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
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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 although it is an unlicensed indication. It is usually well tolerated but there are potential side effects and contraindications to its use. This necessitates stringent monitoring of signs, symptoms and blood results. 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/day with normal TPMT levels, 0.5-1mg/kg/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.
- 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. Request forms for all monitoring bloods will be supplied by the paediatric gastroenterology team.
- 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/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/day.*[212,134] (Grade B;Level III evidence). Levels as defined by laboratory standards.

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) Concurrent allopurinol administration (not an absolute contraindication –dose to be reduced to quarter of normal)
5) 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)
6) Thiopurine induced pancreatitis

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

Red Flag symptoms while on AZA

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

Adverse effects

1) Nausea ,vomiting , diarrhoea, anorexia and dyspepsia
2) Hepatotoxicity
3) Myelosuppression
4) Increased risk of infection
5) Hypersensitivity reactions
6) Rarely pancreatitis

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 1st and 2nd 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 3rd month
Amylase	If there is any complaint of central abdominal pain and/or pancreatitis is suspected

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:

- Neutrophil count < 1 × 10^9 /L
- White blood cells <2.5 × 10^9 /L
- Lymphocytes <0.5× 10^9 /L
- Platelets <150 × 10^9 /L
- AST / ALT > 2 times ULN
- Sore throat with oral or pharyngeal ulceration
- Unexplained bruising /bleeding or appearance of new rash

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. For interpretation see ECCO guidelines (reference 14).

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.

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Guideline review in 2018 resulted in the addition of reference 14 (BSPGHAN guideline), clarification of starting dose and addition of statements on influenza vaccination.

Distribution list/ dissemination method

Pharmacy Services
Trust Intranet

References/ source documents

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14) BSPGHAN IBD working group. Thiopurine Blood Monitoring Guidelines http://bspghan.org.uk/documents/Azathioprine%20Guidelines%20BSPGHAN%20Final.pdf

Appendix 1:

Information on Azathioprine for Inflammatory Bowel Disease (Paediatrics)
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