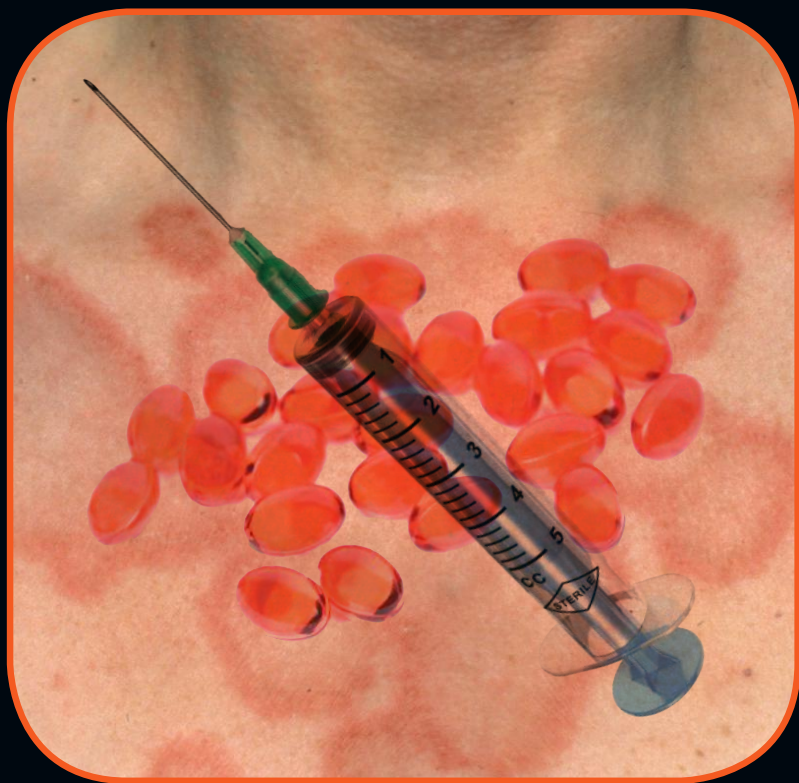


# HANDBOOK OF SYSTEMIC DRUG TREATMENT IN DERMATOLOGY

S E C O N D   E D I T I O N



Sarah H Wakelin | Howard I Maibach | Clive B Archer



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# HANDBOOK OF SYSTEMIC DRUG TREATMENT IN DERMATOLOGY

Second Edition

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## Preface

Since the first edition of this handbook, dermatological therapy has made a quantum leap with the advent of biologics for severe psoriasis. Other advances include a new oral retinoid, oral anticancer therapy and evolving guidelines for prescribing and monitoring established drugs. Our therapeutic power grows, but changes in society mean that those taking drugs are increasingly likely to be elderly, have co-morbidities and to be taking multiple medications – all factors which increase the risk of adverse effects. Coupled with growing patient expectations and recourse to litigation, the prescribing physician must carefully evaluate risks versus benefit and be able to explain these clearly to allow patients to share in the decisions about their care. Doctors may prescribe any medicine for any legitimate purpose if they judge it to be in the best interest of the patient, but if their use is for an indication that is not in the product licence (off label), they are advised to keep good records should there be the need to justify their decision at a later date. Much prescribing for children is 'off label' because clinical trials are usually conducted in adults and there are insufficient data on children for the regulatory authorities.

Ideally, prescribing information would list the harmful effects of every drug, with details of its relation to dose and duration of therapy, preventative measures (if available) and the chance of its occurrence in the population and preferably the individual. However, the full extent of such information is not usually available in daily practice. Rare adverse events are especially difficult to detect, because of the large study size needed to detect these and the possibility of uncorrected biases with observational studies. Not only do 'package inserts' change with time, but they may differ by country of registration.

We hope that the second edition will prove as practical and popular as the first, despite some gain in girth with age! We have not attempted to appraise critically the evidence of effectiveness for different drugs in diseases in order to keep a concise and easy-to-read format. Prescribers are advised to check doses in up-to-date formularies and to consult manufacturers for full product information and details of excipients, for use in rare metabolic diseases such as porphyria and Lapp lactose galactose deficiency. This edition attempts to generalize across countries. However, each country may have special aspects of prescribing that should be considered.

Sarah H. Wakelin

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The clinical image on the cover is from the collection of St John's Institute of Dermatology, King's College London School of Medicine, with permission.

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The editors and publishers are also very grateful to the number of reviewers in the USA who have commented on the international applicability of the advice contained in various sections; they are acknowledged at the end of the relevant sections. However, because of international variations it has not been possible to include all package information about dosages, so readers are encouraged to confirm the position in their own territories.

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## Abbreviations

<b>5-HT</b> 5-hydroxytryptamine	<b>DEXA</b> dual energy X-ray absorptiometry
<b>ACE</b> angiotensin converting enzyme	<b>DHT</b> dihydrotestosterone
<b>ACTH</b> adrenocorticotrophic hormone	<b>DILI</b> drug induced liver injury
<b>AGEP</b> acute generalized exanthematous pustulosis	<b>DISH</b> diffuse idiopathic skeletal hyperostosis
<b>AIDS</b> acquired immunodeficiency syndrome	<b>DLE</b> discoid lupus erythematosus
<b>ALP</b> alkaline phosphatase	<b>DLQI</b> Dermatology Life Quality Index
<b>ALT</b> alanine aminotransferase	<b>DNA</b> deoxyribonucleic acid
<b>ANA</b> antinuclear antibodies	<b>DRESS</b> drug reaction (or rash) with eosinophilia and systemic symptoms
<b>(p)ANCA</b> (perinuclear) antineutrophil cytoplasmic antibody	<b>DVT</b> deep venous thrombosis
<b>AST</b> aspartate aminotransferase	<b>EBV</b> Epstein–Barr virus
<b>AV</b> atrioventricular	<b>ECG</b> electrocardiogram
<b>BAD</b> British Association of Dermatologists	<b>ELISA</b> enzyme linked immunosorbent assay
<b>BCC</b> basal cell carcinoma	<b>EMA</b> European Medicines Association
<b>BCG</b> bacillus Calmette–Guérin	<b>ENL</b> erythema nodosum leprosum
<b>bd</b> twice daily, every 12 hours	<b>FBC</b> full blood count (= CBC)
<b>BMD</b> bone mineral density	<b>FDA</b> (USA) Food and Drug Administration
<b>BMI</b> body mass index	<b>FSH</b> follicle stimulating hormone
<b>BNF</b> British National Formulary	<b>G6PD</b> glucose-6-phosphate dehydrogenase
<b>BP</b> blood pressure	<b>G-CSF</b> granulocyte colony stimulating factor
<b>BSA</b> body surface area	<b>(e)GFR</b> (estimated) glomerular filtration rate
<b>CBC</b> complete blood count (= FBC)	<b>GGT</b> gamma-glutamyl transferase
<b>CBG</b> cortisol binding globulin	<b>GI</b> gastrointestinal
<b>CIN</b> cervical intraepithelial neoplasia	<b>GnRH</b> gonadotrophin releasing hormone
<b>CK</b> creatine kinase	<b>GSH</b> glutathione
<b>CKD</b> chronic kidney disease	<b>HAART</b> highly active antiretroviral therapy
<b>CMV</b> cytomegalovirus	<b>HBV</b> hepatitis B virus
<b>CNS</b> central nervous system	<b>HCV</b> hepatitis C virus
<b>CS</b> glucocorticosteroids	<b>HDL</b> high-density lipoprotein
<b>CSM</b> (UK) Committee for Safety of Medicines	<b>HIV</b> human immunodeficiency virus
<b>CTCL</b> cutaneous T-cell lymphoma	
<b>CXR</b> chest radiograph	
<b>CYP450</b> cytochrome P450	
<b>DCP</b> dexamethasone–cyclophosphamide pulse	

<b>HR</b> heart rate	<b>NRTI</b> nucleoside reverse transcriptase inhibitor
<b>HRT</b> hormone replacement therapy	<b>NSAID</b> non-steroidal anti-inflammatory drug
<b>HSV</b> herpes simplex virus	<b>NYHA</b> New York Heart Association
<b>IBD</b> inflammatory bowel disease	<b>OCP</b> oral contraceptive pill
<b>IFN</b> interferon	<b>od</b> once daily, every 24 hours
<b>Ig</b> immunoglobulin	<b>PIIINP</b> pro-collagen III peptides
<b>IGRA</b> interferon-gamma release assay	<b>PABA</b> para-aminobenzoic acid
<b>IL</b> interleukin	<b>PASI</b> Psoriasis Area and Severity Index
<b>i/m</b> intramuscular, intramuscularly	<b>PE</b> pulmonary embolism
<b>INR</b> international normalized ratio	<b>PGA</b> Physician's Global Assessment
<b>ITP</b> idiopathic (immune) thrombocytopenic purpura	<b>PML</b> progressive multifocal leukoencephalopathy
<b>i/v</b> intravenous, intravenously	<b>PPP</b> Pregnancy Prevention Programme
<b>IVF</b> <i>in vitro</i> fertilization	<b>PSA</b> prostate specific antigen
<b>KS</b> Kaposi's sarcoma	<b>PT</b> prothrombin time
<b>LDL</b> low-density lipoprotein	<b>PTC</b> pseudotumour cerebri
<b>LE</b> lupus erythematosus	<b>PUVA</b> psoralen combined with ultraviolet A
<b>LFT</b> liver function test	<b>PVL</b> Pantan–Valentine leukocidin
<b>LH</b> luteinizing hormone	<b>qds</b> four times daily, every 6 hours
<b>MAOI</b> monoamine oxidase inhibitor	<b>RAR</b> retinoic acid receptor
<b>MCV</b> mean corpuscular volume	<b>RePUVA</b> PUVA with oral retinoid therapy
<b>MF</b> mycosis fungoides	<b>RNA</b> ribonucleic acid
<b>MHRA</b> (UK) Medicines and Healthcare Products Regulatory Agency	<b>RXR</b> retinoid X receptor
<b>MI</b> myocardial infarction	<b>s/c</b> subcutaneous, subcutaneously
<b>MMR</b> mumps, measles, rubella	<b>SCC</b> squamous cell carcinoma
<b>MPD</b> minimal phototoxic dose	<b>SHBG</b> sex hormone binding globulin
<b>MRI</b> magnetic resonance imaging	<b>SLE</b> systemic lupus erythematosus
<b>(CA/HA)-MRSA</b> (community-acquired/hospital-acquired) methicillin-resistant <i>Staphylococcus aureus</i>	<b>SPC</b> Summary of Product Characteristic
<b>MTX</b> methotrexate	<b>SSRI</b> selective serotonin reuptake inhibitor
<b>NHL</b> non-Hodgkin's lymphoma	<b>STAT</b> signal transducer and activator of transcription
<b>NICE</b> (UK) National Institute for Health and Care Excellence	<b>TB</b> tuberculosis
<b>nocte</b> at night	
<b>NMSC</b> non-melanoma skin cancer	

**tds** three times daily, every 8 hours

**TEN** toxic epidermal necrolysis

**TFT** thyroid function test

**TGF- $\beta$**  transforming growth factor-beta

**TPMT** thiopurine methyltransferase

**TSH** thyroid stimulating hormone

**UVA** ultraviolet A

**UVB** ultraviolet B

**VTE** venous thromboembolism

**VZIG** varicella/zoster immunoglobulin

**VZV** varicella zoster virus

**WBC** white blood cell count

**WHO** World Health Organization

## FDA Pregnancy Categories

### Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

### Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

### Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

### Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

### Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

# Acitretin

Peter C.M. van de Kerkhof

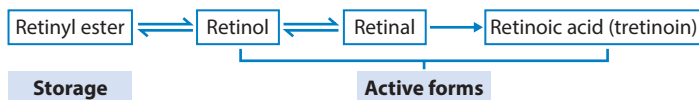
## + Classification & mode of action

By the 1960s, modifications of vitamin A (figure 1) resulted in the discovery of the first generation retinoids, all-*trans*-retinoic acid and 13-*cis*-retinoic acid. Further research led to development of the second generation of retinoids, the monoaromatic retinoids, etretinate and its metabolite, acitretin. Etretinate (which is no longer available) and acitretin are effective treatments for psoriasis and severe congenital disorders of keratinization.

A major problem with systemic retinoids is their teratogenicity, and separation of this from their therapeutic effects has never been achieved. Acitretin has a much shorter half-life than etretinate, but a long duration of pregnancy avoidance post-treatment is still advised, as it transpires that acitretin can be converted to etretinate in the presence of alcohol, and the latter is stored in fat with a half-life of 120 days.

Acitretin is an established treatment for psoriasis and, despite development of biological agents (the biologics), it remains an important therapy due to its unique mode of action. It binds receptors belonging to the steroid-thyroid receptor superfamily. Subsequently, the ligand/receptor complex binds to specific gene regulatory regions to modulate gene expression. Acitretin has antiproliferative and anti-inflammatory properties. In the epidermis, acitretin reduces keratinocyte proliferation and normalizes differentiation and cornification. It also inhibits production of vascular endothelial growth factor and inhibits intraepidermal neutrophil migration. Acitretin inhibits interleukin (IL)-6-driven induction of Th17 cells, which play a pivotal role in the pathogenesis of psoriasis and promote the differentiation of T-regulatory cells.

Unlike other psoriasis therapies, acitretin lacks immunosuppressive effects and this can be useful in patients with a history of internal malignancy, those with a history of skin cancer or severe sun damage, transplant recipients and those with underlying infections such as human immunodeficiency virus (HIV) infection. In addition, there is emerging evidence that acitretin may be successfully combined with biologics.



**FIGURE 1** Simplified diagram to illustrate the three main active forms of vitamin A and a storage form.



## **+ Indications & dermatological uses**

The licensed indications for acitretin are as follows:

- Severe extensive psoriasis that cannot be managed by topical treatment or phototherapy.
- Palmoplantar pustular psoriasis.
- Severe Darier's disease.
- Severe congenital ichthyosis.

Monotherapy is indicated for erythrodermic or pustular psoriasis while combination therapy (with phototherapy) is often used for chronic plaque psoriasis. The efficacy of acitretin monotherapy in chronic plaque psoriasis is limited and dose dependent, with approximately 70% of patients achieving a moderate or greater response. Various studies have reported partial clearance rates of 25–75% with daily doses of 30–40 mg. Lower doses (10 mg or 25 mg daily) have little therapeutic effect, whereas doses of 50 mg and 75 mg daily result in an improvement of at least 75% (PASI 75) in 25% of patients. Complete clearance is rare and adherence at high dosage is often limited by side-effects.

The comparative efficacy of acitretin monotherapy in chronic plaque psoriasis is less than methotrexate and ciclosporin (cyclosporine). However, acitretin in combination with phototherapy (ultraviolet B [UVB] or psoralen combined with ultraviolet A [PUVA]) has an efficacy at least comparable with the other non-biologic systemic treatments. An additional advantage of combination treatment is that lower doses of acitretin and lower cumulative doses of UVA or UVB can be used. Topical therapy such as calcipotriol should be continued with acitretin as it may enable increased efficacy at lower dosage. There is preliminary evidence for improved efficacy in combination therapy with the antidiabetic drug pioglitazone, although further studies are needed. There is also limited evidence for the effective combination of acitretin with etanercept and with hydroxycarbamide (hydroxyurea).

As monotherapy, acitretin is highly effective in erythrodermic and pustular psoriasis. However, its efficacy in nail psoriasis and psoriatic arthritis is only modest.

Another potential therapeutic use of acitretin is the prophylaxis of non-melanoma skin cancer in organ transplant recipients. Acitretin may be considered a first-line systemic therapy for pityriasis rubra pilaris and lichen planus (especially the hyperkeratotic and erosive variants). Acitretin has similar efficacy to antimalarials in the treatment of cutaneous lupus erythematosus.

## **+ Formulations/Presentation**

Branded formulations exist with capsule sizes containing 10 mg and 25 mg of acitretin.

In the USA, there are additional formulations containing 17.5 mg and 22.5 mg acitretin.

## + Dosages & suggested regimens

The recommended **starting dose** is **25–30 mg** or **0.5 mg/kg once daily** for chronic plaque psoriasis, with dose adjustment after 2–4 weeks according to clinical response and side-effects. A lower starting dose of **0.25 mg/kg** is advisable in erythrodermic psoriasis. For pustular psoriasis, the dose should be escalated up to the maximum **maintenance dose** of **75 mg** or **1 mg/kg daily**. An initial flare of plaque psoriasis may occur, but improvement is usually evident by 4 weeks. Optimal response may take over 3 months.

Lower starting doses of **10 mg daily** are indicated for Darier's disease, with maintenance doses of **10–25 mg daily**. Similar low doses can be used in conjunction with phototherapy.

Acitretin should be taken with or after a fat-containing meal to maximize bioavailability.

## + Baseline investigations & considerations

- Pregnancy testing.
- Establishment of highly effective contraception.
- Full blood count (FBC) (complete blood count [CBC]).
- Liver function tests (LFTs).
- Serum urea, electrolytes and creatinine.
- Fasting lipids and glucose.

## + Monitoring

- Pregnancy testing (throughout and beyond treatment in females of reproductive age).
- Fasting lipids and LFTs monthly for the first 2 months then every 3–6 months.
- Fasting glucose if evidence of impaired glucose tolerance.
- Monitor for development of hyperostosis by history (twice yearly) and by skeletal x-ray if symptomatic.
- Growth charts for height and weight in those under 18 years.

## + Contraindications & cautions

The following are contraindications to systemic retinoid therapy:

- Pregnancy (see below).
- Lactation.
- Uncontrolled severe hyperlipidaemia.
- Hypersensitivity to retinoids or excipients.

Patients taking acitretin should not donate blood during treatment and for 3 years after stopping therapy.

Extra caution should be taken when acitretin is prescribed in the following:

- Liver dysfunction.
- Severe renal dysfunction (elimination reduced).
- Hyperlipidaemia.
- Alcohol dependency.
- History of pancreatitis.
- Diabetes (glucose tolerance may be impaired).
- Obesity.
- Arteriosclerosis.
- Contact lens use.
- Serious disorders of the retina.

### + Important drug interactions

- **Ciclosporin** (cyclosporine) metabolism: may be inhibited by acitretin as both drugs are metabolized by the same cytochrome P450 (CYP450) system, leading to a risk of ciclosporin toxicity.
- **Glibenclamide**: acitretin enhances the hypoglycaemic effect of glibenclamide.
- **Methotrexate** and **acitretin**: have been used successfully as combination therapy in those patients in whom all other psoriasis treatments have failed. However, severe hepatotoxicity has been reported, so careful monitoring is mandatory. As methotrexate itself causes hepatotoxicity it is unclear what role, if any, acitretin plays in hepatotoxicity.
- **Oral contraceptive pill (OCP)**: there is an additive effect on the elevation of serum triglycerides and cholesterol but there is no effect on the antioviulatory action of the combined OCP.
- **Phenytoin**: protein binding is reduced by acitretin but the clinical significance of this is unknown.
- **Tetracyclines**: should be avoided during acitretin therapy as both drugs can cause benign intracranial hypertension; the risk may be increased if they are used concurrently.
- **Vitamin A**: intake should not exceed the recommended dietary allowance (4,000–5,000 units/d) so supplements should be avoided.
- **Alcohol**: promotes the esterification of acitretin to etretinate ('back metabolism'), which is far more slowly eliminated. This may prolong the risk of teratogenicity in females of childbearing age.

### + Adverse effects & their management

- **Teratogenicity** is the principal problem with all systemic retinoids. Both natural forms of vitamin A in high dose (but not its pro-vitamin, beta-carotene) and synthetic retinoids are highly teratogenic. Teratogenic effects include cardiac defects, microcephaly, spina bifida and limb defects. Females of childbearing potential with a desire to have children should not be given acitretin due to its long half-life.

- **Hyperlipidaemia** is a concern with long-term therapy. Triglycerides and cholesterol rise during acitretin treatment in about 30% of patients, with an increase in the low-density lipoprotein (LDL) to high-density lipoprotein (HDL) ratio (atherogenic index). This occurs particularly in patients with risk factors for hyperlipidaemia, i.e. excessive alcohol intake, diabetes mellitus, obesity or a family history of hyperlipidaemia. The elevation is dose related and can be managed by dietary control, dose reduction or, in some circumstances, by lipid lowering drugs. If the cholesterol cannot be maintained below 8.5 mmol/L and the triglyceride level below 3.0 mmol/L, treatment should be discontinued.
- **Hepatitis:** a transient modest rise in liver transaminases is common but acute hepatitis and jaundice are rare. Elevation of liver enzymes above 2–3 times the upper limit of normal should lead to discontinuation of treatment. If the elevation of liver enzymes is less than twice the upper limit of normal, the patient can be managed by more frequent monitoring, e.g. every 2 weeks.
- **Mucocutaneous:** in view of the commonly occurring dryness or erosions of the skin and mucous membranes, topical emollients and lip salves should be used routinely. Scaling, dryness, thinning and erythema may also be seen, particularly on the face and palmoplantar skin. Rarer cutaneous manifestations include skin fragility, photosensitivity and development of excessive granulation tissue. Epistaxis may occur occasionally. Petrolatum can be smeared into the nostrils to alleviate dryness.
- **Hair loss** is dose dependent and occurs in up to 75% of patients receiving acitretin, but only a minority are severely affected. Hair loss diminishes over time and is usually reversible within 6 months of discontinuation. Development of curly hair has been reported as a rare effect.
- **Ocular adverse effects** include sore eyes and decreased tolerance of contact lenses, which can be alleviated using eye drops ('artificial tears'). A decrease in night vision has occasionally been reported.
- **Musculoskeletal adverse effects** include arthralgia and myalgia, which are usually mild but may result in reduced exercise tolerance. Long-term (>2 years) treatment with second-generation retinoids has been associated with an increased risk of calcification of extraspinal tendons and ligaments, especially ankles, pelvis and knees, and diffuse idiopathic skeletal hyperostosis (DISH)-like changes in the spine. However, this is not clearly correlated with dose or duration. Routine monitoring with x-rays is therefore not justifiable in asymptomatic patients, but targeted radiography may be indicated for atypical musculoskeletal pain.
- **Premature epiphyseal closure** can occur in children. In view of the effect of retinoids on the growth plates there is a potential risk of decreased growth. However, it is advisable to monitor growth at regular intervals in children who are treated with acitretin.
- **Neurological:** headache, drowsiness and benign intracranial hypertension have occasionally been reported. Subclinical dysfunction of sensory nerve fibres has been detected after 1 month's treatment. Taste disturbance may occur.

- **Systemic:** non-specific symptoms such as nausea, malaise or sweating can sometimes occur.

### + Use in special situations

#### Pregnancy (FDA Category X)

Acitretin is absolutely contraindicated in pregnancy and females should not become pregnant for at least 3 years after stopping treatment. This duration is recommended by the British Association of Dermatologists (BAD), FDA and BNF recommend a 3 year time interval. Pregnancy must be excluded prior to commencing therapy. Females of childbearing age should have a negative pregnancy test not more than 2 weeks before starting acitretin.

Highly effective contraception must be used for 1 month prior to, during and for at least 3 years after cessation of treatment, even in those with a history of infertility. Precise recommendations will differ between countries.

Acitretin therapy should begin on the second or third day of the menstrual cycle.

The patient must be able to understand the risks of acitretin treatment, the consequences of a pregnancy and be able to comply with effective contraception. Information on how to obtain emergency contraception may be provided.

There is no evidence of impaired fertility or mutagenic risk in males who receive acitretin.

#### Lactation

Acitretin is excreted in breast milk and mothers taking this medication should not breastfeed.

#### Children

Acitretin may be used in carefully selected cases under expert supervision, e.g. in severe ichthyosis. The main concern in this age group is the risk of premature epiphyseal closure, though it is not clear if this is relevant with low-dose acitretin. Doses of 0.5–1.0 mg/kg/d may be used, up to a maximum of 35 mg/d, but the maintenance dose should be kept as low as possible. In female children approaching menarche, use of acitretin should be critically reviewed.

### + Essential patient information

Patients should be warned of the possible side-effects and given an up-to-date Drug Information Leaflet as provided by the manufacturer.

Females should avoid pregnancy throughout treatment and for at least 3 years after stopping taking acitretin. Females of childbearing age should sign an acknowledgement form regarding the risks associated with pregnancy.

Patients should not donate blood during or for at least 3 years after treatment. They should avoid tetracyclines, keratolytics, excessive sun exposure and ultraviolet lamps and supplements of vitamin A.

Wax epilation should be avoided due to the risk of increased skin fragility.

*With acknowledgements to Alun V Evans and WAD Griffiths, authors of this chapter in the 1st edition, and to Steven Feldman who reviewed this chapter from an international perspective.*

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# Acne Antibiotics

Alexander Nast & Ricardo N. Werner

## + Classification & mode of action

Certain antibiotics are widely prescribed in the treatment of acne. They decrease the number and function of *Propionibacteria acnes* on the surface of the skin and in the pilosebaceous duct. Tetracyclines and macrolides exert broad-spectrum antibacterial effects by inhibiting bacterial protein biosynthesis, while trimethoprim inhibits bacterial folic acid metabolism. Additional non-antimicrobial actions may be of importance including anti-inflammatory and antioxidative effects on neutrophils, impairment of matrix metalloproteinase activity and inhibition of pro-inflammatory cytokines such as IL-1 $\alpha$  and TNF $\alpha$ . These actions are evident at subantimicrobial doses.

## + Indications & dermatological uses

The use of systemic antibiotics for the treatment of acne is indicated in the following:

- Widespread mild-to-moderate papulopustular (inflammatory) acne.
- Severe papulopustular/moderate nodular acne.
- Severe nodular/conglobate acne (as an alternative to oral isotretinoin).

Topical antiacne therapy with a retinoid and/or benzoyl peroxide or azelaic acid should also be continued in all the above situations.

## + Formulations/Presentation

These include the following:

- Doxycycline: 40 mg, 50 mg, 100 mg capsules; 100 mg dispersible tablets.
- Lymecycline: 408 mg capsules.
- Minocycline: 50 mg, 100 mg tablets and capsules.
- Tetracycline and oxytetracycline: 250 mg tablets.
- Erythromycin: 250 mg, 500 mg tablets and capsules; 125 mg/5 ml suspensions (including sugar-free suspensions).
- Trimethoprim: 100 mg, 200 mg tablets; 50 mg/5 ml suspension.

Erythromycin is formulated as erythromycin base, estolate, ethyl succinate and stearate.

## + Dosages & suggested regimens

Antibiotics work relatively slowly in acne and it may improve adherence if patients are advised accordingly. The initial duration of therapy is **2–3 months**. If there is no improvement after this time, another drug should be considered. Maximum improvement does not usually occur until after **4–6 months**. In more severe cases, oral medication may need to be continued for 2 years or more. As acne is a chronic complaint, once inflammatory lesions have resolved, maintenance topical treatment should be prescribed (retinoids and/or benzoyl peroxide or azelaic acid).

- **First choice treatment:**
  - Doxycycline: 100 mg once daily. (or 50mg–200mg daily)
  - Lymecycline: 408 mg once daily.
  - Tetracycline and oxytetracycline: 500 mg twice daily.
- **Second choice treatment:**
  - Minocycline: 100 mg once daily.
- **Third choice treatment:**
  - Trimethoprim: 300 mg twice daily (unlicensed use).
- **During pregnancy and lactation:**
  - Erythromycin: 500 mg twice daily (not erythromycin estolate).

Although all tetracyclines appear to have comparable efficacy against inflammatory acne lesions, lymecycline and doxycycline are preferred due to their lack of interaction with milk and once-daily dosage. Due to the risk of irreversible pigmentation and other adverse effects with minocycline, it should not be used as a first-line therapy. Published trials show a trend towards superior efficacy for tetracyclines compared with macrolides. Trimethoprim is unlicensed for the treatment of acne, and therefore considered a third choice antibiotic to be used under specialist recommendation.

Failure to respond may be a consequence of the following:

- Poor patient adherence.
- *P. acnes* resistance.
- Inadequate dose or duration of therapy.
- Interactions impairing antibiotic absorption.

## + Baseline investigations & considerations

The emergence of antibiotic resistant strains of *P. acnes* has been clearly documented since the 1990s. However, the clinical relevance of this is unclear as it is not necessarily associated with therapeutic failure. The additional anti-inflammatory actions of antibiotics may be of importance in their effectiveness in acne.



Suspect resistance if:

- The patient has received many long-term sequential oral and/or topical antibiotics.
- Nonresponding patient.
- The patient relapses after the initial response to treatment despite continued therapy.

Prevent resistance by:

- Appropriate dosing.
- Avoid co-prescribing dissimilar oral and topical antibiotics.
- Avoid topical antibiotic monotherapy.
- Limit the use of systemic antibiotics (both indication and duration).
- Encourage excellent adherence.

Treat suspected resistance by:

- Use of therapies that are associated with a lower prevalence of resistance (*P. acnes* resistance to tetracyclines is less prevalent than combined resistance to clindamycin and erythromycin; and strains resistant to tetracycline and doxycycline may not be resistant to minocycline).
- Use of non-antibiotic therapies, i.e. oral isotretinoin, hormonal therapy, non-antibiotic topical therapy.

### + Monitoring

- Routine monitoring is not required before or during treatment of acne with oral antibiotics.
- Baseline investigations and monitoring every 3 months for hepatotoxicity and lupus (ANA and LFTs) have been suggested for patients receiving minocycline.

### + Contraindications

- **Tetracyclines** (doxycycline, minocycline, tetracycline, lymecycline):
  - Severe renal impairment (except doxycycline).
  - Children <12 years.
  - Pregnancy and lactation.
  - Systemic lupus erythematosus or family history of lupus (minocycline).
- **Erythromycin**:
  - QT interval prolongation, and combination with agents that can result in QT interval prolongation (risk of ventricular arrhythmias).
  - Hypokalaemia, hypomagnesaemia.
  - Severe hepatic impairment, history of hepatitis caused by macrolides, cholestasis.
- **Trimethoprim**:
  - Severe renal impairment.

- Haematological disease (thrombopenia, granulocytopenia, megaloblastic anaemia),
- Pregnancy and lactation.

### + Cautions

- **Tetracyclines:**
  - Hepatic impairment.
  - Renal impairment (dose reduction, consider determining drug serum level in long-term therapy – see Systemic Therapy & Kidney Disease).
  - Personal or close family history of lupus-like disorders (minocycline).
  - Myasthenia gravis, due to possible potentiation of neuromuscular blockade.
- **Erythromycin:**
  - Hepatic impairment.
  - Severe renal impairment (risk of irreversible hearing loss).
- **Trimethoprim:**
  - Hepatic impairment.
  - Renal impairment (dose reduction required).
  - Folic acid deficiency.

### + Important drug interactions

Tetracyclines should not be prescribed with the following:

- **Oral retinoids**, due to a potential increased risk of benign intracranial hypertension (see Isotretinoin).
- **Penicillins**, as the bactericidal action of penicillins may be reduced due to pharmacodynamic antagonism.

Care should be taken if tetracyclines are prescribed with the following:

- **Digoxin**, due to increased absorption and potential toxicity of digoxin.
- **Oral anticoagulants:** tetracyclines may enhance anticoagulant effects due to a reduction in prothrombin activity.
- **Salts** of calcium, iron, strontium, bismuth, aluminium, zinc, magnesium, antacids and quinapril (contains magnesium) may reduce absorption of tetracyclines and diminish their effectiveness.
- **Oral contraceptive pills (OCP):** there may be short-term impairment in the contraceptive effects of oestrogen-containing pills due to alteration of gut flora.
- **Oral hypoglycaemic agents:** the glucose lowering effect of sulphonylureas may be increased.
- **Ciclosporin** (cyclosporine) and **methotrexate**, due to possible increased toxicity.
- **Diuretics** (lymecycline).

Erythromycin has numerous drug interactions due to its inhibitory effects on the cytochrome p450 (CYP450) 3A isoenzyme, and the cardiotoxicity of certain drugs may also be increased. It should not be prescribed with the following:

- **Antipsychotic drugs** including droperidol, pimozide, sertindole.
- **Cisapride** (discontinued in the UK and USA), due to the risk of ventricular arrhythmias.
- **Ergot alkaloids** (unlicensed use for headache), due to increased risk of ergotism.
- **Mizolastine**, due to QT prolongation.
- **Simvastatin, lovastatin**, due to increased risk of myopathy.

Care should be taken if erythromycin is prescribed with the following:

- **Atorvastatin and pravastatin**: a lower dose should be used and patients monitored carefully for signs of myopathy. Other statins which are not metabolized by CYP3A4 (rosuvastatin, fluvastatin) may carry less risk of myopathy.
- **Ciclosporin** metabolism may be inhibited, with increased toxicity (see Ciclosporin).
- **Colchicine**, due to increased risk of toxicity (see Colchicine).
- **Coumarin anticoagulants** (e.g. warfarin), due to increased anticoagulant effects.
- **Digoxin** plasma concentrations are raised with risk of toxicity.
- **OCP**: there may be a short-term impairment in the contraceptive effects of oestrogen-containing pills due to alteration of gut flora.
- **Anticonvulsants** (phenytoin, carbamazepine, clozapine and valproic acid), due to decreased metabolic clearance and increased plasma levels.
- **Theophylline**, due to increased plasma theophylline, which may cause nausea, vomiting and seizures.
- **Verapamil**, due to increased risk of cardiotoxicity.

Trimethoprim should not be prescribed with the following:

- **Cytotoxics** (methotrexate, mercaptopurine, azathioprine), due to the increased risk of increased bone marrow toxicity.

Care should be taken if trimethoprim is prescribed with following:

- **Ciclosporin**, due to possible increased nephrotoxicity.
- **Coumarin anticoagulants**, due to possible enhanced anticoagulant effect.
- **Dapsone**: plasma concentrations of both drugs may increase.
- **Pyrimethamine**, due to possible blood dyscrasia.
- **OCPs**, due to possible impact on the contraceptive efficacy.
- **Oral hypoglycaemic agents**, due to possible enhanced effects.
- **Phenytoin, lamivudine, zidovudine, digoxin, procainamide**, due to increased plasma level and potential toxicity.

Oral antibacterial drugs inactivate **oral typhoid vaccine** and should be avoided 3 days before and after administration.

## + Adverse effects & their management

Nonspecific effects of oral antibiotic therapy include the following:

- **Gastrointestinal:** nausea, colic and diarrhoea may occur with all acne antibiotics but are particularly common with erythromycin as it enhances gastroduodenal motility. Symptoms may respond to dividing dosage or occasional use of co-phenotrope (Lomotil®, a mixture of 2.5 mg diphenoxylate hydrochloride and 25 µg atropine sulfate). Treatment with pro-biotic agents (such as Pro-Symbioflor®, a suspension containing *Escherichia coli* and *E. faecalis*), can help to regulate the intestinal flora. Epigastric discomfort is common with doxycycline and may be improved by taking the medication after food (which may decrease absorption up to 20%).
- **Vaginal candidiasis** is a common side-effect. Effective therapy is available without prescription.
- **Generalized drug eruption** and **fixed drug eruptions** are uncommon, although 4% of patients may develop a widespread maculopapular rash with trimethoprim. Stevens–Johnson syndrome, (an immune complex-mediated syndrome involving the skin and mucous membranes, which should be managed in an intensive care unit) and toxic epidermal necrolysis are rare (<0.1%) adverse effects of acne antibiotics.
- **Hormonal contraceptive failure:** broad-spectrum antibiotics have been associated with impaired effectiveness of the combined OCP, due to alteration in large bowel flora and reduced enterohepatic circulation of oestrogen. Although the magnitude of this effect appears modest, additional non-hormonal methods of contraception should be used during the first month of antibiotic therapy. If a woman on long-term acne antibiotic therapy (>3 weeks) commences a combined OCP, additional precautions are not needed. The American College of Obstetricians and Gynecologists advises that tetracycline, doxycycline, ampicillin and metronidazole do not affect oral contraceptive steroid levels.
- **Clostridium difficile-associated diarrhoea** (CDAD) and especially **pseudomembranous colitis** is very rare with oral acne antibiotics. It requires prompt and specific treatment with metronidazole or vancomycin.

Specific drug side-effects include the following:

- **Hyperpigmentation** with minocycline: this may affect various body sites including skin, nails, mucosae, eyes and bones ('black bones') and is due to deposition of black metabolites of the drug. Blue/grey/muddy brown discolouration may be localized or diffuse. The risk is generally related to the duration of treatment, and pigmentation may persist after stopping therapy, especially on sun exposed sites. Q-switched ruby laser therapy may help.
- **Photosensitivity** (phototoxicity) may occur with all tetracyclines, but is especially common with doxycycline and demeclocycline and most rare with minocycline. Phototoxicity appears clinically as exaggerated sunburn, sometimes with oedema and blistering, and may be accompanied by onycholysis.

- **Benign intracranial hypertension** is a rare adverse effect of tetracyclines, especially with doxycycline. It usually occurs within 4 weeks of starting therapy. Symptoms include headache, transient visual disturbances, diplopia, pulsatile tinnitus, nausea and vomiting. It may result in permanent loss of visual fields. If suspected an ophthalmological or neurological examination for papilloedema is required.
- **Minocycline-associated drug hypersensitivity syndrome** is a rare and potentially fatal drug reaction. It occurs within the first 1–2 months of treatment and presents with a generalized rash, lymphadenopathy and fever.
- **Minocycline induced lupus-like syndrome** with hepatitis, polyarthralgia, and positive antinuclear antibodies has been reported rarely (approximately 1 case per 10,000 person-years) especially with prolonged treatment. Perinuclear antineutrophil cytoplasmic antibodies (p-ANCAs) may also occur in some individuals. The risk of developing a lupus-like disorder has been estimated to be increased 2–5-fold during minocycline treatment, so the use of this drug should be carefully evaluated.
- **Oesophagitis** may occur with all tetracyclines, especially doxycycline. Medication should be taken when upright and with plenty of water to reduce the risk. Symptoms usually settle within a few days of drug withdrawal.
- **Tooth staining** is a recognized adverse effect of all tetracyclines. This may affect the primary or secondary dentition and has been reported to develop in adults after prolonged therapy. It occurs due to the ability of this group of antibiotics to chelate calcium ions, leading to their incorporation into teeth, cartilage and bone.
- **Drug induced liver injury** is a very rare adverse effect of tetracyclines (see Systemic Therapy & Liver Disease). Cholestatic hepatitis has been reported as a hypersensitivity reaction to the estolate salt of erythromycin. Symptoms include fever and abdominal pain, with eosinophilia and abnormal LFTs.
- **Idiosyncratic blood dyscrasias** including agranulocytosis, thrombocytopenia and anaemia may occur with trimethoprim.

### + Use in special situations

#### Pregnancy & pre-conception

**Tetracyclines** (FDA Category D) are contraindicated. They cross the placenta and can have toxic effects on fetal development, particularly retardation of skeletal development. Embryotoxicity in early pregnancy has been noted in animals. Use of tetracyclines during the last half of pregnancy may cause permanent discolouration of the infant's teeth.

**Erythromycin** (FDA Category B) may be considered as a suitable oral therapy in severe disease in pregnancy. The estolate salt is contraindicated.

**Trimethoprim** (FDA Category C) should be avoided in pregnancy, as it is a folate antagonist.

**Negative effects on male fertility** have been reported with tetracyclines and erythromycin.

## Lactation

**Tetracyclines** should not be used as they are excreted in breast milk and may cause permanent tooth discolouration and enamel hypoplasia in the developing infant.

**Erythromycin** is excreted in breast milk, but can be considered in severe cases (strict indication).

**Trimethoprim**: due to relatively low rate of excretion in breast milk, trimethoprim can be considered in severe cases (strict indication).

## Children

**Tetracyclines** are contraindicated in young children due to the risk of permanent tooth discolouration. The British National Formulary advises against their use under the age of 12 years due to the risk of permanent dental staining. Organizations in the USA recommend a lower age limit of under 9 years.

**Erythromycin** is licensed for use in childhood and may be considered in severe infantile acne.

## + Essential patient information

Females taking the combined OCP should be warned about the need for increased contraceptive precautions for the first month of oral antibiotic therapy. Patients should be advised about the expectable outcome of therapy (e.g. slow onset of effect) and about the need for excellent adherence to maximize effectiveness. They should also be informed of the specific drug side-effects.

