



British Society of Paediatric Gastroenterology Hepatology and Nutrition

BSPGHAN IBD Working group

Thiopurine (Azathioprine/Mercaptopurine)

Blood Monitoring Guidelines

Recent findings from an audit carried out by the BSPGHAN/RCN IBD Nurse group have demonstrated that thiopurine blood monitoring is disparate across the UK (unpublished survey 2012). Evidence on the specific frequency necessary to reduce the risk of thiopurine toxicity is lacking in published literature therefore the following recommendations are based on 3 specific publications:

- BSG Guidelines for the management of inflammatory bowel disease in adults (2011)
- ECCO/ESPGHAN consensus guidelines on the management of paediatric Crohn's disease (2014)
- BNFC (2016)

BSG guidelines

Evidence around TPMT activity predicting the likelihood of long term adverse effects is limited (Gearry et al, 2003) however, there is a role in measuring activity to identify the 1 in 300 patients who are at risk of severe myelosuppression using standard doses of azathioprine (Gisbert et al, 2006).

Frequency of blood monitoring is based around manufacturers guidelines although the BSG recognise that this is not based on robust clinical evidence.

Suggested blood monitoring frequency:

FBC every 2 – 4/52 for 2/12

FBC every 4 – 8/52 thereafter

These timelines are suggested as a result of the Colombel (2000) paper which demonstrated myelotoxicity in around half of the study group at 2/12 and around two thirds of the group at 4 months. Hepatotoxicity and pancreatitis are discussed however the risk quoted is <5% and there is no recommendation to routinely check LFT's or amylase.

There is no mention of the role of measuring thiopurine metabolites in terms of frequency or otherwise in these guidelines.

ECCO/ESPGHAN guidelines

Recommends checking TPMT status prior to commencing thiopurine therapy (genotype or phenotype) to help identify those patients at risk of severe myelosuppression. The document mentions pancreatitis as a potential side effect (affecting 3 – 4% of patients) however no guidance is given re: adding amylase into the routine blood monitoring protocol. The guidelines state that conventional dosing of aza & MP cause haemotoxicity in up to 13% of patients (Gearry et al, 2004; Hindorf et al, 2006; Kirschner et al, 1998)

The use of 6TGN as a marker for optimal effect of azathioprine is addressed in these guidelines and a level of $>250 \text{ pmol}/8 \times 10^8$ erythrocytes is suggested. Hepatotoxicity correlated with an MMP level of $>5700 \text{ pmol}/8 \times 10^8$ erythrocytes (Dubinsky et al, 2000). There is no recommendation for frequency of testing the 6TGN or MMP level, however, there is an algorithm for patient management when these levels are available.

These guidelines also address the use of allopurinol for those patients who are 6TG shunters (low 6TGN and high MMP) and the thiopurine dose should be reduced (25 – 33% of original dose). Splitting the dose is based on one retrospective study and the guidelines suggest more evidence is necessary to confirm this as an effective strategy. Split dose to be considered.

Suggested blood monitoring frequency:

FBC & LFT's every 1-2/52 for 1/12

Decreasing frequency thereafter but minimum every 3/12 for duration of therapy.

BNF

Suggests TPMT before commencing therapy.

Suggested blood monitoring therapy:

FBC weekly for 4/52

Reduce frequency to at least every 3/12 thereafter.

No mention of LFT's or amylase

Based on the advice from the guidelines, BNF and clinical consensus, the IBD WG suggest the following blood monitoring protocol for paediatric patients on thiopurine therapy:

Pre-screening

1. All patients requiring thiopurine therapy will have a thiopurine methyltransferase (TPMT) genetic or enzymatic screen carried out before commencing therapy.
2. Thiopurine therapy is contra-indicated in patients who are homozygous mutant or have extremely low enzyme activity.
3. All patients must be counselled on the benefits and risks of therapy before commencing treatment (IBD Standards 2015).
4. No need to start at lower dose then titrate up.

Monitoring frequency

1. Monitor FBC and LFTs at baseline week 2, 4, 8 and 12 and then 3 monthly thereafter.
2. Thiopurine metabolites levels are recommended for guiding therapy as clinically indicated (see ECCO/ESPGHAN guidelines & table 1).
 3. Check lipase /amylase **only** if severe abdominal pain or if other concerns about pancreatitis.

To ensure optimisation of therapy:

Azathioprine:

1. Initial dose 2- 2.5 mg/kg/day once a day, with further dose adjustment based on thiopurine metabolites Reduce dose to half if heterozygote or moderately low TPMT activity
2. Review dose if signs of bone marrow suppression eg. WBC <2.5, lymphocytes <0.5, or neutrophils <1.0, platelets <150.
3. Review dose if transaminases x2 above ULN (upper limit of normal)

Mercaptopurine:

1. Initial dose 1-1.5mg/kg/day once a day. Reduce dose to half if heterozygote or moderately low TPMT activity

2. Review dose if signs of bone marrow suppression eg WBC <2.5, lymphocytes <0.5, or neutrophils <1.0, platelets <150.
3. Review dose if transaminases x2 above ULN (upper limit of normal)

In general, most UK groups start with azathioprine. If intolerance to azathioprine in general mercaptopurine can then be tried. (Lees 2008)

A second thiopurine is relatively contraindicated if the patient has had pancreatitis.

Table 1: Metabolite monitoring

6-TGN (pmol/8.108 RBC)	6-MMP (pmol/8.108 RBC)	Possible adverse event or finding	Recommendation
Low (<230)	Low-normal (<5700)	--	Improve compliance or increase thiopurine dose as appropriate
Low or normal	High \geq 5700	Hepatotoxicity and others	Preferred option is to try split dose regimen Or if alternative considered see *
Normal 230-450	High >5700	Normal LFT's	Standard monitoring
Therapeutic (230-450)	Normal or high	Active disease	Consider changing treatment strategy
High levels >450	normal	Myelosuppression	Consider dose reduction and repeat (between 450-550 can be tolerated without changes)

* If allopurinol is used **decrease the dose of thiopurine to a quarter** of the original thiopurine dose

It is essential to monitor for the side effects of allopurinol especially WCC & renal function