Azathioprine (paediatric)

This document provides the necessary information and guidance for the shared care of children and adolescents requiring azathioprine therapy (available on www.noc.nhs.uk/oxparc).

Introduction
Azathioprine is a (non-biologic) disease modifying anti-rheumatic drugs (DMARDs) used in the treatment of inflammatory conditions including systemic lupus erthematosus (SLE), dermatomyositis, uveitis and vasculitis. The optimum therapeutic dose of DMARDs should be achieved to minimise disease progression and joint erosions.

Azathioprine should only be initiated by and under the direction of a consultant paediatric rheumatologist, or a rheumatologist with an interest in paediatric rheumatology.

Dose and administration
Azathioprine is prescribed according to weight (1-3mg / kg of body weight). Doses may be taken at any time of day, with or without food, and should be swallowed whole. It is best taken at the same time every day. It normally takes 4 or more weeks before an effect is seen.

Supply
Azathioprine is taken in tablet form, available in 25mg, 50mg, 100mg. Proprietary liquids are not available and so in children unable to take solid dosage forms, a specially manufactured liquid is required. These are unlicensed preparations and are generally less cost-effective than proprietary products and so should only be used when a child is unable to take a tablet/capsule. Only in exceptional cases should the use of specially manufactured liquids be required.

If a liquid preparation is required, children should be reviewed regularly and changed to the tablets/ capsules when they are able to take these. This can be arranged by GP with follow-up communication with our service.

Adverse effects.
Monitoring levels and frequency of blood tests do differ from the adult rheumatology shared care protocols to reduce the burden of blood tests which have been shown to be unnecessary in paediatric populations or to adjust lab data to normal paediatric physiology.

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

<table>
<thead>
<tr>
<th>Rash or mouth ulcers</th>
<th>Usually mild. If severe withhold until discussed with paediatric rheumatology team. Re-challenge with lower dose once symptoms settle.</th>
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<tbody>
<tr>
<td>Nausea, vomiting or diarrhoea</td>
<td>Look for alternative causes. Administer tablets after meals to reduce nausea. An anti-emetic or dose reduction may help. If symptoms persist discuss with paediatric rheumatology team.</td>
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<tr>
<td>WBC &lt; 4 X 10^9/l</td>
<td>Withhold, repeat WBC, if normal continue, otherwise discuss with paediatric rheumatology team. Leucopenia may be attributed to disease activity.</td>
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<tr>
<td>Neutrophils &lt;1.5 X10^9/l</td>
<td>Withhold until discussed with paediatric rheumatology team. Neutropenia may be attributed to disease activity.</td>
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Platelets <150 X10^9/l

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<thead>
<tr>
<th>Liver function. ALT or AST &gt;120</th>
<th>Withhold until discussed with paediatric rheumatology team. Transaminase increase 3 X normal is common within 2 days of drug administration and may be attributable to an asymptomatic viral infection.</th>
</tr>
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<tbody>
<tr>
<td>MCV &gt; 105 fl</td>
<td>Check folate. GGT, TSH B12. If B12 or folate low, start appropriate supplementation.</td>
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<tr>
<td>Unexplained fall in Albumin &lt;30</td>
<td>Withhold until discussed with rheumatologist</td>
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<tr>
<td>Alopecia</td>
<td>Increase in hair fall is common with disease activity. Alopecia is unlikely to be related to azathioprine in paediatric rheumatology practice. Usually reversible if attributable to azathioprine.</td>
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Notes:
- Azathioprine can be withheld for 2-3 weeks without inducing a flare.
- Azathioprine should not be stopped prior to elective surgery.

Contra Indications and Precautions

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<tr>
<th>Problem</th>
<th>Risk</th>
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<tr>
<td>Pregnancy and breastfeeding</td>
<td>There is no evidence that azathioprine is teratogenic. There are some reports of premature birth and low birth weight, particularly when azathioprine is taken in combination with corticosteroids. It is still better to avoid a pregnancy on azathioprine and contraceptive advice should be given. Breast feeding should be avoided</td>
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<tr>
<td>Chicken pox /Shingles</td>
<td>If a patient develops chicken pox, withhold azathioprine &amp; inform rheumatology team. If a patient who has not had chickenpox is exposed to chicken pox inform rheumatology team. If a patient develops shingles with active skin lesions, withhold azathioprine and inform paediatric rheumatology team.</td>
</tr>
<tr>
<td>Possible increased risk of some types of cancer, including skin cancer</td>
<td>Protect child’s skin from sunburn, with clothing, such as a hat and apply a ‘high protection’ sunscreen to exposed skin.</td>
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Vaccinations
- Live vaccines such as oral polio, rubella, MMR, BCG and yellow fever should not be given due to risk of increased antigenic reaction and possible reduced immunological response.
- Pneumovax is recommended
- Annual flu vaccines are safe and recommended.