*With acknowledgements to W. Cunliffe, author of this chapter in the 1st edition*

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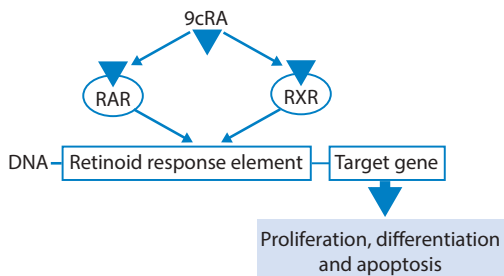
# Alitretinoin

Anand Patel & John English

## + Classification & mode of action

Alitretinoin (9-*cis*-retinoic acid) is an endogenously occurring retinoid which is structurally related to vitamin A. It acts as a pan-agonist at retinoid receptors, binding with high affinity to both retinoic acid receptors (RARs) and retinoid X receptors (RXR). The latter are capable of binding to a range of different nuclear receptors to modulate gene expression (Figure 1). The precise mode of action of alitretinoin in chronic hand eczema remains unclear, but retinoids are known to affect multiple processes at a cellular level including proliferation, differentiation and apoptosis. They may also have anti-inflammatory and immunomodulatory effects, including suppression of nitric oxide and tumour necrosis factor (TNF)-alpha production, impairment of T-cell activation and down-regulation of chemokine synthesis (CXCL9 and CXCL10), thereby impairing the recruitment of inflammatory leukocytes. Alitretinoin has been shown to suppress the expression of co-stimulatory molecules on the surface of antigen-presenting cells, which may be of relevance to a therapeutic effect in contact dermatitis. In contrast to isotretinoin, alitretinoin only has a minimal effect on sebum secretion.

Alitretinoin has a much shorter half-life than acitretin and isotretinoin, and levels of the drug and its metabolites return to the normal range within 2–7 days of stopping established treatment.



**FIGURE 1** Schematic diagram of the retinoic acid receptor (RAR), retinoid X receptor (RXR) and binding to the retinoid response element in the promoter region of a gene.

## + Indications & dermatological uses

- The only licensed indication for alitretinoin in the UK is severe chronic hand eczema that is unresponsive to potent topical steroids in adults. Severe chronic hand eczema is defined by a clinical score – the Physician's Global Assessment (PGA) – and a Dermatology Life Quality Index (DLQI) score of at least 15.

A large randomized placebo controlled study has demonstrated the efficacy of alitretinoin in adult patients with severe chronic hand eczema (referred to as the 'BACH' – Benefit of Alitretinoin in Chronic Hand eczema study). This reported that almost half of all patients receiving the higher (30 mg daily) dose achieved a rating of 'clear' or 'almost clear' at the 24 week endpoint. The lower dose (10 mg daily) was less effective but superior to placebo. Both hyperkeratotic disease and pompholyx/fingertip variants of hand eczema were reported to respond.

Smaller studies have reported benefit in palmoplantar psoriasis, chronic hyperkeratotic palmar psoriasis and chronic foot eczema. Isolated reports are emerging of its benefit in Darier's disease, Hailey–Hailey disease, pityriasis rubra pilaris and mycosis fungoides.

## + Formulations/Presentation

- 10 mg and 30 mg alitretinoin in soft capsules (Toctino®).
- Capsules contain soya bean oil and sorbitol.

A topical formulation of alitretinoin is FDA approved in the USA for use in acquired immunodeficiency syndrome (AIDS) associated Kaposi's sarcoma.

## Special point

Alitretinoin and acitretin are both prescribed by dermatologists and are 'sound alike' drugs. This raises the potential for prescribing and dispensing error with potentially serious consequences and litigation. Prescribing by brand may reduce this risk. Pharmacists who dispense alitretinoin should be alert to the potential for confusion.

## + Dosages & suggested regimens

The usual **starting dose** is **30 mg once daily**. The capsule should be swallowed whole with/after a meal to maximize bioavailability. If side-effects are not tolerated, dosage can be reduced to 10 mg daily. In patients with diabetes, hyperlipidaemia or risk factors for cardiovascular disease, a lower starting dose of **10 mg once daily** is recommended. This can be increased if necessary to a maximum daily dose of 30 mg.



The onset of action is slow, but there is usually some improvement within the first month. UK guidelines recommend that clinical response should be assessed at **12 weeks**, and treatment discontinued if inadequate. For those who respond, the total duration of treatment is recommended to be **12–24 weeks**. It has been reported that some patients who have not responded by these time intervals may nevertheless benefit from more prolonged therapy. Treatment should be stopped once an adequate clinical response (clear or almost clear) has been achieved. Relapse tends to occur slowly over several months and subsequent retreatment may be necessary.

### + Contraindications & cautions

The following are contraindications to systemic retinoid therapy including alitretinoin:

- Pregnancy (see below).
- Hypersensitivity to retinoids or excipients.

Alitretinoin capsules (Tocino®) contain soya bean oil. While soya beans and peanuts are both legumes, each of these foods stand alone in terms of immunogenicity and patients who are peanut allergic do not routinely need to avoid soya-containing products. In cases where the history is unclear, immediate type allergy testing can be undertaken (skin prick tests or specific immunoglobulin [Ig]E measurement) and if negative, a test dose given under clinical supervision.

Blood donation: should be avoided during treatment and for at least 1 month after stopping treatment.

Extra caution should be taken when alitretinoin is prescribed in the following:

- Liver dysfunction/cirrhosis (close monitoring is required; see Systemic Therapy & Liver Disease).
- Renal impairment (alitretinoin metabolites are mainly excreted in the urine; see Systemic Therapy & Kidney Disease).
- Uncontrolled hypothyroidism.
- Uncontrolled hyperlipidaemia.
- Diabetes.
- Depression.
- Disorders associated with ocular dryness.

### + Important drug interactions

- **Ketoconazole:** is a strong inhibitor of cytochrome P450 (CYP450) 3A4 metabolism of alitretinoin that impairs and increases alitretinoin plasma concentrations .

- **Simvastatin:** a slight reduction of simvastatin plasma levels was observed when co-administered with alitretinoin.
- **Vitamin A:** supplements are contraindicated due to the risk of hypervitaminosis/retinoid toxicity.
- **Tetracyclines:** due to the increased risk of benign intracranial hypertension.

### + Baseline investigations & considerations

**Patch testing** should be performed prior to commencing alitretinoin to exclude a significant underlying contact allergy. This is an important consideration as allergic contact dermatitis of the hands may be impossible to distinguish from an endogenous dermatitis on clinical grounds alone.

Patients with diabetes, history of hyperlipidaemia, or risk factors for cardiovascular disease should be identified and screened prior to commencing treatment and closely monitored during treatment. Baseline investigations consist of:

- Pregnancy testing (Pregnancy Prevention Programme, PPP).
- BP.
- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs.
- Fasting lipids & glucose.
- Thyroid function tests (if clinically indicated).

### + Monitoring

- **The PPP** must be followed in females of reproductive age. (See below and Isotretinoin.)
- **Fasting lipids** (cholesterol and triglycerides) should be monitored in order to detect hyperlipidaemia. In the absence of specific advice from the manufacturers, testing every 3 months is reasonable. Monthly monitoring may be indicated for those with diabetes, pre-existing hyperlipidaemia or risk factors for cardiovascular disease.
- **Urea and electrolytes and LFTs** monitoring may be sensible though not specifically advised by the manufacturer.
- **Thyroid function** should be monitored in those with pre-existing disease. In normal individuals low thyroid stimulating hormone (TSH) levels may occur during treatment but thyroid medication is not usually required.

## + Adverse effects & their management

- **Teratogenicity:** in females of childbearing age the PPP must be followed unless the individual has signed a disclaimer that she is not sexually active and at risk of pregnancy. The monitoring requirements are identical with those for oral isotretinoin (see Isotretinoin). In the UK this includes the following:
  - Pregnancy testing prior to commencing alitretinoin, at monthly intervals thereafter during treatment and at 5 weeks after completion of treatment.
  - Females at risk of pregnancy must use adequate contraception for at least 1 month before starting treatment, during treatment and for at least 1 month after stopping treatment.
  - Females should be advised to use at least one method of highly effective contraception and ideally they should use two methods. The progesterone-only oral contraceptive pill (OCP) (mini-pill) or barrier contraception alone are not considered adequate but can be combined with other contraceptive methods. Effectiveness of hormonal contraceptives is not impaired by alitretinoin.
  - Females should be advised to discontinue treatment and to seek prompt medical attention if they become pregnant during treatment or within 1 month of stopping treatment.
- **Hyperlipidaemia:** raised total cholesterol and triglycerides may occur during treatment. This effect is usually dose related and reversible and usually responds to dosage reduction. If these measures fail and hyperlipidaemia is severe, treatment must be discontinued. Hypertriglyceridaemia is associated with an increased risk of pancreatitis, especially if levels exceed 9 mmol/L.
- **Headache and flushing** are the commonest initial adverse effects, and affect about half of all patients. They are a more frequent problem with alitretinoin than other systemic retinoids and tend to improve after several weeks of continued treatment. Simple analgesics and taking the medication shortly before sleep may be helpful.
- **Pseudotumour cerebri (PTC)/benign intracranial hypertension** is a very rare adverse effect common to all retinoids, especially when taken with tetracyclines. Symptoms are severe headache, nausea and vomiting and visual disturbance. If untreated, there is a risk of permanent visual loss.
- **Ocular adverse effects** include blurred vision, conjunctivitis, photosensitivity, impaired night vision, cataracts, keratitis and eye irritation.
- **Cutaneous adverse effects** include flushing and pruritus, dryness, cheilitis, epistaxis, asteatotic eczema, vasculitis and alopecia. Cheilitis and alopecia are less common than with isotretinoin and acitretin respectively. Photosensitivity can occur during treatment with alitretinoin so patients should be advised to avoid use of sun beds and protect their skin against excessive sun exposure.
- **Musculoskeletal adverse effects** common to oral retinoids include exercise induced fatigue, myalgia and arthralgia. These may be associated with

elevation of serum creatine kinase. Radiological changes with long-term retinoid therapy include hyperostosis and spondylitis (rare).

- **Psychiatric disturbance** including depression is a potential adverse effect of all oral retinoids, especially isotretinoin (see Isotretinoin). It is not yet clear if this applies to alitretinoin which has generally been used in older patients with a different psychosocial profile from those with acne. If patents are affected by mood change, the PHQ-9 can be used as a simple screening tool for depression (see Appendix 1).

### + Use in special situations

#### Pregnancy & pre-conception

Alitretinoin is a teratogen and absolutely contraindicated in pregnancy. Females should not become pregnant within 1 month of discontinuing treatment (see Isotretinoin PPP).

Very low amounts of alitretinoin have been detected in the semen of males taking alitretinoin. As with the other oral retinoids, isotretinoin and acitretin, these levels are too low to pose a teratogenic risk to the unborn baby of a female partner.

Topical alitretinoin is FDA Category D.

#### Lactation

Alitretinoin is lipophilic and likely to be distributed to breast milk so it is contraindicated in breastfeeding females.

#### Children

Alitretinoin is only licensed for use in those over 18 years. Clinical trials of high dose 9-*cis*-retinoic acid in childhood malignancy reported PTC as a frequent adverse effect, especially in younger children. There is insufficient evidence at present to support use of alitretinoin in dermatological disease in children.

### + Essential patient information

- Patients should be informed of the reasons for treatment, the likely side-effects and the monitoring requirements.
- It should be explained that treatment will cease if there is an inadequate response at 3 months, after completion of a 6 months' course or earlier if disease remission is achieved.
- Females should be fully informed of the requirements of the PPP.

*With acknowledgements to Raja Sivamani, Jillian Millsop and Vivian Shi who reviewed this chapter from an international perspective.*

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# Androgens

Shirin Zaheri & laisha Ali

## + Classification & mode of action

Androgens belong to class C-19 steroids produced primarily by the testes, adrenal cortex (the major source in females) and ovaries. Testosterone and its more potent  $5\alpha$ -reduced derivative,  $5\alpha$ -dihydrotestosterone (DHT), are the two predominant physiological androgens. The ovaries produce oestradiol. Steroids with oestradiol-like function are called oestrogens. Testosterone and oestradiol circulate in plasma bound to plasma proteins, mainly sex hormone binding globulin (SHBG). The hepatic synthesis of SHBG is stimulated by oestrogens and inhibited by testosterone.

Anabolic steroids are sex hormones with some androgenic activity (increased skeletal muscle mass, increased organic mass of bone and retention of nitrogen). They cause less virilization than androgens in females and are helpful in some dermatological conditions. The actions of anabolic steroids are similar to male sex hormones, with the possibility of causing serious disturbances of growth and sexual development if given to children.

**Danazol** is a synthetic steroid derived from ethisterone. It is a weak androgen with additional antiprogesterogenic and antioestrogenic actions and interferes with gonadal steroid synthesis. It also affects pituitary gonadotrophins, with inhibition of the mid-cycle surge of follicle stimulating hormone (FSH) and luteinizing hormone (LH), as well as altering the pulsatility of LH, and can reduce the mean plasma levels of these gonadotrophins after the menopause.

Danazol has a wide range of actions on plasma proteins, including increasing prothrombin, plasminogen, antithrombin III, alpha-2 macroglobulin, C1 esterase inhibitor, and erythropoietin and reducing fibrinogen, thyroid binding and SHBG. It increases the proportion and concentration of testosterone carried unbound in plasma. In addition, danazol corrects partially or completely the primary biochemical abnormality of hereditary angioedema by increasing the levels of the deficient C1 esterase inhibitor. As a result of this action, the serum levels of the C1 esterase inhibitor and C4 component of the complement system are increased.

The suppressive effects of danazol on the hypothalamic–pituitary–gonadal axis are reversible, cyclical activity reappearing normally within 60–90 days after therapy.

**Stanozolol** is a synthetic derivative of testosterone and has more powerful androgenic effects, hence its use as a performance enhancing drug by bodybuilders. It is no longer licensed for use in the UK, but remains approved by the USA FDA. It suppresses the gonadotrophic functions of the pituitary and

may exert a direct effect upon the testes. It can increase collagen production and decrease the antianabolic action of cortisone. It is also reported to increase fibrinolysis. It corrects the formation of kinin or kinin-like factors, which may be associated with oedema and swelling seen in hereditary angioedema.

### + Indications & dermatological uses

- **Danazol** is licensed for the treatment of endometriosis and benign fibrocystic breast disease. Stanazolol is no longer licensed for use in the UK.
- Danazol has been used in the long-term management of hereditary angioedema in patients who have frequent and/or severe episodes. It has also been used for recalcitrant cholinergic urticaria and lividoid vasculopathy.
- **Stanozolol** has been used for hereditary angioedema and a range of dermatological diseases including hereditary angioedema, vascular manifestations of Behçet's disease, cryofibrinogenaemia and lipodermatosclerosis.

The usage of these drugs for hereditary angioedema prophylaxis may decrease as on-demand self-administered therapy with C1 inhibitor concentrate and bradykinin analogues becomes more widespread.

### + Dosages & suggested regimens

- Danazol: 50 mg, 100 mg and 200 mg capsules.
- Stanazolol: 2 mg tablets, scored 5 mg tablets.

**Danazol:** for hereditary angioedema the initial dose is **200 mg 2–3 times per day**, with dose reductions of 50% at intervals of at least **1–3 months**. If an attack occurs, dosage is increased by increments up to 200 mg/d. Treatment is usually given continuously and dosage should be kept at the lowest effective level. Short-term treatment may also be given before elective surgical interventions. In recalcitrant cholinergic urticaria the usual daily dosage of danazol is 600mg. Doses of up to 800 mg per day are used for endometriosis.

In fertile females, treatment should be started during menstruation, preferably on the first day of the cycle and adequate non-hormonal contraception used (see Use in special situations).

**Stanozolol:** for hereditary angioedema, initial doses range from 2.5 to 10 mg daily according to severity, with maintenance doses of 2 mg daily or on alternate days or 2.5 mg three times weekly.

For vascular manifestations of Behçet's disease the usual dose is 10 mg daily.

### + Baseline investigations & considerations

- FBC (CBC)/LFTs/fasting lipids/glucose.

- Pregnancy test and contraception for females of childbearing potential (see above and Use in special situations).

### + Monitoring

Hepatotoxicity and liver tumours have been reported in rare instances, so the lowest doses should be used with careful monitoring as below:

- FBC.
- LFTs.
- Fasting lipids.
- Fasting glucose.
- Biannual hepatic ultrasonography.
- Clinical assessment of females for features of virilization.

Interactions with laboratory function tests: danazol may interfere with laboratory determination of testosterone or plasma proteins; stanozolol may interfere with thyroid function tests.

### + Contraindications

Both drugs are contraindicated in the following:

- Pregnancy and lactation.
- Androgen sensitive tumours (e.g. prostate cancer).
- Severe impairment of hepatic, renal or cardiac function.
- Thromboembolic disease – active or past history of events.
- Acute porphyria.
- Hypersensitivity to the active drug or excipients.
- Undiagnosed/abnormal vaginal bleeding.

Stanozolol is not recommended for use in pre-menopausal females, those with insulin dependent diabetes and hypercalcaemia/hypercalciuria.

### + Cautions

- Underlying medical disease associated with fluid retention: cardiac, renal and hepatic disorders, migraine, epilepsy, polycythaemia, lipoprotein disorder, diabetes.
- The elderly.
- Patients who have shown marked or persistent androgenic response to previous gonadal steroid therapy.
- Malignant disease – before treatment initiation, the presence of hormone dependent carcinoma should be excluded at least by careful history and clinical examination. The risk of ovarian cancer may be increased.



### + Important drug interactions

- **Anticonvulsant** therapy: use of androgens may increase plasma levels of carbamazepine, phenobarbital and phenytoin.
- **Antidiabetic** therapy: requirements may increase as androgens increase insulin resistance and impair glucose tolerance.
- **Antihypertensive** therapy: requirements may increase due to hypertensive actions of synthetic androgens.
- **Oral anticoagulant** therapy may be potentiated.
- **Gonadal steroid** therapy may be affected by danazol.
- **Migraine** therapy: danazol may provoke migraine and possibly reduce the effectiveness of medication to prevent that condition.
- **Alpha calcidol**: danazol may increase the calcaemic response in primary hypoparathyroidism, necessitating a reduction in dosage of this agent.
- **Ciclosporin** (cyclosporine) and tacrolimus: danazol can increase the plasma level of ciclosporin and tacrolimus, leading to increased renal toxicity.
- **Levothyroxine** activity may be enhanced by stanozolol.
- **Statins**: the risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with statins such as simvastatin, atorvastatin and lovastatin.

### + Adverse effects & their management

- **Androgenic**: mild effects are common and include acne, weight gain, increased appetite and seborrhoea. Menstrual irregularities, vaginal dryness, flushing, changes in libido and a reduction in breast size may also occur. Treatment should be discontinued if signs of virilization develop (hirsutism, pattern hair loss, voice change). If treatment is discontinued promptly, these effects are usually reversible. However, permanent clitoral hypertrophy has occurred with continued therapy. Male fertility and sexual function may be affected (see Use in special situations).
- **Hepatic**: prolonged therapy with large doses increases the risk of hepatic neoplasms and hepatocellular carcinomas. Isolated increases in serum transaminase levels, cholestatic jaundice and benign hepatic adenomata may also occur, so careful monitoring is indicated. Peliosis hepatis has been reported (a condition in which hepatic and sometimes splenic tissue is replaced with blood-filled cysts).
- **Renal**: haematuria has been reported with prolonged use in patients with hereditary angioedema.
- **Metabolic and pro-atherogenic adverse effects** include increased insulin resistance and impaired glucose tolerance with raised plasma glucagon. Increase in low-density lipoprotein (LDL) cholesterol and decrease in high-density lipoprotein (HDL) cholesterol may occur. Routine laboratory monitoring is therefore indicated.

- **Haematological abnormalities** include increased erythropoiesis and polycythaemia, leukopenia, thrombocytopenia, eosinophilia and alteration in clotting factors with prolongation of the prothrombin time (PT).
- **Central nervous system** adverse effects include dizziness, headache, fatigue, insomnia and mood disturbance (anxiety, depression, aggression). Benign intracranial hypertension has been reported (symptoms include severe headache, nausea and visual disturbance). Aggravation of epilepsy and carpal tunnel syndrome may occur.
- **Ophthalmological adverse effects** include blurred vision and altered refraction, which may affect those who wear contact lenses or spectacles.
- **Gastrointestinal adverse effects** include nausea, vomiting, dyspepsia and pancreatitis.
- **Pulmonary:** pleuritic pain, interstitial pneumonitis.
- **Cardiac:** hypertension may be the most significant long-term effect of therapy. Combined with the deleterious alterations in metabolic profile (see above) this may increase cardiovascular risk. Other cardiac effects include palpitations and tachycardia. Thrombotic events include sagittal sinus, cerebrovascular thrombosis and myocardial infarction.
- **Cutaneous adverse effects** include rash and pruritus, photosensitivity, altered skin pigmentation, exfoliative dermatitis and erythema multiforme. Immediate type hypersensitivity has been reported.
- **Musculoskeletal and connective tissue adverse effects** include muscle cramps and tremors, fasciculation, limb pain, joint pain and joint swelling. Premature epiphyseal closure may occur in children and adolescents.
- **Alcohol:** subjective intolerance in the form of nausea and shortness of breath has been reported with danazol.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category X)

Androgens are contraindicated in pregnancy as they may cause virilization of the female fetus. In males, use of synthetic androgens may be associated with reduced spermatogenesis as they inhibit FHS production. Other effects include altered libido and priapism.

#### Lactation

Androgens are contraindicated as it is not known whether they are excreted in human milk.

#### Children

The use of synthetic androgens is not recommended in pre-pubertal children. Risks include precocious sexual development in boys, virilization in girls and premature closure of the epiphyses in both sexes. If used in children, growth should be carefully monitored with radiography if indicated to assess bone age.

### **+ Essential patient information**

- These drugs should not be taken during pregnancy as they may be harmful to an unborn baby.
- Alcohol should be avoided as it may cause sickness or shortness of breath.
- Patients should be advised to stop taking this medicine and consult their doctor if they experience any of the following symptoms: hair loss (especially male baldness); marked increase in facial or body hair; voice change – hoarseness or pitch change; enlargement of the clitoris; altered vision; severe headache and vomiting; stabbing pains and/or unusual swelling in one leg; pain on breathing or coughing; coughing up blood; sudden breathlessness; sudden severe chest pain; or any other severe unexplained symptom.
- Blood tests to monitor liver function are required while taking this medicine. Symptoms that may suggest a liver problem include persistent nausea and vomiting, abdominal pain, or the development of jaundice.

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# Antiandrogens

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## + Classification & mode of action

Antiandrogens are a group of drugs that block the action of androgens by two broad mechanisms:

- Competitive inhibition of binding of androgens (testosterone and dihydrotestosterone [DHT]) to the androgen receptor (androgen receptor antagonists).
- Inhibition of the enzyme 5 $\alpha$ -reductase that converts testosterone to DHT.

**Androgen receptor antagonists** include drugs, such as the steroidal antiandrogens, spironolactone and cyproterone acetate, which also have direct inhibitory effects on androgen synthesis, and the non-steroidal or 'pure' antiandrogens, flutamide and bicalutamide.

**Flutamide** is a potent antiandrogen. Its mechanism of action is inhibiting androgen uptake and inhibiting nuclear binding of androgen in target tissues.

**Bicalutamide** is a newer and potent antiandrogen with similar mechanism of action. These drugs were developed for the treatment of prostate cancer but at lower doses have been found to be effective in the treatment of females with hirsutism.

**Spironolactone** is an aldosterone antagonist and acts as a potassium sparing diuretic. It inhibits the action of aldosterone on the distal renal tubule, increasing sodium and water excretion and reducing potassium excretion. Spironolactone is also a potent antagonist of the androgen receptor as well as an inhibitor of androgen production, hence its use to treat androgen related skin disease in females, namely hirsutism, androgenic alopecia and acne.

**Drospirenone** is a spironolactone analogue with antimineralocorticoid activity. It also counteracts the oestrogen stimulated activity of the renin-angiotensin-aldosterone system, and has also been shown to possess mild antiandrogen activity. It is used in combination with an oestrogen for hormonal oral contraception and hormone replacement therapy.

**Cyproterone acetate** is a synthetic derivative of 17-hydroxyprogesterone, and acts primarily as an androgen receptor antagonist. It also has weak progesterone agonist and glucocorticoid actions and inhibits androgen synthesis. Cyproterone acetate was the first antiandrogen in clinical use and was introduced 1964. A low dose combined preparation containing 2 mg of cyproterone acetate and 50  $\mu$ g of ethinyloestradiol was first marketed in the UK in 1977, and subsequently reformulated with a lower oestrogen dose (Dianette®) to reduce oestrogen related side-effects (oedema, melasma and nausea).

**5 $\alpha$ -reductase inhibitors** specifically prevent the conversion of testosterone to its more potent metabolite DHT. In males with male pattern hair loss, the balding scalp contains miniaturized hair follicles and increased amounts of DHT. Administration of 5 $\alpha$ -reductase inhibitors decreases scalp DHT concentrations and inhibits the process responsible for miniaturization of scalp follicles. Males with a genetic deficiency of type 2 5 $\alpha$ -reductase do not suffer from male pattern hair loss. The enzyme 5 $\alpha$ -reductase exists as two isoenzymes; type 1 is the dominant form in non-genital skin including the scalp and the sebaceous glands, while type 2 is the dominant form in genital skin, the prostate and hair follicles of the scalp, where miniaturization takes place. **Finasteride** selectively inhibits the type 2 isoenzyme whereas **dutasteride** inhibits both type 1 and type 2 5 $\alpha$ -reductase. Although dutasteride reduces serum DHT levels more than finasteride, both drugs have similar efficacy in the treatment of symptomatic benign prostatic hyperplasia where they reduce prostate volume and have similar adverse event profiles.

Other drugs with antiandrogenic effects include the **corticosteroids**, prednisolone and dexamethasone, which inhibit adrenal androgen secretion, particularly when given as a nocturnal dose (see Corticosteroids). **Metformin**, an insulin sensitizing agent, has been suggested to have direct antiandrogen actions on ovarian steroid synthesis as well as improving insulin sensitivity and reducing insulin levels, which leads to a reduction in circulating free androgens. **Cimetidine** has weak antiandrogenic effects due to competitive inhibition of DHT at peripheral androgen receptors. **Gonadotrophin releasing hormone** (GnRH) agonists inhibit pituitary gonadotrophin release and are the most effective inhibitors of testosterone, while **oral contraceptive pills** (OCP) inhibit ovarian androgen secretion. These agents have been reported to be useful in the treatment of skin conditions.

### + Indications & dermatological uses

Dermatological uses include the following (licensed indication \*):

- Finasteride: androgenetic alopecia (in males\*).
- Dutasteride: androgenetic alopecia.
- Flutamide: hirsutism, female pattern hair loss.
- Bicalutamide: hirsutism.
- Spironolactone: female pattern hair loss, acne and hirsutism.
- Drosiprenone: acne.
- Cyproterone acetate as co-cyprindiol (Dianette®): acne (recalcitrant/severe\*) and/or hirsutism (moderate\*) in females. The combined preparation also functions as a hormonal contraceptive, but is not licensed specifically for this purpose. It is not available in the USA.
- Cyproterone acetate (high dose): female hair loss and hirsutism.

Other licensed uses are:

- Finasteride, dutasteride: benign prostatic hyperplasia.
- Flutamide, bicalutamide: metastatic prostate cancer.

- Spironolactone: oedematous conditions including congestive heart failure, nephrotic syndrome, cirrhosis with ascites, malignant ascites and primary aldosteronism.
- Drospirenone: OCP.
- Cyproterone acetate (high dose): male hypersexuality, advanced prostate cancer.

### + Formulations/Presentation

- Finasteride: 1 mg and 5 mg tablets. The 1 mg dosage is indicated for males with androgenetic alopecia.
- Dutasteride: 0.5 mg soft capsules.
- Flutamide: 125 mg tablets.
- Bicalutamide: 25 mg tablets.
- Spironolactone: tablets containing 25 mg, 50 mg and 100 mg of spironolactone. Oral suspension ranging from 5 to 100 mg/5 mL is available on special order.
- Drospirenone: combined preparation of 3 mg drospirenone and 30 µg ethinylloestradiol as oral contraception (Yasmin®) and 0.5 mg of drospirenone and 1 mg of estradiol (Angeliq®) as hormone replacement therapy in post-menopausal females.
- Cyproterone acetate: scored tablets containing 50 mg and 100 mg of cyproterone acetate. A combined preparation, co-cyprindiol, containing cyproterone acetate 2 mg and ethinylloestradiol 35 µg is available as sugar coated tablets (Dianette®).

### + Dosages & suggested regimens

**Finasteride:** the recommended dose for male androgenic alopecia is **1 mg daily**. A higher daily dose (5 mg) is used for the treatment of benign prostatic hyperplasia but does not increase efficacy in hair loss.

**Dutasteride:** the recommended dose for benign prostatic hyperplasia is **0.5 mg daily** and this dose has also been found to be effective in male androgenic alopecia. A placebo-controlled study reported that this dose had superior effects on hair growth and hair count to finasteride. Capsules should be swallowed whole and not chewed or opened, as contact with the contents may cause irritation of the oropharyngeal mucosa.

The onset of effect of these agents in male androgenic alopecia is slow and it usually takes **6 months** to stabilize hair loss. Treatment arrests the progression of disease, but regrowth is partial at best and continued treatment is required to sustain benefit. If treatment is stopped, the beneficial effects begin to reverse by 6 months and return to baseline by 9–12 months. At the recommended dose, finasteride has been shown to improve the anagen (growing phase) follicle count in males with vertex baldness while those given placebo lost anagen hair. The majority of males continue to benefit from long-term

treatment (up to 10 years). Adverse effects are uncommon. Efficacy in females with androgenic alopecia is controversial. No adjustment in dosage is necessary in renal impairment or in the elderly. Finasteride has a much shorter half-life than dutasteride.

**Flutamide:** low doses of **125–250 mg daily** are effective for hirsutism. Dosages of up to 750 mg have been used (i.e. the recommended dose for prostate cancer). Treatment may be given with a combined OCP and in a reverse sequential regimen as below.

**Bicalutamide:** low doses of **25 mg daily** for treatment of hirsutism.

**Spironolactone:** a low **starting dose** of **25–50 mg** daily is recommended to reduce side-effects, followed by dose increases **up to 200 mg** daily as maintenance therapy. (Doses of up to 400 mg daily are used in oedema and ascites.) Medication should be taken with food to aid absorption.

**Drospirenone:** the combined OCP preparation Yasmin® is taken once daily for 21 days, followed by a 7-day tablet free interval.

**Cyproterone acetate:** for the treatment of hirsutism and female pattern hair loss, **50 mg daily** is usually sufficient, although up to **100 mg/d** can be used. Side-effects are dose dependent so the lowest effective dose is advisable. To prevent pregnancy and minimize menstrual irregularities it should be taken daily with the first 10 pills of a combined OCP, i.e. reverse sequential regimen. Co-cyprindol is taken once daily for 21 days, followed by a 7-day tablet free interval when a withdrawal bleed should occur.

### + Baseline investigations, considerations & monitoring

- Females who are overweight or obese (body mass index [BMI]  $\geq 30$ ) should be advised to lose weight as this may improve androgen related symptoms.
- Androgen profile, cortisol and pelvic ultrasound scan in females with severe/progressive hirsutism or acne – especially if associated with menstrual disturbance.
- Pregnancy should be excluded before starting oral antiandrogen therapy.

### Finasteride/dutasteride

- Serum prostate specific antigen (PSA).
- Prostate evaluation by urologist for older males.
- Monitoring: check PSA values regularly and refer to individual's baseline value. PSA usually falls with treatment. Any increase in PSA level may indicate the presence of prostate cancer and needs further evaluation even if within the normal range. PSA levels should return to baseline within 6 months of discontinuing treatment.

### Flutamide/bicalutamide

- Baseline: FBC (CBC), urea and electrolytes, LFTs.

- Monitoring: LFTs monthly for first 4 months, then 3-monthly. Discontinue if alanine aminotransferase (ALT) increases to twice upper limit of normal. Monitor methaemoglobin levels in patients susceptible to the effects of hypoxia.

### Spironolactone

- Baseline: BP, weight and BMI.
- FBC, urea and electrolytes.
- Monitoring: FBC, urea and electrolytes after 2 weeks and after dose increases; discontinue if hyperkalaemia occurs.

### Drospirenone (Yasmin®)

- Baseline: BP, weight and BMI.
- Check medical eligibility criteria for combined OCP.
- The risk of venous thromboembolism (VTE) should be assessed (personal or close family history) as the risk of VTE may be increased in females taking drospirenone than in those taking other low dose combined OCPs (see below).
- Start treatment on the first day of the menstrual period.
- Routine monitoring as for OCP: includes review after 3 months then every 6–12 months with measurement of BP and assessment of new risk factors.

### Cyproterone acetate as co-pyrindiol (Dianette®)

- Baseline: BP, weight and BMI.
- Check medical eligibility criteria for combined OCP.
- The risk of VTE should be assessed (personal or close family history) as VTE occurs more frequently in females taking co-cyprindiol than in those taking low dose combined OCPs (see below).
- Start treatment on the first day of the menstrual period.
- Monitoring as for OCP (see Drospirenone).

### Cyproterone acetate (high dose)

- As above with baseline and regular laboratory monitoring (FBC, urea and electrolytes, glucose, LFTs).

## + Contraindications

All antiandrogens are contraindicated in pregnancy. (See pregnancy & preconception)

Flutamide/bicalutamide:

- Severe hepatic disease.

Spironolactone:

- Hyperkalaemia and severe renal impairment.
- Postural hypotension.
- Addison's disease.



- Drospirenone (Yasmin®):
  - Contraindications to combined OCP.
  - Renal or liver impairment.
  - Adrenal insufficiency.
- Cyproterone acetate as co-pyrindiol (Dianette®):
  - Contraindications for combined OCP including personal or close family history of VTE.
- Cyproterone acetate (high dose):
  - Meningioma or past history of meningioma.
  - Severe depression.

### + Cautions

- Finasteride/dutasteride:
  - Although the overall risk of prostate cancer is decreased, there is an increased risk of high grade disease and PSA tests are more difficult to interpret.
- Flutamide/bicalutamide:
  - Cardiac disease.
  - Hepatic impairment – closer monitoring needed.
  - Renal impairment.
- Spironolactone:
  - Elderly.
  - Renal impairment, diabetes mellitus.
  - Porphyria.
  - Patients suffering from menstrual abnormalities or breast enlargement.
- Drospirenone:
  - As for combined OCP including diabetes, hypertension, age over 35 years, obesity and those at risk of thromboembolic disease, depression. All combined OCPs are associated with an increased risk of VTE, the size of this risk is related to the dose of oestrogen and the progestagen. The risk of a VTE is highest during the first year of treatment or when switching/ restarting after a pill free period of at least 1 month. Epidemiological studies have shown that the incidence of VTE for combined OCPs containing 30–35 µg ethinyloestradiol and drospirenone, cyproterone acetate, gestodene and desorgestrel are similar and about 50–80% higher than for combined OCPs with levonorgestrel.
  - Increased risk of hyperkalaemia (in renal impairment, hepatic impairment and adrenal insufficiency).
- Cyproterone acetate as co-pyrindiol (Dianette®):
  - As for combined OCP (see above).

## + Important drug interactions

- **Finasteride and dutasteride:** combination therapy with an **alpha blocker**, especially tamsulosin may precipitate cardiac failure.
- **Dutasteride:** **verapamil**, **diltiazem**, **isoniazid**, and **macrolide antibiotics** can increase dutasteride serum concentrations.
- **Flutamide:** **corticosteroids** delay its metabolism; avoid concomitant administration of potentially hepatotoxic drugs, excessive alcohol consumption, concomitant administration with theophylline – increases theophylline plasma concentration. It also enhances the anticoagulant effect of warfarin.
- **Bicalutamide:** inhibits **cytochrome P450 (CYP450) 3A4** and should be used with caution with other drugs which are metabolized by this enzyme system, e.g. ciclosporin, cimetidine, calcium channel blockers. It also enhances the anticoagulant effect of warfarin.
- **Spironolactone:** due to the drug's diuretic actions, there is an increased risk of hyponatraemia with **chlorpropamide** and hyperkalaemia with **potassium sparing diuretics**, **ciclosporin**, **trimethoprim**, **non-steroidal anti-inflammatory drugs (NSAIDs)** and **tacrolimus**. The nephrotoxicity of drugs such as NSAIDs may be increased and excretion of digoxin and lithium reduced, so closer therapeutic monitoring is required.
- **Drospirenone:** may worsen **hyperkalaemia** (see Spironolactone). Drug interactions are also relevant to the oestrogenic component in Yasmin® and agents that induce CYP3A4 may increase metabolism of oestrogen and cause loss of efficacy (see formulary for full prescribing information).
- **Cyproterone acetate:** oral **antidiabetic drug** or **insulin** requirements may change. Drugs interactions are also relevant to the oestrogenic component in Dianette® as for Yasmin® (see above and consult full prescribing information).

## + Adverse effects & their management

### Finasteride/dutasteride

- **Infertility:** there have been sporadic reports of infertility and/or poor seminal quality, but in some cases patients had additional risk factors for infertility. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.
- **Sexual adverse effects:** in a placebo-controlled trial, a slight increase in the incidence of sexual adverse effects such as decreased libido, impotence and ejaculatory dysfunction was reported with finasteride. These adverse effects gradually disappeared during prolonged treatment. However, persistence of decreased libido and erectile dysfunction after discontinuation has been reported in post-marketing data. The risk of sexual dysfunction is slightly greater in males taking dutasteride compared with finasteride.

- **Breast cancer** has been reported in males taking finasteride and dutasteride. Physicians should advise patients to report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.
- **Cutaneous adverse effects** include rash and pruritus, urticaria, localized oedema, angioedema, alopecia (primarily body hair loss) and hypertrichosis.

### Flutamide/bicalutamide

- **Hepatotoxicity** ranges from mild transaminitis and jaundice to hepatic necrosis and encephalopathy. It may be less frequent with bicalutamide than flutamide. Careful monitoring is required with early discontinuation if LFTs are deranged.
- **Sexual adverse effects** are common with non-steroidal antiandrogens including loss of libido, gynaecomastia, breast tenderness and galactorrhoea. Dry skin, pruritus and flushing may occur.
- **Gastrointestinal adverse effects** are common and include nausea and dyspepsia.
- **Haematological adverse effects** include anaemia and very rarely methaemoglobinaemia (flutamide).
- **Cutaneous adverse effects** including photosensitivity and a systemic lupus erythematosus-like syndrome have been described.

Bicalutamide: appears to have fewer side-effects than flutamide at the higher doses used in the treatment of prostate cancer.

### Spironolactone

- **Hyperkalaemia** is dose related and more common in the elderly and those with renal impairment or cardiac impairment. It may lead to arrhythmia and cardiovascular collapse. Review other medication (see Important drug interactions) and discontinue if necessary.
- **Non-specific side-effects** such as fatigue, headache and dizziness are common.
- **Gastrointestinal adverse effects** include gastritis and an increased risk of gastroduodenal bleeding (dose related).
- **Sexual adverse effects** include gynaecomastia, breast tenderness, loss of libido and alteration in voice pitch. These are usually reversible on discontinuation but in rare instances breast enlargement and voice change may persist. Menstrual irregularities are common with doses above 100 mg daily and may be improved by combination with an OCP or cyclical therapy (days 4–21 of menstrual cycle).
- **Cutaneous adverse effects** include pruritus, alopecia, immediate type hypersensitivity and severe cutaneous adverse reactions (DRESS and Stevens–Johnson syndrome).
- **Other adverse effects** include osteomalacia, agranulocytosis, eosinophilia, thrombocytopenia and hyponatraemia.

Carcinogenicity has not been established in large epidemiological studies, though isolated reports have raised concerns especially when long-term treatment is considered in young females.

### Drospirenone (Yasmin®)

- **Combined oral contraceptive adverse events:** arterial and venous thromboembolism, hypertension, weight gain, depression, headache and melasma.
- **Hyperkalaemia** is a potential adverse effect due to the drug's potassium sparing diuretic actions, but large studies in healthy female users have not shown this metabolic abnormality.

### Cyproterone acetate as co-pyrindiol (Dianette®)

- **Combined oral contraceptive adverse effects** (see above).

### Cyproterone acetate (high dose)

- **Cardiovascular adverse effects** include arterial and venous thromboembolism.
- **Hepatotoxic adverse effects** include hepatitis, jaundice and liver tumours (benign and malignant).
- **Sexual adverse effects** include decreased libido, erectile dysfunction, reversible inhibition of spermatogenesis, gynaecomastia, galactorrhoea and hot flushes.
- **Metabolic adverse effects** include changes in body habitus (central obesity).
- **Neurological adverse effects** include meningiomas (at doses of 25 mg daily and above), depression.
- **Other adverse effects** include anaemia, osteoporosis, fatigue and lassitude.

### + Use in special situations

#### Pregnancy & pre-conception

FDA pregnancy categories:

Bicalutamide, cyproterone acetate, drospirenone, dutasteride, finasteride: X.

Flutamide: D.

Spironolactone: C.

