowel Disease and some children with conditions like autoimmune diseases or transplant recipients need an immunosuppressant drug to achieve long term control of inflammation. Azathioprine is the first line immunosuppressant in inflammatory bowel disease. It is usually well tolerated but there are potential side effects and contraindications to its use. Azathioprine is a pro-drug, which is split rapidly in the liver to 6-mercaptopurine and then metabolised to the active metabolite 6-thioguanine. Thiopurine Methyl Transferase (TPMT) is an enzyme involved in the pathway. Testing TPMT activity helps to identify patients at risk of early profound myelosuppression and is recommended prior to treatment. Myelosuppression may still occur in the presence of normal TPMT activity, which also does not identify patients at risk of other toxic or allergic adverse effects, therefore regular monitoring of signs, symptoms and blood results are necessary.

This guideline has been formulated to provide guidance to professionals involved in the prescribing or monitoring of children on azathioprine.

Broad recommendations

- Decision to start azathioprine in children will be taken by the named Paediatric Consultant working within the EoEPGN after counselling of patient and parents/guardian.
- Patient information leaflet and Blood monitoring schedule should be provided to the patient and parents. (Attached Patient Info Sheet- Appendix 1)
- Thiopurine Methyl Transferase (TPMT) level should be checked and results should preferably be available prior to commencement of azathioprine. This can be checked by sending 5 mL of EDTA blood to Chemical Pathology. The results take 1-2 weeks. Blood transfusion within the last three months may give spurious results.
- The dose prescribed for individual patient is at the discretion of the Consultant prescribing it but will usually be a starting dose of 2.0-2.5mg/kg once a day with normal TPMT levels, 0.5-1mg/kg once a day if TPMT levels are low and it should not be prescribed if TPMT is very low/absent as defined by laboratory standards.
- Clinical response to azathioprine will be assessed in follow up clinics and will be based on clinical symptoms, signs and blood results. Response may take up to 10-14 weeks after the start of treatment.
- Thiopurine metabolites (6TGN, 6MMP) can be measured to guide dosing. This is usually after 8 week treatment or if there is concern about efficacy or compliance
- Blood tests to monitor unwanted side effects of the drug should be carried out as per the Guidelines under the supervision of the Hospital Consultant.

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Request forms for all monitoring bloods will be supplied by the paediatric gastroenterology team. Amylase if not routinely measured but should be done urgently if abdominal pain is reported.

- Patient should be made aware of warning signs and symptoms which they need to report urgently. (Patient Info Sheet)
- Patients of reproductive age group, both male and female, should be advised to avoid pregnancy whilst taking azathioprine and for 3 months after discontinuation. This should be clearly documented.

Dosage and administration

If patient has normal TPMT status the initial recommended starting dose is **2-2.5 mg/kg once a day** ^{2,12,13,14} orally *with or after food often tolerated better if taken at night* and can be titrated according to response. (Grade A;Level II evidence). Children with Low TPMT activity should be started at a dose between 0.5-1mg/kg once a day.^{212,134} (Grade B;Level III evidence). Levels as defined by laboratory standards. Azathioprine is available as 25mg and 50mg tablets and 50mg in 5ml oral solution (unlicensed Special)

Contraindications to use of Azathioprine

- 1) Known hypersensitivity to the Drug ^{2,13}
- 2) Significant haematological impairment
- 3) Moderate to severe renal or hepatic insufficiency (azathioprine may be prescribed specifically for autoimmune liver disease)
- 4) In adolescent girls who may be pregnant or hope to become pregnant in near future. (Azathioprine should not be started without careful assessment of risk versus benefit in such patients)
- 5) Thiopurine induced pancreatitis
- 6) Severe infection
- 7) TPMT deficiency (reduce dose if levels are low)

Cautions

- 1) Increased risk of haematological toxicity with co-trimoxazole / trimethoprim
- 2) Patients on azathioprine must not have live vaccines such as Oral Polio, Oral Typhoid, MMR, BCG, nasal influenza and Yellow fever. Due to risk of orofaecal transmission other family members should receive Inactive Polio Vaccine if needed.
- 3) Concurrent allopurinol administration (not an absolute contraindication and can be used to manage hypermetabolism: (see section E)– Azathioprine dose to be reduced to quarter of normal)
- 4) Patients should try to avoid any contact with people who have active chicken pox or shingles and should report any such contact to their GP or Hospital Specialist for consideration of Varicella zoster Immunoglobulin.
- 5) Anticoagulant effect of warfarin may be impaired with azathioprine

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- 6) Increased sun-protection to be advised (sun-screen against UVA/UVB) given reports of 4-5 fold increased risk of non-melanoma skin cancers in patients on thiopurines (ref Ulrich)
- 7) Patients on azathioprine are recommended to have injected influenza vaccination annually.