Up to date advice on vaccines can be obtained from website / paediatric rheumatology team.

Drug interactions (refer also to BNF or SPC)
NSAID’s in addition to the recommended doses of azathioprine are not contraindicated.
- There is a significant interaction between allopurinol and azathioprine and so these should not be used concurrently without first discussing with the specialist team.
- Co-trimomazole and Trimethoprim should be avoided as they can increase the risk of bone marrow problems.
- Warfarin – INR may be reduced
- ACE inhibitors

Monitoring
Pre treatment assessment by Rheumatologist
FBC, ESR, CRP, LFT’s and U&E’s will be checked prior to commencement.
A specific test called TPMT may be ordered to test for an increased risk of abnormal blood tests while on azathioprine. (TMPT is the enzyme thiopurine methyltransferase that metabolises azathioprine).

**Monitoring by GP**
The burden of blood monitoring in children is less than in adults to reduce distress and loss of school. Safety is not compromised by this.

FBC, ESR, CRP and LFT’s, U&E’s monthly for 6-12 months. If the patient’s condition is stable the frequency of monitoring may be extended to 6-8 weeks with agreement of the paediatric rheumatology team. Blood results should be recorded in the shared care card.

If a second DMARD is introduced as a combination, then the frequency of monitoring should be increased to the initial starting levels.

**Patient / Parent information leaflet**
Parents and patients will be supplied with an information leaflet.

**Shared Care Responsibilities**
Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients should be under regular follow-up which provides an opportunity to discuss drug therapy.

**a) Rheumatology Consultant**
- Pre treatment assessment and recommendation of the appropriate DMARD to be prescribed.
- Write to the GP requesting shared care and outline shared care protocol criteria.
- Pre treatment counselling to include rationale for treatment, benefits, potential side effects, precautions and monitoring requirements ensuring patients/parents/guardians understand their role in reporting adverse effects promptly. Patients (where possible) and parents/guardians consent to treatment should be sought and recorded.
- Issue written patient drug information, shared care monitoring booklet, contact telephone number.
- Ensure clinical supervision of the patient is done by follow-up as appropriate.
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments.
- Provide telephone /e-mail support in the event of any serious adverse reactions by a member of the medical team.
- Additional support for patients and members of the primary care team, via the rheumatology telephone Advice-line.

**b) General Practitioner**
- Prescribing the azathioprine as per recommendation of consultant
- Provision of services related to the shared care agreement as listed in the GMS contract, in respect of near patient testing.
- Ensuring blood tests are taken in accordance with this paediatric rheumatology unit information sheets which have been adapted for paediatric purposes from the National Guidelines for the monitoring of second line drugs (BSR 2009)
- Monitor for adverse effects as detailed above.
- Checking and recording of blood test results.
- Advise the consultant rheumatologist of any changes in the patient’s condition, any adverse drug reactions, or if the patient fails to attend for blood monitoring.
- Ensuring that all clinical staff involved in the provision of this service have the relevant knowledge and skills.

**c) The patient/parent/guardian**
- Attending for blood monitoring.
- Ensuring shared care card is kept up to date
- Reporting any adverse side effects to medication to the GP or a member of the hospital rheumatology team.
- Ensuring that they bring the shared care card and a list of all medications to the surgery and outpatient consultations.

**Contact Numbers**

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<th>Nuffield Orthopaedic Centre.</th>
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<tr>
<td>Rheumatology Registrar on call</td>
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<td>Bleep Rheumatology Registrar on call</td>
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<tr>
<td>Website (contains all shared care protocols some basic information to understanding blood results)</td>
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<td>Email enquiries</td>
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<td>Rheumatology Advice line (Answer phone)</td>
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Copies of all these sheets are available for general use by GP’s via www.noc.nhs.uk/oxparc, the unit or the PCT Intranet (www.oxfordshirepct.nhs.uk under General Practice / Prescribing and Medicines Management / Shared Care Protocols)

These guidelines are based on:

- Oxford Heatherwood and Wexham Park Rheumatology Depts Shared Care Agreement 2010
- National Guidelines for monitoring second line drugs. British Society for Rheumatology 2009
- Azathioprine Oxford and Berkshire Regional Rheumatology Guidelines 2010