**Antiandrogens** are contraindicated during pregnancy due to the risk of feminization of the male fetus. Small amounts of finasteride/dutasteride have been detected in the semen of males taking this medication. It is not known whether a male fetus may be adversely affected by *in utero* exposure to the semen of a male treated with finasteride or dutasteride, but condom use is advised. Likewise, it is advised that pregnant females should not handle crushed or broken tablets.

**Finasteride/dutasteride** have been reported to adversely affect sperm counts and quality in healthy males and an impairment of male fertility cannot be excluded. **Flutamide** and **bicalutamide** have both been shown to affect adversely male fertility.

#### Lactation

Antiandrogens are contraindicated during breastfeeding. Canrenone, the principal metabolite of spironolactone, has been detected at low levels in breast milk, so an alternative method of infant feeding should be instituted.

Cyproterone acetate and drospirenone (Yasmin®) may lead to a reduction in the volume of milk produced and to a change in its composition. Minute amounts of these active substances are excreted with the milk. These amounts may affect the child, particularly in the first 6 weeks post-partum.

### Children

Antiandrogen therapy is not relevant in paediatric dermatology as the skin disorders they are used to treat do not occur before puberty. Spironolactone is licensed for non-dermatological indications.

#### + Essential patient information

- Females should be advised of the need to avoid pregnancy during antiandrogen therapy.
- Counselling for the risks and benefits of combined hormonal contraception for Yasmin® and Dianette®.

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# Antibiotics Commonly Used for Skin Infections

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Antibiotics are drugs with therapeutic activity against living organisms, the term being usually reserved for drugs active against bacteria. They are commonly described as either bacteriostatic or bactericidal, depending on whether at any given concentration they inhibit or kill the bacteria. Site of infection, strain of organism and drug concentration are all important in determining this characteristic. This chapter is concerned with the antibiotics most commonly used in dermatology, including broad- and narrow-spectrum drugs. One of the problems dominating antibiotic usage is the rising prevalence of resistance among bacteria, either because of intrinsic drug resistance or acquired resistance due to mutation or transfer of plasmid based resistance genes.

## Penicillins

### + Classification & mode of action

Penicillins are bactericidal because they inhibit bacterial cell wall synthesis leading to death of the micro-organism. The basic structure of a penicillin consists of a thiazolidine ring, a  $\beta$ -lactam ring and a variable side-chain. They are usually divided into penicillinase-sensitive (e.g. benzylpenicillin/penicillin G and phenoxymethylpenicillin/penicillin V) or penicillinase-resistant penicillins (e.g. methicillin, flucloxacillin), broad-spectrum penicillins, antipseudomonal penicillins and mecillinams. All penicillins are readily and actively secreted by the renal tubules and most are eliminated, almost completely unchanged, in the urine.

### + Indications & dermatological uses

- Penicillins are first-line drugs for infections by *Staphylococcus aureus*, *Streptococcus pyogenes* group A, *Treponema pallidum* and meningococcal septicaemia, as well as yaws, actinomycosis and diphtheria. Most *S. aureus* strains are resistant to benzylpenicillin because they produce penicillinases.
- Flucloxacillin is resistant to degradation by this enzyme and therefore is effective against penicillin-resistant staphylococci. Penicillin V (also known as phenoxymethylpenicillin) has similar antibacterial properties

to benzylpenicillin, but it is less active and produces variable plasma concentrations.

In dermatology, flucloxacillin is indicated for pyodermas such as extensive impetigo, early furunculosis and erysipelas and cellulitis. If the patient is acutely unwell, i/v penicillins, e.g. piperacillin, should be considered. Oral penicillin V has a role in prophylaxis against recurrent streptococcal cellulitis in patients with lymphoedema.

Infection with *S. aureus* strains resistant to methicillin (MRSA) and to flucloxacillin has become a serious concern as it is endemic in many hospitals and is also becoming a problem in the community setting. The hospital-acquired strains (HA-MRSA) show multiple drug resistance, whereas community-acquired strains (CA-MRSA) usually show resistance to a smaller range of penicillins, e.g. methicillin. Treatment of MRSA is guided by the sensitivity of the infecting strain and local hospital eradication policy regime.

Strains of CA-MRSA, unlike HA-MRSA, usually carry a gene encoding the Panton–Valentine leukocidin (PVL) toxin. This is a virulence determinant and is associated with multiple skin and soft tissue infections such as abscesses. PVL positive strains may also occur without methicillin resistance, but even then flucloxacillin is usually ineffective and may increase PVL production. In such cases rifampicin and clindamycin are usually recommended.

### + Formulations/Presentation

- Penicillin V: tablets (250 mg); oral solution (125 mg/5 mL or 250 mg/5 mL).
- Benzylpenicillin sodium powder: 600 mg vials.
- Flucloxacillin: capsules (250 mg or 500 mg); oral solution (125 mg/5 mL or 250 mg/5 mL); injection either i/m, slow i/v or i/v infusion (250 mg or 500 mg vial).

### + Dosages & suggested regimens

**Penicillin V:** in adults, 500 mg every 6 hours, can be increased up to 1 g every 6 hours in severe infections. In children up to 1 year, 62.5 mg every 6 hours; 1–6 years, 125 mg every 6 hours; 6–12 years, 250 mg every 6 hours. If the infection is severe, the dose can be increased up to 12.5 mg/kg every 6 hours.

**Benzylpenicillin:** in adults, 0.6–1.2 g every 6 hours, by i/m injection, slow i/v injection or infusion. Increased dosages (by i/v route only) and frequency of injection may be indicated in severe infection. In children 1 month–18 years, 25 mg/kg every 6 hours (see children's formulary for further information in severe infections).

**Flucloxacillin:** in adults, 250–500 mg every 6 hours, at least 30 minutes before food or 2 hours after food, or by i/m injection, usually for 7 days. By slow i/v injection or by i/v infusion, 0.25–2 g every 6 hours. In children 1 month–2 years, 62.5–125 mg every 6 hours; 2–10 years, 125–250 mg every 6 hours.

For these short half-life penicillins, high peaks are much less important than duration of exposure, so for parenteral administration, continuous i/v infusion may optimize therapy.

### + Baseline investigations & considerations

No investigations are required. Patients should be asked about previous hypersensitivity reactions to  $\beta$ -lactam antibiotics (see Special point).

### + Monitoring

Monitoring is not necessary unless the patient is on a prolonged course of flucloxacillin or is known to have renal or hepatic impairment.

### + Contraindications

Penicillins are contraindicated in patients with known penicillin or  $\beta$ -lactam antibiotic hypersensitivity (see Special point).

### + Cautions

- Chronic renal impairment: reduce dose of flucloxacillin if the estimated glomerular filtration rate (eGFR) is less than 10 mL/min/1.73 m<sup>2</sup> (see Systemic Therapy & Kidney Disease).
- Hepatic impairment (flucloxacillin).
- Elderly and those with serious underlying disease (increased risk of hepatitis with flucloxacillin).

### + Important drug interactions

There are few significant drug interactions. The following should be noted:

- **Neomycin** reduces the absorption of penicillin V.
- **Oral anticoagulant** actions (and INR) can be altered by penicillins, in particular the broad-spectrum penicillins; close monitoring is required.
- **Methotrexate** excretion may be reduced by penicillins, increasing the risk of toxicity.
- **Oral typhoid vaccine** may be inactivated by penicillins, as other antibiotics.



### + Adverse effects & their management

- **Gastrointestinal (GI):** minor GI upset and diarrhoea is a common problem, while antibiotic associated colitis is very rare. The penicillin must be stopped immediately and treatment given with oral vancomycin or metronidazole.
- **Hypersensitivity reactions** vary according to the underlying immunological mechanism (as below). Immediate drug withdrawal is usually needed, and treatment may be required (e.g. anaphylaxis therapy, corticosteroids). If further treatment with the antibiotic is essential, drug desensitization may be considered.
- **Immediate type hypersensitivity** reactions with urticaria, angioedema and anaphylaxis may follow parenteral or oral therapy. **Serum sickness** type hypersensitivity reactions with fever, arthralgia and rashes can occur.
- **Drug rashes** are usually morbilliform ('measles-like'), but a range of drug eruptions can occur, including Stevens–Johnson syndrome, acute generalized exanthematous pustulosis and toxic epidermal necrolysis.
- **Hepatitis and cholestatic jaundice** are very rare idiosyncratic adverse effects, especially with flucloxacillin. The onset may be delayed for up to 2 months post-treatment and may persist for months. Risk factors include age over 55 years and duration of therapy over 2 weeks.
- Other very rare reactions include interstitial nephritis, haemolytic anaemia, leukopenia, thrombocytopenia and coagulation disorders.

### + Use in special situations

#### Pregnancy (FDA Category B)

Penicillins are not known to be harmful in pregnancy.

#### Lactation

Penicillins are not known to be harmful in lactation. Trace amounts of penicillins are excreted in human breast milk.

#### Children

It is safe to use penicillins in children when clinically indicated. The dosing is according to age and weight.

#### Elderly

Penicillin V is not known to cause any problems in the elderly but careful note should be made of concurrent drugs to avoid interactions.

#### Special point: immediate hypersensitivity

Patients with IgE (immediate type) hypersensitivity to penicillins may be reactive to the  $\beta$ -lactam ring that is common to all penicillins (including cephalosporins, carbapenems and monobactams) or the R-group side-chain that distinguishes different penicillins from one another. Although early studies reported a

cross-reactivity rate of 5–10% between cephalosporins and penicillin allergy in patients with IgE mediated penicillin allergy, most penicillin allergic patients can tolerate third and fourth generation cephalosporins because the R-side-chain (rather than the  $\beta$ -lactam ring) appears to play the dominant role in cephalosporin allergy.

The use of *in vivo* skin tests (skin prick tests and intradermal tests) is well validated for  $\beta$ -lactam antibiotics. Commercial reagents are available in many countries, minor determinant mix. *In vitro* diagnostic immunoassays are generally more expensive and less specific. Finally, drug provocation testing may be required to exclude cross-reactivity.

### + Essential patient information

Patients should be informed about the side-effect profile of penicillins.

## Erythromycin & clarithromycin

### + Classification & mode of action

Macrolides, including erythromycin and clarithromycin, are antibiotics whose structure is based on a large macrocyclic lactone ring. They act by inhibiting protein synthesis through binding to ribosomes and are mainly bacteriostatic.

### + Indications & dermatological uses

- Erythromycin is the most widely used macrolide. It is active mainly against Gram-positive organisms such as staphylococci and streptococci. Staphylococci and streptococci may become erythromycin resistant, including as many as 50% of staphylococci strains. However, erythromycin may be active against many penicillin resistant staphylococci. Uses include staphylococcal and streptococcal pyodermas, especially in penicillin allergic patients, erythrasma and acne. Macrolides may be more effective than penicillins for the treatment of cellulitis. Macrolides may also be used for atypical mycobacterial infections and for Lyme disease and syphilis.
- Clarithromycin is an erythromycin derivative with a slightly greater activity and greater tissue concentrations. Although not widely used in dermatology, it is licensed for treatment of skin infections and is also used for the treatment of atypical mycobacterial infections.

### + Formulations/Presentation

- Erythromycin: 250 mg, 500 mg tablets and capsules, 125 mg/5 mL suspensions (including sugar-free suspensions).
- Clarithromycin: 250 mg, 500 mg tablets, 125 mg/5 mL suspension, granules 250 mg/sachet.

### + Dosages & suggested regimens

**Erythromycin:** adults and children over 8 years: 250–500 mg every 6 hours or **0.5–1 g every 12 hours; up to 4 g daily** in divided doses in severe infections. Younger children: 1 month–2 years: **125 mg every 6 hours**; 2–8 years: **250 mg every 6 hours**. Doses are doubled for severe infections. Lyme disease: 500 mg four times daily for 14–21 days. By i/v infusion: adult and child severe infections, 50 mg/kg daily by continuous infusion or in divided doses every 6 hours, mild infections (oral treatment not possible), 25 mg/kg daily.

**Clarithromycin:** adults and children over 12 years: **250 mg every 12 hours for 7 days**, increased in severe infection up to **500 mg every 12 hours** for up to **14 days**. By i/v infusion into larger proximal vein: 500 mg twice daily. For younger children (1 month–12 years) the dosage depends on body weight: <8 kg: 7.5 mg/kg twice daily; 8–11 kg: 62.5 mg twice daily; 12–19 kg: 125 mg twice daily; 20–29 kg, 187.5 mg twice daily; 30–40 mg, 250 mg twice daily.

### + Baseline investigations & considerations

No routine investigations/monitoring are required in the absence of renal impairment.

### + Contraindications

- Erythromycin or clarithromycin hypersensitivity.
- Severe hepatic impairment, history of hepatitis caused by macrolides, cholestasis.
- Clarithromycin is contraindicated in patients with prolonged QT intervals, ventricular dysrhythmias and hypokalaemia.

### + Cautions

#### Erythromycin

- Maximum dose of 1.5 g daily in severe renal impairment (risk of hearing loss).
- Avoid in acute porphyria.

- Neonates under 2 weeks: risk of hypertrophic pyloric stenosis.
- Pre-disposition to QT interval prolongation, therefore caution with concomitant use of drugs that prolong QT interval and electrolyte disturbances.

### Clarithromycin

- Caution is advised in hepatic impairment as clarithromycin is mainly excreted by the liver.
- The dosage should be reduced in moderate to severe renal impairment.

### + Important drug interactions

Macrolide antibiotics have numerous drug interactions due to inhibitory effects on the cytochrome P450 (CYP450) 3A4 isoenzyme, and enhancing the cardiotoxicity of certain drugs. Prescribers are advised to consult an updated drug formulary.

Macrolides should not be prescribed with the following:

- **Antipsychotic drugs** including droperidol, pimozide, sertindole.
- **Cisapride** (no longer available in UK), due to the risk of ventricular dysrhythmias.
- **Ergot alkaloids** (unlicensed use for headache), due to increased risk of ergotism.
- **Mizolastine**, due to QT prolongation.
- **Simvastatin**, lovastatin, due to increased risk of myopathy.

Care should be taken if erythromycin or clarithromycin are prescribed with the following:

- **Atorvastatin and pravastatin**: a lower dose should be used and patients monitored carefully for signs of myopathy (muscle pain and weakness). Other statins that are not metabolized by CYP3A4 (rosuvastatin, fluvastatin) may carry less risk of myopathy. Measurement of serum creatine kinase (CK) is helpful as modest elevations (up to five times upper limit of normal) are common and usually related to exercise. A rise in CK of more than 10 times above the upper limit of normal can indicate significant myopathy and a risk of rhabdomyolysis, which is a medical emergency.
- **Calcium channel blockers**: the risk of hypotension or shock is increased with erythromycin and clarithromycin. In elderly patients at risk, azithromycin is the macrolide of choice.
- **Ciclosporin** (cyclosporine) metabolism may be inhibited, with increased toxicity (see Ciclosporin).
- **Colchicine**, due to increased risk of colchicine toxicity (see Colchicine).
- **Coumarin** anticoagulants (e.g. warfarin), due to increased anticoagulant effects with risk of serious haemorrhage. Close monitoring of INR is essential.
- **Digoxin** plasma concentrations are raised with risk of toxicity.
- **Methyl prednisolone** metabolism may be inhibited.

- **Oral contraceptives:** there may be a short-term impairment in the contraceptive effects of oestrogen-containing pills due to alteration of gut flora.
- **Oral hypoglycaemic agents/insulin:** the concomitant use of macrolides and certain oral hypoglycaemic agents and/or insulin can result in significant hypoglycemia. Careful monitoring of glucose is recommended.
- **Phenytoin, carbamazepine, clozapine and valproate,** due to decreased metabolic clearance and increased plasma levels.
- **Theophylline,** due to increased plasma theophylline which may cause nausea, vomiting and seizures.
- **Verapamil,** due to increased risk of cardiotoxicity

### + Adverse effects & their management

#### Erythromycin

- **Cholestatic hepatitis** can occur with erythromycin estolate.
- **Gastrointestinal:** nausea and colicky pains are common, with occasional vomiting and diarrhoea. Symptoms may be improved by giving a lower dose (250 mg four times daily).
- **Hypersensitivity reactions** are rare. They include Stevens–Johnson syndrome and toxic epidermal necrolysis.
- **Reversible hearing loss** and tinnitus have been reported after large i/v doses, and in renal impairment.
- **Other effects** include pancreatitis, cardiac effects, myasthenia-like syndrome/exacerbation of myasthenia gravis.

#### Clarithromycin

The adverse reaction profile is similar to that of erythromycin:

- **Hepatitis** and cases of fatal hepatic failure have been reported. Advise patients to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop.
- **Tooth and tongue discolouration,** smell and taste disturbances, stomatitis and glossitis.
- Less commonly: arthralgia, myalgia, headache.
- Very rarely: dizziness, insomnia, nightmares, anxiety, confusion, psychosis, paraesthesia, convulsions, hypoglycaemia, renal failure, intestinal nephritis, leukopenia and thrombocytopenia.

Patients who are hypersensitive to clindamycin may also be hypersensitive to clarithromycin, so caution is required if they are prescribed clarithromycin.

### + Use in special situations

#### Pregnancy (FDA Category B)

Erythromycin crosses the placenta but is not known to be harmful in pregnancy. The manufacturers advise avoiding clarithromycin in pregnancy unless the potential benefit outweighs the risk.

#### Lactation

Only small amounts of erythromycin are found in breast milk and this is not known to be harmful. The manufacturers advise avoiding clarithromycin in lactation unless the potential benefit outweighs the risk.

#### Children

Both drugs are available in paediatric formulations. Remember the risk of pyloric stenosis in neonates.

#### Elderly

Consider underlying renal impairment which may affect drug dosage for clarithromycin.

## Clindamycin

### + Indications & dermatological uses

Clindamycin is a lincosamide antibiotic with activity against Gram-positive cocci and many anaerobes. It has a bacteriostatic effect by inhibiting bacterial ribosomal translocation. It can be used as an alternative to macrolides for erysipelas or cellulitis and for infections associated with MRSA. Topical clindamycin is licensed for use in acne and bacterial vaginosis.

### + Formulations/Presentation

Capsules (75 mg, 150 mg), i/m and i/v preparations.

### + Dosages & suggested regimens

The usual adult oral dose is **150–300 mg** every **6 hours** and up to 450 mg every 6 hours in severe infection. The recommended dose of clindamycin in children is 3–6 mg/kg every 6 hours.

A regimen of **300 mg clindamycin twice daily** and **300 mg rifampicin** (see below) **twice daily for 10 weeks** has been reported to be effective in the treatment of hidradenitis suppurativa.

Deep i/m or i/v infusion in 2–4 divided doses/d may be used as an alternative to oral therapy or in severe infection. Injections containing benzyl alcohol should be avoided in neonates.

### + Baseline investigations & considerations

In neonates and infants being treated for greater than 10 days: LFTs and renal indices.

### + Monitoring

LFTs and renal indices weekly for prolonged therapy (>10 days) in neonates and infants.

### + Contraindications & cautions

- Diarrhoea and colitis.
- Acute porphyria.

### + Important drug interactions

- **Erythromycin** should not be prescribed concurrently as its antibacterial actions may be impaired by clindamycin.
- **Neuromuscular blocking agent** effects may be enhanced and the effects of cholinesterase inhibitors prolonged.
- **Oral typhoid vaccine** is inactivated by antibacterials.

### + Adverse effects & their management

- ***Clostridium difficile*-associated diarrhoea (CDAD)** is the most frequent cause of pseudomembranous colitis, which is the most serious common adverse effect of clindamycin. Although CDAD can occur with almost all antibiotics (including  $\beta$ -lactams), it is classically linked to clindamycin use. Symptoms may develop several weeks after ceasing therapy. The drug should be discontinued immediately if marked diarrhoea or colitis develops (severe abdominal pains with passage of blood and mucus). If allowed to progress, it may lead to toxic megacolon, peritonitis and fatal septicaemic shock.

The disease is likely to follow a more severe course in elderly or debilitated patients. Diagnosis can be confirmed by colonoscopic demonstration of pseudomembranous colitis and culture of the stool for *C. difficile* or assay of the stool specimen for *C. difficile* toxin. Treatment is usually with oral vancomycin 125–500 mg four times a day for 7–10 days. Hypertoxin producing strains of *C. difficile* can be refractory to antimicrobial therapy and may require colectomy. Probiotics taken for the duration of antibiotic treatment and the following 2 weeks may have a protective effect. CDAD must be considered in all patients who present with diarrhoea following antibiotic use.

Other adverse effects include the following:

- **Jaundice and hepatitis.**
- **Taste disturbance, oesophagitis, oesophageal ulceration.**
- **Hypersensitivity reactions** including urticaria, anaphylactoid reactions.
- **Dermatological:** generalized mild-moderate morbilliform-like skin rashes are the most frequently reported rashes. Rare cases of erythema multiforme, Stevens–Johnson syndrome, pruritus, vaginitis, exfoliative or vesiculobullous dermatitis and toxic epidermal necrolysis have been reported.
- Induration, pain and abscess formation after i/m injection; thrombophlebitis after i/v injection.
- **Haematological adverse effects** include eosinophilia, neutropenia and thrombocytopenia.

### + Use in special situations

#### Pregnancy (FDA Category B)

Clindamycin is not known to be harmful in pregnancy.

#### Lactation

It is excreted in breast milk, but the amount is probably too small to be significant.

#### Children

Licensed from aged above 1 month in the UK. A syrup formulation containing 75 mg clindamycin/5 mL may be obtained from outside the UK.

#### Elderly

Clindamycin should be used with caution in frail elderly patients due to their increased susceptibility to complications of CDAD.

### + Essential patient information

Patients should be fully informed about the risk of diarrhoea and colitis and advised to discontinue the drug immediately and to contact a doctor if symptoms develop. Capsules should be swallowed with a glass of water.



## Rifampicin

Rifampicin is a complex, synthetically modified antibiotic of the rifamycin group and has a concentration dependent, prolonged postantibiotic effect. It is bactericidal and very effective against *Mycobacterium tuberculosis*, many atypical mycobacteria and Gram-positive cocci such as *S. aureus*.

### + Indications & dermatological uses

Rifampicin is always used in combination with other antimicrobials, such as clarithromycin or clindamycin, to prevent the rapid emergence of resistant strains. It is licensed for use in the following infections:

- Tuberculosis: for all forms of disease in combination with other drugs.
- Atypical mycobacterial infections.
- Leprosy: in combination with at least one other active antileprosy drug.
- Brucellosis.
- Legionnaires' disease.
- Serious staphylococcal infections.

Dermatological uses include PVL-positive *S. aureus*. Benefit has also been reported in recalcitrant pustular/follicular diseases including hidradenitis suppurativa, folliculitis de calvans/tufted folliculitis.

Rifampicin is also used in asymptomatic carriers to eliminate *Neisseria meningitidis* and *Haemophilus influenzae*.

### + Formulations/Presentation

Rifampicin is available as 150 mg and 300 mg capsules and a 100 mg/5 mL syrup.

### + Dosages & suggested regimens

In adults it is usual to prescribe **450–600 mg/d** as a single dose before breakfast. Concomitant antacid administration may reduce absorption, so rifampicin should be given at least 1 hour before the ingestion of antacids.

### + Baseline investigations & considerations

Liver biochemistry (LFTs) may be checked at baseline but monitoring is generally not necessary during treatment. Rifampicin may inhibit standard microbiological assays for serum folate and vitamin B12, so alternative assay methods should be considered.

### + Contraindications

Severe liver impairment or jaundice.

### + Cautions

- Liver impairment: a reduced dose is indicated due to impaired elimination with regular monitoring of liver enzymes every 2–4 weeks during therapy.
- Alcohol dependence: regular monitoring of liver enzymes is advised.

### + Important drug interactions

Rifampicin is a potent inducer of certain CYP450 enzymes. Concurrent administration of rifampicin with other drugs that are also metabolized through these pathways may accelerate the metabolism and reduce the activity of these other drugs with loss of therapeutic effectiveness. The number of potential interactions is large and includes the following:

- **Antiarrhythmics, calcium channel blockers and cardiac glycosides** (digoxin).
- **Oestrogens, progestogens** in hormonal contraceptives and **hormone antagonist** (antioestrogens, e.g. tamoxifen). Advise patients to use alternative, non-hormonal methods of birth control during rifampicin therapy.
- **Antipsychotics, anxiolytics, barbiturates and anticonvulsants** (phenytoin).
- **Anticoagulants** (e.g. coumarins).
- **Azole antifungals**.
- **Antiretrovirals** (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine). When rifampicin is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of this drug combination is contraindicated.
- **Antibacterials** (e.g. clarithromycin, dapsone, doxycycline, fluoroquinolones).
- **Corticosteroids**.
- **Oral hypoglycaemic agents** for diabetes. Diabetes may become more difficult to control.
- **Immunosuppressive agents** (e.g. ciclosporin [cyclosporine], sirolimus, tacrolimus).
- **Thyroid hormone** (levothyroxine).
- **Statins** metabolized by CYP3A4 (e.g. simvastatin).
- **Theophylline**.

### + Adverse effects & their management

Rifampicin is generally regarded as a relatively safe drug, but the following adverse reactions have been described:

- **Cutaneous adverse effects** that are mild and self-limiting consist of flushing and pruritus with or without a rash. Urticaria and more serious cutaneous adverse drug reactions are uncommon. Exfoliate dermatitis, bullous dermatoses, erythema multiforme/Stevens–Johnson syndrome and vasculitis have been reported rarely.
- **Gastrointestinal adverse effects** are common and consist of anorexia, nausea, vomiting, abdominal discomfort and diarrhoea.
- **Hepatitis** is usually characterized by transiently elevated transaminases. Hyperbilirubinaemia can occur in the early days of treatment due to competition between rifampicin and bilirubin for hepatic excretion.
- **Thrombocytopenia** with or without purpura may occur, and is in association with intermittent therapy. Eosinophilia, leukopenia and agranulocytosis have also been reported.
- **A flu-like syndrome** consisting of episodes of fever, chills, headache, dizziness and bone pain has mainly been reported with intermittent or irregular therapy and may represent drug hypersensitivity. Anaphylaxis has also been described.
- **Red-orange discolouration** of the urine, sweat, sputum and tears is common and may lead to permanent staining of soft contact lenses.

### + Use in special situations

#### Pregnancy (FDA Category C)

Animal data indicate that there is a potential risk to the fetus but there is no confirmatory information in humans. Caution is therefore advised but depending on the condition under treatment, the benefits may outweigh any risk.

#### Lactation

Rifampicin is excreted in breast milk at low concentrations. The amounts are considered too small to be harmful.

#### Children

Rifampicin is used in special situations such as tuberculosis in childhood.

### + Essential patient information

- The drug should be stopped immediately if purpura develop and should not be given again.
- Patients should be advised how to recognize signs of liver disorders, and to stop treatment immediately and seek advice if symptoms such as persistent nausea, vomiting, malaise, jaundice or bruising develop.

## Fluoroquinolones

The fluoroquinolones or 4-quinolones are antibiotics whose principal use in dermatology is the treatment of Gram-negative infections. Their mode of action is by inhibition of DNA synthesis. Generally only one of these agents, ciprofloxacin, is used in dermatology. Other fluoroquinolones include norfloxacin and ofloxacin.

### + Indications & dermatological uses

Ciprofloxacin is used in the treatment of lower respiratory tract, GI, urinary tract and genital tract infections. In dermatology, it is used for Gram-negative infections of the skin and soft tissue and Gram-negative folliculitis.

### + Formulations/Presentation

Ciprofloxacin is available in 100 mg, 250 mg, 500 mg and 750 mg tablets, a strawberry flavoured suspension of 250 mg/5 mL and powder for i/v infusion.

### + Dosages & suggested regimens

For most skin infections the usual dose is 250–750 mg twice daily for 7–14 days, depending on severity. For unresponsive cellulitis the higher dose of 750 mg twice daily is used. Ciprofloxacin is well absorbed after oral administration and rarely needs to be given parenterally.

### + Monitoring

Routine monitoring is not essential.

### + Contraindications

Patients with known hypersensitivity to quinolones.

### + Cautions

Lower dosages are used in patients with renal impairment (see Systemic Therapy & Kidney Disease).

Use with caution in patients with cardiac disease due to possible QT interval prolongation.

### + Important drug interactions

- Drugs causing **QT interval prolongation**.
- Ciprofloxacin inhibits the enzyme **CYP1A2** and thus may cause increased serum concentration of concomitantly administered drugs metabolized by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine). Co-administration of ciprofloxacin and tizanidine (a muscle relaxant) is contraindicated.
- **Methotrexate** excretion may be inhibited, leading to toxicity

### + Adverse effects & their management

- **Hypersensitivity** and **anaphylactic reactions** have been described.
- **Phototoxicity** may occur, so avoid excess sunlight or artificial ultraviolet (UV) exposure.
- **QT interval prolongation** may occur in patients with cardiac disorders, electrolyte imbalance (hypokalaemia, hypomagnesaemia) and drugs therapy (see above).
- **Tendonitis and tendon rupture** (especially the Achilles tendon) may occur even within the first 48 hours of treatment. Inflammation and rupture can also occur up to several months after therapy. The risk is increased in elderly patients and those receiving corticosteroids. The drug should be discontinued at any sign of tendonitis and care taken to rest the affected limb.
- **Seizure threshold** may be lowered in predisposed patients with CNS disorders. Polyneuropathy, depression and psychosis have been reported.
- **Haemolytic reactions** may occur in patients with glucose-6-phosphate dehydrogenase deficiency.
- **Hepatitis** ranging from mildly abnormal LFTs to hepatic necrosis and life-threatening hepatic failure.

### + Use in special situations

#### Pregnancy (FDA Category C)

Effects on immature cartilage have been observed in animal studies, so as a precaution, it is preferable to avoid in pregnancy.

#### Lactation

Ciprofloxacin is excreted in breast milk and should not be used in lactation due to the potential risk of joint damage.

#### Children

Ciprofloxacin is associated with an increased risk of musculoskeletal disorders in children and is therefore not recommended except in severe infections.

## Elderly

Elderly patients and females may be more sensitive to QT prolonging medications. Therefore, caution should be taken when using ciprofloxacin in these populations.

### + Essential patient information

Advise about signs and symptoms of tendonitis and hepatitis.

### + Further reading

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# Antifungals

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Systemic antifungal drugs are highly effective in treating superficial dermatomycoses acquired in temperate climates. Unfortunately, tropical and deep fungal infections often remain recalcitrant to treatment despite high dose prolonged therapy with newer agents. Topical treatment is often adequate for localized superficial yeast and dermatophyte infection, but nail and scalp infections usually require systemic therapy to enable adequate delivery of drug to the infected hair shafts and nail plates.

Fungi are broadly divided into moulds and yeasts. A mould is made up of multinucleate filaments called hyphae, which can be divided by septae and grow continuously from their apical tip. Yeasts are unicellular and usually oval in shape. They mainly replicate by budding. Some fungi including *Candida* and dimorphic species (such as *Aspergillus*) are able to switch between producing hyphae and yeast forms depending on the environment. Hyphal forms are usually necessary for invasion of cells and tissue, whereas yeast forms appear to be important for dissemination to distant sites.

The plasma membrane of fungal cells contains ergosterol rather than cholesterol as in mammalian cells and the majority of antifungal drugs exert their selective effects by interfering with the enzymatic pathway of ergosterol biosynthesis (see Table 1). However, some of these enzymes are also involved with cholesterol metabolism. The majority of antifungal drugs are fungistatic (inhibiting fungal cell growth) at concentrations achievable at sites of infection. Only a minority have the advantage of being fungicidal (kill fungal cells), which enables more effective clearance of fungal infections with a shorter course of treatment, and less evolution of drug resistance.

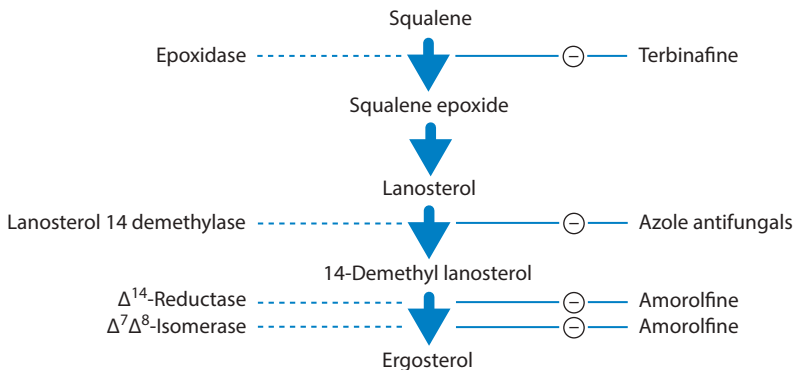
The main categories of antifungal drugs are listed in Table 1, which summarizes their classification and mechanism of action (see also Figure 1). The systemic antifungal drugs used in dermatology (terbinafine, azoles and griseofulvin) are discussed in more detail.

Patients at risk from superficial fungal infections include children (tinea capitis), the elderly (onychomycosis), the immunosuppressed, animal handlers (zoophilic tinea corporis), athletes (tinea pedis, tinea cruris) and those with diabetes (candidiasis). Human immunodeficiency virus (HIV) infection may predispose individuals to more severe and more frequent infections, particularly onychomycosis, which may fail to respond to conventional doses of antifungals.

**TABLE 1** Classification and mechanism of action of antifungal drugs

Group	Examples	Mode of action	Main indications
<b>Azoles</b> Imidazoles	Clotrimazole Econazole Ketoconazole Miconazole	Inhibit C-14 sterol demethylase via cytochrome P450 leading to a reduction in ergosterol	Tinea infections <i>Candida</i> skin infections Vaginal candidiasis
	Tioconazole		Onychomycosis
Triazoles	Itraconazole Fluconazole		Oropharyngeal candidiasis Vaginal candidiasis Sporotrichosis Tinea skin infections Onychomycosis
	Voriconazole Posaconazole		<i>Fusarium</i> , <i>Mycetoma</i> , chromoblastomycosis Coccidioidomycosis <i>Scedosporium</i> , <i>Candida</i>
<b>Allyamines</b>	Terbinafine Naftifine	Inhibit squalene epoxidase causing squalene accumulation	Tinea infections
<b>Echinocandins</b>	Caspofungin Micafungin Anidulafungin	Inhibit (1-3)- $\beta$ -D-glucan synthase a component of fungal cell wall	Invasive aspergillosis Invasive candidiasis
<b>Morpholines</b>	Amorolfine	Inhibits 14 reductase epoxidase causing squalene accumulation	Dermatophyte onychomycosis
<b>Polyenes</b>	Amphotericin B (Nystatin) (Natamycin)	Binds to ergosterol in fungal cell walls and disrupts membrane structure	Invasive candidiasis Invasive aspergillosis Cryptococcosis Sporotrichosis
<b>Others</b>	Griseofulvin	Disrupts microtubule function in nuclear division	Tinea infections Onychomycosis
	Flucytosine (5-fluorocytosine)	Inhibits DNA and RNA synthesis	Cryptococcosis Invasive candidiasis





**FIGURE 1** Points of action of antifungal drugs in the pathway of ergosterol biosynthesis.

## AZOLE ANTIFUNGAL DRUGS

### + Classification & mode of action

Azole antifungals are a synthetic group of fungistatic agents with a broad spectrum of activity. They are based on a 5-member ring structure and classified into two groups: **imidazoles** and **triazoles**. They bind to the iron atom in the haem component of lanosterol-14 demethylase (or CYP51A1, P45014DM) a cytochrome P450 enzyme that converts lanosterol to ergosterol, a major fungal wall component. This leads to arrested fungal growth. Triazoles have a higher specificity of binding than imidazoles, leading to increased potency. Over-expression of CYP51A1 or impairment of energy dependent facilitated diffusion of azoles into fungal cells are mechanisms underlying drug resistance.

Most imidazole antifungal drugs are only formulated for topical use (clotrimazole, miconazole, econazole) to treat the skin and nails. Ketoconazole is the exception, but is no longer recommended for systemic use due to the risk of hepatotoxicity. Triazoles (itraconazole, fluconazole, voriconazole, posaconazole) are used systemically and have a higher specificity against fungal cytochrome P450 (CYP450) than imidazoles and less human toxicity. Fluconazole has good activity against fungal yeast forms but lacks activity against moulds, whereas itraconazole has a wider spectrum of action, but less reliable bioavailability. Voriconazole and posaconazole are used for invasive

fungal infections. The adverse effects of voriconazole include hepatitis, hair loss, nail changes, phototoxicity and squamous cell carcinoma.

The widespread therapeutic and prophylactic use of azole antifungal drugs has led to an increase in the rate of drug resistance. This can relate to the ability of some fungal species to switch from yeast to hyphal forms in the presence of azole drugs.

## Itraconazole

Itraconazole is highly lipophilic and well absorbed with a prolonged half-life. The therapeutic effect in the skin is achieved by passive diffusion into basal keratinocytes, a high rate of excretion in sebum and to a lesser degree, excretion in sweat. Extensive tissue (protein) binding in skin and hair has been demonstrated, so the active drug persists for several weeks after stopping therapy.

### + Indications & dermatological uses

The licensed dermatological indications for itraconazole are:

- Dermatophytoses caused by tinea species (tinea corporis, tinea pedis, etc.).
- Onychomycosis caused by dermatophytes and/or yeast.
- Pityriasis versicolor.
- Vulvovaginal and oropharyngeal candidiasis.

Itraconazole has a broad spectrum of antifungal action, and is also widely used to treat systemic fungal infections (e.g. aspergillosis, candidiasis, cryptococcosis and histoplasmosis), deep mycoses (e.g. sporotrichosis, chromoblastomycosis, paracoccidioidomycosis and histoplasmosis) and for prophylaxis of fungal infection in patients with neutropenia and HIV.

It is effective in both a continuous and pulsed regimen for fungal nail infection. *Candida* onychomycosis responds very well to pulsed itraconazole; however, non-dermatophyte moulds causing onychomycosis (such as *Scytalidium*) do not respond. When treating onychomycosis with systemic drugs, the causative organism should therefore be identified and host factors such as co-morbidities and concurrent medication carefully considered as well as the extent and severity of disease.

Itraconazole also has antiangiogenic effects and inhibits hedgehog signalling pathways, and is currently undergoing trials in various malignant diseases.

### + Formulations/Presentation

- 100 mg capsules.

- Oral liquid (10 mg/mL) is suitable for children and HIV/immunosuppressed patients with oral or oesophageal candidiasis.
- i/v infusion for systemic fungal infections.

**+ Dosages & suggested regimens**

See Table 2. Itraconazole should be taken immediately after a meal to maximize absorption. Absorption is impaired by any drug which reduces gastric acidity. The treatment regimen and dosage vary according to indication. In the treatment of fungal nail disease, improvement may be slow and full benefit not apparent until after treatment has been completed.

**TABLE 2** Indications and dosage regimens of itraconazole for skin disease

Indication	Dose
Vulvovaginal candidiasis	200 mg twice daily for 1 day
Pityriasis versicolor	200 mg once daily for 7 days
Tinea corporis, tinea cruris	100 mg once daily for 15 days or 200 mg once daily for 7 days
Tinea pedis, tinea manuum Tinea capitis in younger children (unlicensed)	100 mg once daily for 30 days or 200 mg twice daily for 7 days 3–5 mg/kg/d up to 200 mg daily for 2–6 weeks or pulsed regimen (see Use in special situations – Children)
Oropharyngeal candidiasis	100 mg once daily for 15 days
Onychomycosis (dermatophyte or <i>Candida</i> )	200 mg once daily for 3 months or a pulsed regimen of 200 mg twice daily for 7 days a month, i.e. subsequent courses repeated after 21 day intervals. 2 pulses for fingernails, 3 pulses for toenails

**+ Baseline investigations & considerations**

- Mycology should confirm a fungal infection before starting treatment for suspected onychomycosis.
- LFTs in patients with history of liver disease.
- Pregnancy testing and ensure adequate contraception in females of childbearing age.

**+ Monitoring**

LFTs in patients with pre-existing liver disease, those taking continuous treatment over a month or if receiving other hepatotoxic drugs.

## + Contraindications & cautions

Contraindications:

- Hypersensitivity to itraconazole or related azoles.
- Acute porphyria.
- Pregnancy.

Use itraconazole only after careful consideration and with caution:

- Liver disease: use at reduced dosage if the benefit outweighs risk of hepatotoxicity. LFTs should be monitored.
- Cardiac failure: itraconazole has been associated with congestive cardiac failure after high doses and long treatment courses. Caution is advised in patients at high risk of heart failure, i.e. the elderly and those with cardiac disease. Baseline echocardiography may be indicated.

## + Important drug interactions

As itraconazole is mainly metabolized by **CYP3A4**, potent inhibitors of this enzyme may increase its bioavailability. Examples are: ritonavir, indinavir, clarithromycin and erythromycin. Likewise enzyme inducers including rifampicin, may reduce bioavailability. Itraconazole may also inhibit the metabolism of many other drugs metabolized by CYP3A4 and lead to an increased risk of toxicity.

