

BNSSG Paediatric Shared Care Guidance

Please complete all sections

Section 1: Heading

Drug	Azathioprine
Amber <i>one month</i>	
Indication	Azathioprine is an immunosuppressive drug, which is effective in Crohn's disease and Ulcerative Colitis as a second line treatment and also as a steroid sparing agent.
Speciality / Department	Paediatric Gastroenterology
Trust(s)	University Hospitals Bristol NHS Foundation Trust

Section 2: Treatment Schedule

Usual dose and frequency of administration <i>(Please indicate if this is licensed or unlicensed for this age group and any relevant dosing information)</i>	Under the care of the paediatric gastroenterology team: Initially 2mg/kg once daily, increased up to 2.5mg/kg once daily (maximum 3mg/kg once daily). In patients with intermediate enzymatic activity or heterozygous TPMT, dose should be reduced to 1mg/kg.
Route and preferred formulation <i>(Please indicate licensed or unlicensed preparation)</i>	Oral 25mg and 50mg tablets Unlicensed 50mg/5mL suspension
Duration of treatment	Long term

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist)

Baseline tests to be done by secondary care
Secondary care: FBC, U&Es, LFTs, Thiopurine Methyl Transferase (TPMT) level (not reliable if red blood cells have been transfused within the previous 3 months)
Subsequent tests - where appropriate <i>(Please indicate who takes responsibility for taking bloods and interpreting results. If the drug is dosed by weight please also indicate intended frequency of weight monitoring/dose adjustment)</i>
Secondary care: FBC, LFTs and U&Es on week 2 and week 4.

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Primary care:

If bloods are stable, FBC, LFT and U&Es on week 8 and week 12 then 12 weekly thereafter:

Test	Frequency	Who by	Action/Management
Full Blood Count values:			
WBC 2.5 - 4 x 10 ⁹ /L (mild)	Week 8, Week 12, 12 weekly thereafter	Primary care	Discuss with hospital team. Dose should be reduced and FBC repeated.
WBC 1.5-2.5 x 10 ⁹ /L (moderate)			Withhold drug and repeat in 1 week. Discuss with hospital team.
WBC <1.5 x 10 ⁹ /L (severe)			Stop drug and refer to hospital team.
Neutrophils <1.0x 10 ⁹ /L			Repeat and discuss with hospital team if still low.
Lymphocytes <0.5 x 10 ⁹ /L			Repeat and discuss with hospital team if still low.
Platelets <150 x 10 ⁹ /L			Repeat and discuss with hospital team if still low.
LFTs Elevation of liver enzymes (ALT, AST, ALP)			If >2 fold but <4 fold, repeat and if still high discuss with hospital team. If >4 fold, withhold medication, repeat and discuss with hospital team. Azathioprine is hepatotoxic.
U&Es Renal Impairment	If creatinine is outside of specific limit for patient given by secondary care, use generic table given below. If creatinine falls outside of reference range, contact hospital team to discuss. Reference table for children's creatinine levels shown below.		

Creatinine reference table for children

Female		Male	
Age range	Reference interval	Age range	Reference interval
0 - 14 days	27 - 77 µmol/L	0 - 14 days	27 - 77 µmol/L
14 days - 1 year	14 - 34 µmol/L	14 days - 1 year	14 - 34 µmol/L
1 year - 3 years	15 - 31 µmol/L	1 year - 3 years	15 - 31 µmol/L
3 years - 5 years	23 - 37 µmol/L	3 years - 5 years	23 - 37 µmol/L
5 years - 7 years	25 - 42 µmol/L	5 years - 7 years	25 - 42 µmol/L
7 years - 9 years	30 - 47 µmol/L	7 years - 9 years	30 - 47 µmol/L
9 years - 11 years	29 - 56 µmol/L	9 years - 11 years	29 - 56 µmol/L
11 years - 12 years	36 - 64 µmol/L	11 years - 12 years	36 - 64 µmol/L
12 years - 13 years	36 - 67 µmol/L	12 years - 13 years	36 - 67 µmol/L
13 years - 14 years	38 - 74 µmol/L	13 years - 14 years	38 - 76 µmol/L
14 years - 15 years	43 - 75 µmol/L	14 years - 15 years	40 - 83 µmol/L

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15 years - 16 years	44 - 79 µmol/L	15 years - 16 years	47 - 98 µmol/L
16 years - 17 years	48 - 81 µmol/L	16 years - 17 years	54 - 99 µmol/L
17 years - Adult	45 - 84 µmol/L	17 years - Adult	59 - 104 µmol/L

Frequency of ongoing follow up by secondary care <i>(Please indicate how often child will continue to be seen by secondary care i.e. at least every 6 months)</i>	3 monthly
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Section 4: Side Effects

Please list only the most pertinent side effects and management. Please provide guidance on when the GP should refer back to the specialist. For everything else, please see BNFc or SPC.