Red Flag symptoms while on Azathioprine

Patients should report the following warning symptoms immediately to their GP or Hospital Consultant: (Patient info sheet)

- 1) Significant new rash (check FBC for dyscrasia)
- 2) Severe infections, fever , chills
- 3) Sore throat >5 Days
- 4) Moderate to severe upper/central abdominal pain (check amylase)
- 5) Abnormal bruising or bleeding.
- 6) Severe nausea, vomiting or diarrhoea
- 7) Chicken pox rash

Other Adverse effects

- 1) Nausea, vomiting, diarrhoea, anorexia and dyspepsia (5-8% patients)
- 2) Hepatotoxicity
- 3) Myelosuppression
- 4) Increased risk of infection
- 5) Hypersensitivity reactions
- 6) Rarely pancreatitis (3-4% of patients, usually presents in first 6 weeks of treatment, is independent of dose and is most often a hypersensitivity reaction. It usually requires discontinuation of azathioprine)

Monitoring of Blood Biochemistry and Haematology Results

A) Pre-Treatment assessment: FBC, LFT, TPMT activity^{2,13}, Varicella Status ^{2,10}

B) Monitoring: ^{2,10,12}

FBC	Fortnightly in the 1 st and 2 nd month then monthly for the next 4/12, then 3 monthly from the 6th month onwards till any dose change.
LFT	As above
CRP/ESR	As clinically indicated to assess disease activity
U&E	At least once monthly from start, then 3 monthly from 3 rd month
Amylase	If there is any complaint of central abdominal pain and/or pancreatitis is suspected

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Consider need for increased monitoring if dose is increased. A local audit of blood monitoring demonstrated poor compliance with weekly blood tests and no side effects from Azathioprine that would have been detected by weekly testing (Dr Briars, personal communication). The frequency of FBC monitoring is in line with UK best practice and ECCO guideline (14).

C) Action on abnormal results:

- If any of the following noted urgent Medical review is needed if child is unwell or inform named Consultant if child is well:
- Sore throat with oral or pharyngeal ulceration
- Unexplained bruising /bleeding or appearance of new rash

Blood test results		Action
Total WBC	2.5 - 4 x 10 ⁹ /L	Reduce dose and repeat FBC.
	1.5 - 2.5 x 10 ⁹ /L	Withhold drug and repeat in 1 week. Consider restarting at lower dose with weekly FBC monitoring.
	<1.5 x 10 ⁹ /L	Withdraw treatment.
Neutrophils	< 1.0 x 10 ⁹ /L	Repeat and discuss with Consultant
Lymphocytes	< 0.5 x 10 ⁹ /L	Repeat and discuss with Consultant if still low
Platelets	<150 x 10 ⁹ /L	Repeat and discuss with Consultant
AST/ALT/ALP	>2 fold rise	Repeat and if still high discuss with named Consultant
	>4 fold rise	Withhold medication, repeat and discuss with named Consultant

D) Exposure to Chicken pox infection or Clinical infection

Follow guidance from Immunisation against infectious disease. (Green Book)

http://www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Greenbook/DH_4097254

Immunisation against Varicella should be considered prior to starting immunosuppression in those without protective antibodies.

E) Monitoring of metabolites

Consider measuring 6TGN and 6MMP in patients with raised liver enzymes, cytopenia or suboptimal response.

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6-TGN	6-MMP	Possible adverse event or finding	Interpretation	Recommendation
Low [<230]	Normal [<5700]	-	Under-dosing or low compliance	Increase compliance or thiopurine dose as appropriate
Low [<230]	High [≥5700]	Hepatotoxicity and others	TPMT hyper-metaboliser	Consider allopurinol co-treatment and thiopurine dose reduction to 25–33% of standard dose, or change medication
Therapeutic [230–450]	Normal or high	Refractoriness	Therapy failure	If clinically resistant, change medication
High [>450]	Normal	Myelosuppression	Low TPMT activity [heterozygote or homozygote]	Change drug category if homozygote, or reduce dose to half if heterozygote
High	High	Myelosuppression and hepatotoxicity	Overdosing	Reduce dose and if clinically resistant, change drug category

Clinical audit standards

- Pre-treatment blood tests performed and documented.
- Written information given to patient/family and documented.
- Monitoring of blood tests within guidelines.
- Actions taken on the basis of side effects clearly documented.

Summary of development and consultation process undertaken before registration and dissemination

This guideline has been drafted based on local and National guidelines that exist for the use of azathioprine in adult patients and recent scientific evidences available for the recommendations. During its development it has been circulated for comment within the NNUH Paediatric Directorate and Pharmacy Department. It was then reviewed by the East of England Paediatric Gastroenterology Network and comments have been incorporated into the final version where appropriate.

The guideline was revised by Dr Briars and Dr Morris in 2015. The patient front sheet for documenting side effects has been superseded by Paradox database and is therefore deleted. The interval for FBC monitoring has been increased from weekly to fortnightly in the first month in line with UK best practise and after an audit had demonstrated poor compliance with weekly bloods and an absence of clinical benefit. Guideline review in 2018 resulted in the addition of reference 14 (BSPGHAN guideline), clarification of starting dose and addition of statements on influenza

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vaccination. Review in 2022 by Dr Morris and Ros Howe revised rationale and added section E.

Distribution list/ dissemination method

Pharmacy Services
Trust Intranet

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The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update 2020 <https://doi.org/10.1093/ecco-jcc/jjaa161>

Appendix 1:

Information on Azathioprine for Inflammatory Bowel Disease (Paediatrics)
[Trustdocs Id: 9724](#)