The following should not be given with itraconazole: mizolastine, cisapride, triazolam, oral midazolam, dofetilide, quinidine, pimozide, statins metabolized by CYP3A4 (atorvastatin, lovastatin and simvastatin)

Caution is advised with the following drugs:

- **Calcium channel blockers** due to pharmacological interactions and additive negative inotropic effects which may precipitate cardiac failure.
- **Cardiac glycosides** (digoxin).
- **Ciclosporin** (cyclosporine), **tacrolimus** and **sirolimus** metabolism is inhibited. Reduced dosage and monitoring of drug levels may be required.
- **Coumarin anticoagulants**: effect may be enhanced.
- **Inhaled corticosteroids**: metabolism may be impaired with long-term itraconazole leading to iatrogenic Cushing's syndrome.
- **HIV protease inhibitors** such as ritonavir, indinavir, saquinavir.

## + Adverse effects & their management

- **Gastrointestinal**: nausea and abdominal pain are the most common side-effects and are generally mild. Side-effects are dose dependent therefore the dose can be reduced.
- **Hepatitis**: this is very uncommon (<1/10,000) but potentially serious. The risk is increased in pre-existing liver disease, with prolonged therapy (>1 month) and high dosage. Patients should be advised of the signs and symptoms of

hepatitis (see below) and treatment stopped immediately. In most cases, LFTs normalize after withdrawal of treatment.

- **Dermatological:** pruritus, acute generalized exanthematous pustulosis, urticaria, Stevens–Johnson syndrome and photoallergic reactions have been reported. Adverse cutaneous reactions are more common in immunosuppressed patients.
- **Cardiovascular:** see Cautions
- Headache, dizziness, hypersensitivity reactions, thrombocytopenia and decreased libido can also occur.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category C)

Itraconazole is embryotoxic and teratogenic in animals and is contraindicated in pregnancy except for life-threatening infections. Effective contraception must be in place during treatment and until the next menstrual period following treatment cessation. It may cause menstrual irregularities.

#### Lactation

Small amounts of itraconazole are excreted in human breast milk so should not be taken during lactation.

#### Children

Itraconazole is unlicensed in children under the age of 12 years but it has been proven to be safe, effective and well-tolerated. It is commonly prescribed for tinea capitis due to *Trichophyton* species. Its efficacy is comparable to griseofulvin and terbinafine, with high complete cure rates when given for 2–3 weeks. Itraconazole is superior to terbinafine for the treatment of *Microsporum* species, but griseofulvin remains the treatment of choice in many countries due to its lower cost. The duration of treatment is 2–6 weeks and dosage is based on weight and formulation, up to a maximum of 200 mg daily. The dose for capsules is 5 mg/kg/d and for oral solution is 3 mg/kg/d.

For tinea capitis treatment can be given continuously for 2–6 weeks or as a pulsed regimen of 1 week itraconazole then 2 weeks off between each pulse, for up to 3 pulses in total. The schedule for pulsed treatment for onychomycosis is the same as in adults with a dose of 5 mg/kg.

#### Elderly

Care should be taken in those at risk of cardiac failure, and taking drugs which may interact with itraconazole. The prevalence of onychomycosis in the elderly is high but generally morbidity is low; therefore, the risks/benefits of treating onychomycosis with any oral antifungal should be carefully considered before embarking on potentially lengthy courses of treatment.

#### Special point

In addition to antifungal properties, itraconazole inhibits the hedgehog signalling pathway, similar to vismodegib (see Vismodegib). This may account

for the drug's teratogenic effects. Itraconazole shows activity against basal cell carcinoma in humans and may have therapeutic potential in oncology.

### + Essential patient information

Females of childbearing age should avoid pregnancy and use effective contraception.

Patients should be informed of the signs and symptoms of liver dysfunction, e.g. anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine, and advised to discontinue treatment and seek medical advice if affected.

## Fluconazole

Fluconazole is very well absorbed after oral administration and does not undergo first pass metabolism, so serum concentrations are identical whether administered orally or parentally. Unlike itraconazole, it is highly water soluble and absorption is not affected by food intake or gastric acidity. It is distributed widely throughout the body and appears to be eliminated from the skin more slowly than from the plasma. Most of the drug is excreted unchanged in the urine.

### + Indications & dermatological uses

- Genital candidiasis, oropharyngeal candidiasis.
- Systemic candidiasis including candidaemia and disseminated candidiasis.
- Superficial mycoses: tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor and dermal candidiasis.

Other uses include:

- Tinea capitis in children (off label).
- Recalcitrant toenail onychomycosis (off label).
- Prophylaxis or treatment of systemic mycoses such as cryptococcosis and candidosis in HIV infection, treatment of histoplasmosis and coccidiomycosis and prevention of fungal infections in immunocompromised patients.

### + Formulations/Presentation

- 50 mg, 150 mg and 200 mg capsules; a 150 mg single capsule pack is available for sale to the public for the treatment of vaginal candidiasis.
- Oral suspension: 50 mg/5 mL, 35 mL oral suspension, 200 mg/5 mL, 35 mL oral suspension.
- i/v infusion.

### + Dosages & suggested regimens

- Genital candidiasis: **150 mg** as single oral dose.
- Oropharyngeal/oesophageal candidiasis: **50 mg daily** (100 mg maximum daily in recalcitrant infection) given for **7–14 days**.
- Chronic atrophic candidiasis associated with dentures: **50 mg daily** for **14 days**.
- Oesophageal and mucocutaneous candidiasis: **50 mg** for **14–30 days**. In unusually difficult cases of mucosal candidal infections the dose may be increased to **100 mg daily**.
- Tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor and dermal candidiasis: **50 mg daily** for **2–4 weeks** (up to 6 weeks in tinea pedis).

Other reported regimens (unlicensed) include pulse dosing of 150 mg fluconazole once weekly for tinea corporis and tinea cruris, and 300 mg once weekly for 6–9 months for onychomycosis. However, fluconazole is not licensed for the treatment of nail disease and has lower efficacy than other licensed drugs, so should only be considered when these are contraindicated or not tolerated.

### Special point

Resistant strains of *Candida* may emerge during prolonged treatment with fluconazole. *C. krusei*, *C. glabrata* and certain strains of *C. albicans* are also primarily resistant to this drug.

### + Baseline investigations & considerations/Monitoring

- Baseline/pre-therapy: FBC (CBC), renal function and LFTs in those with underlying illnesses. Pregnancy test.
- During therapy: repeat LFTs after 6 weeks of treatment.

### + Contraindications

- Fluconazole should not be used in patients with known hypersensitivity to it or related azoles.
- Pregnancy.

### + Cautions

Dose reduction required in renal impairment as fluconazole is mostly excreted unchanged by the kidneys.

### + Important drug interactions

- **Fluconazole** may inhibit both the 3A4 and 2C9 isoforms of CYP450.
- **Rifampicin**: modest reduction in fluconazole levels due to CYP450 induction by rifampicin.
- **Phenytoin**: levels may be increased, so monitoring required.
- **Ciclosporin**: levels may be increased so monitoring required.
- **Hydrochlorothiazide** may increase levels of fluconazole.

### + Adverse effects & their management

The adverse effect profile of fluconazole is similar to itraconazole (see above) but fluconazole is less frequently associated with **hepatotoxicity**. Adverse events usually occur with treatment duration of over 1 week but most are reversible when the drug is discontinued.

### + Use in special situations

#### Pregnancy (FDA Category C)

Fluconazole is contraindicated in pregnancy as it has been associated with birth defects in the children born to mothers taking high dose long-term treatment. Pregnancy should be excluded before starting therapy and females of childbearing age should use adequate contraception.

#### Lactation

Fluconazole is excreted in breast milk at similar levels to plasma, and should not be used during lactation.

#### Children

Fluconazole is licensed for use in children, including neonates in the treatment of mucosal candidiasis, invasive candidal infections and cryptococcal infections, but not for superficial skin infection. Clearance is faster than in adults so higher doses are needed (up to 12 mg/kg/d for severe infection). Fluconazole has been reported to be effective in childhood tinea capitis at doses of 6 mg/kg/day for 3–6 weeks with comparable efficacy to griseofulvin and the advantage of a shorter treatment duration.

## Ketoconazole

Ketoconazole was the first broad-spectrum imidazole for oral use in the treatment of systemic mycoses. However, in 2013 the European Medicines Association (EMA) issued advice against the use of oral ketoconazole for treatment of fungal infections due to the risk of severe liver damage and



availability of safer alternatives. Ketoconazole hepatotoxicity ranges from asymptomatic transient raised transaminases and alkaline phosphatase to severe derangement and death. Females over the age of 40 years on long-term therapy appear at highest risk. Liver damage may progress despite immediate drug withdrawal. Although the estimated incidence of severe hepatotoxicity is less than 1 in 10,000, in view of this serious hazard and availability of safer drugs, the EMA advises that its use is no longer justified.

Ketoconazole was previously licensed for use in candidiasis, dermatophytosis and malassezia folliculitis at doses of 200–400 mg daily. Topical ketoconazole is still available in cream and shampoo formulations for the treatment of seborrhoeic dermatitis and pityriasis versicolor.

## Terbinafine

### + Classification & mode of action

Terbinafine is a synthetic allylamine which is highly effective against a broad spectrum of dermatophyte infections. It inhibits the biosynthesis of fungal ergosterol at the point of squalene epoxidase. This leads to accumulation of the intermediate squalene, which appears to be fungicidal, and deficiency of the end product ergosterol, which is fungistatic. Ergosterol is an integral component of fungal cell membranes and squalene is thought to interfere with fungal membrane function and cell wall synthesis. Although the biosynthesis of cholesterol relies on the activity of squalene epoxidase, terbinafine has a much lower binding affinity for the mammalian enzyme and therefore demonstrates selective toxicity to fungal systems.

Terbinafine is well absorbed after oral dosage (especially after a high fat meal/with acidic food) and reaches peak plasma concentrations within about 2 hours. Primary metabolism occurs in the liver and involves at least seven CYP450 enzymes. Inactive metabolites are slowly eliminated, mainly in the urine. The polyfunctional nature of terbinafine as a substrate reduces potential drug interactions. Terbinafine inhibits CYP2D6, and the activity of this enzyme may not return to normal for months following cessation of a prolonged course of treatment.

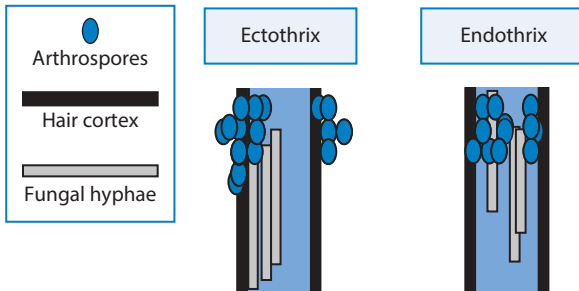
Terbinafine is preferentially taken up into fat, and reaches high concentrations in the sebum, skin and nails. It is delivered to the stratum corneum primarily by sebum and to a lesser extent by diffusion through the dermoepidermis. During the first 2 weeks of therapy, concentrations within the stratum corneum increase to 75 times greater than plasma concentrations. It is also incorporated into the hair matrix. The long terminal half-life of 200–400 hours may reflect its slow elimination from tissues such as skin and adipose. The clinical efficacy of terbinafine is related to high drug levels at the site of infection and sustained fungicidal activity following discontinuation of therapy.

### + Indications & dermatological uses

The licensed indications of terbinafine are dermatophyte infections of the skin and nails where oral therapy is appropriate (site, severity, etc.).

Terbinafine is the most active antidermatophyte agent. It is the treatment of choice for dermatophyte onychomycosis, with superior long-term results in toenail disease than griseofulvin, ketoconazole, fluconazole and itraconazole. Clinical trials have shown greater or equal efficacy compared with other antifungals, with the benefit of a shorter treatment period. It is also highly effective in treating chronic dermatophyte infections on the hands, feet and body.

Terbinafine is also an effective treatment for tinea capitis, though not yet licensed in the UK for treating children. It is however, licensed for this complaint in the USA and parts of Europe. The commonest causative agents for tinea capitis vary from one part of the world to another. In urban settings in Europe and the USA, the main dermatophyte fungi causing tinea capitis are *Trichophyton* species, which cause an endothrix pattern of infection where arthrospores are most abundant within the hair shaft (see Figure 2).



**FIGURE 2** Different arthrospore distribution in ectothrix and endothrix fungal hair infection.

Systemic terbinafine is usually ineffective at treating superficial yeast infections such as candidosis and pityriasis versicolor.

### + Formulations/Presentation

- Scored tablets containing terbinafine hydrochloride equivalent to 250 mg terbinafine.
- Oral granules that can be sprinkled on food have been approved by the USA FDA for use in children aged 4 years or over.
- Topical formulation (terbinafine hydrochloride 1%, 5%) cream.

### + Dosages & suggested regimens

The usual adult dose is **250 mg once daily**. The duration of treatment depends on the site and severity of the infection. It is usually 2–6 weeks in tinea pedis, 2–4 weeks in tinea cruris, 4 weeks in tinea corporis, 6 weeks–3 months in nail infections (occasionally longer in toenail infections). Additional topical or surgical treatment to infected nails may improve cure rates. The maximum clinical effect in nail infections may not be seen for several months after cessation of treatment until the healthy nail has grown.

Although unlicensed in children in the UK, studies have confirmed good cure rates in tinea capitis.

- Child over 1 year, bodyweight 10–20 kg: 62.5 mg once daily.
- Child bodyweight 20–40 kg: 125 mg once daily.
- Child bodyweight over 40 kg: 250 mg once daily.

The duration of treatment for tinea capitis depends on the causative organism. *Trichophyton* species show good response rates within 4 weeks of treatment. *Microsporum* infection requires prolonged therapy of 6 weeks or more. The difference in clinical response may be related to the ectothrix infection pattern of *Microsporum* spp. as opposed to the endothrix pattern associated with the genus *Trichophyton*, with a consequent decreased accessibility of antimycotics to the fungal spores on the surface of the hair shaft in the former.

Treatment of onychomycosis in patients with HIV infection may require higher dose therapy, e.g. 500 mg daily. Additional use of a topical antifungal preparation and avulsion of diseased nail may improve cure rates in severe toenail onychomycosis.

### + Baseline investigations & considerations

Mycological confirmation of infection and causative organism should ideally be obtained before starting treatment, especially when prolonged treatment is likely (onychomycosis).

### + Monitoring

It is now recommended to check LFTs at baseline, then every 4–6 weeks during treatment.

### + Contraindications

- Terbinafine hypersensitivity.
- Severe renal or liver impairment.

### + Cautions

- **Psoriasis:** exacerbation has been reported very rarely with terbinafine.
- **Systemic and cutaneous lupus erythematosus** may be exacerbated or induced.
- **Hepatic impairment:** hepatic clearance of terbinafine is reduced in liver disease and as it may also cause hepatotoxicity, its use should be avoided in liver disease.
- **Renal impairment:** reduce dosage by half if estimated glomerular filtration rate (eGFR) is less than 50 mL/min/1.73 m<sup>2</sup> and no suitable alternative is available.

### + Important drug interactions

- **CYP450 enzyme inducers** (e.g. rifampicin) and inhibitors (e.g. cimetidine) may accelerate or reduce terbinafine metabolism respectively, and its dosage may need adjustment.
- **CYP2D6 mediated drug metabolism** is inhibited by terbinafine. Patients taking drugs metabolized by this enzyme ( $\beta$ -blockers, SSRIs, MAOIs type B) may require closer monitoring.
- **Oral contraceptive metabolism** is not usually affected but there have been sporadic reports of menstrual disturbances/breakthrough bleeding.
- **Warfarin:** rare cases of increased or decreased prothrombin time have been reported so closer monitoring is indicated.

### + Adverse effects & their management

- **Mild gastrointestinal** effects including abdominal discomfort, anorexia, nausea and diarrhoea are common (>2%). They may settle with continued treatment. Loss of taste/a metallic taste is not uncommon and although usually reversible, permanent taste loss has been reported.
- **Dermatological:** include pruritus, urticaria, hair loss, photosensitivity, induction or exacerbation of subacute cutaneous or systemic lupus erythematosus, exacerbation of psoriasis and serious **cutaneous adverse reactions** (acute generalized exanthematous pustulosis, Stevens–Johnson syndrome and toxic epidermal necrolysis). Treatment should be discontinued immediately if a progressive rash develops.
- **Hepatotoxicity** is very rare. It may present with hepatitis or cholestasis. Treatment should be discontinued immediately if signs of liver dysfunction develop.
- **Other non-specific:** include headache, flu-like symptoms, occasionally with arthralgia or myalgia.
- **Psychiatric:** have been reported very rarely.
- **Blood disorders** (including leukopenia and thrombocytopenia) have been reported very rarely.

### + Use in special situations

#### **Pregnancy & pre-conception (FDA Category B)**

Although there is no evidence of harm, the use of terbinafine is not recommended in pregnancy unless potential benefit outweighs risk.

#### **Lactation**

Avoid as terbinafine is excreted in milk and the ratio of this drug in milk to plasma after oral administration is 7:1.

#### **Children**

Although not licensed for use in children in the UK, terbinafine has been shown to be well-tolerated and effective. The drug may have a higher clearance and shorter half-life in this age group. It has recently been licensed by the FDA for use in children from the age of 4 years in the USA. For dosages in tinea capitis, see page 68.

### + Essential patient information

Patients should be advised to seek prompt medical attention if they develop a new or worsening rash or signs and symptoms of liver dysfunction (e.g. jaundice, right upper abdominal pain, nausea, fatigue, vomiting, dark urine or pale stools). They should be advised to report any signs of taste disturbance, smell disturbance and or depressive symptoms.

## Griseofulvin

### + Classification & mode of action

Griseofulvin was first obtained from the mould *Penicillium griseofulvum* in 1939 and has been used as an oral therapy for superficial fungal infection since the 1960s. It has fungistatic actions and is most effective against dermatophytes that cause tinea (ringworm) infections. It is deposited in newly formed keratin in the skin and hair and is thought to confer resistance against fungal infection by inhibiting the formation of fungal microtubules. Griseofulvin may also have anti-inflammatory and immunomodulatory effects.

GI absorption varies considerably between individuals, mainly because the drug is insoluble in the upper GI tract. Peak serum levels are usually found about 4 hours after ingestion, and higher blood levels can usually be attained if griseofulvin is taken after a fatty meal. Absorption is also improved by a reduction in particle size. It is metabolized in the liver and excreted in the urine, faeces and in sweat.

The duration of treatment depends on the length of time required for the infected keratin to be shed, which may be several months. Effective delivery to the skin depends upon eccrine sweating, and can be impaired in disease where the sweat ducts are obstructed.

### + Indications & dermatological uses

- Superficial dermatophyte infections (nail, skin, hair) where topical therapy has failed or is inappropriate (severe or widespread disease). Griseofulvin has specific activity against dermatophytes. It is a long-established treatment for infections of the scalp and nails and has been used safely in children for many years, being available as both tablet and suspension preparations. However, it has a bitter taste and prolonged treatment may be required. For nail infection, newer more effective antifungal drugs are preferred. Griseofulvin is licensed to treat tinea capitis in children, and is still widely used in this context, but newer drugs (itraconazole and terbinafine) appear to be equally effective with shorter treatment durations. Griseofulvin is not effective against *Candida*, *Pityrosporum*, *Scopulariopsis* or *Scytalidium* spp.
- There have been anecdotal reports of benefit from griseofulvin treatment in a range of dermatological conditions including lichen planus and eosinophilic fasciitis, and recent research has highlighted a potential antitumour effect.

### + Formulations/Presentation

- Microsize tablets containing 125 mg and 500 mg griseofulvin.
- Ultramicrosize tablets containing 125 mg and 250 mg griseofulvin.
- A peppermint flavoured oral suspension containing 125 mg/5mL griseofulvin is useful for treating children.

### + Dosages & suggested regimens

The usual adult dose (microsize preparation) is **500 mg/d** in a single or divided dose taken after meals. Where the ultramicrosize preparation is available, the dose is **375 mg/d**. For children, see Use in special situations.

### + Baseline investigations & considerations

No routine investigations are needed for short courses (up to 6 weeks).

### + Monitoring

During therapy: FBC and LFTs after 3 months.

### + Contraindications

- Hypersensitivity to griseofulvin or any component of the formulation.
- Severe liver disease.
- Porphyrias, particularly acute intermittent; also best avoided in variegate and porphyria cutanea tarda.
- Systemic lupus erythematosus (SLE).
- Pregnancy.

### + Cautions

- Hepatic impairment.
- Penicillin allergy: hypersensitivity cross-reaction between penicillins and griseofulvin is possible.
- Photosensitivity: avoid exposure to intense sunlight to prevent photosensitivity reactions.

### + Important drug interactions

- Griseofulvin may decrease the blood level of drugs metabolized by **CYP3A4** and adjustment of their dosage may be required.
- **Coumarin** anticoagulant activity (warfarin) is decreased so closer monitoring is required.
- **Oral contraception**: metabolism is increased and contraceptive failure may occur, so additional precautions are required during griseofulvin treatment and for 1 month afterwards.
- **Ciclosporin**: serum levels are decreased by griseofulvin.

### + Adverse effects & their management

The most common side-effects of griseofulvin are listed below. Serious reactions are extremely rare.

- **Headache**: is a common adverse reaction and is due to a reduction in vascular tone. It usually improves with continued treatment. Nausea, diarrhoea and vomiting are frequent side-effects. These may be helped by dividing the dose.

- **Dermatological:** are rare and include urticaria, photosensitivity, erythema multiforme and toxic epidermal necrolysis. A dermatophytide (id or 'ide') allergic reaction is occasionally seen after starting oral antifungal medication including griseofulvin. This usually presents with widespread follicular papules, especially on the face and may be mistaken for a drug rash.
- **Neuropsychiatric:** have been reported including confusion, drowsiness, impaired concentration and peripheral neuropathy. The sedative effects of alcohol may be enhanced.
- **SLE:** may be exacerbated or precipitated.
- **Alcohol:** toxic effects are enhanced by griseofulvin and alcohol ingestion may precipitate a disulfiram-like reaction.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category C)

Griseofulvin disrupts the mitotic spindle and is capable of inducing aneuploidy (abnormal segregation of chromosomes following cell division) and causing embryo toxicity. Rare cases of conjoined twins have been reported following griseofulvin therapy in early pregnancy. Females should not take the drug during pregnancy or become pregnant within 1 month of stopping treatment. Men should not father children within 6 months of treatment.

#### Lactation

Griseofulvin should be avoided in lactation as its safety is not established.

#### Children

Griseofulvin is the only licensed treatment for treatment of superficial fungal infections including tinea capitis in children under the age of 12 years. In children, the recommended dose is **10 mg/kg/d (maximum 500 mg daily)**. The duration of treatment varies from 2 to 4 weeks in tinea corporis and 2–4 months in tinea unguem. The recommended duration of griseofulvin treatment for tinea capitis is **6–12 weeks**. To avoid treatment failure, however, the dosage may need to be increased to **20 mg/kg/d (maximum 1 g daily)** for the same period of time. This is particularly advisable in patients with endothrix infection (see Table 3).

Griseofulvin is ineffective in at least one-third of children with tinea capitis, most likely due to inadequate dosing, poor adherence and insufficient treatment duration. Adjunctive therapy with an antifungal shampoo (ketoconazole or selenium sulphide) is recommended for the first 2 weeks to minimize transmission to others. Prolonged treatment is required to clear kerion (12–16 weeks) but the routine additional use of systemic corticosteroids confers no benefit and is not recommended.



**TABLE 3** Oral antifungal agents for tinea capitis in children

Agent	Dosage
Griseofulvin*	10–20 mg/kg/d for 6–12 weeks
Terbinafine (for <i>Trichophyton tonsurans</i> )	<20 kg: 62.5 mg/kg 20–40 kg: 125 mg/kg >40 kg: 250 mg – all daily for 1 month
Itraconazole	3–5 mg/kg/d (max 100 mg/d) for 2–6 weeks Or weekly pulses of 5 mg/kg/d every 4 weeks for 2–3 months
Fluconazole	3–6 mg/kg/d for 3–6 weeks

\*Licensed in the UK for treatment of tinea capitis in children.

Children with tinea capitis on treatment may continue to shed fungal spores for several months and do not need to be excluded from school. Children in contact with tinea capitis should be examined very carefully for signs of infection (which may be as little as a few broken hairs) and given oral antifungals if infection is confirmed. Asymptomatic carriers do not routinely need oral antifungals but should be given an antifungal shampoo at least twice weekly.

**+ Essential patient information**

- Adults should be advised to avoid alcohol.
- Adults should avoid driving or operating machinery if affected by drowsiness.
- Adults should be advised about contraceptive and family planning precautions and the reduced effectiveness of oral contraceptives.

*With acknowledgements to Wanda Robles, author of this chapter in the 1st edition.*

**+ Further reading**

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# Antihistamines

Tabi A. Leslie & Clive E. Grattan

Systemic antihistamines are commonly prescribed to relieve the symptoms of itch (pruritus). They are widely used in many dermatological conditions associated with itch including urticaria, pruritic dermatoses such as eczema, chronic pruritus, insect bites and stings. Antihistamines are also useful in treating patients with allergic drug reactions and as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis and histaminergic angioedema.

This chapter mainly describes the use of  $H_1$  antagonists in dermatology. There is a short section on the dermatological uses of  $H_2$  antagonists and doxepin, which has both  $H_1$  and  $H_2$  antagonist effects.

## + Classification & mode of action

$H_1$  antihistamines are classified as first generation, which are sedating; (these include chlorpheniramine, diphenhydramine, promethazine and hydroxyzine) and newer antihistamines which are relatively non-sedating, and include loratadine, desloratadine, cetirizine, levocetirizine, fexofenadine, acrivastine, bilastine, ebastine, mizolastine and rupatadine (see Table 1).

Acting on  $H_1$  receptors in the skin, histamine induces vasodilation, increased vascular permeability, itching and smooth muscle contraction as well as in the respiratory and gastrointestinal (GI) tracts. All  $H_1$  antihistamines reversibly act on  $H_1$  receptors as inverse agonists. Some of the sedating (first-generation) antihistamines have additional antimuscarinic, antiadrenergic, antiserotonergic antagonizing or local anaesthetic effects.

$H_1$  antihistamines are generally well-absorbed after oral administration. The time course of action is variable, although symptomatic relief usually begins within 15–30 minutes, lasts for 1–2 hours and in some cases lasts for 12–24 hours or longer. It is usually maximal within 1–2 hours and continues for 3–6 hours or longer.

Cetirizine, levocetirizine, loratadine, desloratadine and mizolastine have a slower onset and prolonged duration of action, peak blood levels from 45 minutes and lasting for at least 24 hours. Therefore, they are effective when given once as a daily dosage.

Most  $H_1$  antihistamines are extensively metabolized in the liver by cytochrome P450 (CYP450) enzymes (particularly CYP2D6 and CYP3A4) except cetirizine, levocetirizine, fexofenadine and, to a lesser extent, mizolastine. Some antihistamines have active  $H_1$  antihistamine metabolites. Desloratadine

and cetirizine are the active metabolites of loratadine and hydroxyzine, respectively. Some H<sub>1</sub> antihistamines and their metabolites are eliminated predominantly by renal mechanisms (acrivastine, cetirizine and levocetirizine, an isomer of cetirizine). These antihistamines, including mizolastine and rupatadine, cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood–brain barrier only to the slight extent.

Prolonged use of H<sub>1</sub> antihistamines may lead to some reduction in effectiveness, although tolerance of sedative effects of classical antihistamines is much more common than tachyphylaxis of antihistamine effects.

### + Indications & dermatological uses

- The licensed indications of most antihistamines include **urticaria** with or without **angioedema**. Second-generation (non-sedative) antihistamines are the drugs of choice for daytime symptoms. First-generation antihistamines may be useful to relieve symptoms at night because of their sedating properties, but they are not recommended during the day.
- Sedating antihistamines may be useful in the treatment of **pruritus** caused by other dermatological conditions such as atopic eczema. Hydroxyzine is approved for use in pruritus caused by contact or atopic dermatitis.
- H<sub>1</sub> antihistamines are also used for **type I hypersensitivity reactions** including anaphylaxis. Most are approved for allergic rhinoconjunctivitis. Chlorphenamine and promethazine are approved for use in anaphylaxis.
- Some antihistamines have antiemetic properties, such as diphenhydramine and promethazine. These may be used in motion sickness, Ménière's disease and other vestibular disorders. Diphenhydramine is available as a standard over-the-counter night-time sleep aid in the UK and is widely used for urticaria in the USA.

### + Formulations/Presentation

The generic names and dosages of oral antihistamine tablets in the UK are listed in Table 1.

The following are available in solution or syrup form: cetirizine, chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, desloratadine and promethazine.

Some drugs can be given parenterally, but this frequently causes local irritation. Chlorphenamine can be given i/v or i/m at a dose in adults of 10 mg, repeated if required with a maximum of four doses in 24 hours. Parenteral use is usually reserved for anaphylaxis, or if there is difficulty swallowing in patients with angioedema.

Some topical antihistamines are available but prolonged use should be avoided because of a relatively high risk of contact sensitization.

**TABLE 1** Generic names and dosages and suggested regimens of antihistamines used in dermatology in the UK

Generic name	Oral dose (adult and child 12–18 y)	Oral dose (child under 12 y)
Non- or low-sedating antihistamines		
Acrivastine	8 mg tds	Unlicensed
Bilastine	20 mg od	Unlicensed
Cetirizine	10 mg od	1–2 y: 250 µg/kg bd 2–6 y: 2.5 mg bd 6–12 y: 5 mg bd
Desloratadine	5 mg od	1–6 y: 1.25 mg od 6–12 y: 2.5 mg od
Fexofenadine	180 mg od	Unlicensed
Loratadine	10 mg od	2–12 y, <30 kg: 5 mg od 2–12 y, >30 kg: 10 mg od
Mizolastine	10 mg od	Unlicensed
Rupatadine	10 mg od	Unlicensed
Sedating antihistamines		
Alimemazine	10 mg bd/tds (max. 100 mg/d) <i>Elderly</i> : 10 mg od/bd	2–5 y: 2.5 mg tds/qds 5–12 y: 5 mg tds/qds
Chlorphenamine	4 mg 4–6 hourly (max. 24 mg/d) <i>Elderly</i> : max. 12 mg/d	1–24 mo: 1 mg bd 2–6 y: 1 mg 4–6 hourly (max. 6 mg/d) 6–12 y: 2 mg 4–6 hourly (max. 12 mg/d)
Diphenhydramine	25–50 mg 4–6 hourly (max 24 mg/d)	6.25–25 mg tds/qds (max 5 mg/kg or 300 mg daily)
Hydroxyzine	25 mg nocte (up to 25 mg tds/qds if required)	6 mo–6 y: 5–15 mg nocte (up to 50 mg tds/qds) 6–12 y: 15–25 mg nocte (up to 50–100 mg daily tds/qds)
Promethazine	10–20 mg tds/qds	2–5 y: 5 mg bd (or 5–15 mg nocte) 5–10 y: 5–10 mg bd (or 10–25 mg nocte) >10 y: 10–20 mg bd (or 25 mg nocte, up to 25 mg bd if required)

### + Dosages & suggested regimens

Antihistamines are usually given orally. Standard doses for their administration in urticaria with or without angioedema are given in Table 1. The recommended first-line treatment is with non-sedating second-generation H<sub>1</sub> antihistamines. If standard dosing is not effective in chronic urticaria, increasing the dosage up to fourfold is recommended. For patients who do not respond to a fourfold increase in dosage second-line therapies should be added to the antihistamine. Treatment options include montelukast 10 mg daily, omalizumab 300 mg by s/c injection every 4 weeks or immunosuppressant drugs, e.g. ciclosporin.

### + Baseline investigations & considerations

No routine monitoring is required.

### + Contraindications & cautions

- **Mizolastine** is partly metabolized by CYP3A4. Increased levels of this drug may predispose to serious cardiovascular adverse effects (see below) so it should not be given at doses greater than those recommended. It should not be given to patients in whom there may be impaired drug metabolism, such as those with liver disease, the elderly or those taking drugs that inhibit CYP450 (see Important drug interactions). Patients should be instructed not to drink grapefruit juice, which inhibits CYP450. Patients with cardiac disease may be at increased risk of cardiac adverse effects, and this drug should not be given to patients with a bradycardia, QT prolongation, arrhythmias or electrolyte imbalance.
- **Antihistamines** with substantial **antimuscarinic (anticholinergic)** activity (mainly first-generation/sedating) should be used with caution or avoided in patients with narrow-angle glaucoma or increased intraocular pressure, prostatic hypertrophy, bladder neck obstruction, stenosing peptic ulcer, pyloroduodenal obstruction, asthma and chronic obstructive airways disease, hyperthyroidism, cardiovascular disease and hypertension. Caution should be applied to the elderly who may be more susceptible to side-effects.
- **Acute intermittent porphyria** may be precipitated by certain antihistamines. Chlorphenamine, desloratadine, loratadine and fexofenadine are considered safe. Severe liver disease: avoid sedating antihistamines as they increase the risk of coma.
- **Severe renal impairment:** reduced dosage or frequency of dosing may be required.
- **Seizure disorders:** use non-sedating antihistamines in preference.

### + Important drug interactions

- **Mizolastine** should not be given with drugs that can inhibit **CYP450**, as these may increase its plasma levels and predispose to cardiac toxicity. These include:azole derivatives such as antifungals, macrolides (clarithromycin, erythromycin). Grapefruit juice also inhibits CYP450 and should be avoided. Mizolastine should not be given with drugs that may **prolong the QT interval**, such as class IA and III antiarrhythmic agents (quinine, quinidine, sotalol, amiodarone or halofantrine), antipsychotic drugs (haloperidol or thioridazine) or doxepin.
- **Central nervous system (CNS) depressants**, such as barbiturates, anxiolytics, opioid analgesics and alcohol, may have additive CNS depressive effects to those of the sedating antihistamines.
- **Monoamine oxidase inhibitors**, used less frequently than in the past, are contraindicated with chlorphenamine as they may prolong and intensify the anticholinergic and sedative effects. Although widely cited as a potential interaction with other antihistamines, with the exception of cyproheptadine, this has not been confirmed clinically.
- The vasopressor effect of epinephrine may be blocked and reversed by phenothiazine-type antihistamines (promethazine).

### + Adverse effects & their management

Serious toxicity rarely occurs.

- **Sedation** occurs predominantly with first-generation antihistamines because they are highly lipid-soluble and cross the blood–brain barrier readily, blocking central as well as peripheral  $H_1$  receptors. However, sedation and impaired performance may also occur with second-generation drugs, so these cannot be considered universally non-sedating. A significantly lower incidence of sedation has been reported with fexofenadine and loratadine compared with cetirizine and acrivastine. Headache, dizziness, lassitude, sleep disturbances, abnormal co-ordination and muscular weakness may also occur. In some patients effects disappear spontaneously after 2–3 days. All patients, particularly those who perform potentially hazardous tasks such as driving motor vehicles or operating machinery, **MUST** be warned of these effects. Sedative effects may also be potentiated by other CNS depressants, such as sedatives, anxiolytics and alcohol.
- **Paradoxical stimulation** (excitement) also occurs predominantly with first-generation antihistamines. Restlessness, insomnia, tremors, euphoria, nervousness, delirium and seizures may occur, particularly in children.
- **Cardiovascular adverse effects** are uncommon, and are usually limited to overdose situations, or where elevated drug plasma concentrations have occurred as a result of drug interactions, impaired liver function or old age. With most antihistamines, adverse cardiac effects are due to anticholinergic or quinidine-like effects, and include tachycardia, palpitation, widen-

ing of the QRS complex and arrhythmias. Hypertension and hypotension may occur. Mizolastine, rupatadine and bilastine may have the potential to prolong the QT interval and, therefore, should be used with caution in patients with cardiac disease.

- **Gastrointestinal adverse effects** include epigastric pain, anorexia, nausea, vomiting, diarrhoea and constipation. Administering the drug with meals or with milk can decrease symptoms. Cholestasis, hepatitis and jaundice have been reported rarely. Increased appetite and weight gain may occur with cyproheptadine and mizolastine.
- **Hypersensitivity reactions:** prolonged topical use of antihistamines should be avoided because of the risk of developing allergic contact dermatitis. Dermatitis can recur following subsequent topical or systemic exposure to the drug or to a chemically related drug such as a local anaesthetic. Photoallergic dermatitis has also been reported. Immediate-type hypersensitivity reactions to oral antihistamines have been reported rarely, and include urticaria, angioedema, and bronchospasm.
- **Anticholinergic effects** occur predominantly with first-generation antihistamines, and include dryness of the mouth, nose and throat, dysuria, urinary retention, impotence, gastric reflux, constipation, vertigo, visual disturbance, blurred vision, diplopia, tinnitus, acute labyrinthitis, insomnia, tremor, nervousness, irritability and facial dyskinesia. In addition, tightening of the chest, thickening of bronchial secretion, wheezing, nasal stuffiness, sweating, chills, early menses, toxic psychoses, headache, faintness and paraesthesias have occurred at above-licensed doses.
- **Haematological adverse effects** are rare and include agranulocytosis, haemolytic anaemia, leukopenia, thrombocytopenia and pancytopenia.

### + Use in special situations

#### Pregnancy/Lactation

The manufacturers of antihistamines advise avoidance of their use during pregnancy. There is no evidence of teratogenicity, apart from for hydroxyzine (FDA Category C), which has been associated with toxicity when given in high doses in animal studies.

Other first-generation antihistamines are considered generally safe to use during pregnancy. While no antihistamine can be considered entirely safe in pregnancy, if one is required, chlorphenamine (FDA Category B) may be used in the first two trimesters. It should be avoided if possible in the third trimester because of a rare association with neonatal seizures. Other adverse effects in neonates include irritability and tremor.

Loratadine and cetirizine (Category B) are now recommended as the treatment of choice when any perceived risks are outweighed by potential benefits.

Promethazine (FDA Category C) may interfere with several immunological urinary pregnancy tests and also interferes with blood grouping in the ABO system.



Bilastine should be avoided in pregnancy, and the manufacturer of rupatadine (FDA Category B) advises caution.

Most antihistamines can be found in breast milk to varying degrees but are not known to be harmful. However, manufacturers advise avoiding their use in mothers who are breastfeeding. Antihistamines may also inhibit lactation. If chlorphenamine is taken during lactation, the infant should be monitored for adverse effects (drowsiness and irritability).

### + Essential patient information

Patients should be warned about the sedative effects of  $H_1$  antihistamines and that additive CNS depression may occur if taken with other sedatives and alcohol. The elderly may be more at risk. Sedation and impaired psychomotor function can occur without a sensation of sleepiness.

### Children

Doses are given in Table 1. Major side-effects of the older antihistamines include drowsiness, although paradoxical stimulation may occur. Drowsiness may reduce after a few days of treatment and is less of a problem with the newer antihistamines.

Several newer antihistamines are licensed for use in children (see Table 1). Cetirizine was safely used in a large cohort of children aged 12–24 months in the Early Treatment of the Atopic Child (ETAC) Study.

## $H_2$ Antihistamines

There is controversy about the use of  $H_2$  antagonists in urticaria, although some authors have found them useful when given in combination with  $H_1$  antagonists. This combination has been reported to be of benefit in symptomatic dermographism and acute allergy syndromes.  $H_1$  and  $H_2$  receptor activation can cause vasodilation and increased vascular permeability, while  $H_1$  receptors mediate itch and flare. Theoretically therefore,  $H_2$  receptor antagonists may reduce whealing. Their dermatological use is unlicensed and they should not be used as monotherapy.

**Ranitidine** can be given at doses of **150 mg twice daily** and is usually chosen rather than cimetidine, as it does not inhibit CYP450.

$H_2$  antagonists should be given with caution in renal and hepatic impairment, pregnancy and breastfeeding and cardiovascular impairment.

Adverse effects of ranitidine include rashes, altered bowel habit, dizziness, somnolence or fatigue, confusion, headache, liver dysfunction, bradycardia or atrio-ventricular block and blood disorders.

Additional adverse effects of cimetidine include interstitial nephritis, gynaecomastia, impotence and myalgia.

Like  $H_1$  antagonists,  $H_2$  antagonists have also been reported to cause urticaria and angioedema.

## Doxepin

Doxepin is a tricyclic antidepressant with potent  $H_1$  and  $H_2$  antihistamine effects. Although unlicensed, it is a useful drug in the treatment of adult urticaria and pruritus, particularly if night-time sedation is required. An **initial dose of 25 mg/d** at night is usually sufficient, and may be adjusted to response. An alternative low-dose regimen is **10 mg** two or three times a day. Dosages used in dermatology are usually much less than psychotropic dosage, which is up to 300 mg daily. Anticholinergic and sedative effects are dose limiting in these patients.

