



## Complete Summary

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### GUIDELINE TITLE

Guidelines for prescribing azathioprine in dermatology.

### BIBLIOGRAPHIC SOURCE(S)

Anstey AV, Wakelin S, Reynolds NJ, British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. Br J Dermatol 2004 Dec;151(6):1123-32. [54 references] [PubMed](#)

### GUIDELINE STATUS

This is the current release of the guideline.

## COMPLETE SUMMARY CONTENT

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## SCOPE

### DISEASE/CONDITION(S)

Autoimmune and immune-mediated dermatologic conditions, including:

- Systemic lupus erythematosus
- Dermatomyositis
- Pemphigus vulgaris
- Atopic dermatitis
- Psoriasis
- Bullous pemphigoid
- Chronic actinic dermatitis
- Pyoderma gangrenosum
- Pityriasis rubra pilaris
- Wegener's granulomatosis

- Cutaneous vasculitis

### **GUIDELINE CATEGORY**

Counseling  
Evaluation  
Treatment

### **CLINICAL SPECIALTY**

Dermatology

### **INTENDED USERS**

Physicians

### **GUIDELINE OBJECTIVE(S)**

To provide evidence-based recommendations for routine safety monitoring of patients treated with azathioprine, including pretreatment assessment of red blood cell thiopurine methyltransferase activity

### **TARGET POPULATION**

Patients in the United Kingdom who are treated with azathioprine for autoimmune and immune-mediated dermatologic conditions

### **INTERVENTIONS AND PRACTICES CONSIDERED**

1. Pretreatment thiopurine methyltransferase (TMPT) measurement
2. Azathioprine doses and dose adjustments
3. Monitoring for toxicity, including full blood counts (FBCs) and liver function tests (LFTs)
4. Provision of patient information and informed consent regarding risks of azathioprine, including risk of malignancy

### **MAJOR OUTCOMES CONSIDERED**

- Morbidity and mortality from adverse drug reactions, including susceptibility to infection and rate of tumorigenesis
- Response rate to treatment

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

## **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

The aim of the search strategy was to identify recent and past publications relating to the clinical pharmacology of azathioprine that were relevant to its current usage within dermatology. The evidence gathered includes some derived from disciplines other than dermatology, such as gastroenterology, where azathioprine usage is high and experience with thiopurine methyltransferase (TPMT)-guided prescribing is established.

### *Types of Studies*

Randomized, double-blind, placebo-controlled trials; well-designed controlled trials without randomization; well-designed cohort or case-control analytical studies; evidence from multiple time series with or without intervention; opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

### *Search Strategy for Identification of Studies*

A computer-assisted search of the online bibliographic databases Medline, PubMed and Embase was carried out to identify potentially relevant papers published between 1966 and 2003. Other databases searched included the Royal College of Physicians Guidelines database, CINAHL, the Cochrane library, DARE, AMED and HMIC. The following search terms were used: azathioprine; 6-mercaptopurine; dermatology; adverse drug reactions; clinical monitoring; TPMT; thiopurine methyltransferase. Citations were limited to those in English, French, Spanish, Italian and German. Manual searches of the reference lists from the relevant papers were performed in order to identify additional studies that may have been missed by the computer-assisted strategy. These guidelines include evidence derived from the key papers identified by the search strategy.

## **NUMBER OF SOURCE DOCUMENTS**

Not stated

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Weighting According to a Rating Scheme (Scheme Given)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

### **Levels of Evidence**

**I:** Evidence obtained from at least one properly designed, randomized controlled trial

**II-i:** Evidence obtained from well-designed controlled trials without randomization

**II-ii:** Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one centre or research group

**II-iii:** Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence

**III:** Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees

**IV:** Evidence inadequate due to problems of methodology (e.g., sample size, or length of follow-up, or conflicts of interest)

## **METHODS USED TO ANALYZE THE EVIDENCE**

Systematic Review

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

Not stated

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Particular emphasis has been placed on assessing the risks and benefits of azathioprine therapy for patients with dermatological disease. These guidelines attempt to establish an explicit link between evidence and recommendations for clinical usage. This is sometimes difficult, as decisions in clinical medicine occur in the context of single patients and do not always relate to the context from which a guideline recommendation has been made.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

### **Strength of Recommendations**

- A. There is good evidence to support the use of the procedure
- B. There is fair evidence to support the use of the procedure
- C. There is poor evidence to support the use of the procedure
- D. There is fair evidence to support the rejection of the use of the procedure
- E. There is good evidence to support the rejection of the use of the procedure

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

These guidelines have been subjected to expert review by nondermatologists (acknowledged) with recognized expertise in the prescribing of azathioprine.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Grades of recommendations (**A-D**) and levels of evidence (**I-IV**) are defined at the end of the "Major Recommendations" field.