Side effects and management		
Referral back to specialist	Problem	Management
	Gastrointestinal tolerance (such as diarrhoea, nausea/vomiting and/or loss of appetite)	Tolerance to these side effects should occur within 2 weeks. Nausea can be reduced by taking with food, dividing the dose or taking at night. If symptoms persist refer back to hospital team.
	Severe rash	Stop drug and refer back to hospital team.
	Fever, flu-like symptoms, myalgia and arthralgia	Refer back to hospital team who may consider switching from azathioprine to 6-mercaptopurine.
	Alopecia	Usually resolves spontaneously despite continuing treatment – link between azathioprine and alopecia uncertain.
	Signs of bone marrow suppression: severe or persistent infection, sore throat, oral ulceration, fever and/or unexplained bruises or bleeding	Check FBC (see below) and discuss with specialist clinician. Azathioprine should be stopped in all but minor infections as the body defences may be reduced and delay recovery. Bone marrow suppression is reversible if azathioprine is stopped early enough.
	Raised amylase or symptoms suggesting pancreatitis	Stop drug and refer to hospital team. Usually occurs within first 6 weeks. This is usually

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		reversible on stopping treatment.
	Chicken pox/shingles	Stop drug, commence oral aciclovir and refer to hospital team.
<p>Patients receiving azathioprine are at an increased susceptibility to viral, fungal and bacterial infections.</p> <p>Serious rare side effects: Pneumonitis is a very rare side effect that is reversible on discontinuation.</p> <p>There is a 4-5 fold increased risk of non-melanoma skin cancers before the age of 50 years. There is a low risk of lymphoma for any given patient.</p>		

Section 5: Other Issues

(e.g. Drug Interactions, Contra-indications, Cautions, Special Recommendations)

Please list only the most pertinent and the action for GP to take (For full list please see BNFC or SPC)

Issues	Interactions	
	Drug	Significance/Action
	Allopurinol	The azathioprine dose should be reduced to 25% of the original dose.
	Aminosalicylates	Aminosalicylate derivatives inhibit the TPMT enzyme. Therefore lower doses of azathioprine may need to be considered when administering concomitantly.
	Captopril and Enalapril	Haematological abnormalities (especially in renal impairment)
	Clozapine	Avoid concomitant use – increased risk of agranulocytosis
	Cytostatic/ myelosuppressive agents (i.e. Penicillamine)	Should be avoided due to enhanced myelosuppression.
	Co-trimoxazole and Trimethoprim	Information limited and interaction not established. There is a possible increased risk of haematological toxicity.
	Cimetidine and Indometacin	Myelosuppressive effects
	Live vaccines (Varicella vaccine, MMR, BCG, oral polio, oral typhoid, yellow fever and Fluenz Tetra nasal spray)	Risk of generalised infections when given with live vaccine. Avoid concomitant use.
Warfarin	Anticoagulant effect may be reduced. Warfarin doses may need to be increased.	
<p>Contra-indications: hypersensitivity to azathioprine, significant haematological impairment, excessive sunbathing and exposure to UV light (increased risk of non-melanoma skin cancers), patients with hypoxanthine-guanine phosphoribosyltransferase deficiency and pregnant patients or those likely to become pregnant.</p>		

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	<p>Caution: Renal & liver impairment, contact specialist clinician as reduced dose is likely to be needed.</p> <p>Special recommendations:</p> <ul style="list-style-type: none"> - Patients should avoid people who have active chickenpox or shingles – report any such contact to GP/hospital specialist - Care should be taken to avoid use of azathioprine during EBV infection due to the risk of EBV-associated lymphomas - A diminished response to live attenuated vaccines (polio, oral typhoid, MMR, BCG, Varicella, Fluenz nasal influenza and yellow fever) is likely and such a response to hepatitis B has been observed among patients treated with combination of azathioprine and corticosteroids - Report immediately any evidence of infection, unexpected bruising or bleeding or other manifestation of bone marrow depression - Present in breast milk in low concentrations. Mothers should not breastfeed whilst on azathioprine. No evidence of harm in small studies – use if potential benefit outweighs risk.
Reminder to ask patient about specific problems	N/A

Section 6: Advice to the patient

Advice for prescribing clinician to inform patient

1. Explain the importance and need for regular blood tests.
2. Patients should wear protective clothing and a high factor sunscreen during the summer.
3. Parents/carers/patients should be aware they should report any signs or symptoms of bone marrow suppression, for example, any bruising or bleeding, infection or any other side effects.
4. Patients not immune to chickenpox/shingles and who have been in contact with individuals with chickenpox/shingles should report this to their GP.
5. Therapeutic effect may take up to 10 to 14 weeks after the start of treatment.

Section 7: Generic principles of shared care for **SECONDARY CARE**

Core responsibilities

1. Initiating treatment and prescribing for the length of time specified in **section 1**.
2. Undertaking the clinical assessment and monitoring for the length of time specified in **section 1** and thereafter undertaking any ongoing monitoring as detailed in **section 3**.
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. if blood test is due.
5. To provide advice to primary care when appropriate.
6. Review in frequency specified in **section 3** and adjust dose for child's age/body weight as appropriate.
7. Review concurrent medications for potential interaction prior to initiation of drug specified in **section 1**.
8. Stopping treatment where appropriate or providing advice on when to stop.
9. Reporting adverse events to the MHRA.
10. Reminder to ask patients about particular problems see **section 5**.

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Section 8: Generic principles of shared care for PRIMARY CARE

Core responsibilities

1. Responsible for taking over prescribing after the length of time specified in **section 1**.
2. Responsible for any clinical assessment and monitoring if detailed in **section 3** after the length of time specified in **section 1**.
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see **section 5**.

Section 9: Contact Details

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Section 10: Document Details

Date prepared	October 2017
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Section 11: Collaboration

Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

1. Nil

Section 12: References

Please list references

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5. Fraser A, Gibbs K, 2010. BNSSG Azathioprine Shared Care Guideline
6. Turner D, Levine A, Escher JC, et al. Management of pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence-based Consensus Guidelines. JPGN 2012; 55: 340-361
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