A topical formulation of doxepin is licensed for use as an antipruritic.

### + Important drug interactions

Doxepin is metabolized by CYP450, and can prolong the QT interval, causing arrhythmias and heart block. It should not be given with other drugs that do the same (see above), or with monoamine oxidase inhibitors. It has multiple drug interactions (see formulary for further information).

### + Adverse effects & their management

- Adverse effects include sedation, convulsions, hepatic and haematological reactions, **antimuscarinic effects** (such as dry mouth, blurred vision, constipation and urinary retention), sweating, hypotension and syncope, hyponatraemia and weight gain.
- Due to its **sedative effects** and associated risk of falls, doxepin should be used with caution in the elderly.
- Doxepin has also been reported to cause **urticaria** and **angioedema**. Topical use of doxepin may cause allergic contact dermatosis.
- High doses of doxepin (150–300 mg/day) are associated with **electrocardiological abnormalities**. Doses usually used in dermatology are much lower. However, it should be used with caution or avoided in patients with cardiac disease.
- Avoid in glaucoma, urinary retention, liver disease.
- Caution in epilepsy, thyroid disease.

### + Use in special situations

#### Pregnancy

Doxepin (FDA Category C; B for topical use) should not be used in pregnancy because of limited available information.

#### Lactation

Doxepin should be avoided in lactation, since accumulation of metabolite may cause sedation and neonatal respiratory depression.

#### Children

Doxepin is not recommended in children under 12 years.

*With acknowledgements to Ruth Sabroe and Anne Kobza Black, authors of this chapter in the 1st edition and Garrett Coman who reviewed this chapter for the international perspective.*

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# Antimalarials

Mark Goodfield

## + Classification & mode of action

Antimalarials are the first choice oral therapy for all patients with cutaneous lupus erythematosus (LE), as well as the majority with systemic forms of the disease. They have been widely used since their introduction in 1894, particularly since the 1950s.

Hydroxychloroquine, mepacrine and chloroquine are all effective in the management of systemic lupus erythematosus (SLE), various forms of cutaneous lupus and rheumatoid arthritis, and are also used in a variety of other cutaneous disorders. They are safe when used appropriately, and generally well-tolerated: they are probably under-prescribed.

**Chloroquine** and **hydroxychloroquine** are **4-aminoquinolones**, while **mepacrine** (quinacrine), a **9-aminoacridine**, has an extra benzene ring but is otherwise structurally similar. This structural change leads to a different side-effect profile. The mode of action of antimalarials in dermatological disease is still uncertain, although recent research has led to a clearer understanding of their mode of action. Antimalarials inhibit toll-like receptors, particularly TLR9 and TLR7, thus reducing levels of tumour necrosis factor (TNF) $\alpha$  and type 1 interferons, which are important mediators of inflammation in lupus. This probably has more relevance to their efficacy than the previously reported actions on phago/lysosomal function and interruption of antigen processing.

The antimalarials outlined above are well-absorbed orally and bind particularly to pigmented tissues, including the retina. They are metabolized by the liver and excreted renally, with a prolonged half-life of 40–50 days. There is a great inter-individual variability in blood levels between patients taking similar drug doses and the onset of therapeutic effect varies between drugs.

## + Indications & dermatological uses

- All forms of cutaneous LE including discoid lupus erythematosus (DLE) and subacute LE.
- SLE with disease symptoms including arthralgia, myalgia, fatigue, rashes and alopecia.
- Other rheumatic diseases, including rheumatoid arthritis and juvenile chronic arthritis.

Hydroxychloroquine and chloroquine are both licensed in the UK for treatment of DLE and SLE, as well as 'skin conditions aggravated by sunlight'. Mepacrine is currently unlicensed for use in skin and connective tissue disorders.

Several randomized, controlled trials provide evidence that antimalarials are useful in suppressing disease activity in SLE, particularly skin manifestations and fatigue. Fewer studies demonstrate efficacy in cutaneous lupus specifically. Discontinuing hydroxychloroquine in stable SLE may lead to increased disease activity. The drugs may also reduce the risk of thrombotic episodes in patients with antiphospholipid antibody syndrome, and reduce serum lipids.

In addition to cutaneous lupus, other evidence-based dermatological indications for antimalarials include:

- Polymorphic light eruption.
- Cutaneous sarcoidosis.
- Porphyria cutanea tarda.

Quinolone antimalarials have also been found to be useful in benign cutaneous lymphocytic infiltration (Jessner's), reticular erythematous mucinosis syndrome, dermatomyositis, urticarial vasculitis, alopecia areata and lichen planus.

### + Formulations/Presentation

- Hydroxychloroquine is available as 200 mg tablets.
- In the UK, chloroquine is dispensed as 250 mg tablets of chloroquine phosphate (containing 150 mg chloroquine base).
- Chloroquine sulphate syrup is available at a concentration of 68 mg/5 mL (containing 50 mg/5 mL chloroquine base). Chloroquine sulphate is currently difficult to obtain in tablet form.
- Chloroquine sulphate 250 mg and 500 mg tablets are the most readily available forms in the USA.
- Mepacrine hydrochloride is available as 100 mg scored tablets.

### + Dosages & suggested regimens

There is little evidence of comparative efficacy of different antimalarials in skin disease, but hydroxychloroquine is used in preference to chloroquine due to its safety profile. Most patients will need repeated courses of therapy, or even continuous treatment, to deal with flares and adequately suppress disease. Cigarette smoking seems to impair the efficacy of antimalarials, but the mechanism remains unclear. Combinations of antimalarials, particularly hydroxychloroquine and mepacrine, are more effective than either alone.

#### Hydroxychloroquine sulphate

**Initial dose: 400 mg daily; maintenance dose: 200–400 mg daily; maximum dose: 400 mg daily or 6.5 mg/kg ideal bodyweight.** In obese patients it is important to calculate the ideal bodyweight in order to avoid excess dosage. Tablets are not scored, but due to a long half-life, the daily dosage can be varied (e.g. 200 mg day 1 then 400 mg day 2 etc.) to avoid exceeding recommended limits.

The onset of effect is slow, because of tissue distribution in fat and the mode of action, and may take **up to 12 weeks**. Beneficial effects take a similar period to wear off. Approximately 60% of patients with DLE respond within 6 months, but there may be some loss of efficacy with continued treatment, requiring the addition of mepacrine to regain disease control.

### Mepacrine hydrochloride

The usual dosage is **50–100 mg daily**, but doses **up to 400 mg daily** have been used. Yellow skin discolouration is inevitable and may be severe at higher doses. The onset of action is about 3–6 weeks. It may be used as monotherapy or combined with hydroxychloroquine

### Chloroquine phosphate or sulphate

Chloroquine base is usually given at a dose of **150 mg daily** (= 200 chloroquine sulphate or 250 mg chloroquine phosphate). The maximum recommended dose is **2.5 mg/kg/d** based on ideal bodyweight. Its onset of action is more rapid and may be as short as 1 month.

Chloroquine carries a higher risk of retinopathy (see Adverse effects & their management) than hydroxychloroquine, possibly because it crosses the blood–retinal barrier more easily, so it should be used only after other antimalarials have failed. There are inadequate data on chloroquine to advise a safe maximum dose and cumulative dosage may be important, so treatment is usually limited to courses of 6 months.

## + Baseline investigations & considerations

The 2009 Royal College of Ophthalmologists recommendations for good practice in rheumatology and dermatology for hydroxychloroquine are as follows:

- Ask about visual impairment (which is not corrected by glasses). Examine near visual acuity of each eye (with glasses where appropriate). If the patient cannot read N.5 or N.6 on the reading chart (with reading glasses on), a referral should be made, first to an optician to correct any refractive error, then to an ophthalmologist if the impairment is still present. (See Appendix 2 for reading chart.)
- FBC (CBC), renal indices and LFTs.

## + Monitoring

- Monitor patients annually, enquiring about visual symptoms, rechecking acuity and assessing for blurred vision using the reading chart. Referral to an ophthalmologist is recommended in the following situations:
  - Visual impairment or eye disease detected at baseline.

- Development of changed acuity or blurred vision (as assessed by reading chart) while on treatment.
- Patients who ultimately require long-term treatment (>5 years).

### Special point

The American Academy of Ophthalmology (AAO) provided updated guidelines for the ophthalmic monitoring of patients on hydroxychloroquine in 2011. **Baseline screening** is recommended as both a reference point as well as to rule out undiagnosed maculopathy, which may preclude the use of hydroxychloroquine. **Annual screening** should begin **after 5 years of therapy** (or upon onset of therapy in those with maculopathy or unusual risk factors as defined by the AAO) and should include at least an objective test (multifocal electroretinogram, spectral domain optical coherence tomography or fundus autofluorescence) in addition to a 10-2 visual field. mfERG can be used in the place of a visual field. Clinical examination is also important, although should not be relied upon for detection of maculopathy as gross changes in macular appearance represent late stage disease. The AAO guidelines represent the most comprehensive, up-to-date and evidence based framework for screening for ophthalmic complications of hydroxychloroquine toxicity (see further reading). The above guidelines are only for adults; no specific guidelines have been provided by ophthalmic societies in the screening of paediatric patients.

- Haematology and biochemistry.

**Mepacrine:** FBC (CBC) every 3 months.

**Hydroxychloroquine** and **chloroquine:** FBC, renal and LFTs every 6 months.

### + Contraindications

Hydroxychloroquine and chloroquine should be avoided in individuals with a history of hypersensitivity to either drug. (Mepacrine is not contraindicated.)

### + Cautions

- Avoid if possible in patients with **pre-existing maculopathy**, e.g. age related macular degeneration. The decision to start this medication in a patient with maculopathy should be done in close co-ordination with their ophthalmologist.
- **Hepatic impairment.**
- **Renal impairment:** mild-moderate – the doses should be reduced (hydroxychloroquine, for example may be reduced to 200 mg three times a week). Avoid in severe renal impairment (glomerular filtration rate [GFR] <10 mL/min). Routine therapeutic blood monitoring is not currently available for antimalarials.
- **Neurological disorders**, especially epilepsy.

- **Myaesthesia gravis** may be exacerbated.
- **Glucose-6-phosphate dehydrogenase (G6PD) deficiency.**
- **Intermittent and variegate porphyria.**
- **The elderly** due to reduced renal and hepatic function.

### + Important drug interactions

- **Antacids** reduce absorption of hydroxychloroquine and chloroquine.
- Chloroquine and hydroxychloroquine increase the risk of ventricular arrhythmias with **amiodarone**.
- **Cimetidine** may decrease the metabolism of chloroquine, and increase its plasma levels.
- Chloroquine and hydroxychloroquine antagonize the action of **antiepileptic** drugs.
- Chloroquine and hydroxychloroquine increase plasma levels of **digoxin**.
- Chloroquine and hydroxychloroquine increase plasma **ciclosporin** (cyclosporine) concentration.
- **Penicillamine** plasma concentration and toxicity may be increased by both chloroquine and hydroxychloroquine.

### + Adverse effects & their management

- **Ocular adverse effects**, specifically an irreversible retinopathy with blindness, are the major risk associated with chloroquine and hydroxychloroquine treatment. The maculopathy may progress even after the cessation of the drug. Low dose hydroxychloroquine carries a very small risk of this complication, while mepacrine has negligible ocular toxicity.

Early retinopathy with antimalarials takes the form of a non-specific fine pigmentary stippling in the macular area and loss of the foveal light reflex. This may develop into irreversible bull's eye maculopathy and widespread retinal pigment epithelial atrophy, associated with a central scotoma, loss of visual acuity and peripheral visual field loss. Corneal deposits, and impairment of accommodation are reversible, dose related side-effects.

The incidence of clinically significant retinopathy with hydroxychloroquine is low and appears related to long-term treatment (>5 years). It remains unclear if cumulative dosage or duration of treatment is of most relevance. Toxicity has been reported to increase sharply after a cumulative dose of 1000 g hydroxychloroquine; intermittent treatment, for example for 6 months, is therefore preferred. Many patients with cutaneous lupus can be adequately managed by limiting antimalarial therapy to the spring and summer seasons. Risk factors are listed in Table 1 (*overleaf*).

If visual abnormalities or symptoms occur the drug should be discontinued and the patient monitored for possible progression after cessation of therapy.



**TABLE 1** Risk factors for hydroxychloroquine retinopathy

Duration	>5 years
Cumulative dosage	>1000 g
Age	Elderly
Co-morbidities	Renal, hepatic impairment, obesity
Ocular disease	Retinal or macular complaints

- **Common adverse effects** include gastrointestinal (GI) disturbance, headache and pruritus. These are usually mild. More serious but rare adverse effects include hepatic damage, myopathy, neuropathy and psychosis.
- **Cutaneous adverse effects** include skin and mucous membrane pigmentation, depigmentation of hair, alopecia and exfoliative dermatitis. Serious cutaneous adverse reactions including acute generalized exanthematous pustulosis (AGEP) and toxic epidermal necrolysis have been reported with hydroxychloroquine. Mepacrine causes reversible yellow discolouration of the skin when used in maintenance doses of 100 mg daily, and may occasionally cause severe lichenoid eruptions (preceded by itch). Psoriasis may be worsened by chloroquine and hydroxychloroquine.
- **Haematological adverse effects** of antimalarials include a small but significant risk of marrow suppression, and haemolysis in G6PD deficiency.
- **Overdosage:** antimalarials are very toxic in overdose, especially in infants, so safe storage is essential.

**+ Use in special situations**

**Pregnancy**

The use of hydroxychloroquine (FDA Category C) in pregnancy is controversial. The manufacturers recommend avoidance of hydroxychloroquine in pregnancy and breastfeeding, because of a theoretical risk of cochlear damage. However, stopping hydroxychloroquine when pregnancy is discovered makes little sense because of the long half-life. Separate studies in the UK and North America have found that continuation of hydroxychloroquine in pregnant patients with SLE is probably safe. There is considerable experience of pregnancy in patients safely receiving antimalarials as prophylaxis in malaria endemic regions, and UK obstetricians are happy to continue hydroxychloroquine in patients in *in vitro* fertilization (IVF) programmes.

Chloroquine (FDA Category D) is contraindicated in pregnancy, except for treating and preventing malaria. Because mepacrine is unlicensed, the manufacturers have no data on its use in pregnancy and breastfeeding.

## Lactation

Small amounts of antimalarials are excreted in breast milk, therefore mothers taking these drugs should not breastfeed. However, the same is true for lactation as pregnancy, in terms of experience obtained from malarial prophylaxis.

## Children

Quinolones and mepacrine are not licensed for use in children. When essential, hydroxychloroquine should be used at the minimum effective dose and not exceed 6.5 mg/kg/d or 400 mg. Tablets of 200 mg can therefore not be used in children weighing <31 kg. Chloroquine is sometimes used in specialist units at a daily dose of 4 mg/kg/d for ease of administration.

### + Essential patient information

- Patients should be warned to stop treatment and seek advice from the prescribing doctor if they develop visual symptoms such as reduced acuity, abnormal colour vision or blurred vision.
- Patients prescribed chloroquine should be specifically counselled about the risk of permanent visual loss.

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# Antivirals for HerpesViruses

David J. Eedy

## + Classification & mode of action

Herpesviruses are members of a large family of DNA viruses that cause disease in humans and animals. At least five species are extremely widespread in humans, namely herpes simplex virus (HSV-1 and HSV-2) (both of which can cause orolabial and genital infections), varicella zoster virus (VZV) (that causes chickenpox and shingles), Epstein-Barr virus (EBV) (the cause of infectious mononucleosis), and cytomegalovirus (CMV). HSV and VZV are neurotropic and following primary infection, establish long-term asymptomatic latency in the ganglia of sensory nerves. Reactivation of latent virus leads to enhanced replication and cell lysis and disease symptoms. Other human herpesviruses establish latency in lymphoid cells and can play a role in oncogenesis.

Most viral illnesses including HSV and VZV are self-limiting and do not require specific antiviral therapy. However, occasionally serious complications such as encephalitis and disseminated infections can occur, especially in neonates or immunocompromised patients (such as transplant recipients, cancer patients and those with human immunodeficiency virus [HIV] infection), and exposure to VZV infection in early pregnancy results in congenital varicella syndrome in up to 5% of pregnancies.

Antiherpes drugs inhibit viral DNA synthesis and viral replication by inhibiting viral DNA polymerase, which results in premature chain termination. **Aciclovir** (acyclovir) is the prototype guanosine analogue antiherpes drug and requires activation by viral thymidine kinase. It has a low water solubility and poor gastrointestinal (GI) absorption, with low oral bioavailability (15–30%) so i/v administration is required to achieve consistent high plasma levels. The poor oral bioavailability is improved by esterification to the pro-drug **valaciclovir** (**valacyclovir**), which is hydrolysed to aciclovir (acyclovir) via hepatic first-pass metabolism and increases the bioavailability 3–5-fold to approximately 70%. The superior pharmacokinetics of valaciclovir allows a reduced dosage frequency that may improve clinical efficacy and compliance. The therapeutic activity of aciclovir against herpesviruses is as follows: HSV >VZV >EBV >CMV.

**Penciclovir** has a similar spectrum of activity and potency against HSV and VZV but due to a very low oral bioavailability it is only used topically. **Famciclovir** is a pro-drug of penciclovir that improves the oral bioavailability of penciclovir to over 70%. The active triphosphate form of penciclovir has been shown to have more persistent antiviral activity in HSV infected cells than aciclovir, and this may lead to an increase in efficacy.

Drug resistance is an emerging threat to the clinical utility of antiviral drugs, especially following their long-term use in immunocompromised patients. Aciclovir resistance in HSV is usually associated with mutations in the viral thymidine kinase gene, rather than DNA polymerase, as this enzyme is not essential for viral replication. Strains resistant to aciclovir are almost always cross-resistant to penciclovir and famciclovir. Resistant infections can be managed by foscarnet or cidofovir, but both are more toxic than aciclovir. **Foscarnet** is inhibitory for all herpesviruses and HIV and inhibits viral nucleic acid synthesis by interacting directly with viral DNA polymerase or reverse transcriptase. Foscarnet resistant strains of herpesvirus have been described and in this situation i/v cidofovir should be considered (an unlicensed use).

### + Indications & dermatological uses

- **Aciclovir** is licensed for use in HSV and VZV infection.
- **Valaciclovir** is licensed for HSV and VZV infection and CMV prophylaxis in organ transplant recipients.
- **Famciclovir** is licensed for use in shingles and genital herpes.
- **Foscarnet** is licensed for unresponsive HSV infection in immunocompromised patients and CMV retinitis in HIV patients.

### HSV infection

**Primary HSV infection** of the **mouth and lips** (gingivostomatitis) or eyes in immunocompetent individuals is usually managed with topical aciclovir or penciclovir. Oral aciclovir may provide modest clinical benefit in preventing subsequent recurrent orolabial herpes. Severe infection, neonatal HSV and immunocompromised individuals require systemic therapy.

Primary and recurrent **genital HSV infection** is usually treated with an oral antiviral drug. This reduces virus shedding, symptoms and healing time, but does not significantly reduce the risk of further recurrence. **Long-term prophylactic therapy** with aciclovir or valaciclovir may be considered in patients with frequently recurring, debilitating genital herpes which is impairing the quality of life. It reduces the rate of clinical recurrence by about 90% and subclinical shedding is markedly reduced, but not eliminated. Aciclovir has been used safely for up to 10 years. **Shorter-term prophylaxis** (e.g. special events or risk periods) reduces the overall risk of recurrence by about 70% in those with sun-induced recurrences of HSV.

Long-term HSV prophylactic regimes may also be useful in the treatment of disabling recurrences of herpetic whitlow and HSV related erythema multiforme.

Prophylactic oral aciclovir is used in late pregnancy (from 36 weeks) to reduce viral shedding in females with recurrent genital herpes and prior to organ transplantation.

## VZV infection

In healthy children, primary infection with VZV (chickenpox) is usually benign and self-limiting. However, in adolescents and adults chickenpox is more severe and oral antiviral therapy should be started within 24 hours of onset of the rash. This shortens the healing time and duration of fever and symptoms. Starting aciclovir after this time point appears to be of no value in uncomplicated adult varicella.

Systemic therapy is recommended for immunocompromised patients to reduce the risk of pneumonitis. Pregnant females and immunocompromised patients who are not immune to VZV require specialist advice and may require urgent treatment with varicella zoster immunoglobulin following exposure to chickenpox.

Oral antiviral treatment is indicated in **herpes zoster (shingles)** to reduce the severity and duration of acute pain, reduce complications (post-herpetic neuralgia) and reduce viral shedding. Treatment should be started within 72 hours of the onset of the rash. Additional treatment with prednisolone may accelerate resolution of acute pain but does not reduce post-herpetic neuralgia. Valaciclovir and famciclovir have been shown to be superior to aciclovir in reducing herpes zoster associated pain and are generally preferred due to their more convenient dosing regimens. Administration of aciclovir i/v increases the rate of healing and resolution of acute neuritis in immunocompetent patients with shingles compared with oral therapy, but does not appear to confer any improved long-term benefits.

Immunocompromised patients require i/v therapy for 7 days to reduce the risk of disseminated VZV infection. In those who are severely immunocompromised oral therapy may be administered for 6 months.

## + Formulations/Presentation

- Aciclovir: 200 mg and 800 mg tablets; 200 mg, 400 mg and 800 mg dispersible tablets; and suspensions of 200 mg/5 mL, 400 mg/5 mL (with sugar-free versions available). Powder to reconstitute for slow i/v infusion. Topical aciclovir 5% cream and 3% eye ointment.
- Valaciclovir: 250 mg and 500 mg tablets.
- Famciclovir: 125 mg, 250 mg and 500 mg tablets.
- Penciclovir: 1% cream for herpes labialis. Not recommended under 12 years.
- Foscarnet sodium is only available as a solution for i/v infusion.

## + Dosages & suggested regimens

Non-genital HSV infection (primary gingivostomatitis/herpes labialis).  
oral aciclovir:

- Adults and children over 2 years: **200 mg 5x/d for 5 days** (double the dose if immunocompromised or absorption impaired).
- Infants aged 1 mo–2 y: half adult dose.

Intravenous aciclovir is recommended to achieve higher blood levels than oral aciclovir in severe infections (disseminated infection, extensive eczema herpeticum, neonatal infection, HSV encephalitis):

- Adults and children over 12 years: **5 mg/kg tds for 5 days**. Obese individuals should receive a dosage based on their ideal bodyweight.
- Neonates, infants and children up to 12 years: see children's formulary for dosage according to body surface area or bodyweight.

Valaciclovir:

- Adults: **500 mg bd for 5 days** (up to 10 days if new lesions appear or healing incomplete; double the dose in immunocompromised).
- Adults and children over 12 years: **two 2 g doses** with a **12 hour interval** for treatment of acute herpes labialis.

### Primary genital HSV infection

- Oral aciclovir: **200 mg 5x/d** or **400 mg tds for 5 days** (longer if new lesions appearing). Increase dose to 400 mg 5x/d in immunocompromised.
- Valaciclovir: **500 mg bd for 5 days** (up to 10 days if new lesions appear or healing incomplete; double the dose in immunocompromised).
- Famciclovir: **250 mg tds for 5 days**.

### Recurrent genital HSV infection

- Oral aciclovir: **200 mg 5x/d**, **400 mg tds for 3–5 days** or **800 mg tds for 2 days**. In immunocompromised, give 400 mg tds for 5–10 days.
- Valaciclovir: **500 mg bd for 3–5 days** (double the dose and treat up to 10 days in immunocompromised).
- Famciclovir: **125 mg bd for 5 days** or **1 g bd for 1 day** (500 mg bd for 5–10 days in immunocompromised).

Alternatively, topical therapy with aciclovir or penciclovir may be used for recurrent HSV. Treatment should be commenced at the onset of symptoms. Penciclovir is not recommended under the age of 12 years.

### Prophylactic regimens for frequently recurring genital herpes

- Short-term prophylaxis: aciclovir **400 mg bd for 1 week**.
- Long-term prophylaxis: aciclovir (**400 mg bd** or **200 mg tds**); valaciclovir **500 mg once daily** (increase to twice daily for very frequent recurrences); famciclovir **250 mg bd**. Long-term prophylactic therapy is usually interrupted after 6–12 months to assess recurrence frequency.

### Primary VZV infection (chickenpox)

- Oral aciclovir: **800 mg 5x/d for 7 days**, in both normal and immunocompromised patients.

### Herpes zoster (shingles)

- Oral aciclovir: **800 mg 5x/d for 7 days** for adults and children over 12 years. In severely immunocompromised patients 800 mg qds can be administered

for up to 6 months. In younger children, 20 mg/kg (up to 800 mg) qds (unlicensed).

- Intravenous aciclovir: **10 mg/kg tds** for acute herpes zoster affecting the trigeminal nerve (forehead and eyelids).
- Valaciclovir: **1g tds for 7 days** in adults and immunocompromised children over 12 years.
- Famciclovir: **500 mg tds for 7 days** (or 10 days in immunocompromised) or **750 mg 1–2×/d for 7 days**.

### Aciclovir resistant HSV and VZV

Foscarnet sodium i/v 40 mg/kg tds by slow infusion for 2–3 weeks or until lesions healed. It is licensed for use in aciclovir resistant mucocutaneous HSV infections and may also be effective in aciclovir resistant VZV infections.

### Special point

Chickenpox vaccination, with live attenuated VZV, is not part of the current routine UK childhood immunization programme. It is recommended for non-immune healthcare workers, older children/adults and close family contacts of immunocompromised individuals.

Passive immunity is conferred by administration of varicella zoster immunoglobulin, which should be given to high risk individuals within 4 days of contact (British National Formulary [BNF] advises 10 days) with chickenpox or herpes zoster. High risk individuals include neonates, non-immune pregnant females and immunocompromised patients – including those who have received systemic corticosteroids in the previous 3 months (>40 mg prednisolone daily for more than 1 week).

Despite recent attempts, no effective vaccine has yet been developed for HSV infection.

### + Baseline investigations & considerations

- Routine monitoring is not required for aciclovir, valaciclovir and famciclovir.
- Foscarnet: renal indices, electrolytes, calcium and magnesium.

### + Monitoring

Renal indices, electrolytes, calcium and magnesium should be monitored frequently during foscarnet therapy.

### + Contraindications

Hypersensitivity to the antiviral agent.



### + Cautions

- Aciclovir i/v: maintain adequate hydration and reduce dose in renal failure. Dose limiting toxicities of i/v aciclovir are renal insufficiency and CNS side-effects.
- Valaciclovir; caution with high doses in hepatic impairment and reduce dose of i/v infusion in renal failure.
- Famciclovir: reduce dose in renal impairment.
- Aciclovir and penciclovir creams can cause transient stinging, burning or numbness. They should not be used in the mouth.

### + Important drug interactions

- Aciclovir and valaciclovir: increased nephrotoxicity with **ciclosporin** (cyclosporine) and possibly with tacrolimus.
- Increased plasma concentrations of aciclovir with **mycophenolate**.
- Excretion of aciclovir reduced by **probenecid**.
- Plasma concentrations of **theophylline** may be increased.
- Excretion of famciclovir is possibly reduced by **probenecid**.
- Foscarnet with **pentamidine** isetionate increases the risk of hypocalcaemia.

### + Adverse effects & their management

Oral antiherpes virus drugs are generally well-tolerated.

- **Aciclovir** has been infrequently associated with nausea, diarrhoea, rash, headache, pruritus, photosensitivity and very rarely renal insufficiency, hepatitis, jaundice, neuropsychiatric effects (dizziness, confusion, drowsiness, hallucinations psychosis, convulsions), tremor and fever. Anaemia, thrombocytopenia or leukopenia have been described.
- **Valaciclovir** has similar adverse effects but in higher dose may be associated with confusion, hallucinations, nephrotoxicity and uncommonly severe thrombocytopenic syndromes, especially in immunocompromised patients.
- **Famciclovir** may be associated with headache, diarrhoea and nausea. Urticaria, rash and hallucinations or confusion (predominantly in the elderly) have been reported.
- Intravenous **foscarnet** may cause a range of adverse effects including GI effects, neuropsychiatric disturbance, renal impairment and bone marrow toxicity. It requires careful monitoring for electrolyte disturbance especially hypocalcaemia.
- **Aciclovir** and **penciclovir** creams can cause transient stinging, burning or numbness. Ophthalmic use of aciclovir can give rise to local irritation and rarely, blepharitis or very rarely hypersensitivity.

## + Use in special situations

### Pregnancy

- Aciclovir and valaciclovir (both FDA Category B) are not known to be harmful in pregnancy, but the manufacturers advise to use only when potential benefits outweigh risk. No increase in the frequency of congenital abnormalities has been recognized in infants born to females who took aciclovir during pregnancy, and the drug has been used safely in neonates.
- Famciclovir (FDA Category B): avoid but use only when potential benefits outweighs risk.
- Foscarnet (FDA Category C): avoid use.

### Lactation

- Aciclovir and valaciclovir: significant amounts are found in milk; it is not known to be harmful but should be used with caution.
- Famciclovir: insufficient data exist.
- Foscarnet: avoid.

### Children

- Aciclovir is licensed for use in children and is the treatment of choice.
- Valaciclovir is licensed for use in children over 12 years for CMV infection.
- Famciclovir is not licensed for children and not generally recommended due to limited safety data.
- Foscarnet is not licensed for use in children. Dosages of 40 mg/kg tds can be given for severe mucocutaneous HSV infection

## + Essential patient information

Patients should be advised about additional symptomatic treatment of their infection with oral analgesics and to maintain adequate fluid intake. It should be explained that a person who has not had chickenpox or the varicella vaccine can catch chickenpox from a person with shingles and that the person is infectious until their lesions have dried (usually 5–7 days). While chickenpox is spread by respiratory droplets and skin contact, only direct skin contact with shingles carries the risk of infection.

Seek urgent specialist advice for ocular infection with cold sores or shingles.

*With acknowledgements to Stephen K. Tying who reviewed this chapter from an international perspective.*

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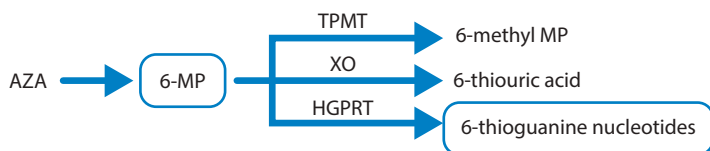
# Azathioprine

Sarah H. Wakelin

## + Classification & mode of action

The synthetic purine analogue azathioprine (AZA) was initially developed as an immunosuppressant in the 1960s, but is now most widely prescribed for its anti-inflammatory actions, especially in the treatment of skin and bowel disease and lupus.

AZA is a pro-drug and after oral ingestion and absorption it is rapidly hydrolysed non-enzymatically to an imidazole derivative (methylnitroimidazole) and 6-mercaptopurine (6-MP). Although 6-MP is also available for oral administration, AZA is usually preferred as its bioavailability is more reliable. 6-MP undergoes metabolism by competing enzymatic pathways to form various active metabolites (thioguanine nucleotides) and inactive metabolites (Figure 1). Thioguanine nucleotides are incorporated into the DNA and have an antiproliferative effect, especially on lymphocytes and other haemopoietic cells. The principal deactivating pathways are regulated by the enzymes thiopurine methyltransferase (TPMT) and xanthine oxidase (XO). Impairment of these pathways, due to inherent low enzyme activity or drug interactions can lead to accumulation of potentially toxic levels of thioguanine nucleotides and the risk of life-threatening bone marrow suppression. Tests to measure TPMT activity are now widely available and play a key role in the safe and effective prescribing of AZA.



TPMT = thiopurine methyl transferase  
XO = xanthine oxidase  
HGPRT = hypoxanthine phosphoribosyl transferase  
AZA = azathioprine  
MP = mercaptopurine

**FIGURE 1** Metabolism of azathioprine via different enzyme pathways. Active metabolites are boxed.

### + Indications & dermatological uses

The UK licensed indications for AZA are listed below. There are no FDA-approved dermatological indications in the USA.

- Pemphigus vulgaris.
- Systemic lupus erythematosus.
- Dermatomyositis/polymyositis.

AZA has also been widely used as a steroid-sparing treatment for bullous pemphigoid, and in this context appears to have similar efficacy to mycophenolate mofetil. Good clinical evidence supports its use as an oral monotherapy in the treatment of atopic dermatitis and it has been shown to be of benefit in chronic actinic dermatitis and parthenium allergic contact dermatitis.

AZA is also used to treat a range of vasculitides including Wegener's granulomatosis, Behçet's disease, Henoch-Schönlein purpura and severe cutaneous leukocytoclastic vasculitis. Small studies have reported benefit in pyoderma gangrenosum, lichen planus, erythema multiforme and pityriasis rubra pilaris.

### + Formulations/Presentation

- Generic and branded formulations tablet sizes of 25 mg and 50 mg.
- Preservative-free powder to reconstitute for i/v injection.

### + Dosages & suggested regimens

The onset of action is slow, and therapeutic effects may take several months. Empirical dosing of **1–3 mg/kg/d** is recommended in the package insert, with adjustment within these limits according to response and side-effects. This may be given as a single or divided dose and taken with food to reduce gastric upset.

Use of a low starting dose of **0.5–1 mg/kg/d** for the first 4 weeks may minimize the risk of side-effects such as nausea. Dosage may then be increased according to baseline TPMT levels and the FBC (CBC), especially the white blood cell count (WBC).

Several UK authors have recommended a schedule for maintenance doses based on TPMT activity as in Table 1. Units of measurement and category boundaries may differ in other countries and prescribers are advised to contact their laboratory for further advice.

Patients with absent TPMT activity should not receive AZA (see Baseline investigations & considerations). In exceptional situations a greatly reduced dose (5–10%) has been used with very close haematological and metabolite monitoring. The effects of treatment may also be slow to wear off after ceasing treatment due to persistence of active drug metabolites. Therapy should be discontinued if there is no improvement after 3 months.

**TABLE 1** Recommended dosages of azathioprine (AZA) based on thiopurine methyltransferase (TPMT) activity

TPMT range	Maintenance AZA dose mg/kg
Absent <10 pmol/h/mg Hb	Contraindicated
Intermediate/carrier 10–25 pmol/h/mg Hb	1.0–1.5
Normal/high >26 pmol/h/mg Hb	2.0–3.0

### + Contraindications & cautions

- Hypersensitivity to AZA or 6-MP is an absolute contraindication as AZA hypersensitivity syndrome is potentially life-threatening.
- Very low/absent or unknown TPMT levels (see Baseline investigations & considerations).

The following contraindications are also listed in the package insert:

- Severe infection.
- Pancreatitis.
- Severely impaired hepatic function or bone marrow depression.
- Pregnancy (unless benefits outweigh risks).
- Lactation.
- Malignancy is a contraindication to any form of immunosuppression including AZA, due to the possible increased risk of disease progression.

**Human immunodeficiency virus (HIV)** infection is not a contraindication and there is growing experience of safe use of AZA and other immunosuppressive drugs in HIV-positive patients. In this situation, it is used in those who are stabilized on highly active antiretroviral therapy (HAART). HIV screening should be considered prior to starting AZA and close liaison carried out with infectious disease specialists prior to initiating therapy in HIV-positive individuals.

**Hepatitis B virus (HBV)** is an important consideration as up to one-third of the world's population has evidence of past or active infection with this virus. HBV carriers are at risk of a disease flare on treatment with immunosuppressants and acute liver failure on drug withdrawal. Screening for HBV surface antigen (HBsAg) and anti-HBV core antibodies (antiHBc) should be considered in all patients and non-immune individuals at risk of infection should receive immunization against HBV. Testing LFTs alone is inadequate as these may be normal in infected individuals. The risk for hepatitis C virus (HCV) infected individuals is unclear, but all patients seropositive for HBV and HCV should be discussed with a hepatologist or infectious disease specialist as prophylactic antiviral therapy may be required (see Systemic Therapy & Liver Disease).

### + Important drug interactions

- **Angiotensin converting enzyme (ACE)** inhibitors may increase the risk of anaemia or leukopenia in those with renal impairment.
- **Allopurinol** inhibits XO and leads to accumulation of active metabolites with potentially life-threatening myelotoxicity. If co-administration is essential, it has been suggested that the dose of AZA should be reduced to one-quarter or one-third of the routine dose, with very careful haematological monitoring.
- **Live-attenuated vaccines** (see Table 2) should not be given to patients receiving AZA or other immunosuppressants. Inactivated vaccines are safe. (See Department of Health Green book for latest UK recommendations on vaccines and vaccination.)
- **Ribavirin** inhibits an enzyme in the purine salvage pathway and has been reported to cause severe pancytopenia.
- **Warfarin** resistance has been reported, and increased warfarin dosing may be required with close monitoring of anticoagulation.
- Other drugs that can cause **bone marrow depression** should be avoided, including other immunosuppressants, trimethoprim, cotrimoxazole and clozapine.

**TABLE 2** Live-attenuated vaccines

BCG
Intranasal influenza vaccine
Measles, mumps, rubella
Oral polio
Oral typhoid
Varicella zoster (chickenpox)
Yellow fever

### + Baseline investigations & considerations

- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs
- TPMT activity (see Dosages & suggested regimens).
- Hepatitis B & C serology.
- HIV testing if at risk.

- Varicella zoster virus (VZV) serology in patients without reliable history of chickenpox. VZV vaccine should ideally be given to the non-immune several weeks prior to starting AZA (as it is a live vaccine), but the disadvantages of delaying immunosuppressant therapy may not be justified.
- Influenza and pneumococcal vaccination are recommended for people who are on immunosuppressant medication. Ideally these inactive vaccines should be administered at least 2 weeks before therapy is started.
- Cervical screening should be up-to-date. A pre-treatment gynaecological review is recommended in females with a history of cervical intraepithelial neoplasia (CIN) as immunosuppressants increase the risk of progression to invasive disease and reduce the success of treatment.
- Dermatological examination and treatment of skin cancer and actinic keratoses is recommended for transplant recipients and seems appropriate for all patients in whom long-term treatment is likely.
- TPMT activity testing may be unreliable for up to 60 days after red cell transfusions due to interference by donor TPMT activity. Diuretics, some non-steroidal anti-inflammatory drugs (NSAIDs) and aminosaliclates such as sulfasalazine may have inhibitory effects on TPMT but the clinical relevance of these is unclear.

### + Monitoring

- Weekly FBCs for the first 8 weeks then monthly or no less than every 3 months (manufacturer's recommendations). Any downward trend in the neutrophil count should be noted, as an early decrease that is still within the normal total WBC range may herald more severe neutropenia.
- There is no recommended schedule for monitoring renal or liver function, but they should be checked regularly during the first few months of therapy (e.g. every 1–2 weeks) as hepatotoxicity can be seen during this period. In patients stabilized on therapy, FBC and LFTs should be checked at least every 3 months.
- Measurement of thioguanine nucleotides is not routinely undertaken in dermatology but may be useful to assess adherence and guide dose adjustment. Levels of thioguanine nucleotides have been found to correlate with clinical remission rates in patients with inflammatory bowel disease (IBD).

### + Adverse effects & their management

- **Gastrointestinal:** nausea is the commonest adverse effect of AZA and usually settles with continued treatment. It may be helped by dividing the daily dose and taking medication with food or co-prescription of an antiemetic.



- **Hypersensitivity:** idiosyncratic drug hypersensitivity to AZA is uncommon and usually starts within the first few weeks of treatment. Symptoms are often non-specific and flu-like with nausea, malaise, arthralgia. Urticarial, maculopapular and vasculitic rashes may occur. In severe cases hypotension and shock may occur with possible fatality. Treatment should be discontinued if hypersensitivity is suspected. Any rechallenge should be attempted in hospital with a reduced dose. Some patients may tolerate 6-MP as an alternative therapy.
- **Hepatitis:** mild abnormalities of transaminases ( $<2$  times upper limit of normal) are not uncommon and may settle with continued treatment. Deteriorating or sustained elevations of LFTs require dose reduction or discontinuation of therapy. Acute drug induced liver injury may be hepatocellular (high transaminases) or cholestatic (high bilirubin and alkaline phosphatase). The latter usually takes longer to resolve. A chronic pattern of liver injury termed nodular regenerative hyperplasia has been reported in transplant recipients and patients with IBD.
- **Haematological:** bone marrow suppression is one of the most serious adverse effects and can be fatal. As measurement of baseline TPMT does not identify all patients at risk of severe bone marrow suppression, it is essential that all patients are carefully monitored by regular measurement of FBC. Leukopenia is commonest, but anaemia or thrombocytopenia may also occur. These may develop suddenly or slowly over several months. Mild lymphopenia ( $0.5\text{--}1.0 \times 10^9/\text{L}$ ) is often observed and does not usually lead to complications. Macrocytosis is also common and can be helpful to monitor compliance. B12 and folate deficiency should be excluded.