#### Azathioprine Indications in Dermatology

The main area of azathioprine use in dermatology is in the treatment of autoimmune dermatoses, in particular bullous pemphigoid (**Grade B; level IV**), and pemphigus vulgaris (**Grade B; level II-iii**) where azathioprine is used as a steroid-sparing agent. Accumulating evidence also suggests a role for azathioprine as a single agent in the treatment of severe, recalcitrant atopic dermatitis (**Grade A; level I**). Double-blind, placebo-controlled trials have shown azathioprine to be of benefit in chronic actinic dermatitis (**Grade A; level I**) and Behçet's disease (**Grade A; level I**). It may also be effective as monotherapy in the treatment of severe, recalcitrant psoriasis (**Grade C; level IV**). Azathioprine is sometimes used in the treatment of other rare dermatological conditions including Wegener's granulomatosis, pyoderma gangrenosum, pityriasis rubra pilaris, lupus erythematosus and lichen planus, but evidence to support its usage in these conditions is anecdotal (**Grade C; level IV**).

#### Azathioprine Contraindications

Azathioprine is contraindicated in patients with known hypersensitivity to the drug (**Grade A; level III**). Evidence of teratogenicity with azathioprine in humans is equivocal, but adequate contraceptive precautions are advised when either partner is taking azathioprine. Azathioprine is also contraindicated in pregnancy (except where benefit may outweigh risk such as in allograft recipients) (**Grade A; level II-ii**). 6-Mercaptopurine (6-MP) has been identified in colostrum and in the breast milk of women receiving azathioprine treatment. Women on azathioprine should therefore be advised to bottle feed their babies. It is strongly recommended that azathioprine should not be used in patients whose thiopurine methyltransferase (TPMT) status is unknown (**Grade A; level II-ii**). Very low or absent TPMT activity is a contraindication to the usage of azathioprine because of the high risk of life-threatening pancytopenia (**Grade A; level II-ii**). Concurrent treatment with allopurinol results in an important drug interaction which may cause significant myelosuppression, and should therefore be avoided (**Grade A; level III**).

There are concerns that azathioprine treatment increases the risk of developing a malignancy. Accumulating evidence suggests that this risk is smaller than was originally feared. Nevertheless, patients should be advised of this risk, and it is

recommended that azathioprine treatment should not usually be initiated or continued in patients with known malignancy (**Grade A; level III**).

### **Pretreatment Thiopurine Methyltransferase Assessment**

Although there are currently no published prospective studies for dermatological conditions which demonstrate improved prognosis, TPMT screening prior to azathioprine treatment is considered by some clinicians to be essential (**Grade A; level II-ii**).

- Pretreatment thiopurine methyltransferase (TPMT) measurement should be performed in all patients prescribed azathioprine for treatment of dermatological conditions

### **Azathioprine Dosage**

The recommended dosage of azathioprine for dermatological indications is 1 to 3 mg kg<sup>-1</sup> daily, adjusted within these limits according to response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing azathioprine. Care should be taken when prescribing azathioprine in the elderly: it is recommended that the dosage used is at the lower end of the range. There are currently no data to support prescribing azathioprine in doses outside the above range. However, modified dosage regimens based on TPMT activity have been published for both adults and children (**Grade C; level III**), and are the logical progression of this pharmacogenetic assessment.

Azathioprine should not be used in patients with very low / absent TPMT activity (deficient), as the danger of severe and prolonged myelosuppression is significant (**Grade A; level II-ii**). Patients with inflammatory bowel disease and low TPMT activity have been shown to be at increased risk of azathioprine toxicity. Thus, for patients with low TPMT activity, alternative systemic therapies should be considered (**Grade A; level II-ii**). If a trial of azathioprine is deemed appropriate in this situation, a low-dosage regimen should be used (0.5 to 1 mg kg<sup>-1</sup> daily) and extra care taken with haematological surveillance (**Grade B; level III**).