There are no specific guidelines for dose reduction according to haematological parameters. Mild reductions in haemoglobin, a leukocyte count  $3\text{--}4 \times 10^9/\text{L}$  or platelet count of  $70\text{--}100 \times 10^9/\text{L}$  may be managed by reducing the dose of AZA by 50% and further close monitoring. The original dose can be resumed if values normalize, but treatment should be discontinued if indices continue to fall.

- **Malignancy:** thiopurines have been in clinical use for several decades, and there is evidence that they have a good safety record in terms of carcinogenicity. The exception is **non-melanoma skin cancer (NMSC)**, where they increase the risk of photo-carcinogenesis. In transplant recipients, long-term use of AZA combined with other immunosuppressants raises the risk of NMSC development more than 200-fold. AZA may carry a proportionally higher risk than other immunosuppressants as the absorption spectrum of 6-TG peaks at 340 nm (within the ultraviolet A [UVA] spectrum). Irradiation of 6-TG substituted DNA induces free radicals formation, which subsequently causes irreparable DNA damage. In the short term this manifests as increased UVA sensitivity; in the longer term, carcinogenesis. It is therefore important that those treated with AZA are advised about sun protection, self-examination and the need to report any suspicious skin lesions.

It remains controversial whether AZA treatment of dermatological disease carries any increased risk of internal malignancy. Studies in transplant recipients and those with IBD have shown increased rates of lymphoma

(including hepatosplenic T-cell lymphoma), but these appear to relate to the intensity of immunosuppression and underlying bowel disease, respectively. For treatment periods of less than 1 year, there is no obvious risk for dermatology patients. Those requiring longer-term therapy, can be advised that any increase in risk appears small.

- **Infection:** AZA may increase the risk of infection even in the absence of neutropenia. In practice, this does not appear to be a common clinical problem among dermatology patients. However, patients taking AZA may be susceptible to more severe infection with VZV. Non-immune individuals may require VZ immunoglobulin or prophylactic aciclovir (acyclovir) if they have significant exposure to chickenpox or herpes zoster.
- **Pancreatitis** has been reported in patients with underlying IBD.

### + Use in special situations

#### Pregnancy

There is no conclusive evidence that thiopurines are teratogenic, but they cross the placenta and are categorized as risk group D by the FDA (evidence of fetal risk, which may be outweighed by maternal benefits in life-threatening/serious disease), so their prescription in pregnant females requires careful consideration. Human studies have shown that AZA does not affect sperm quality or male fertility.

#### Lactation

Negligible amounts of AZA and its metabolites are present in breast milk, and although the World Health Organization (WHO) has advised that the risks to the infant outweigh any benefit, recent evidence does not support this.

#### Children

AZA is licensed for use in childhood and has been reported to be safe and effective for severe atopic eczema. High doses may be needed (2.5–3.5 mg/kg) to achieve remission. Long-term use needs careful consideration as the risk of skin cancer increases with treatment duration, so photo-protection is essential in this age group. Nausea and loss of appetite can be a problem in children, and may be helped by taking medication with food in the evening.

#### Elderly

The elderly take more medication and are therefore are at increased risk of drug interactions. They are also more susceptible to the adverse effects of AZA, so lower dosages should be considered.

### + Essential patient information

Patients should be informed of the reasons for treatment and whether the drug is being used for a licensed indication or not. It should be explained that

the onset of action is slow and that benefit may not appear until after 2–3 months' treatment.

The dermatologist should ensure that patients clearly understand the need for regular blood monitoring in order to minimize the risk of adverse effects and are able to comply with this. Patients should be warned that they are at increased risk of infection and should seek urgent medical attention if they develop the following symptoms and signs:

- High fever/severe flu-like illness.
- Severe sore throat.
- Unexplained bruising or bleeding.
- Jaundice.

The increased risk of skin cancer should be discussed and patients given practical information about sun protection and skin surveillance. In patients requiring longer-term use, the possible increased risk of malignancy, especially lymphoma should be discussed. In fertile females, advice should be given regarding the possible risks of AZA in pregnancy.

*With acknowledgements to Francisco A. Kerdel who reviewed this chapter from the international perspective.*

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# Azole Anthelmintics

Mahreen Ameen

## + Classification & mode of action

The anthelmintic drugs that are most commonly used in dermatology are the two benzimidazole carbamates, **albendazole**, which was first approved in 1983, and **mebendazole**, which was introduced in 1972. These long-established agents are used in both human and veterinary medicine. Thiabendazole (thiabendazole) is no longer used systemically due to serious adverse effects and its topical use is not advocated for treatment of cutaneous larva migrans unless systemic therapy is contraindicated.

Both albendazole and mebendazole have broad-spectrum anthelmintic activity. They are most commonly prescribed for the treatment of nematode infestations including roundworm, whipworm, threadworm and hookworm. Albendazole and mebendazole have a number of mechanisms of action: they act as vermicides by causing selective degenerative alterations in the tegument and intestinal cells of the worm, and by impairing cellular metabolism, thereby leading to immobilization and death of the parasite.

Albendazole and mebendazole are poorly absorbed following ingestion, and absorption is greatly enhanced if taken with food, especially a fatty meal. Administration on an empty stomach is only appropriate when intraluminal parasites are targeted. Both drugs undergo extensive first-pass metabolism in the liver and metabolic activation and detoxification depend on cytochrome P450 (CYP450) 2C and flavin mono-oxygenases. The oral bioavailability of mebendazole is reported to be less than 20%, which is significantly less than that of albendazole, and is a consequence of both poor absorption and rapid first-pass metabolism.

## + Indications & dermatological uses

Soil transmitted helminthiasis, which can parasitize the human gastrointestinal (GI) tract is responsible for GI infection in millions of people worldwide. In comparison, helminths are uncommon causes of skin diseases. Azole anthelmintic drugs are indicated as treatment for the following infestations: Mebendazole: pinworm (threadworm), roundworm; whipworm and hookworm. Licensed in UK and FDA approved.

Albendazole: FDA approved for pork tapeworm (trichinosis) hydatid disease caused by dog tapeworm (*Echinococcus granulosus*). Unlicensed in UK.

The following are off label uses:

- Cutaneous larva migrans: this is the commonest helminth infestation of the skin. It is characterized by a serpiginous rash and intense pruritus and is

acquired from direct contact of the skin with soil or sand contaminated by dog or cat hookworm, followed by percutaneous penetration and migration of larvae within the epidermis.

- Gnathostomiasis: this is caused by the nematode *Gnathostoma* sp. and is endemic in South Eastern Asian and Latin American countries. It is acquired by consuming raw or insufficiently cooked meat or fish. Ingested larvae cause cutaneous or, less frequently, visceral disorders.
- Trichinosis similarly is caused by eating undercooked pork or wild game and is caused by the nematode *Trichinella spiralis*. It is endemic worldwide and presents with facial oedema, particularly peri-orbitally, splinter haemorrhages, fever and myalgia.

### + Formulations/Presentation

Availability may differ according to country. Generally, albendazole is the treatment of choice and mebendazole is usually only considered as a second-line drug if albendazole is unavailable. Albendazole (200 mg and 400 mg) and mebendazole (100 mg and 500 mg) are formulated as chewable tablets and as an oral suspension (100 mg/5 mL).

### + Dosages & suggested regimens

- Cutaneous larva migrans: albendazole **400 mg daily for 3–5 days**. Ivermectin is an alternative treatment (see Ivermectin).
- Gnathostomiasis: albendazole **400–800 mg daily for 21 days** or ivermectin 0.2 mg/kg for 1–2 days. Cure rates are high and comparable for both drugs, but the relapse rate may be higher with albendazole.
- Trichinosis: albendazole **400 mg bd for 8–14 days** or mebendazole **200–400 mg tds for 3 days**.

### + Baseline investigations & considerations/Monitoring

- None routinely required.
- FBC (CBC) and LFTs if underlying haematological or hepatic abnormalities are suspected or when high dose/long-term benzimidazole therapy is considered. Repeat during treatment if abnormal.

### + Contraindications & cautions

- Albendazole and mebendazole are not recommended for use during pregnancy and children under the age of 2 years.
- Hepatic impairment: both drugs must be used with caution in those with hepatic impairment as they are metabolized in the liver and therefore

severe liver disease may result in higher plasma levels of the parent drug and metabolites. In cutaneous larva migrans alternative topical treatments should be considered to avoid the risks associated with systemic therapy.

### + Important drug interactions

- **Cimetidine**, an inhibitor of CYP450, may suppress the metabolism of the benzimidazoles and increase the bioavailability of the active metabolites of albendazole. Cimetidine does not appreciably raise serum mebendazole level as these are low due to its poor systemic absorption.
- **Antiepileptics**: carbamazepine, phenobarbitone (phenobarbital) and phenytoin can decrease the half-life of albendazole and mebendazole, leading to a decrease in their serum concentration.
- **Dexamethasone**: can increase plasma levels of albendazole by up to 50%.
- **Metronidazole**: there have been reports of Stevens–Johnson syndrome and toxic epidermal necrolysis occurring when high doses of either metronidazole or mebendazole are given concomitantly.

### + Adverse effects & their management

Albendazole and mebendazole have a similar adverse effect profile, with fewer effects reported for mebendazole, probably because of very low absorption. In spite of these, albendazole is considered a safe drug given the extensive clinical experience using it over decades.

- **Gastrointestinal adverse effects** (>1%) include nausea, vomiting, diarrhoea and abdominal pain. This is usually self-limiting and does not require special treatment. However, children especially must be monitored for dehydration, which may require active treatment if the individual is not able to tolerate oral fluids.
- **Headaches and dizziness** are the next most commonly reported side-effects and can be managed with simple analgesics.
- **Hypersensitivity reactions** including rash, pruritus and urticaria have been reported less frequently. These are usually not severe and can be managed with antihistamines and/or topical steroids. Telogen effluvium may also occur.
- **Hepatitis** elevation of liver enzymes may occur (with a frequency of only 0.035%) but is usually self-limiting without serious sequelae. There is an increased risk of this with long-term therapy. The detection of elevated liver enzymes seldom necessitates discontinuation of drug therapy. Closer monitoring is recommended in patients with underlying liver disease.
- There have been very rare reports of **acute liver failure, bone marrow suppression** with agranulocytosis and aplastic anaemia.

### + Use in special situations

#### Pregnancy

Albendazole and mebendazole (both FDA Category C) are not recommended in pregnancy because animal studies have found that they are teratogenic and embryotoxic. Therefore, it is not recommended that they are administered during pregnancy or in females thought to be pregnant. Females of childbearing age should be advised to avoid conception during and for one month after completion of treatment. However, clinical trials have also demonstrated a lack of adverse birth outcomes after deworming pregnant females with mebendazole. Therefore, pregnancy is not an absolute contraindication to benzimidazoles but it is suggested that treatment should be avoided in the first trimester of pregnancy.

#### Lactation

Low concentrations of albendazole and its active metabolite are detectable in breast milk after a single dose of albendazole 400 mg. However, these low levels are not considered to be harmful to the infant. Therefore, there is no absolute contraindication to the use of albendazole in breastfeeding mothers. There are very limited data on the presence of mebendazole in breast milk, but given its low bioavailability it is unlikely to be significant.

#### Children

The benzimidazoles are generally not recommended in children under the age of 2 years. However, clinical data suggest that the incidence of adverse effects is likely to be the same in young children as in older children. Therefore, both albendazole and mebendazole can be used from the age of 12 months if the risks of not treating outweigh the risks of drug related adverse effects.

*With acknowledgements to Garrett Coman who reviewed this chapter from an international perspective.*

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# Ciclosporin

Murtaza Khan & John Berth-Jones

## + Classification & mode of action

Ciclosporin (cyclosporine) is a lipophilic cyclic undecapeptide (11 amino acid residues) with a molecular weight of 1202 daltons. It is the original calcineurin inhibitor and was first isolated in 1970 from the soil fungus *Tolypocladium inflatum* during a search for antifungal agents. The drug was found to have immunosuppressive actions and its use revolutionized solid organ transplant medicine. It was inadvertently found to be effective in the treatment of psoriasis in 1979.

Ciclosporin exerts immunomodulatory effects mainly by preventing the activation of T-lymphocytes which are implicated in the pathogenesis of inflammatory skin disorders such as psoriasis and atopic dermatitis. It binds to a cytoplasmic protein, cyclophilin, forming a complex that inhibits the activity of calcineurin. In T cells calcineurin normally activates nuclear factor of activated T cells (NFATc), which promotes the production of interleukin-2 (IL-2) and numerous other cytokines that initiate the activation and proliferation of T cells. In addition, the drug inhibits the release of histamine from mast cells which may in part explain its usefulness in urticaria.

Gastrointestinal (GI) absorption varies according to food intake and gut motility and plasma levels vary between individuals. This variation is reduced by the use of microemulsion formulations. Ciclosporin is metabolized by the cytochrome P450 (CYP450) enzyme system (predominantly CYP3A4 and CYP3A5) in the liver and therefore has many potential drug interactions. Its metabolites are predominantly eliminated in the bile so alteration in renal function does not increase blood levels significantly.

## + Indications & dermatological uses

Ciclosporin has been used for the treatment of inflammatory bowel disease, nephrotic syndrome and rheumatoid arthritis. It is widely used in the prevention of transplant rejection.

- The licensed dermatological indications in the UK for the use of ciclosporin are severe psoriasis and severe atopic eczema.

Ciclosporin has been shown to greatly improve the quality of life in patients with psoriasis in randomized controlled trials. It is effective in the management of severe chronic plaque psoriasis, erythrodermic psoriasis and pustular psoriasis. In addition, it improves joint disease in psoriatic arthritis. In the USA, ciclosporin is approved for the treatment of adult patients with severe or recalcitrant psoriasis. It leads to an approximate PASI 75 of 70% at 12



weeks. Ciclosporin is widely used for the treatment of severe atopic dermatitis (atopic eczema), although not FDA approved for this indication. The rapid onset of action of ciclosporin is particularly useful for short-term control of atopic dermatitis and it has been shown to be effective and well-tolerated in children aged 2–16 years.

There are numerous reports of off-label uses of ciclosporin in dermatology, including the following:

- Behçet's disease.
- Chronic urticaria.
- Connective tissue diseases including scleroderma and dermatomyositis.
- Immunobullous disorders such as pemphigus and epidermolysis bullosa acquisita.
- Lichen planus.
- Nodular prurigo (prurigo nodularis).
- Palmo–plantar pustulosis.
- Photodermatoses such as chronic actinic dermatitis and solar urticaria.
- Pyoderma gangrenosum.
- Toxic epidermal necrolysis.

### + Formulations/Presentation

Differences may occur in the bioavailability of the various formulations and brands of ciclosporin. For dermatological use, the modified microemulsion forms of ciclosporin, Neoral or Gengraf (in the USA), are usually prescribed as they offer better bioavailability than the non-modified form. Physicians should specify the brand when prescribing and should not switch randomly between brands.

Several branded formulations are available in the UK in the following forms:

- Capsules: 25 mg and 100 mg ciclosporin (Neoral, Gengraf, modified), 25 mg, 50 mg and 100 mg ciclosporin (Sandimmune, non-modified).
- Oral solution: sugar-free solution containing ciclosporin 100 mg/mL. This may be mixed with orange or apple juice to improve the taste but not with grapefruit juice. Avoid milk due to the unpleasant taste
- Sandimmune is also available in a concentrate for i/v infusion containing ciclosporin 50 mg/mL.

### + Dosages & suggested regimens

- Ciclosporin should be taken as two divided doses per day.

For psoriasis: for non-urgent cases, the recommended **starting dose** is **2.5–3.0 mg/kg/d**, which can be titrated up to **5 mg/kg/d** over 6–8 weeks. For severe or urgent cases in which a rapid effect is required, treatment should be initiated at **5 mg/kg/d**. Improvement is usually apparent within **6 weeks** and the drug should be discontinued if there is an inadequate response after

**3 months** of therapy. Once sufficient improvement is observed the dose should be slowly reduced by 0.5–1 mg/kg/d to the lowest effective dose.

Treatment should be limited to intermittent short courses lasting 3–6 months, which are usually sufficient for the control of most cases of psoriasis. However, some patients with severe disease may require therapy for several years, exceeding the limit of **1 year of continuous therapy** recommended in the FDA guidelines. In this situation the lowest effective dose should be used with meticulous monitoring for side-effects. In obese patients, ideal bodyweight should be used for dose calculation. Due to the risk of renal toxicity continuous use of ciclosporin for more than 2 years is not recommended.

For atopic dermatitis: ciclosporin is licensed in the UK for short-term treatment (usually up to 8 weeks). Although not FDA approved for this indication, there are similar guidelines for its widespread use in the USA. Ciclosporin is effective and well-tolerated in adults and is highly effective and probably better tolerated in younger children. Ciclosporin can be used at a starting dose of **5 mg/kg/d** for the first **2–4 weeks**, by which time a clinical response is expected. Thereafter the dose is gradually tapered. An alternative approach is to start with a lower dose (e.g. 2.5 mg/kg/d). The use of ciclosporin for longer term, i.e. up to 12 months, for adults with severe atopic dermatitis has been studied and shown to be generally safe and effective.

### + Baseline investigations & considerations

- BP should be monitored on at least two occasions, preferably 2 weeks apart.
- Physical examination to exclude infection and skin malignancy.
- Patients should be advised to follow recommended guidelines for cancer screening, e.g. cervical smear, breast imaging, prostate cancer screening.
- Mean value of creatinine and eGFR should be recorded on 2 occasions 2 weeks apart.
- FBC (CBC), electrolytes, uric acid, LFTs and fasting lipids.
- Human immunodeficiency virus (HIV) test, if at risk of infection.
- During treatment with ciclosporin, vaccination may be less effective so the use of live attenuated vaccines should be avoided.

### + Monitoring

- BP should be monitored every 2 weeks for the first 2 months of treatment and then monthly thereafter. BP should be maintained below 140/90 mmHg.
- Serum creatinine, eGFR and electrolytes should be measured every 2 weeks for the first 2 months then every 2 months. A rise in creatinine of 25% above baseline/ fall in eGFR by more than 25% (30% originally recommended), even if within the normal range, should prompt dose reduction by 1mg/kg/day and retesting after 2 weeks. If values do not improve, treatment should be discontinued.

- Fasting lipids should be measured as appropriate.
- Drug levels are not routinely monitored when ciclosporin is used at doses up to 5 mg/kg/d. However, this can sometimes be useful, e.g. to assess suspected non-adherence or drug interaction.

### Special point

The serum creatinine is related to muscle mass. Patients with a low muscle mass may have significant nephrotoxicity even though their serum creatinine remains within the normal range, so baseline values should always be considered.

### + Contraindications & cautions

Ciclosporin should generally be avoided in the following circumstances:

- Impaired renal function.
- Uncontrolled hypertension.
- Malignancy.
- Active infection.
- Concomitant ultraviolet (UV) B or psoralen and ultraviolet A (PUVA) therapy.
- Severe hepatic dysfunction.
- Immunodeficiency.

HIV-associated psoriasis is often severe and refractory to first-line therapies. Ciclosporin may be used in special cases after careful evaluation and with the expert advice of an infectious disease specialist. Close monitoring for adverse effects is essential.

### + Important drug interactions

Ciclosporin interacts with a large number of drugs and a database for drug interactions such as the British National Formulary (BNF) should be consulted for a full list. Some of the important interactions are listed below:

- **Nephrotoxic drugs:** other nephrotoxic drugs should be avoided as far as possible, although the concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) often occurs.
- **Statins** should generally not be co-administered with ciclosporin, as there are metabolic interactions including inhibition of the metabolism of statins by CYP450, increasing the risk of myopathy. However, some statins (e.g. pravastatin) are not metabolized by CYP450 and the use of these medications reduces the risk.
- **CYP450 inducers and inhibitors:** ciclosporin is metabolized by the hepatic CYP450 system, primarily CYP3A4 and CYP3A5. This leads to a number of potential drug interactions that may increase or decrease levels of ciclosporin (Table 1).
- **Grapefruit juice** is also a CYP450 inhibitor and should be avoided while taking ciclosporin. It also increases the absorption of ciclosporin from the gut.

**TABLE 1** Cytochrome P450 (CYP450) inducers and inhibitors

CYP450 inducers (reduce ciclosporin levels)	CYP450 inhibitors (increase ciclosporin levels)
Rifampicin	Macrolide antibiotics (erythromycin, clarithromycin)
Phenobarbital	Ciprofloxacin
Carbamazepine	Fluoxetine
Phenytoin	Ketoconazole, itraconazole, fluconazole
St John's wort	Omeprazole
	Cimetidine

- **Methotrexate** and ciclosporin should not be co-prescribed if possible, as each drug can reduce the elimination of the other.
- **Aciclovir** (acyclovir) and other antiviral drugs may increase the risk of nephrotoxicity (see Antivirals for HerpesViruses).
- **Antimalarials** (chloroquine and hydroxychloroquine) increase the plasma concentration of ciclosporin (see Antimalarials).

### + Adverse effects & their management

- **Hypertension:** ciclosporin raises BP largely through a peripheral vascular effect. If the systolic BP rises above 140 mmHg or diastolic BP rises above 90 mmHg, the BP should be checked again in 2 weeks. If it remains elevated the dose of ciclosporin should be reduced by 25–50% or treatment with an antihypertensive should be considered. Nifedipine is a useful drug as it has a nephroprotective effect when used in combination with ciclosporin. However, both drugs may cause gingival hyperplasia so monitor for this at each visit.
- **Nephrotoxicity:** ciclosporin causes nephrotoxicity by mechanisms thought to include renal vasoconstriction and hypoxia leading to the formation of free radicals. The effects are related to dose and duration of treatment so intermittent short courses are preferable. It also upregulates transforming growth factor-beta (TGF- $\beta$ ) expression in juxtaglomerular cells, which promotes renal fibrosis. A rise in creatinine of >25% requires dose reduction (see monitoring). The creatinine level usually normalizes within 4–8 weeks of cessation of the drug. Continued use can result in irreversible chronic renal failure.
- **Metabolic:** hyperkalaemia, hypercalciuria and hypomagnesaemia (which may cause muscle cramps). Hyperkalaemia is thought to be due to renal tubular resistance to aldosterone. The risk is increased when administered with potassium-sparing diuretics and aldosterone antagonists.

- **Hyperuricaemia** may occur due to reduced urate clearance.
- **Malignancy:** patients treated with ciclosporin are at increased risk of **non-melanoma skin cancers**, especially squamous cell carcinoma. This risk is significantly increased in patients previously exposed to PUVA therapy. Some studies have also reported an increased incidence of lymphoma. Patients taking ciclosporin on a long-term basis should have examinations of their skin, lymph nodes and abdomen every 6 months.
- **Gingival hyperplasia:** gum hypertrophy is a known side-effect of ciclosporin. It is worsened by poor oral hygiene. If gingival hyperplasia develops patients should be advised to see a dentist and in severe cases it may be necessary to withdraw ciclosporin.
- **Neurological:** patients taking ciclosporin often report paraesthesia or tremor, and seizure threshold may be lowered.
- **Hepatotoxicity:** liver dysfunction is sometimes seen in transplant patients taking ciclosporin and is uncommon at the lower doses used in psoriasis. As the drug is eliminated mainly in the bile, any liver disorder should prompt a reduction in the dose or discontinuation of the drug.
- **Hypertrichosis** is common.
- **Miscellaneous:** sebaceous hyperplasia has mainly been reported in transplant recipients. Fatigue, headache, flu-like symptoms, and GI disturbances occur occasionally. Nausea and reflux may be helped by changing to a liquid formulation.

### + Use in special situations

#### Pregnancy (FDA Category C)

Ciclosporin has not been shown to be teratogenic in humans. There is considerable experience of its use in mothers following organ transplantation without any established serious hazard to the unborn child. There are some reports of an association with premature labour. The manufacturer recommends avoiding ciclosporin in pregnancy unless the benefits to the mother justify potential risks to the fetus.

#### Lactation

Ciclosporin is excreted in breast milk and mothers taking the drug should not breastfeed.

#### Children

Ciclosporin is not licensed in the UK for use in children less than 16 years, or FDA approved for psoriasis patients less than 18 years. However, it has been used in patients as young as 1 year of age in nephrotic syndrome, juvenile dermatomyositis and organ transplantation without serious side-effects. As in adults, the main risks are renal toxicity and hypertension.

#### Elderly

Elderly patients should be monitored with particular care for nephrotoxicity

### + Essential patient information

The important side-effects should be explained and supplemented with written information. Patients should be advised to attend appointments for clinical assessments and blood tests on a regular basis. Advice regarding the avoidance of sunlight, interacting drugs and grapefruit juice should be given. Patients should also be warned that any change in formulation should only be done under physician supervision.

*With acknowledgements to Rachael Morris-Jones and Anne Powles, authors of this chapter in the 1st edition, and Eric Sorensen and Wilson Liao who reviewed this chapter from an international perspective.*

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# Clofazimine

Eglantine Lebas & Stephen L. Walker

## + Classification & mode of action

Clofazimine is a riminophenazine dye and a cornerstone of the multidrug therapy (MDT) of leprosy. It was first synthesized in 1954 as an antituberculous drug but found to lack effectiveness, and was later marketed under the brand 'Lamprene' as a treatment for leprosy. Clofazimine is usually prescribed in combination with rifampicin and dapsone. Since 1995, the World Health Organization (WHO) has supplied MDT free of cost for leprosy sufferers in endemic countries.

Clofazimine is highly lipophilic and tends to be deposited in fatty cells and cells of the reticuloendothelial system. It has both antimycobacterial and immunomodulatory properties. It has a slow bactericidal effect against *Mycobacterium leprae* and preferentially binds to the guanine bases of bacterial DNA, thereby inhibiting bacterial proliferation. It also increases activity of bacterial phospholipase A2 leading to accumulation of lysophospholipids, which inhibit cell wall integrity and bacterial proliferation. Clofazimine has inhibitory actions on macrophages, neutrophils and T-lymphocyte proliferation, blocking Kv1.3 channels in the latter, which are essential for memory T-cell proliferation.

## + Indications & dermatological uses

Clofazimine is indicated for the treatment of leprosy. It is only available on a named patient basis in the UK and USA and is used as follows in leprosy:

- Multibacillary leprosy in combination with rifampicin and dapsone.
- Erythema nodosum leprosum (ENL).

Due to its immunosuppressive actions, clofazimine has been used in the management of chronic discoid lupus erythematosus, granulomatous cheilitis, chronic graft-versus-host disease, necrobiosis lipoidica, pyoderma gangrenosum and other neutrophilic dermatoses such as Sweet's syndrome. Although not a first-line treatment for these diseases, it can be considered in refractory cases.

It has been used to treat *Mycobacterium avium* complex infections in patients with acquired immunodeficiency syndrome (AIDS) and has a role in the management of multidrug resistant and extensively drug resistant tuberculosis.

## + Formulations/Presentation

Oil-wax based capsules containing 50 mg and 100 mg clofazimine (red-brown microcrystalline powder). Food increases the rate of absorption and bioavailability.

## + Dosages & recommended regimens

The WHO's recommended dosage of clofazimine in MDT of multibacillary leprosy is **300 mg once a month** and **50 mg daily** for the rest of the month for at least 12 months. MDT is supplied in blister packs. Monotherapy should never be used in the treatment of leprosy as it leads to drug resistance.

The WHO recommends that ENL reactions in lepromatous leprosy, which are often recurrent and chronic in nature, are managed by experienced clinicians. Clofazimine is used most commonly in persons with multibacillary leprosy who are at risk of developing ENL reactions or who have recurrent or chronic ENL. It may be given at higher doses of **300 mg a day** for a maximum of 3 months followed by **200 mg daily** for 3–6 months. The **maximum recommended duration** of high dose clofazimine is **12 months**. For chronic inflammatory dermatoses the usual effective dose is 100–200 mg/d.

## + Baseline investigations & considerations/Monitoring

- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs.
- Glucose.

## + Contraindications & cautions

- Hypersensitivity to clofazimine.
- Soft contact lenses may be discoloured.

## + Important drug interactions

**Antimycobacterial drugs:** clofazimine may reduce the absorption of rifampicin, but this is not thought to be clinically relevant and they are often co-prescribed.



## + Adverse effects & their management

- **Skin discolouration** is a very common adverse effect of treatment with clofazimine, occurring in approximately 80% of individuals. The discolouration can range from pink to dark brown/black. It can be very distressing for some patients, but slowly resolves after drug discontinuation. In leprosy patients pigmentation tends to be most prominent on the face and in lesions, and this can lead to further stigmatization and depression. Discolouration of mucous membranes and most bodily fluids and secretions also occurs. Hair may darken.
- **Ichthyosis**, particularly of the limbs and skin dryness with pruritus are also common and resolve with cessation of the drug. Emollients can be helpful. Other dermatological effects that have been reported rarely include acneiform eruptions and photosensitivity.
- **Gastrointestinal (GI)** adverse effects are common affecting up to 50% of patients, and include nausea, vomiting, abdominal pain and diarrhoea. Rarely, a severe painful and sometimes fatal enteropathy can occur due to the formation of clofazimine crystals in the tissues (sometimes referred to as clofazimine crystal storing histiocytosis). Lymphadenopathy and splenic infarction may occur. Clofazimine should be discontinued immediately if patients develop severe GI symptoms. This may prevent unnecessary surgery.
- Other non-specific adverse effects include headache and fatigue. Blood glucose levels may be elevated.

## + Use in special situations

### Pregnancy (FDA Category C)/Lactation

Clofazimine crosses the placenta and appears in breast milk in relatively large amounts. Breast milk may turn pink and nursing infants of mothers taking clofazimine have developed skin discolouration. The WHO recommends that pregnant or breastfeeding females who have multibacillary leprosy should be treated with standard MDT that includes clofazimine.

### Children

Children with multibacillary leprosy aged 10–14 years are treated with a MDT regimen including 150 mg clofazimine once a month and 50 mg on alternate days of the month. Children under 10 years are treated with a monthly dose of 6 mg/kg/ then the equivalent of 1 mg/kg/d. The dosage interval of clofazimine can be increased to achieve smaller daily doses.

### Elderly

No special precautions are required.

*With acknowledgements to Arjida Woolons and Martin M. Black, authors of this chapter in the previous edition, and Toby Maurer who reviewed this chapter from an international perspective.*

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# Colchicine

Malcolm W. Greaves

## + Classification & mode of action

Colchicine is a pseudoalkaloid obtained from the meadow saffron (autumn crocus *Colchicum autumnale*) and other *Colchicum* spp. that have been used for medicinal purposes since the time of ancient Greece. It occurs as pale to greenish yellow crystals and is irritating to skin. It is water soluble and oxidizes rapidly on light exposure, so must be stored in the dark.

On ingestion, colchicine is rapidly absorbed (peak plasma levels 30–120 min after oral administration) and is mainly metabolized in the liver, although 10–20% is excreted unchanged in the urine.

Colchicine has anti-inflammatory actions, mainly through inhibition of polymorphonuclear mobility, adhesion and chemotaxis. It also possesses antimitotic activity since it prevents aggregation of the microtubular cytoskeleton, thus inhibiting mitosis and causing metaphase arrest. It is immunosuppressive due to reduced expression of cellular adhesion molecules with resultant inhibition of T-cell activation. Cellular secretion of pro-collagen is reduced, and collagenase production is increased. Colchicine also suppresses activation of caspase 1 and release of interleukin (IL)-1 $\beta$  from stimulated macrophages.

## + Indications & dermatological uses

Colchicine is licensed only for use in gout and familial Mediterranean fever. Dermatological uses, mainly supported by uncontrolled studies, include the following:

- Recurrent aphthous stomatitis.
- Behçet's disease.
- Neutrophilic dermatoses including Sweet's disease and pyoderma gangrenosum.
- Dermatitis herpetiformis (in patients intolerant of dapsone), epidermolysis bullosa acquisita and linear IgA disease.
- Leukocytoclastic vasculitis, especially urticarial vasculitis.
- Scleroderma.
- Cutaneous amyloidosis.

Erythema nodosum and genital lesions in women have been shown to respond but there is no clear effect on oral ulceration in Behçet's disease. Except for some forms of mucocutaneous Behçet's disease, where colchicine has been shown to be effective in double blind studies, it is not a first-line agent for any of the above conditions.

### + Formulations/Presentation

Tablets contain 0.5 mg of colchicine. They should be stored in an airtight container and protected from exposure to light.

### + Dosages & suggested regimens

For dermatological conditions the the starting dose is **0.5mg daily**, increasing to **1–1.5 mg** in divided (0.5 mg) doses, as tolerated. The dose tolerated by the patient is usually dependent on gastrointestinal (GI) side-effects.

### Special point

Colchicine has a narrow therapeutic window and is extremely toxic in overdose. Specialist advice should be obtained promptly. There may be a delay of hours to days before toxicity is apparent and as little as 6–7 mg of colchicine has caused death. Acute toxicity manifests as cholera-like symptoms and signs with dehydration, electrolyte disturbance, metabolic acidosis, renal failure and shock. Convulsions, muscle paralysis, neuropathy and respiratory distress are common. Chronic toxicity may cause leukopenia, aplastic anaemia, myopathy and alopecia.

### + Baseline investigations & considerations

- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs.

### + Monitoring

- FBC (CBC) and differential white cell count every month.
- LFTs and renal indices 3-monthly.

### + Contraindications

- Haematological disease.
- Severe renal impairment or haemodialysis (colchicine cannot be removed by dialysis or exchange transfusion).

### + Cautions

- Elderly or debilitated patients may be especially susceptible to cumulative toxicity, leading to GI, renal, hepatic, cardiac or haematological complications.

- Gastrointestinal hepatic or cardiac disease, due to the increased risk of toxicity.
- Renal impairment or concurrent use of nephrotoxic drugs, due to increased toxicity.

Do not use in patients with chronic kidney disease stage 5 (glomerular filtration rate [GFR] <15 mL/min).

### + Important drug interactions

- **Macrolide antibiotics** (erythromycin, clarithromycin and others) increase the risk of colchicine toxicity, due to interactions with the cytochrome P450 (CYP450) 3A4 microsomal enzyme system.
- **Ciclosporin** (cyclosporine) concentrations are increased by colchicine, with an increased risk of nephrotoxicity and neuromuscular adverse effects.
- **Vitamin B12** absorption may be impaired by colchicine resulting in megaloblastic anaemia.
- **Statins and fibrates** may cause acute myopathy when given with colchicine. Patients should be advised to report any muscular pain or weakness.
- Other potential interactions include drugs metabolized by **CYP3A4** including azole antifungals, antiviral drugs and cardiac medication.

### + Adverse effects & their management

Colchicine is usually well-tolerated.

- **Mild Gastrointestinal upset** is common (vomiting, diarrhoea, abdominal pain) and usually responds to dosage adjustment; failing this, the drug should be withdrawn. Colchicine can less commonly cause malabsorption syndrome affecting B12, fat, protein, actively transported sugars and electrolytes. Other GI effects include stomatitis and paralytic ileus.
- **Bone marrow suppression:** agranulocytosis, thrombocytopenia and aplastic anaemia can occur after prolonged treatment. Administration of granulocyte colony stimulating factor (G-CSF) should be considered in such cases.
- **Myopathy and neuropathy:** this occurs especially in patients with renal impairment. The myopathy is proximal, with elevated serum creatinine phosphokinase and the neuropathy is axonal. Myopathy recovers on withdrawal of colchicine, but neurological recovery may be slow.
- **Dermatological:** these include urticaria and rarely Stevens–Johnson syndrome, toxic epidermal necrolysis and alopecia universalis, and very rarely porphyria cutanea tarda.

There have been isolated reports of bladder spasm, renal damage and haematuria and hypothyroidism.

### + Use in special situations

#### Pregnancy (FDA Category C)

Colchicine is teratogenic in animals and there is some evidence of teratogenicity or of fetal chromosomal abnormalities in humans, so it should be avoided in pregnancy. There have been sporadic reports of oligospermia and azoospermia.

#### Lactation

Colchicine can be found in breast milk so it should be avoided during lactation.

#### Children

Safe use of colchicine has been reported in a small number of children. Colchicine has been reported to be useful as an adjuvant treatment with systemic corticosteroids in children with linear IgA disease. It is also an alternative to dapsone in children who are glucose-6-phosphate dehydrogenase (G6PD) deficient.

### + Essential patient information

- Patients should be advised to reduce dosage of colchicine if weakness, anorexia, nausea, vomiting or diarrhoea occurs.
- Patients should also be informed of the dangers of overdosage.
- Colchicine can adversely affect the fetus, so pregnancy should be avoided during treatment.

*With acknowledgements to Ruth Sabroe, author of this chapter in the 1st edition.*

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# Corticosteroids

Clive B. Archer

## + Classification & mode of action

Synthetic corticosteroids (glucocorticoids, glucocorticosteroids, steroids) are analogues of endogenous adrenal steroid hormones and are widely used in dermatology. They have anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictor actions. The effects of steroids are mediated predominantly by binding to intracellular glucocorticoid receptors, which then bind to specific DNA sequences that regulate gene transcription. Corticosteroids also have non-genomic actions such as interactions with cellular membranes and receptors. Corticosteroids thereby reduce inflammation via several molecular mechanisms, suppressing the many inflammatory genes that are activated in chronic inflammatory diseases and repressing the expression of pro-inflammatory proteins.

**Prednisolone** and **methylprednisolone** are the steroids most commonly used in medicine. The relatively high mineralocorticoid activity of cortisone and hydrocortisone with consequent fluid retention makes them unsuitable for long-term therapy.

After absorption corticosteroids bind to the carrier protein, transcortin (cortisol binding globulin) and albumin. Transcortin levels are decreased in liver disease, kidney disease, hypothyroidism and obesity. This may therefore increase the level of free corticosteroid in these conditions. Liver disease also results in decreased albumin levels and potentially increased steroid side-effects. Steroids are metabolized by the liver to water-soluble metabolites that are excreted by the kidneys.

The relative potencies and approximate equivalent doses of steroids compared with hydrocortisone are shown in Table 1.

**Prednisone** is generally used instead of prednisolone in the USA. It is a pro-drug that is converted to prednisolone in the liver. However, there is 20% less on conversion and liver failure may impair conversion further. The onset of action is also slower.

**TABLE 1** Relative potencies and approximate equivalent doses of corticosteroids compared with hydrocortisone (reproduced with the permission of Guy's and St Thomas' NHS Foundation Trust)

Drug	Relative glucocorticoid (anti-inflammatory) potency	Relative mineralocorticoid potency	Equivalent anti-inflammatory dose* (mg)
Hydrocortisone (Cortisol)	1	1	100
Prednisolone	4	0.8	25
Methylprednisolone	5	0.5	20
Triamcinolone	5	0	20
Betamethasone	25	0	4
Dexamethasone	25	0	4

\*applies only to oral or i/v administration

## + Indications & dermatological uses

The following corticosteroids are licensed for systemic use in the suppression of inflammatory and allergic disorders:

- Betamethasone.
- Deflazacort.
- Dexamethasone.
- Methylprednisolone.
- Prednisolone.
- Triamcinolone.

Parenteral hydrocortisone is indicated for the treatment of anaphylactic shock and angioedema.

Corticosteroids have been widely used in dermatology since the 1950s. Some of the diseases for which they are commonly prescribed are as follows:

- Dermatitis: acute contact dermatitis, atopic dermatitis, chronic actinic dermatitis, exfoliative dermatitis due to drugs.
- Connective tissue diseases: lupus erythematosus (all types), dermatomyositis, mixed connective tissue disease, relapsing polychondritis, eosinophilic fasciitis.
- Immunobullous diseases: pemphigus (all types), bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestationis, linear IgA disease, epidermolysis bullosa acquisita.
- Vasculitis: hypersensitivity vasculitis, polyarteritis nodosa, Wegener's granulomatosis.
- Neutrophilic dermatoses: Sweet's syndrome, pyoderma gangrenosum, Behçet's disease.



- Other dermatoses: lichen planus, sarcoidosis, acute severe urticaria, angioedema, Stevens–Johnson syndrome (but not toxic epidermal necrolysis), large haemangiomas.

### + Formulations/Presentation

Includes the following:

- Prednisolone: 1 mg, 2.5 mg, 5 mg and 25 mg tablets; 2.5 mg, 5 mg enteric coated tablets (note decreased gastric absorption); 5 mg scored soluble tablets.
- Betamethasone: 0.5 mg scored tablets; 0.5 mg scored soluble tablets.
- Triamcinolone: aqueous suspension for injection. As acetone 10 mg/mL, 40 mg/mL; as hexacetone 5 mg/mL, 20 mg/mL.
- Deflazacort: 1 mg, 6 mg, 30 mg tablets.
- Dexamethasone: 0.5 mg tablets.
- Methylprednisolone: 2 mg, 4 mg, 16 mg, 100 mg tablets; 40 mg, 125 mg, 500 mg, 1 g and 2 g powder for reconstitution with water (as sodium succinate).
- Hydrocortisone: 100 mg/mL solution for injection (as sodium phosphate); 100 mg powder for reconstitution with water (as sodium succinate).

### + Dosages & suggested regimens

Steroids given for immunosuppression are usually given as a **single daily dose** in the morning to minimize adrenal suppression. Prednisolone has predominant glucocorticoid activity and is used for most purposes. It has the advantage over more potent steroids of allowing fine dose adjustment.

The starting dose of prednisolone varies according to the skin disease, its severity and concurrent disorders such as hepatic impairment. The BNF recommends a daily **starting dose of 10–20 mg**, up to **60 mg in severe disease**. In dermatological practice it may be necessary to use higher doses to gain initial disease control, e.g. **60–100 mg** prednisolone daily in pemphigus.

In children, a typical short course high dose regimen is 1–2 mg/kg/d for 3–5 days. If treatment is required for >7 days, the dose is usually reduced gradually.

A high dose pulsed i/v regimen with **500 mg–1 g methylprednisolone** daily for 3 days may be faster acting and more effective than oral therapy, but these advantages have yet to be fully validated and controlled prospective studies are lacking.

For androgen excess syndromes, a unique regimen is indicated involving night time suppressive therapy with low dose treatment (below physiological levels) to suppress the early morning peak of adrenocorticotrophic hormone (ACTH) that stimulates adrenal androgen production (see Antiandrogens).

The rate of drug withdrawal depends mostly on disease activity. Rapid withdrawal may precipitate disease flares in some disorders. The **maintenance dose** should be kept at the minimum required for the shortest length of time

in order to minimize side-effects. Alternate day dosing may reduce adverse effects by allowing time for the hypothalamic–pituitary–adrenal (HPA) axis to recover.

Soluble formulations of prednisolone or betamethasone may be of advantage in treating severe oral inflammatory disease (lichen planus, pemphigus) as they can be held in the mouth before swallowing to obtain a local anti-inflammatory effect.

### Special point: Adrenal suppression

The approximate physiological daily secretion of cortisol by the adrenal cortex is 20 mg (equivalent to about 5 mg prednisolone daily). Short courses of high dose prednisolone (2 weeks or less) do not require tapering as, although suppressed, the HPA axis recovers promptly.

In patients on long-term prednisolone therapy, once a daily dose of 7.5 mg has been reached, dose reduction should be slower to allow the HPA axis to recover, e.g. 1–2.5 mg weekly.

Patients taking oral corticosteroids must continue systemic therapy during periods of stress such as infection, trauma or surgery, either orally or by injection. Extra steroids are needed for up to 3 days during periods of acute illness to prevent an **acute adrenal crisis**. Patients who have been taking 5 mg or more of prednisolone for more than 4 weeks are at risk of an adrenal crisis during periods of high stress. Patients who have completed a short course of treatment (3 weeks or less) within the previous week also require corticosteroid replacement during acute stress.

### + Baseline investigations & considerations

- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs.
- Urinalysis for glucose and/or blood glucose – if at risk of diabetes.
- Fasting lipid profile – if at risk of hyperlipidaemia.
- Dual energy X-ray absorptiometry (DEXA) scan of lumbar spine and hips – if long-term treatment is required.
- BP and weight.
- Growth chart for height and weight for children.

### + Monitoring

After 1 month then every 2–3 months:

- BP.
- Urinalysis for glucose.
- Urea and electrolytes.
- DEXA scan after 6 months, 12 months then yearly.
- Consider ophthalmological review for cataracts and raised intraocular pressure.

### + Contraindications

Systemic infection including latent tuberculosis (unless specific antimicrobial therapy is given).

### + Cautions

Corticosteroids should be used with caution in patients with the following pre-existing disease which might be exacerbated:

- Diabetes mellitus.
- Hypertension or congestive heart failure.
- Glaucoma.
- Osteoporosis.
- Active peptic ulcer disease.
- Liver failure.
- Severe affective disorders/history of corticosteroid induced psychosis.
- Previous steroid myopathy.
- Kidney failure.
- Recent myocardial infarction (risk of cardiac rupture).

### + Important drug interactions

- **Antacids** can reduce the absorption of prednisolone if given in high doses.
- **Anticonvulsants**: increased clearance of corticosteroids occurs with carbamazepine, phenytoin and phenobarbitone.
- **Antibiotics**: increased clearance of corticosteroids occurs with rifampicin and isoniazid.
- **Ciclosporin** (cyclosporine) increases the plasma concentration of prednisolone.
- **Coumarin** anticoagulant efficacy may be enhanced by high dose corticosteroids, so closer monitoring is required to avoid bleeding.
- The therapeutic effects of **hypoglycaemic agents** (including insulin), **antihypertensive** therapy and **diuretics** are antagonized by corticosteroids.
- Corticosteroids may increase the risk of **benign intracranial hypertension** if given with **retinoids** and **tetracyclines**.

### + Adverse effects & their management

- **Fluid and electrolyte imbalance** (mineralocorticoid) effects are slight with prednisolone, methylprednisolone and triamcinolone, and negligible with betamethasone and dexamethasone. They include hypertension, sodium and water retention and potassium loss. The risk of hypokalaemia is increased when given with acetazolamide, loop diuretics and thiazide diuretics.

- **Sudden death** and life-threatening ventricular arrhythmias have been associated with pulsed methylprednisolone therapy, possibly as a consequence of rapid electrolyte shifts. All patients receiving such therapy should preferably have cardiac monitoring and daily monitoring of electrolytes.
- **Glucocorticoid effects** are the main problem associated with long-term corticosteroid therapy. They include osteoporosis, diabetes mellitus and Cushing's syndrome.
- **Corticosteroid myopathy** typically affects the proximal muscles of the pelvic then shoulder girdle. The patient should be asked if they have difficulty rising from chairs and climbing stairs. Exercising and slow tapering of the corticosteroid dose may help.
- **Peptic ulcer disease:** it is uncertain if corticosteroids increase the risk of peptic ulcer disease, and if so, the effect is modest. There is clearer evidence that they increase the risk of peptic ulceration when given with non-steroidal anti-inflammatory drugs (NSAIDs). Treatment with proton pump inhibitor or an H<sub>2</sub>-antagonist seems appropriate in patients with a history of peptic ulcer disease or those who develop symptoms of gastritis. The potential advantage of soluble or enteric coated preparations (with consequent reduced gastric absorption) versus plain tablets to reduce the risk of peptic ulceration remains uncertain. As corticosteroid therapy may mask the signs of a perforated peptic ulcer or other visceral perforation, patients taking these drugs who develop significant abdominal pain warrant urgent specialist attention.
- **Neuropsychiatric adverse effects** include euphoria, irritability, anxiety, sleep disturbance, cognitive impairment, depression, labile mood and suicidal thoughts. Psychotic symptoms include mania, delusions and aggravation of schizophrenia. Particular care is required when systemic corticosteroids are given to patient with existing or a previous history of severe affective disorders.
- **Cardiovascular disease** risk is increased in those on long-term corticosteroids. Thrombophlebitis may also occur.
- **Cutaneous adverse effects** include atrophy, telangiectasia and striae. Truncal acne may occur, but usually clears on corticosteroid withdrawal. Corticosteroids impair fibroblast production of type 1 collagen and delay wound healing.
- **Ocular adverse effects** include corneal thinning, glaucoma and posterior subcapsular cataracts. Children are at increased risk of cataracts and regular slit lamp examinations should be considered in those on long-term treatment.
- **Leukocytosis** is a common finding due to reduced neutrophil margination.
- **Infection:** susceptibility is increased and infections may be more severe. Clinical signs and symptoms of opportunistic infections and tuberculosis may be suppressed. Chickenpox is of particular concern since this usually minor illness may be fatal in immunosuppressed patients. Patients taking corticosteroids without a definite history of chickenpox should avoid close personal contact with chickenpox or herpes zoster and if exposed they

should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobulin (VZIG) is required in non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should ideally be given within 3 days of exposure. If a diagnosis of chickenpox is confirmed, the illness warrants special care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased. Similarly, patients should be advised to avoid contact with measles, and if exposed without prior immunity, to seek prompt medical attention for prophylaxis with normal immunoglobulin.

- **Hypersensitivity reactions** including anaphylaxis may occur rarely.

### Special point: Osteoporosis

Bone loss is one of the most important adverse effects of corticosteroid therapy even in low doses. Mechanisms include glucocorticoid inhibition of osteoblast function and induction of osteoclast and osteocyte apoptosis. Bones with a high trabecular content like vertebrae are most vulnerable. Asymptomatic fractures may occur in up to 50% of patients receiving long-term glucocorticoid therapy, and minimal trauma fractures occur at higher bone mineral density (BMD) than with other primary or secondary causes of osteoporosis. The greatest rate of bone loss occurs during the first 6–12 months of therapy, so early preventative measures are important. A DEXA scan is the investigation of choice to assess BMD.

A computerised tool, FRAX®, developed by The World Health Organization (WHO) has recently become available online ([www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)). It provides an assessment of fracture risk in those aged 40 and over, taking into account different osteoporosis risk fractures, including long-term (> 3 months) corticosteroid therapy and BMD, if available. Clinical risk factors for the assessment of fracture probability are shown in Table 2. The World Health Organization (WHO) classification of bone densitometry results is based on comparison with the mean value for adults of the same age and sex:

- A normal value for BMD is within 1 standard deviation of the score (T score 0 to –1).
- Osteopenia is defined as BMD value 1–2.5 standard deviations below the mean (T score –1 to –2.5).
- Osteoporosis is diagnosed when the T score is –2.5 or lower.

Intervention to prevent osteoporosis should start as soon as corticosteroids are prescribed. Lifestyle measures, such as exercise, stopping smoking and restricting alcohol consumption, should be recommended for all patients.

**Bisphosphonates** are the agents of choice for treatment and prevention of osteoporosis. They slow the rate of bone turnover. Alendronic acid or risedronate sodium (given daily or once a week) are first-choice drugs and disodium etidronate is an alternative (given in 2-week cycles every 13 weeks).

**Calcium** and **vitamin D supplementation** should be considered, especially in patients whose dietary intake is unreliable. The recommended dosages are 1,000–1,500 mg calcium and 800 IU vitamin D daily. Milk, hard cheese and

**TABLE 2** Clinical risk factors used for the assessment of fracture probability.

- Age
- Sex
- Low body mass index  $\leq 19\text{kg/m}^2$
- Previous fragility fracture, particularly of the hip, wrist and spine including morphometric vertebral fracture
- Parental history of hip fracture
- Current smoking
- Alcohol intake of three or more units daily

**Secondary causes of osteoporosis including**

- Rheumatoid arthritis
- Untreated hypogonadism in men and women
- Prolonged immobility
- Organ transplantation
- Type 1 diabetes
- Hyperthyroidism
- Gastrointestinal disease
- Chronic liver disease
- Chronic obstructive pulmonary disease

yoghurt are good sources of calcium. Vitamin D-rich foods include salmon, mackerel and tuna. Ultraviolet exposure is another consideration, as individuals who avoid the sun or expose little skin are at increased risk of vitamin D deficiency.

Calcitonin also inhibits osteoclastic bone reabsorption and may be a more suitable option in children and young adults.

Gonadal hormone replacement therapy with oestrogen supplements for post-menopausal females reduces the risk of fractures. The oestrogen receptor modulator **raloxifene**, which has potent agonist effects on bone and antioestrogen effects on the uterus and breast, may be a good alternative.

**Testosterone** replacement should be considered in males with low testosterone levels.

- **Avascular necrosis** (osteonecrosis) of bone may occur with high dose or prolonged corticosteroid therapy. The femoral head is most commonly affected and disease may occur bilaterally. Other sites include the femoral condyles and head of humerus. Symptoms of pain or reduced movement at one or more joints should prompt further investigation. Magnetic resonance imaging (MRI) is more sensitive for diagnosing early avascular necrosis than radiography. Specialist referral is warranted in suspected cases.

### **+ Use in special situations**

#### **Pregnancy & pre-conception (FDA Category C)**

All corticosteroids cross the placenta to a variable degree. Betamethasone and dexamethasone cross the placenta readily, while 88% of prednisolone is inactivated. In humans there is no convincing evidence that systemic corticosteroids cause an increase in fetal abnormalities such as cleft lip. The main risk when they are administered for prolonged periods or repeatedly during pregnancy is intrauterine growth retardation. There is also a theoretical risk of neonatal adrenal suppression, but this usually resolves spontaneously after birth.

Menstrual irregularities may follow depot i/m corticosteroid therapy, but are uncommon with oral therapy. Sperm counts may be decreased but this does not usually impair fertility.

#### **Lactation**

Corticosteroids are excreted in small amounts in breast milk. However, doses of up to 40 mg daily of prednisolone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this should be monitored for signs of adrenal suppression.

#### **Children**

Long-term corticosteroids cause growth suppression in children. Full catch up growth may not be attained after medication is discontinued. Normal growth is achieved on 5 mg prednisolone per day for a child with 1 m<sup>2</sup> surface area. Alternate day dosing may reduce growth suppression but can have reduced therapeutic effectiveness against the disease being treated.

### **+ Essential patient information**

The Medicines Control Agency has documented the recommended advice that should be given to patients who are prescribed long-term systemic corticosteroids (see below). It is important to tell patients prescribed systemic corticosteroids (especially for >7 days) about their possible adverse effects and of the actions they may need to take. It is also important to inform patients about the benefits of treatment. Specifically, they should be advised:

- Not to stop taking corticosteroids suddenly.
- To see a doctor if they become unwell.
- Of the increased susceptibility to infections, especially chickenpox (see above).
- Of the serious side-effects that may occur.
- To read and keep the patient information leaflet.
- Always to carry the Steroid Treatment Card and to show it to any health professional involved in their treatment. Patients may also be advised to wear a Medical Alert bracelet.

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*With acknowledgements to Fiona Keane, the author of this chapter in the 1st edition.*

### + Further reading

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# Cyclophosphamide

Olga Golberg & Karen Harman

## + Classification & mode of action

Cyclophosphamide is an antineoplastic drug from the nitrogen mustard group of alkylating agents, which also include melphalan and chlorambucil. The primary mechanism of action is DNA cross-linking, by irreversibly binding an alkyl group to the guanine base of DNA. This leads to the inhibition of DNA replication and cell division. Cyclophosphamide causes immunosuppression by affecting T-cell mediated and humoral immunity, mainly proliferating B-lymphocytes. It is well absorbed after oral administration, with a bioavailability of greater than 75%. Cyclophosphamide is converted in the liver to active metabolites, such as phosphoramidate mustard and toxic compounds by specific cytochrome P450 (CYP450) isoenzymes. The half-life of the drug is 3–12 hours. Its metabolites are excreted in the urine and have an irritant effect on the bladder mucosa.

## + Indications & dermatological uses

The main use of cyclophosphamide is in combination with other agents in the treatment of a wide range of lymphomas, leukaemias and solid tumours. It is also used as an immunosuppressant in severe, refractory autoimmune disorders. The only approved dermatological indication is in advanced mycosis fungoides; all the other dermatological uses of cyclophosphamide are unlicensed. The main uses in dermatology include:

- Immunobullous diseases: pemphigus (vulgaris, foliaceus), pemphigoid (bullous, cicatricial).
- Vasculitides: refractory cutaneous vasculitis, polyarteritis nodosa, antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (e.g. Wegener's granulomatosis), cryoglobulinaemic vasculitis, autoimmune connective tissue disease associated vasculitis.
- Connective tissue diseases: systemic and cutaneous lupus erythematosus, dermatomyositis, Behçet's disease.
- Pyoderma gangrenosum.

## + Formulations/Presentation

- Tablets contain 50 mg cyclophosphamide.
- Vials containing 500 mg of cyclophosphamide powder to reconstitute for i/v injection and infusion. This may be used to prepare an elixir for oral use.

## + Dosages & suggested regimens

High doses and complex regimens are used in the treatment of malignant diseases, before bone marrow transplantation and for severe autoimmune disease. Dermatological diseases are usually managed with lower doses of **50–200 mg/d** and seldom require more than **2.5 mg/kg/d**. Cyclophosphamide is commonly used in conjunction with systemic corticosteroids. Regimens vary from daily oral administration to fortnightly or monthly pulses, or a combination of these. Studies comparing pulsed i/v and daily oral cyclophosphamide therapies in vasculitis suggest equal efficacy but a lower cumulative dosage and rate of complications with pulsed regimens. However, the risk of relapse may be higher. Large comparative trials of differing doses and regimens are lacking for dermatological conditions.

A well-established **pulse and oral regimen with corticosteroids** reported by Parischa and co-workers for the treatment of pemphigus is as follows:

- Days 1–3: 100 mg dexamethasone in 500 mL of 5% glucose as an i/v infusion over 2 hours.
- Day 2: 500 mg cyclophosphamide added to the dexamethasone i/v infusion (this constitutes one DCP [dexamethasone–cyclophosphamide pulse]).
- Days 4–28: oral cyclophosphamide 50 mg daily with conventional daily doses of oral corticosteroids.

The cycle is repeated every 28 days until clinical remission is achieved and oral steroids withdrawn (phase I: typically 3–4 months). DCPs continue in 28-day cycles with 50 mg oral cyclophosphamide inbetween the pulses for a further 9 months (phase II), then oral cyclophosphamide 50 mg daily continued for another 9 months (phase III). Treatment is then withdrawn (phase IV) and patients followed-up for 10 years.

This protocol has been reported to induce long-term remission and possible cure of pemphigus, indicating a disease modifying effect. It has also been used for other dermatological diseases. Modifications to this regimen include using i/v methylprednisolone (250–1000 mg on 3–5 days) instead of dexamethasone. Another approach is to combine conventional daily oral corticosteroids with monthly i/v cyclophosphamide pulses (15 mg/kg).

To induce remission in ANCA associated systemic vasculitis, cyclophosphamide is often used as a first-line drug as follows:

- Oral cyclophosphamide 2 mg/kg/d (up to 200 mg/d) for 3 months then continued or reduced to 1.5 mg/kg/d if remission achieved.

Or

- Cyclophosphamide i/v 15 mg/kg (max 1500 mg) given in 500 mL of 0.9% saline or 5% dextrose over 1 hour. Requires pre-hydration with 1 L normal saline and oral intake of 3 L/d for 3 days. The first 3 pulses are given 2 weekly, thereafter at 3-week intervals.

In this context, cyclophosphamide is discontinued after 3–6 months, and alternative maintenance therapy established with azathioprine or methotrexate

due to the risks of bladder and gonadal toxicity with prolonged therapy. A reduced dose should be used in elderly patients and renal impairment (see below).

Cyclophosphamide should be given early in the day and a high fluid intake maintained throughout the day to encourage frequent bladder voiding.

**Special point**

Several rheumatological guidelines advise dose reduction in the elderly or those with impaired renal function to reduce the risk of toxicity. Dose reductions for continuous low dose oral cyclophosphamide:

- Age >60 years: reduce the dose by 25%.
- Age >75 years; reduce the dose by 50%.

Dose reductions for pulsed cyclophosphamide are shown in Table 1.

**TABLE 1** Dose reductions for pulsed cyclophosphamide

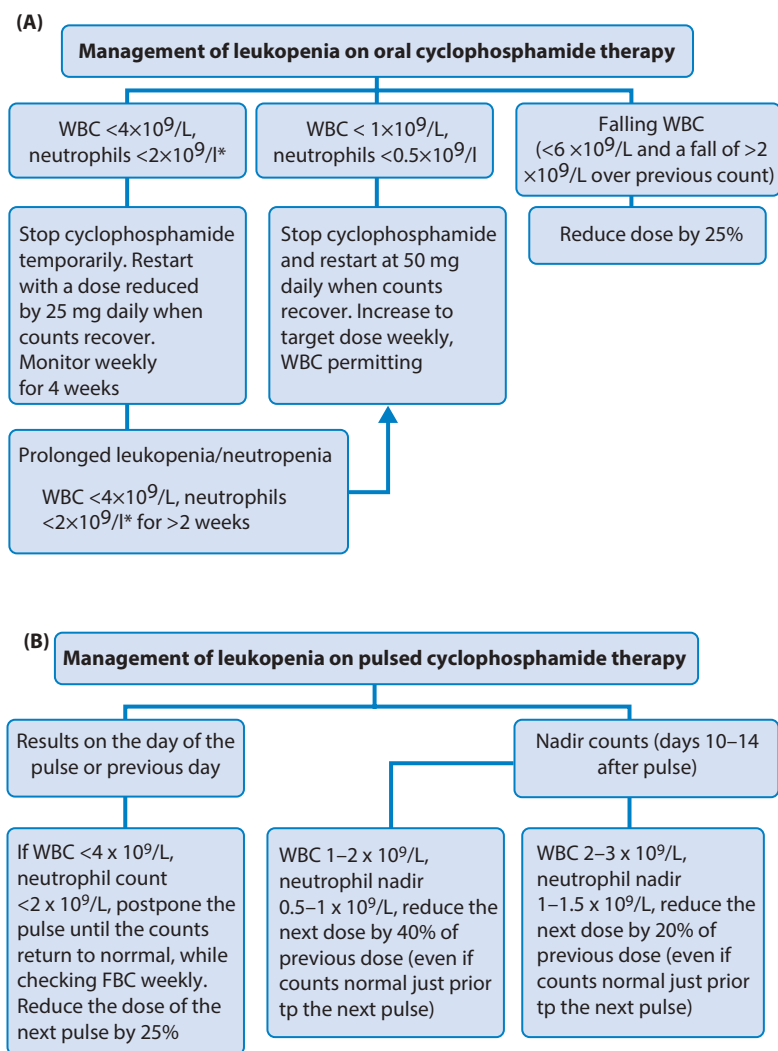
Age (years)	Creatinine 150–300 µmol/L	Creatinine 300–500 µmol/L
<60	15 mg/kg/pulse	12.5 mg/kg/pulse
60–70	12.5 mg/kg/pulse	10 mg/kg/pulse
>70	10 mg/kg/pulse	7.5 mg/kg/pulse

**+ Contraindications**

- Previous urinary malignancy (urinary tract transitional cell carcinoma).
- Haemorrhagic cystitis.
- Bone marrow depression/severe leukopenia (see Figure 1A and B).
- Pregnancy and lactation.
- Hypersensitivity to cyclophosphamide.
- Serious underlying infection.

**+ Cautions**

- Previous or concurrent mediastinal irradiation – risk of cardiotoxicity.
- Hepatic impairment – reduce dose.
- Hepatitis B and C virus.
- Previous tuberculosis (TB) or risk of TB.
- Renal impairment – reduce dose if creatinine >120 µmol/L (see above).
- Elderly – reduce dose (see above).



**FIGURE 1A,B** Management of leukopenia on (A) oral and (B) pulsed cyclophosphamide therapy (data from Lapraik *et al.* 2007). \*The lower value of the normal neutrophil range may vary from centre to centre and should be checked against the local laboratory reference range. WBC: white blood cell count.

## **+ Baseline investigations & considerations**

- FBC (CBC) and differential white blood cell count to ensure normal neutrophil count.
- LFTs and renal function.
- Urinalysis.
- Pregnancy test in females of childbearing age.
- Hepatitis B (HBV) and C (HCV) serology: HBV and HCV carriers are at risk of a disease flare on immunosuppressant treatment. Non-immune individuals should receive immunization against HBV. All patients seropositive for HBV and HCV should be discussed with hepatology or infectious disease specialists, as prophylactic antiviral treatment may be required.
- Varicella zoster (VZV) serology (if no history of chickenpox).
- HIV serology.
- TB risk should be assessed in all patients by clinical examination, history of previous infection, chest radiograph (CXR) and, if appropriate, a tuberculin test or IGRA as for patients being screened for antitumour necrosis factor (TNF) therapy (see TNF Antagonists).
- Influenza and pneumococcal vaccinations are recommended and should be administered at least 2 weeks before commencing cyclophosphamide. Influenza vaccine should be given every year.
- Contraception: should be established in males and females prior to therapy and continued for at least 3 months after treatment has ceased.
- Cervical screening should be up-to-date and a gynaecological review undertaken in females with a history of cervical intraepithelial neoplasia (CIN).

## **+ Monitoring**

### Oral cyclophosphamide:

- FBC (CBC) weekly for the first month, 2 weekly for the next 2 months, then monthly; consider decrease to every 3 months if stable after 3–6 months.
- Renal function, LFTs monthly for 3–6 months, then every 3 months if stable.
- Urinalysis monthly; after 3–6 months, every 3 months if stable.
- Urine cytology if haematuria or after cumulative dose of 50 g.

### Pulsed cyclophosphamide:

- Check FBC and renal function prior to the first pulse of each cycle (on same or preceding day); adjust dose if leukopenia/neutropenia (see Adverse effects & their management and Figure 1).
- Nadir FBC should be checked between days 10–14 after pulsing (the nadir in WBC usually occurs after 8–14 days with recovery after 18–25 days).
- If dose of cyclophosphamide or interval between pulses changes, nadir FBC should be also checked (day 10).
- Renal function should be measured daily prior to infusions.
- Urinalysis monthly.

Lifelong urinalysis every 6 months has been recommended following prolonged treatment due to the risk of bladder cancer.

### + Important drug interactions

- **Diabetes therapy:** cyclophosphamide may potentiate the hypoglycaemic effects of sulphonylurea drugs and may alter glycaemic control.
- **Allopurinol** potentiates the bone marrow toxicity of cyclophosphamide.
- **Barbiturates** and **clozapine** can increase the risk of agranulocytosis.
- **Digoxin** absorption may be reduced by cyclophosphamide.
- **Itraconazole** and **fluconazole** may increase the risk of adverse effects with cyclophosphamide.
- **General anaesthesia** – alert anaesthetist if cyclophosphamide has been used within 10 days (as it enhances effects of suxamethonium).
- **Live vaccinations** are contraindicated during and for 3 months after cyclophosphamide therapy.

### + Adverse effects & their management

Alkylating agents are potent immunosuppressives. Their use is reserved for severe disease because of concerns about serious side-effects.

- **Haematological: leukopenia** is dose related and can be used as a dosage guide during treatment (Figure 1). Following a single dose, spontaneous recovery usually occurs within 21 days. Anaemia and thrombocytopenia may occur.
- **Bladder toxicity** and **haemorrhagic cystitis** have been attributed to a toxic metabolite, acrolein, and appear to be related to the cumulative dose of cyclophosphamide. Reactivation of a human BK polyoma virus may also play a role. Haemorrhagic cystitis is associated with an increased risk of bladder cancer (see below). Urine microscopy should be performed regularly to detect early problems. Microscopic non-glomerular haematuria is a significant risk factor for the development of bladder cancer. If five or more red blood cells/high power field appear in the urine, cyclophosphamide should be discontinued. **Haematuria** often resolves after a few days but if it persists or is macroscopic, urology referral is indicated. Vigorous hydration before and throughout therapy reduces the risk of haemorrhagic cystitis – the aim is for a minimal urine output of 100 mL/h (2–3 L/d). Long-term sequelae of this cystitis are bladder fibrosis and contracture. Mesna protects the urinary epithelium by reacting with the toxic metabolite acrolein. It should be considered in patients treated with i/v cyclophosphamide and is used routinely in those who receive high dose treatment or have had previous urothelial toxicity. Mesna can be given orally or i/v. When used with pulsed i/v cyclophosphamide, the oral dose of mesna should be 40% of the cyclophosphamide dosage in mg, given 2 hours prior to the pulse and repeated 2 and 6 hours after the pulse of cyclophosphamide. The dose of

i/v mesna should be 20% of the cyclophosphamide dosage in mg and given with the pulse and then at 2 and 6 hours.

- **Malignancy:** cyclophosphamide is specifically associated with an increased risk of **bladder cancer**. Studies suggest the risk is dose related, especially with cumulative doses exceeding 36 g. The risk of acute leukaemia, non-melanoma skin cancer and other solid tumours may also be increased. These can develop several years after treatment is discontinued.
- **Infection:** risk is related to the severity and duration of drug induced leukopenia. A WBC nadir  $\leq 3 \times 10^9/L$  has been associated with severe and fatal infections in patients on cyclophosphamide therapy. Opportunistic infections such as *Pneumocystis jiroveci* (*carinii*) infection may occur and prophylactic antibiotic therapy may be indicated. The risk of infection is greater in the elderly and those receiving simultaneous treatment with high dose steroids.
- **Chickenpox or shingles** contact in non-immune patients may lead to **severe infection**, and VZV immunoglobulin should be considered.
- **Gastrointestinal:** nausea, vomiting and anorexia are common and dose related complications of cyclophosphamide therapy. They can be managed with dose reduction and effective antiemetic medications, e.g. i/v ondansetron before pulse therapy. Abdominal pain, diarrhoea and oral mucositis may occur. Haemorrhagic colitis and hepatotoxicity are rare.
- **Dermatological:** alopecia (anagen effluvium) occurs in 5–30% of patients and is dose dependent. Hair regrowth occurs in most patients even with continued treatment. Diffuse hyperpigmentation, especially of palmoplantar skin and nail pigmentation may occur. Severe cutaneous adverse drug reactions (including Stevens–Johnson syndrome/toxic epidermal necrolysis) have been reported.
- **Cardiac and pulmonary:** pulmonary fibrosis, interstitial pneumonitis and cardiomyopathy are rare and associated with high doses of cyclophosphamide used in the treatment of malignancy. The drug should be discontinued if cardiac or pulmonary toxicity is suspected.
- **Hypersensitivity** to cyclophosphamide may rarely occur, including anaphylaxis. Possible cross-reactivity with other alkylating agents has been reported.
- **Infertility:** cyclophosphamide interferes with spermatogenesis and oogenesis. Amenorrhoea, azoospermia and irreversible sterility may occur with prolonged therapy. Risk factors for cyclophosphamide induced infertility include: age >30 years, long-term therapy, cumulative dose >10 g. Expert advice should be sought for patients of reproductive age to discuss the option of sperm or oocyte banking.
- **Minor adverse effects** have been observed with pulsed i/v cyclophosphamide and some are thought to be specific to this method of administration. These include facial flushing, palpitations and hiccups occurred during i/v infusion, whereas malaise, headache and taste alteration developed soon after DCP.

### + Use in special situations

#### Pregnancy (FDA Category D)

Cyclophosphamide is a known teratogen and should not be used in pregnancy except in life-threatening situations. Pre-natal exposure in the first trimester has been associated with absent digits, abnormal facies, cleft palate and hernias. Pregnancy should be avoided for at least 3 months after cyclophosphamide treatment in females and males.

#### Lactation

Cyclophosphamide is contraindicated in lactation as large quantities of active metabolites are excreted in milk. Breastfeeding should not commence for 36 hours after stopping treatment.

#### Children

Cyclophosphamide is not recommended for treatment of skin disease in children as it may cause irreversible loss of fertility.

### + Essential patient information

Patients should be informed of the reasons for treatment, possible side-effects and the need for regular blood monitoring. They should be specifically advised:

- To take cyclophosphamide in the morning and ensure good hydration (2–3 L of fluid a day) and frequent bladder voiding.
- To seek immediate medical help if they develop symptoms such as sore throat, fever, easy bruising/bleeding, pallor, shortness of breath and cough.
- To use effective contraception during and for at least 3 months after treatment.
- About the risk of infertility.
- To report any contact with VZV if non-immune.
- To ensure sun protection.

*With acknowledgements to Harvey Smith and Martin Black, authors of this chapter in the 1st edition, and Robert A. Brodsky who reviewed it from an international perspective.*

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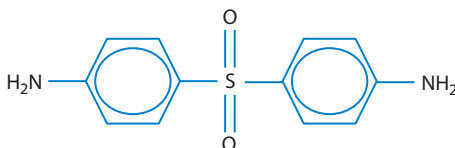
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# Dapsone

Catherine Borysiewicz & Jonathan Leonard

## + Classification & mode of action

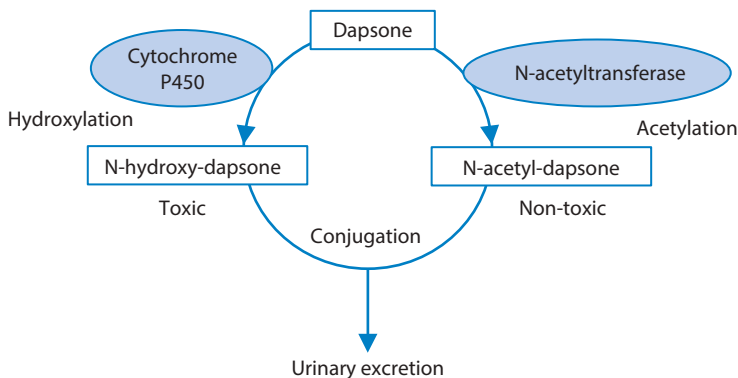
Dapsone (4',4'-diaminodiphenyl sulphone) was first introduced in the 1940s for treatment of leprosy and remains an important therapy against *Mycobacterium leprae*. It is structurally related to the sulfonamides (Figure 1) and shares their antimicrobial action, i.e. impairing microbial synthesis of folate from para-aminobenzoic acid (PABA) by competitive inhibition of the enzyme dihydropteroate synthetase.



**FIGURE 1** Chemical structure of dapsone.

Dapsone also has anti-inflammatory actions that account for much of its use in dermatological diseases. The mechanism of this action is unclear but thought to be due to inhibition of neutrophil function (chemotaxis and myeloperoxidase activity) and release of inflammatory mediators. It may also have a local anti-inflammatory effect. Dapsone inhibits the signal transduction cascade common to chemotactic stimuli, suppressing neutrophil recruitment and local production of toxic products.

Dapsone is readily absorbed with good bioavailability (>85%) and a relatively long half-life (14–18 hours) allows once daily dosing. It is distributed across all body organs and crosses the blood–brain barrier and placenta. Dapsone is metabolized in the liver through a combination of hydroxylation (cytochrome P450 [CYP450] dependent) into hydroxylamines which are toxic and implicated in the haematological side-effects of the drug, and acetylation (N-acetyl transferase dependent) into mono-acetyl dapsone which is non-toxic. These products are then conjugated and excreted through the urine (Figure 2).



**FIGURE 2** Metabolism of dapsone.

### + Indications & dermatological uses

Dapsone is licensed for the treatment of leprosy and dermatitis herpetiformis and *Pneumocystis jiroveci* (*carinii*) pneumonia prophylaxis in immunodeficient subjects (especially acquired immunodeficiency syndrome [AIDS]). It is also of benefit in a number of dermatoses characterized by neutrophilic infiltrates:

- Immunobullous dermatoses – linear IgA disease, chronic bullous dermatosis of childhood, bullous pemphigoid and cicatricial pemphigoid.
- Neutrophilic dermatoses – erythema elevatum diutinum, Sweet's syndrome, subcorneal pustular dermatosis, leukocytoclastic vasculitis, pyoderma gangrenosum and delayed pressure urticaria.
- Other inflammatory dermatoses including acne and rosacea, Behçet's disease, relapsing polychondritis and granuloma faciale.
- Severe, necrotic brown recluse spider bites.

### + Formulations/Presentation

Dapsone is available as white scored 50 mg and 100 mg tablets.

### + Dosages & suggested regimens

The World Health Organization (WHO) recommended dose for leprosy is 1–2 mg/kg/d.

- Multibacillary leprosy: regimens combining 3 drugs are recommended to avoid development of resistant strains, using dapsone with rifampicin and clofazimine for at least 2 years.
- Paucibacillary leprosy: combined with rifampicin for 6 months.

For most dermatological conditions an **initial dose of 50 mg daily** should be given for the first week to ensure there is no immediate adverse effect and then adjusted according to the clinical response. The minimum drug requirement for the majority of conditions lies between **1–2 mg/kg/d**. In practice the dose is usually increased by weekly 50 mg increments to achieve control of the symptoms. The clinical response in dermatitis herpetiformis (DH) is prompt and skin lesions start to resolve within 48 hours. However, some patients with DH are resistant to dapsone and require higher doses. The **maximum dosage** should not exceed **300 mg/d**. If side-effects are not tolerated, then additional use of sulfamethoxypyridazine or sulfapyridine should be considered to limit the dose of dapsone and reduce dose related adverse effects.

The rash of DH is gluten dependent and the mainstay of therapy in the long term is a strict gluten free diet (GFD). Patients who adhere to a strict GFD are slowly able to reduce their minimum dapsone requirement and eventually wean off dapsone altogether though it takes 2 years on average for the rash to be controlled by GFD alone. Dapsone has no effect on the associated gluten sensitive enteropathy.

### + Baseline investigations & considerations

- FBC (CBC) and reticulocyte count.
- Urea, electrolytes and creatinine.
- LFTs.
- Glucose-6-phosphate dehydrogenase level (G6PD) in patients from ethnic groups at risk of deficiency (see below).
- Assess patients for any medical condition (e.g. cardiorespiratory) that might be exacerbated by a minor reduction in haemoglobin level.
- Urinalysis.

### + Monitoring

- FBC, reticulocytes, urea and electrolytes, LFTs weekly for first month, then monthly for 2 months then every 3–6 months if no increase in dosage.
- Urinalysis every 3 months.
- Measure methaemoglobin levels if patients are symptomatic.
- Urgent FBC if patients develop symptoms suggesting agranulocytosis.

### Special point

G6PD deficiency is the most common disease producing enzyme deficiency worldwide. It is an X-linked inherited disorder and most commonly affects persons of African, Asian, Mediterranean or Middle-Eastern descent. Prevalence of the deficiency is correlated with the geographic distribution of malaria, and it is thought that the defect may confer some protection against this infection. Sporadic gene mutations may affect all populations, and different mutations result in different levels of enzyme deficiency, and disease manifestations. Some people with G6PD deficiency are asymptomatic.

G6PD catalyses the reduction of NADP to NADPH via the pentose phosphate pathway, which is the only method of NADPH generation in erythrocytes (Figure 3). They are therefore more susceptible to oxidative stress in the context of infection and certain drugs and dietary triggers. Deficiency of G6PD greatly increases this vulnerability and can lead to neonatal hyperbilirubinaemia and acute or chronic haemolysis.

### + Contraindications

- Dapsone hypersensitivity.
- Previous adverse reaction to sulfonamides.
- Acute porphyria.
- Severe ischaemic heart disease or pulmonary disease.
- Severe anaemia – treat before starting dapsone.
- Severe G6PD deficiency.

### + Cautions

- Cardiac, peripheral vascular and pulmonary disease – particularly in the elderly who may not tolerate minor reductions in haemoglobin concentration.
- Other conditions predisposing to haemolysis.
- Dapsone can artifactually lower glycosylated haemoglobin levels in patients with Type II diabetes and impair disease monitoring.
- Dapsone can be used with great caution at low dose and with close monitoring in those with mild degrees of G6PD deficiency.

### + Important drug interactions

- **Probenecid:** reduces urinary excretion of dapsone increasing plasma concentration.
- **Rifampicin:** induces dapsone metabolism and enhances urinary excretion.
- **Cimetidine:** inhibits formation of toxic hydroxylamine metabolites and increases the therapeutic/toxic ratio.
- **Trimethoprim:** decreases renal clearance of dapsone and increases the risk of toxicity.

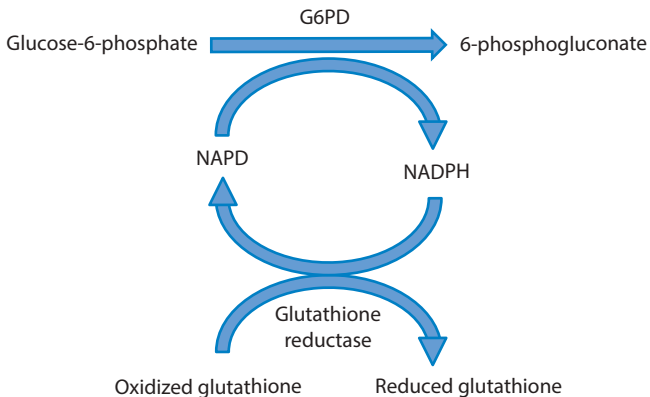
### + Adverse effects & their management

- **Haemolysis and haemolytic anaemia** are dose related and due to reduced erythrocyte survival. Mild haemolysis with a drop in haemoglobin of 1–2 g/dL (10–20 g/L) occurs in most patients at a standard therapeutic dose. Hydroxylated metabolites of dapsone cause oxidation of glutathione, which

in its reduced state plays an important role in maintaining erythrocyte cell membrane integrity. Underlying G6PD deficiency impairs the ability to maintain adequate reserves of reduced glutathione and therefore predisposes individuals to severe haemolysis (see above).

- **Methaemoglobinaemia** is caused by the reaction of hydroxylated metabolites of dapsone with oxyhaemoglobin (containing  $\text{Fe}^{2+}$ ) in the presence of oxygen, leading to formation of a ferric compound ( $\text{Fe}^{3+}$ ) that has reduced capacity for oxygen transport. Raised levels of methaemoglobin can lead to symptoms of headache, shortness of breath and lethargy and a bluish discolouration to lips and fingertips. Methaemoglobin normally undergoes reduction by a NADPH dependent enzyme methaemoglobin reductase and there is an adaptive increase with time. Patients with a deficiency of the enzyme are more susceptible.