In patients with high TPMT activity (see Appendix 2 in the original guideline document for laboratory ranges), the azathioprine dose should be at the higher end of the range of 1 to 3 mg kg<sup>-1</sup> daily. It is probably safe to treat these patients from the outset with dosages of azathioprine towards the top end of this dosage range provided the usual measures are taken to monitor for myelosuppression. However, azathioprine intolerance unrelated to TPMT activity is not uncommon, and a lower initial dose of azathioprine is advocated by some authors for the first month of therapy, even in patients with high TPMT activity. In patients with inflammatory bowel disease, high TPMT activity predicts treatment failure with azathioprine. Thus, in dermatology patients with high TPMT activity, azathioprine dosage should be at the top of the recommended dose range of 1 to 3 mg kg<sup>-1</sup> daily. In patients who fail to respond to 3 months of this dosage regimen, and in whom no adverse effects occur, dosage above the 1 to 3 mg kg<sup>-1</sup> daily range might be considered for a trial period (**Grade C; level III**). However, if this approach is adopted, care should be taken in monitoring for myelosuppression and possible hepatotoxicity.

- If no therapeutic response is observed within 3 months of starting azathioprine, treatment should usually be withdrawn.
- In patients with very low/absent TPMT activity (deficient), azathioprine is contraindicated.
- In patients with low TPMT activity, azathioprine should either not be prescribed or, if used, the dose should be low (0.5 to 1 mg kg<sup>-1</sup> daily) with careful monitoring for myelosuppression.
- In patients with normal or high TPMT activity, azathioprine dosage should commence at the top of the 1 to 3 mg kg<sup>-1</sup> daily dosage range. In patients who fail to respond, and in whom no adverse effects occur, dosage above the 1 to 3 mg kg<sup>-1</sup> daily range might be considered for a trial period.

### **Monitoring for Azathioprine-Induced Toxicity**

It is advised that dermatologists carry out weekly blood tests (full blood counts [FBCs] and liver function tests [LFTs]) until maintenance dose is achieved, followed by regular monitoring reducing to a minimum of once every 3 months for the duration of therapy (**Grade A; level I**).

For higher dosages and for patients with hepatic or renal impairment, initial blood count monitoring more frequently than once weekly is advised. Return to weekly FBCs and LFTs should also follow an increase in dosage in azathioprine in patients already established on this treatment. It is also advised that patients on azathioprine be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or jaundice. In patients with low TPMT activity (3 to 8 nmol h<sup>-1</sup> mL<sup>-1</sup> red blood cells), monitoring for FBC and LFTs should be more frequent than outlined above due to the increased risk of toxicity. Acute pancreatitis is a rare but well-recognized side-effect of azathioprine treatment. In azathioprine-treated patients with acute abdominal pain and/or severe vomiting, acute pancreatitis should be considered and serum amylase measured.

Monitoring for azathioprine toxicity should include:

- Weekly monitoring of full blood count (FBC) and liver function tests (LFTs) for the first 4 weeks of therapy, or until the maintenance dose is achieved; reducing to a minimum of once every 3 months for the duration of therapy.
- More frequent monitoring of FBC and LFTs is advised in patients with hepatic or renal impairment, in the elderly and in those treated with high doses of azathioprine.
- Increase in dosage of azathioprine should be accompanied by return to weekly FBC and LFTs for 4 weeks, reducing to a minimum of once monthly or every 2 months for the duration of therapy.

### **Azathioprine-Induced Susceptibility to Infection**

- Azathioprine in combination with prednisolone is associated with an increased risk of infection, which may be fatal in the elderly. Dermatologists are advised to use the minimum necessary doses of immunosuppressive therapies to control immunobullous diseases in the elderly (**Grade A; level II-ii**).
- Live vaccines are contraindicated for patients receiving azathioprine (**Grade A; level III**).

- Killed vaccines may elicit a diminished immune response in patients receiving azathioprine (**Grade B; level II-ii**)

### **Azathioprine-Related Malignancy**

- Dermatologists should make patients aware of the possible increased risk of malignancy related to long-term azathioprine therapy (**Grade B; level IV**).
- Skin photoprotection should be advised when relevant (**Grade B; level IV**).

### **Patient Information and Informed Consent**

- Before azathioprine is prescribed, the clinician should provide the patient with an azathioprine patient information sheet, and discuss the anticipated benefits and possible side-effects.

### **Definitions:**

#### **Levels of Evidence**

**I:** Evidence obtained from at least one properly designed, randomized controlled trial

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**II-ii:** Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one centre or research group

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**III:** Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees

**IV:** Evidence inadequate due to problems of methodology (e.g., sample size, or length of follow-up, or conflicts of interest)

#### **Grade of Recommendations**

- A. There is good evidence to support the use of the procedure
- B. There is fair evidence to support the use of the procedure
- C. There is poor evidence to support the use of the procedure
- D. There is fair evidence to support the rejection of the use of the procedure
- E. There is good evidence to support the rejection of the use of the procedure

### **CLINICAL ALGORITHM(S)**

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations" field).

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Prevention of adverse effects associated with azathioprine through pretreatment assessment and toxicity monitoring

### POTENTIAL HARMS

- Adverse drug reactions with azathioprine occur in 15 to 28% of patients and include myelosuppression, nausea and vomiting, rash, pancreatitis and hypersensitivity.
- Care should be taken when prescribing azathioprine in the elderly: it is recommended that the dosage used is at the lower end of the range.
- Azathioprine should not be used in patients with very low/absent thiopurine methyltransferase (TPMT) activity (deficient), as the danger of severe and prolonged myelosuppression is significant. Patients with inflammatory bowel disease and low TPMT activity have been shown to be at increased risk of azathioprine toxicity.
- Hepatotoxicity is a recognized complication of azathioprine therapy.
- Acute pancreatitis is a rare but well recognized side-effect of azathioprine treatment.
- Infection in elderly patients with bullous pemphigoid treated with azathioprine and prednisolone has been identified as a significant cause for mortality, particularly when compared with rates of such fatal infections in patients treated with prednisolone alone.
- The inhibitory effect of azathioprine on the immune surveillance system could, on theoretical grounds, lead to an increased rate of malignancy with long-term therapy.
- Idiosyncratic hypersensitivity reactions with azathioprine are recognized, but are rare.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

Contradictions to azathioprine:

- It is strongly recommended that azathioprine should not be used in patients whose thiopurine methyltransferase (TPMT) status is unknown
- Known hypersensitivity to azathioprine (or 6-mercaptopurine [6-MP])
- Azathioprine is contraindicated in patients who may be pregnant or hope to become pregnant in the near future (except where benefit may outweigh risk)

- Women taking azathioprine should not breast feed their babies
- Very low or absent TPMT activity
- Concurrent allopurinol treatment
- Concurrent malignant disease where azathioprine treatment may increase the risk of disease progression
- Renal or hepatic insufficiency (relative contraindication)
- Administration of live vaccines to patients receiving azathioprine is contraindicated on theoretical grounds.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary to depart from the guidelines in the interests of specific patients and in special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

#### Audit of Azathioprine Prescribing

This paper includes highlighted recommendations for good practice in relation to the prescribing of azathioprine. Any one of these could be used to establish agreed local standards of care against which audit could be performed. For example, "Indications for Usage of Azathioprine" might be one area, taking into account the licensed indications for azathioprine and the conditions for which there is good evidence to support its use from randomized controlled trials. There is now a broad consensus among United Kingdom (U.K.) dermatologists that pretreatment thiopurine methyltransferase (TPMT) measurement is necessary for improved safety and more effective dosage selection for patients treated with azathioprine. Thus, audit on usage of TPMT screening could follow the development of agreed local standards of care concerning this investigation. Routine monitoring of azathioprine toxicity is another area where recommendations are made, and locally agreed standards could precede an audit to assess compliance with that standard. Perhaps the most novel audit project concerns what dermatologists tell their patients. The recommendations for patient information in this document exceed what most dermatologists currently do. A patient information sheet has also been developed by the British Association of Dermatologists (BAD) (available on the patient section of the BAD website: <http://www.bad.org.uk/public/leaflets/>) to be used in combination with detailed patient-focused discussion of the merits and hazards of this drug.

### IMPLEMENTATION TOOLS

Audit Criteria/Indicators  
Patient Resources

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness  
Patient-centeredness  
Safety

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Anstey AV, Wakelin S, Reynolds NJ, British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. Br J Dermatol 2004 Dec;151(6):1123-32. [54 references] [PubMed](#)

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2004 Dec

### GUIDELINE DEVELOPER(S)

British Association of Dermatologists - Medical Specialty Society

### SOURCE(S) OF FUNDING

British Association of Dermatologists

### GUIDELINE COMMITTEE

British Association of Dermatologists Therapy and Guidelines Committee

### COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

No additional funding was received by the authors of these guidelines to support this work. None of the authors has a conflict of interest to declare.

## **GUIDELINE STATUS**

This is the current release of the guideline.

## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [British Association of Dermatologists Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

Audit criteria are discussed in the original guideline document.

## **PATIENT RESOURCES**

The following is available:

- Azathioprine. Patient information leaflet. London (England): British Association of Dermatologists; 2007 Jun. 3 p. Available from the [British Association of Dermatologists Web site](#).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## **NGC STATUS**

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