Methaemoglobinaemia does not need treatment unless patients are symptomatic – if the level is  $>20\%$  then dapsone should be discontinued; at a level  $>30\%$  additional measures can be taken. Cimetidine can reduce methaemoglobin levels by inhibition of CYP450, which reduces synthesis of the toxic hydroxylated metabolites (Figure 2). It can be prescribed at a dose of 400 mg tds for mild methaemoglobinaemia. More severe cases may require treatment with oxygen and i/v methylene blue 1% solution to restore the iron in haemoglobin to its reduced oxygen carrying state.



**FIGURE 3** Glutathione maintenance in erythrocytes.

- **Agranulocytosis** is a rare side-effect occurring in about 1:10,000 prescriptions and due to a direct toxic effect of hydroxylated metabolites. It is usually gradual in onset occurring within 2–16 weeks of starting therapy, but may be sudden. It may also arise late in the course of treatment. A significant drop in neutrophil count can present with fever, mouth ulcers and sore throat. It may be accompanied by thrombocytopenia. Regular monitoring of the blood count is therefore mandatory.

- **Sulphaemoglobinaemia** arises from direct combination of dapsone with haemoglobin. It is rarely of clinical relevance.
- **Dapsone hypersensitivity syndrome** is a serious side-effect and usually takes the form of DRESS (drug reaction [or rash] with eosinophilia and systemic symptoms) type reaction. It is estimated to occur in approximately 1% of patients. The onset is usually within 4–6 weeks of starting therapy, but may be delayed up to 6 months. Patients present with fever, a morbilliform rash that progresses to exfoliative dermatitis, lymphadenopathy, hepatitis with elevated liver enzymes, peripheral eosinophilia and atypical lymphocytes. If not recognized, the condition deteriorates and there is a significant risk of death. The drug should be withdrawn immediately.
- **Severe cutaneous reactions** including toxic epidermal necrolysis and Stevens–Johnson syndrome have also been reported.
- **Gastrointestinal adverse effects** such as anorexia, nausea and vomiting may occur and can limit patients' ability to tolerate and continue treatment. Hepatitis, jaundice, cholestasis and abnormal LFTs may occur.
- **Peripheral motor and sensory neuropathies** have been reported rarely. They are dose related and caused by axonal damage. Headache, insomnia, malaise and rarely, psychoses have been reported.
- **Renal adverse effects** include proteinuria and, very rarely, nephrotic syndrome.

### + Use in special situations

#### Pre-conception

Animal studies have shown that dapsone can reduce the number of sperm and their motility, potentially reducing male fertility though there is no clear evidence for this in humans.

#### Pregnancy (FDA Category C)

Dapsone can cross the placenta and should be avoided in pregnancy if possible. It has however, been used safely with no evidence of teratogenicity since its introduction in 1947. Folic acid 5 mg daily should be given to females who are pregnant. The greatest risk is in the last trimester when it may lead to neonatal haemolysis and methaemoglobinaemia.

#### Lactation

Dapsone is secreted in breast milk and absorbed by the infant, giving rise to mild haemolytic anaemia. The risk to the infant is considered small unless it has G6PD deficiency.

#### Children

Dapsone has been used safely in infants and children at doses of 1–2 mg/kg/d.

### + Essential patient information

Patients should be advised of the need to attend for regular monitoring and to seek urgent medical attention if affected by the following:

- Sore throat, mouth ulcers, purpura, bleeding – may indicate agranulocytosis/ bone marrow suppression.
- Shortness of breath, angina, jaundice – may indicate significant haemolysis.

*With acknowledgements to Arjida Woolons and Martin M. Black, authors of this chapter in the 1st edition.*

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# Fumaric Acid Esters

Silja Domm, Kristian Reich & Ulrich Mrowietz

## + Classification & mode of action

Fumaric acid esters (FAE) were first reported as an effective treatment for psoriasis by the German chemist, Schreckendiek, in 1959. A mixture of dimethylfumarate (DMF) and three salts of ethyl hydrogenfumarate (Fumaderm®, Fumaderm® initial) was approved for the treatment of psoriasis in Germany in 1994, where it remains a first-line systemic therapy and the most widely prescribed drug for chronic plaque psoriasis.

DMF is thought to be the active ingredient in Fumaderm® and is regarded as a pro-drug as it is rapidly bound to glutathione (GSH) before absorption to form a stable adduct. It also undergoes hydrolysis to monomethylfumarate (MMF). Both the DMF–GSH adduct and MMF can be detected in the blood after oral DMF administration.

FAEs have immunomodulatory actions without being immunosuppressants. Their therapeutic effects may relate to protecting cells against oxidative stress. Binding of DMF to GSH seems to be a crucial step and causes a shift in cellular redox balance. This leads to activation and stabilization of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which induces the production of many cytoprotective proteins. These include the enzymes NADPH-quinone-oxidoreductase-1 and heme-oxygenase-1 which catalyse the reduction and detoxification of highly reactive quinones and heme respectively, and glutathione transferase. Incubation of cells with DMF leads to an initial GSH-depletion (due to its binding), which is followed by a subsequent rise in intracellular GSH levels. Effects of MMF appear to be related to binding to the membrane receptor hydroxycarboxylic acid receptor 2 and modulation of downstream pathways.

The immunomodulatory effects of Fumaderm® in psoriasis may relate to a shift towards type II dendritic cells releasing interleukin (IL)-10 instead of IL-12 and IL-23, and a subsequent induction of IL-4 producing Th2 cells.

## + Indications & dermatological uses

In 2013, the USA FDA and EMA licensed a formulation containing DMF for the treatment of adults with relapsing remitting multiple sclerosis. This differs from Fumaderm, which contains a mixture of DMF and ethyl hydrogenfumarate.

Fumaderm® was authorized for the treatment of moderate to severe psoriasis in adults in Germany in 1994, but is not licensed elsewhere in the European Union or USA.

FAE therapy has been reported to benefit other dermatological diseases, including disseminated granuloma annulare, necrobiosis lipoidica and sarcoidosis.

## + Formulations/Presentation

Branded formulation with tablet size of 30 mg (Fumaderm® initial) and 120 mg (Fumaderm®) containing DMF and three salts of ethyl hydrogenfumarate.

## + Dosages & suggested regimens

Therapy with FAE should be initiated with one tablet of **Fumaderm® initial** daily and a weekly dose increase to a maximum of three tablets per day to improve gastrointestinal (GI) tolerance. After 3 weeks, treatment is continued with **Fumaderm® tablets** with a similar dose escalation until a satisfactory clinical response is achieved. The **maximum** dose is **two tablets tds** (see Table 1). There is evidence from a retrospective study that many patients respond well to three or four tablets a day and that further dose increases bring little clinical benefit. If patients suffer from GI side-effects or flushing, it may be advisable to reduce the frequency of dosing and use a twice rather than three times a day regimen, e.g. 1–0–2 instead of 1–1–1 tablets per day. As a general guide, if side-effects occur dosage should be reduced to the last tolerated dose. A further dose increase can be reattempted if necessary and may be better tolerated after a longer treatment period.

**TABLE 1** Dosage regimen for Fumaderm® therapy in psoriasis

	Fumaderm® initial	Fumaderm®
Week 1	1–0–0	
Week 2	1–0–1	
Week 3	1–1–1	
Week 4		1–0–0
Week 5		1–0–1
Week 6		1–1–1
Week 7		2–1–1
Week 8		2–1–2
Week 9		2–2–2

During **maintenance therapy** the dosage is gradually reduced to the lowest dose that is necessary to maintain efficacy; two to four tablets per day in most patients. In a small minority very low doses (<120 mg daily) may be effective. Therapeutic dosage is not related to bodyweight or disease activity and is not predictable in advance.

A clinical response is expected within **6 weeks**, although the onset of action is highly variable due to the personal dosing regimen. Full therapeutic effects may take several months. Treatment should be discontinued if there is insufficient improvement by **24 weeks**. Prolonged maintenance therapy may

be considered for disease control. A meta-analysis of randomized controlled trials for moderate-to-severe psoriasis reported that FAE therapy had similar efficacy to methotrexate.

As no relapse or rebound phenomena occur after cessation of treatment with FAE, therapy can be discontinued abruptly if necessary due to adverse effects or lack of efficacy.

### + Baseline investigations & considerations

- FBC (CBC) with differential WBC.
- Urea, electrolytes and creatinine.
- LFTs.
- Urinalysis.

### + Monitoring

During the first 3 months of therapy the following should be checked every 2 weeks, thereafter monthly:

- FBC.
- Urea, electrolytes and creatinine.
- LFTs.
- Urinalysis.

The differential FBC should be checked to identify any downward trend in the lymphocyte count, which is a common adverse effect of FAE therapy. If leukocytes decrease below  $3000/\mu\text{L}$  or lymphocytes below  $500/\mu\text{L}$ , treatment should be stopped. If the lymphocyte count decreases below  $0.7 \times 10^9/\text{L}$  the dosage should be halved and FBC retested after 2–4 weeks. If there is no recovery a further dose reduction is necessary.

Eosinophilia is a common finding and usually appears after 4–10 weeks of treatment. It is usually transient without clinical implications. If a persistent eosinophilia of 25% or more occurs treatment should be stopped. Less commonly observed side-effects include elevated serum creatinine (>30% increase above baseline value). Dosage should be reduced and treatment discontinued if these abnormalities persist.

Proteinuria is usually transient and reversible after dose reduction and normally without clinical relevance.

### + Contraindications

FAE are contraindicated in the following situations:

- Chronic GI diseases including chronic gastritis and active or recent peptic ulceration.
- Severe liver or kidney diseases.

- Pregnancy.
- Lactation.
- Chronic diseases associated with reduced levels or function of leukocytes.

### Special point

DMF has recently been identified as a potent contact allergen which has been used as a mould retarding agent for leather items of clothing and furniture. It is unknown if this is of clinical relevance when considering oral therapy; however, there is a theoretical risk of eliciting a widespread dermatitis in patients with known contact hypersensitivity to DMF.

### + Cautions

- Renal impairment/proteinuria.
- Lymphopenia.

FAEs do not appear to have an immunosuppressive effect and there is no apparent increase in the rate of common infections associated with their use. There have however, been recent isolated reports of **progressive multifocal leukoencephalopathy** associated with long-term use in patients with lymphopenia below the threshold of 500  $\mu$ L (see Adverse effects & their management).

### + Important drug interactions

FAE have no known important interactions with other drugs. Experience of combination therapy with FAE and methotrexate, psoralen, retinoids, ciclosporin (cyclosporine) or other systemic psoriasis therapy remains very limited and is not recommended, but may be considered in exceptional cases with close monitoring. Concomitant use of potentially nephrotoxic agents should be avoided.

### + Adverse effects & their management

- **Gastrointestinal:** complaints such as diarrhoea, abdominal pain, stomach cramps and nausea are very common adverse effects of FAE and are dose dependent. They affect up to two-thirds of patients and if severe may lead to discontinuation of treatment. These symptoms are most troublesome in the first 3 months of treatment and tend to improve with time. Taking medication with milk or other dairy products, or mebeverine hydrochloride taken 30 minutes prior to ingestion may improve GI tolerance.
- **Flushing:** 30–50% of patients experience flushing after taking FAEs. This can vary from mild redness and increased warmth for a few minutes to severe and long-lasting facial redness with associated headaches. Drug

withdrawal may be necessary in severe cases. Recently it was shown that the main metabolite of DMF, MMF, a potent agonist of the hydroxy-carboxylic acid receptor 2 expressed on epidermal Langerhans cells and keratinocytes, induces synthesis of vasoactive prostaglandins D2 and E2 that cause flushing. Cyclo-oxygenase inhibitors such as aspirin may be helpful in reducing symptoms.

- **Haematological:** abnormal haematological parameters especially lymphopenia and eosinophilia are common and reversible on dose reduction or withdrawal (see Monitoring for specific advice).
- **Hepatotoxicity:** changes in LFT are rare and normalize rapidly after dose reduction or cessation of treatment in most patients. Rarely, an isolated increase in ALT levels or bilirubin has been observed at the beginning of treatment. Dose reduction or discontinuation of treatment should be considered if transaminases or GGT rise over twofold the upper limit of normal, and no other cause for the increase is found.
- **Malignancy:** no increased overall risk of malignancy has been reported in short- or long-term use of FAE. There are conflicting data regarding a possible occurrence of melanoma as two case reports describe the detection of melanoma in patients treated with Fumaderm® for psoriasis. On the other hand, experimental data in a mouse model of melanoma growth and metastasis, DMF show inhibitory effects and prolong overall survival.
- **Nephrotoxicity:** renal side-effects are rare and usually resolve after dose reduction or cessation of treatment (see Monitoring). There have been rare isolated reports of Fanconi syndrome secondary to FAE therapy. This is characterized by glycosuria, proteinuria and hyperphosphaturia, and is caused by proximal tubular dysfunction. It is fully reversible with drug discontinuation.
- **Progressive multifocal leukoencephalopathy (PML)** has been reported in two patients treated with FAE. This condition develops when latent JC virus infection becomes reactivated in patients with immunosuppression. Prolonged lymphopenia may have been a relevant risk factor in these cases.

### + Use in special situations

#### Pregnancy (FDA Category C)/Lactation

Animal studies of DMF have shown evidence of embryo-fetal toxicity. There are no established human studies on FAE in pregnancy and the manufacturers advise that Fumaderm® is contraindicated in pregnancy and lactation.

#### Children

FAE are not licensed for use in children and adolescents and experience in this age group is very limited. However, they have been reported in single cases and small case series to be effective and safe and may be an attractive therapeutic alternative to systemic immunosuppressants. Careful counselling and detailed information should be provided to the parents and their informed consent obtained.

## Elderly

FAE can be used in the elderly in the absence of the contraindications listed above. The lack of known drug interactions and lack of immunosuppressive effects is a particular advantage in this age group who often suffer from comorbidities and the need for co-medication.

### + Essential patient information

Detailed patient information is important to improve adherence and reduce treatment drop out due to adverse effects. Dose regimens can be tailored to individual patients if adverse effects are not tolerated.

The onset of action is relatively slow and additional topical psoriasis therapy should be continued at the beginning of treatment. Patients should clearly understand the need to comply with regular blood testing to minimize the risk of adverse effects.

*With acknowledgements to Robert Chalmers, author of this chapter in the 1st edition, and Melinda Gooderham, who reviewed this chapter from an international perspective.*

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# Hydroxycarbamide

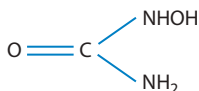
Ekaterina Burova

## + Classification & mode of action

Hydroxycarbamide (hydroxyurea) was first synthesized in 1869 and then forgotten until 100 years later, when it was used to treat solid tumours. It was approved by the FDA in 1967 for the treatment of chronic myeloid leukaemia. Subsequently, the drug was reported to be effective in the management of psoriasis and of benefit in patients who had failed to respond to methotrexate or had underlying liver disease.

Hydroxycarbamide is an S-phase specific antimetabolite that inhibits DNA synthesis (but not RNA synthesis) through its action on ribonucleotide diphosphate reductase. This enzyme catalyses formation of deoxyribonucleotides from ribonucleotides, which in turn are used in the synthesis of DNA. Repair of DNA damaged by chemicals or irradiation is also inhibited. It is postulated that hydroxycarbamide's effects in psoriasis are due to a reduction in keratinocyte proliferation in the basal layer of the epidermis or on proliferating lymphoid cells. It also has antiretroviral effects in human immunodeficiency virus (HIV) infection, inhibiting viral DNA synthesis, and acts in synergy with nucleoside reverse transcriptase inhibitors (NRTIs). Some effects of hydroxycarbamide may be mediated by nitric oxide.

Hydroxycarbamide has a low molecular weight (76 Da) (Figure 1). It is nearly completely absorbed within 2 hours following oral ingestion and widely distributed in the body. It is metabolized in the liver then mainly eliminated by the kidneys, with 80% of an oral or i/v dose recovered in urine within 12 hours. It crosses the blood–brain barrier. There are wide differences in pharmacokinetics in individuals that may influence its effectiveness.



**FIGURE 1** Structure of hydroxycarbamide.

## + Indications & dermatological uses

The licensed indications of hydroxycarbamide in the UK and USA are:

- Chronic myeloid leukaemia.
- Cancer of the cervix (in conjunction with radiotherapy).
- Sickle cell disease: to reduce the frequency of crises and requirements for transfusion.

It is also used in polycythaemia vera, essential thrombocythaemia and other malignant diseases. All dermatological use of hydroxycarbamide is off label.

It may be considered as a systemic therapy for severe psoriasis in patients who have failed to respond to licensed drugs such as methotrexate, acitretin or ciclosporin (cyclosporine) and is also a second-line drug in patients with underlying HIV infection. In general, it is less effective than conventional systemic therapy. Hydroxycarbamide is more effective in the treatment of plaque psoriasis than pustular psoriasis or guttate psoriasis and does not appear to be effective in palmoplantar pustulosis.

### + Formulations/Presentation

- Hard capsules containing 500 mg hydroxycarbamide.
- Film coated scored tablets containing 100 mg and 1000 mg hydroxycarbamide.

Capsules and tablets should be taken with water or a small quantity of food to disguise the bitter taste. In those who are unable to swallow, capsules may be opened into water and drunk immediately. If the prescribed dose requires breaking the tablet, this should be performed away from food and any spilled powder carefully discarded. Patients should be warned not to allow the powder to come into contact with skin and mucous membranes. Anyone handling the drug should wear disposable gloves. Hydroxycarbamide should be stored safely, away from children and pets.

### + Dosages & suggested regimens

The usual adult **starting dose** in psoriasis is **500 mg–1 g daily** in one or two divided doses. A typical **maintenance dose** is **1–1.5 g daily** with a **maximum** recommended dose of **2 g daily** (20–30 mg/kg). It has been used at doses of up to 3 g a day, subject to tolerance.

The onset of action is slow with clinical response taking **up to 12 weeks**. Reported response rates have varied widely and there is a lack of clinical trial data to support its use. Nevertheless, it may be of benefit in individual cases, especially as maintenance therapy after control of psoriasis is obtained with other systemic medication. Treatment should be discontinued after 12 weeks if the response is inadequate.

Most dermatological experience with hydroxycarbamide is as a monotherapy but there have been isolated reports of its use with other systemic treatment, including biologics. A lower daily dose of 600 mg hydroxycarbamide has been advocated for use in HIV in combination with other antiretroviral therapy.

### + Baseline investigations & considerations

- FBC (CBC) and differential white blood cell count (WBC).
- Urea, electrolytes and creatinine.
- LFTs.
- Serum urate.



- Urinalysis.
- HIV hepatitis B & hepatitis C virus infection.
- B12 and folate.
- Baseline examination of skin for malignancy and ensure cervical screening is up-to-date.
- Consider testing varicella antibody status if a history of chickenpox is uncertain. Varicella zoster vaccination should also be given to the non-immune prior to treatment. Those eligible should receive their 'shingles vaccination' prior to starting therapy. (In the USA this is recommended for those over 60 years and in the UK, those aged 70–79 years.)
- Influenza and pneumococcal vaccination are recommended prior to starting hydroxycarbamide, followed by annual influenza vaccination.
- Radiotherapy: an exacerbation of erythema caused by previous or simultaneous irradiation may occur.

### + Monitoring

- Bone marrow toxicity may occur at any stage during the treatment. Therapy with hydroxycarbamide requires close supervision.
- FBC and differential WBC should be checked once every 1–2 weeks for at least the first 6 weeks. Intervals between tests can gradually increase every 4 weeks to a maximum interval of 2–3 months long term.
- B12 and folate should be checked in patients with mean corpuscular volume (MCV) >105 fL to exclude co-existent deficiencies, which can be masked by drug induced macrocytosis.
- LFTs, urea, electrolytes and creatinine should be monitored at regular intervals. Once stable this can be reduced to every 3–6 months. A full skin examination for malignancy should be conducted every 6 months (see below).

### + Contraindications

- Bone marrow suppression. Hydroxycarbamide often causes bone marrow suppression (see below) and is therefore contraindicated in patients with leukopenia: WBC  $<2.5 \times 10^9/L$ ; thrombocytopenia:  $<100 \times 10^9/L$ ; or severe anaemia.
- Hypersensitivity to hydroxycarbamide.
- Severe renal and liver impairment.
- Pregnancy and lactation (see below).

### + Cautions

- Unstable and fulminant psoriasis.
- Mild to moderate renal impairment.

- Hyperuricaemia.
- Hepatic impairment.
- HIV infection: hydroxycarbamide may affect the efficacy and toxicity of antiretroviral medication so close collaboration with HIV physicians is advised.
- Severe photodamage, actinic dysplasia or history of cutaneous squamous cell carcinoma.

### + Important drug interactions

- **Antiretroviral drugs.** If used in combination with NRTIs didanosine and stavudine, their toxicity is enhanced (risk of including pancreatitis, hepatitis and peripheral neuropathy) so dose reduction and expert advice from a HIV physician is required.
- **Clozapine** (antipsychotic), due to increased risk of agranulocytosis.
- **Uricosuric therapy** may need to be adjusted as hydroxycarbamide may raise serum urate levels.
- **Digoxin** absorption may be reduced.
- **Interferon-alpha** administration has been associated with vasculopathy including digital infarcts and gangrene in patients with chronic myeloid leukaemia who also received hydroxycarbamide.
- **Live vaccines** should be avoided by patients receiving hydroxycarbamide and those living in the same household. These include oral polio, mumps, measles, rubella (MMR), bacillus Calmette–Guérin (BCG) and yellow fever.

### + Adverse effects & their management

- **Myelosuppression** is the major concern. Is dose dependent and usually manifests first with neutropenia, followed by thrombocytopenia and anaemia. Treatment should be stopped immediately if:
  - Haemoglobin decreases by 3 g/L.
  - WBC  $<2.5 \times 10^9/L$  (dose reduction and increase monitoring if  $<4 \times 10^9/L$ ).
  - Neutrophils  $<1 \times 10^9/L$ .
  - Platelet count  $<100 \times 10^9/L$ .

Haematological recovery usually occurs within 2 weeks. Treatment may then be restarted at a reduced dose.

- **Macrocytosis:** a raised median cell volume (MCV) and megaloblastic change is often seen at the start of the treatment and is usually self-limiting. Morphological changes are similar to pernicious anaemia, but are not related to B12 or folic acid deficiency.
- **Skin and mucosal toxicities** are common adverse effects in patients with myeloproliferative neoplasms and may be related to cumulative dosage. **Painful leg ulcers**, resembling pyoderma gangrenosum are characteristic, especially in the malleolar area in patients with polycythaemia vera.

Aphthous ulcers of the oral and genital mucosa may occur and painful erosive stomatitis and glossitis. The drug should be discontinued if ulcers develop. Leg ulcers are often difficult to treat and slow to heal. Atrophic skin changes may be localized to the acral areas or generalized and a dermatomyositis-like eruption may occur, probably related to drug induced phototoxicity. Palmoplantar erythema is a frequent finding. Other reported effects include diffuse hyperpigmentation, sclerodermatous change, leukocytoclastic vasculitis, melanonychia and alopecia.

- **Malignancy:** actinic keratosis and rare cases of cutaneous squamous cell carcinomas have been reported so regular skin examination and sun protection advice is recommended, and are essential in geographic locations exposed to high levels of ultraviolet (UV) radiation. Treatment related actinic keratoses and intraepidermal carcinoma resolve within months of discontinuing hydroxycarbamide. Secondary leukaemia has been reported in patients on long-term hydroxycarbamide treatment for myeloproliferative disorders. This may be drug or disease related.
- **Serum urate levels** may be increased resulting in gout or uric acid nephropathy, especially if used with other cytotoxic agents. It is important to maintain adequate fluid intake during treatment.
- **Gastrointestinal toxicity** is usually mild and may manifest with anorexia, nausea, vomiting, constipation, diarrhoea and abdominal pain.
- **Neurological:** hydroxycarbamide may cause headache, dizziness and malaise.
- **Varicella zoster exposure:** may lead to severe infection in the non-immune who should receive varicella immunoglobulin (VZIG) if exposed to chickenpox and herpes zoster.

### + Use in special situations

#### Pre-conception

Spermatogenesis: hydroxycarbamide may be genotoxic. Males receiving treatment are therefore advised to use condoms during and for at least 3 months after therapy. They should be informed about the possibility of sperm conservation before starting treatment.

#### Pregnancy (FDA Category D)

Females of childbearing age should avoid becoming pregnant, and use effective contraception. Hydroxycarbamide crosses the placenta and animal studies have shown it to be a teratogen, producing a range of skeletal malformations, though the risk in humans is unclear. Patients on hydroxycarbamide wishing to conceive should stop treatment 3–6 months before pregnancy if possible. In case of exposure to hydroxycarbamide during pregnancy in female patients or pregnant partners of male patients treated by hydroxycarbamide, a careful obstetric follow-up with ultrasound examination should be considered. Hydroxycarbamide can pass into body fluids (urine, faeces, semen, vaginal fluid) and these should not be handled by pregnant women.

## Lactation

Hydroxycarbamide is excreted in human milk. Because of the potential for serious adverse reactions in infants, breastfeeding must be discontinued.

## Children

Hydroxycarbamide has been used widely in children over the age of 2 years with sickle cell disease and is usually tolerated at doses up to 25–30 mg/kg/day.

## Elderly

The elderly may be more susceptible to the adverse effects of hydroxycarbamide due to reduced renal function, so a reduced dose is recommended.

### + Essential patient information

Patients should be advised to seek urgent medical advice if they experience unexplained bleeding, bruising, sore throat, oral ulceration or fever.

*With acknowledgements to Annmarie Powell and John Coterill, authors of this chapter in the 1st edition, and Amanda Oakley who reviewed this chapter from an international perspective.*

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# Interferons

Louise A. Fearfield

## + Classification & mode of action

Interferons (IFNs) are glycoprotein cytokines, first discovered in the 1950s by Isaacs and Lindeman. They have immunomodulatory, antiproliferative and anti-infective actions and are released by host cells in response to pathogens or tumour cells. They are especially important in protection against viral infection. Three classes of IFNs are recognized (Types I–III IFN) and these differ in their protein sequence, receptors, genetic loci and cell types responsible for their production.

Type I IFNs have an alpha ( $\alpha$ )-helical structure and include IFNs- $\alpha$ 2 and -beta ( $\beta$ ). There are many subtypes of IFN- $\alpha$ , but only one form of IFN- $\beta$ . Type II IFN in humans is IFN-gamma (IFN- $\gamma$ ) and Type III IFNs (IFN-lambda, IFN- $\iota$ ) have only recently been described.

**IFN- $\alpha$**  is produced by B-lymphocytes and macrophages, and is induced by foreign cells, virus infected cells, bacteria and tumour cells. **IFN- $\beta$**  is primarily produced by fibroblasts but also by epithelial, endothelial cells and macrophages, and is induced by viral and other foreign particles. **IFN- $\gamma$**  is produced by natural killer cells and T lymphocytes, and is induced by foreign antigens via specific receptors. IFN- $\iota$  appears to play an important role in the protection of epithelial surfaces.

Binding of microbial antigens to receptors such as membrane bound Toll-like receptors or cytoplasmic receptors can trigger release of IFNs, which bind to specific receptors on the same or neighbouring cells to activate signal transducer and activator of transcription (STAT) complexes. These regulate the expression of hundreds of interferon-stimulated genes with antiviral function. Some STATs are activated by both Type I and Type II IFNs, but each IFN type can also activate unique STATs.

The antiproliferative effects of IFNs include a direct effect on tumour cells with prolongation of the cell cycle, inhibition of the expansion of T-cell clones and activation of cytotoxic T cells. Other actions include increasing p53 activity and upregulation of major histocompatibility complex molecules MHC I and MHC II.

IFNs have been used to treat a range of diseases, but their licensed indications are limited. The addition of polyethylene glycol (PEG) to the interferon through a process of pegylation, prolongs the half-life of the IFN compared with its native form.

## IFN- $\alpha$

### + Indications & dermatological uses

Various formulations of IFN- $\alpha$  are commercially available and differ in their individual product licenses. Indications include the treatment of chronic viral hepatitis, various haematological malignancies, renal cancer and carcinoid. The licensed dermatological indications in the UK are as follows below.

#### Adjuvant therapy of malignant melanoma

The cure rate following surgical removal of early melanoma is high, but patients with more advanced disease (stage IIB/IIC/III disease [Table 1 *overleaf*]) are at higher risk of recurrence and should be considered for adjuvant therapy. Adjuvant IFN- $\alpha$  has been used for over 10 years at various regimens (low, medium and high dose >10 MU/dose). High dose IFN- $\alpha$ 2b (HDI) has been shown to prolong disease-free survival, but its effects on overall survival are unclear and treatment is associated with significant toxicity. IFN- $\alpha$  is licensed as an adjuvant therapy in patients who are disease-free after surgery but are at high risk of systemic recurrence. European consensus guidelines from 2012 concluded that IFN- $\alpha$  may be offered to patients with stage II and stage III melanoma as an adjuvant therapy as it increases disease-free survival. However, the 2010 British Association of Dermatology melanoma guidelines do not recommend its routine use for primary or stage III melanoma, due to the lack of clear evidence for overall survival benefit.

The antitumour actions of IFNs in melanoma are not fully understood, and may be immunomodulatory rather than cytotoxic. Effects of HDI in melanoma include recruitment of T lymphocytes and dendritic cells into the tumour and downregulation of the MEK/ERK MAPK pathway that plays a role in tumour cell metastasis. Over the last 5 years significant advances have been made in the treatment of melanoma with novel targeted therapies. These therapies include BRAF and MEK inhibitors as well as immunomodulatory therapies such as Ipilimumab and anti-PD1 agents. Currently they are used mainly in stage IV disease, but have recently been used as adjuvant therapy of stage IIC and above. There are some current trials investigating combination adjuvant therapy with HDI and the targeted therapies including Ipilimumab and the BRAF inhibitors. Addition of HDI to conventional chemotherapy with agents such as cisplatin and dacarbazine does not appear to confer any benefit in stage IV disease.

#### Refractory cutaneous T-cell lymphoma

In refractory early stage mycosis fungoides (MF), transformed MF and folliculotropic MF, a combination of skin directed therapy such as psoralen UVA (PUVA) plus low dose immunomodulators (e.g. IFN or bexarotene) may be effective. Studies of IFN- $\alpha$ 2b have shown overall response rates of 45–74% with complete responses of 10–27%. Various dose schedules have been used and it appears that response rates are higher for larger doses and for early stage disease. IFN has also been used in combination with acitretin.

**TABLE 1** The 2009 American Joint Committee on Cancer (AJCC) melanoma staging system

Stage (M)	Primary tumour (pT)	Lymph nodes (N)	Metastases (M)
IA	<1 mm, no ulceration, mitoses < 1 mm <sup>2</sup>		
IB	<1 mm, with ulceration or mitoses ≥ 1 mm <sup>2</sup>		
IIA	1.01–2 mm, with ulceration 2.01–4 mm, no ulceration		
IIB	2.01–4 mm, ulceration >4 mm, no ulceration		
IIC	>4 mm, with ulceration		
IIIA	Any Breslow thickness, no ulceration	Micrometastases 1–3 nodes	
IIIB	Any Breslow thickness, with ulceration Any Breslow thickness, no ulceration Any Breslow thickness, no ulceration	Micrometastases 1–3 nodes 1–3 palpable metastatic nodes No nodes, but in-transit or satellite metastasis(es)	
IIIC	Any Breslow thickness, with ulceration Any Breslow thickness, with or without ulceration  Any Breslow thickness, with ulceration	Up to three palpable lymph nodes Four or more nodes or matted nodes or in-transit disease + lymph nodes No nodes, but in-transit or satellite metastasis(es)	
IV, M1a			Skin, subcutaneous or distant nodal disease
IV, M1b			Lung metastases
IV, M1c			All other sites or any other sites of metastases with raised lactate dehydrogenase

In the rare circumstances where mitotic count cannot be accurately determined, a Clark level of invasion of either IV or V can be used to define T1b melanoma. Every patient with melanoma should be accurately staged using the AJCC system; this may include performing a sentinel lymph node biopsy when recommended by the Specialist Skin Cancer Multidisciplinary Team. Staging should be updated following relapse.

### Kaposi's sarcoma in association with HIV disease

Kaposi's sarcoma (KS) remains the most commonly diagnosed malignancy in HIV-infected patients, and is an acquired immunodeficiency syndrome (AIDS)-defining diagnosis. The incidence of KS has sharply declined since the widespread use of highly active antiretroviral therapy (HAART). The first-line approach to management of HIV associated KS is the initiation/consideration of HAART under the guidance of a HIV physician. HAART may be combined with systemic and local therapy. Treatment options include IFN- $\alpha$  and chemotherapy. For local disease, radiotherapy, intralesional chemotherapy or cryotherapy may be used. Partial responses in classic (non-HIV associated) KS have also been reported with IFN, but this is a non-licensed indication. IFN- $\alpha$  is licensed for the treatment of AIDS patients with progressive, asymptomatic KS who have a CD4 count  $>250/\text{mm}^3$ . AIDS patients with CD4 counts  $<250/\text{mm}^3$  or those with a history of opportunistic infections or constitutional symptoms, are unlikely to respond.

Unlicensed uses of IFN- $\alpha$  include the following:

### Non-melanoma skin cancer

Aggressive non-melanoma skin cancers are therapeutically challenging and may demand radical, disfiguring surgery. Benefit has been reported in patients with extensive inoperable or recurrent basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) given peri- and intralesional IFN- $\alpha$ , three times per week for 3 weeks, with complete tumour elimination in almost half of those treated and partial clearance/stable disease in most of the remainder. IFN may be a therapeutic option in the management of inoperable tumours, but its role in the management of advanced BCC is likely to diminish since the advent of vismodegib (see Vismodegib), which is licensed for this indication in the UK.

### Condyloma accuminatum

Locally administered IFN- $\alpha$  has been found to increase the rate of clearance if tolerated and adverse effects are mild, but treatment is limited to patients with recalcitrant infection in whom other therapy has failed. Systemically administered IFN- $\alpha$  appears ineffective.

### Infantile haemangiomas

Large infantile haemangiomas are a therapeutic challenge and may cause life-threatening complications. Several studies have reported the effectiveness of IFN- $\alpha$  (2a and 2b) in treating these vascular lesions. IFN- $\alpha$  inhibits endothelial cell migration and proliferation and specific vascular growth factors. As this mode of action is different to corticosteroids, it can be used in lesions that are unresponsive to steroids, and it does not need to be given during the proliferation phase in order to be effective. The onset of action is slower than corticosteroids, and treatment may need to be continued for up to 12



months. Due to toxicity, IFN- $\alpha$  is only indicated for induction of early regression in life-threatening corticosteroid-resistant infantile haemangiomas where propranolol (see Propranolol) has failed or is contraindicated. The most serious adverse effect in infants is a potentially irreversible spastic diplegia.

### Miscellaneous diseases

Clinical improvement has been reported in patients with cutaneous lupus erythematosus, treated with IFN- $\alpha$ , but disease tends to relapse rapidly on stopping therapy. Benefit has also been reported in small numbers of patients with Ofuji's papuloerythroderma, lichen planus, recurrent genital herpes and chronic urticaria. IFN- $\alpha$  has been recommended for severe eye involvement in Behçet's syndrome and familial Mediterranean fever resistant to colchicine treatment.

The combination of pegylated IFN- $\alpha$  with ribavirin and rituximab is emerging as a promising treatment in hepatitis C virus associated mixed cryoglobulinemia. Limited data also suggest that IFN may induce remissions in recalcitrant Churg–Strauss syndrome.

## IFN- $\beta$

IFN- $\beta$  is approved for treatment of multiple sclerosis. It has also been used to treat a number of viral infections including herpes simplex virus and human papilloma virus and malignant melanoma, but is of no greater benefit than IFN- $\alpha$  and its current use in dermatological diseases is extremely limited, so it is not discussed further.

## IFN- $\gamma$

The only licensed indication is chronic granulomatous disease where IFN- $\gamma$  has been shown to decrease the frequency of serious infections. The use of IFN- $\gamma$  in dermatology is unlicensed and includes the following (see below).

### Atopic dermatitis

The immunopathogenesis of atopic dermatitis (atopic eczema) is complex and incompletely understood. On the basis of the finding that peripheral blood mononuclear cells of patients with atopic dermatitis produce lower levels of IFN- $\gamma$  spontaneously and in response to stimuli, a number of investigators have studied the clinical effects of recombinant IFN- $\gamma$  therapy in severe atopic dermatitis. Placebo randomized controlled trials have confirmed the effectiveness of IFN- $\gamma$  in patients with severe atopic dermatitis, but drawbacks include cost, frequent injections and a high rate of flu-like symptoms so its use is limited to a small minority of patients who are unresponsive to conventional therapy. With increased understanding of the importance of IFN- $\gamma$  in defence against viral infection, IFN- $\gamma$  therapy may prove most suitable for patients with

severe eczema who suffer from recurrent widespread viral infection such as eczema herpeticum.

### Miscellaneous

Various other diseases have been reported to respond to IFN- $\gamma$  include Behçet's disease, psoriatic arthritis, scleroderma, keloids, leishmaniasis (both cutaneous and refractory visceral forms) and eosinophilic pustular folliculitis. IFN- $\gamma$  appears to be less effective than IFN- $\alpha$  in the treatment of malignant melanoma, HIV associated KS and cutaneous lymphoma.

### + Formulations/Presentation

- IFN- $\alpha$ 2b is available in 1 mL and 2.5 mL vials containing 10 million units/mL ready for injection and in pre-filled syringes and injection pen devices.
- IFN- $\gamma$  is available in 0.5 mL vials containing 200  $\mu$ g/mL.
- All preparations should be stored at 2–8°C.

### + Dosages & suggested regimens

There are a few standardized regimens for treatment of dermatological disease with IFNs though doses have varied between different clinical trials. Some examples are given in Table 2.

**TABLE 2** Dosage regimens for therapy with interferons

IFN- $\alpha$			
Condylomata accuminatum	Malignant melanoma	Follicular lymphoma	HIV related Kaposi's sarcoma
Intralesionally 1 million units/lesion for up to 5 lesions in a single course Lesions should be injected 3 times weekly on alternate days for 3 weeks An additional course may be administered at 12–16 wk	20 million IU/m <sup>2</sup> i/v 5 days a week for 4 weeks 10 million IU/m <sup>2</sup> s/c 3 d/wk (every other day) for 48 weeks	5 mIU s/c 3 days/week for 18 months	5 mIU s/c daily if combined with HAART IM or s/c 30 million units/m <sup>2</sup> 3 times a week until disease progression or maximal response has been achieved after 16 weeks of treatment Dose reduction is frequently required
IFN- $\gamma$			
Atopic dermatitis (unlicensed in UK) 50 $\mu$ g/m <sup>2</sup> once daily by s/c injection 0.5 or 1.5 million units/m <sup>2</sup> 3 times a week by s/c injection			

### + Baseline investigations & considerations

- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs.
- Glucose.
- Lipids.
- Thyroid stimulating hormone (TSH).
- Urinalysis.
- ECG if pre-existing cardiac abnormalities.

### + Monitoring

IFN- $\alpha$  (and IFN- $\beta$ ):

- FBC with differential WCC and LFTs weekly during induction phase then monthly throughout therapy.
- Urea, electrolytes and creatinine and lipids: every 1–3 months.

IFN- $\gamma$ :

- FBC, U&E, urea, electrolytes and creatinine, LFTs and urinalysis: every 1–3 months.

### + Contraindications

For detailed advice, the individual product literature should be consulted. General contraindications to IFN therapy include:

- Hypersensitivity to specific interferons.
- Severe cardiac, renal or hepatic dysfunction.

### + Cautions

Use with caution in patients with seizure disorders, depression and the elderly.

### + Important drug interactions

- **Metronidazole** and **atorvastatin**: increased risk of peripheral neuropathy, neurotoxic effects.
- **Theophylline**: associated with decreases in clearance and increases in plasma concentration and elimination half-life of theophylline.
- **Zidovudine** (AZT): may result in severe bone marrow toxicity, most often manifested as granulocytopenia and/or thrombocytopenia.

## + Adverse effects & their management

- **Flu-like symptoms** such as fatigue, fever myalgia, arthralgia, headache, sweating and chills affect most patients during the first weeks of treatment with all IFNs. They are usually manageable with simple analgesics and by administering IFN injections in the evening. Symptoms may improve with continued therapy as tolerance develops.
- **Psychiatric** (all IFNs but predominantly IFN- $\alpha$ ): side-effects are common, especially depression, and more rarely, suicidal ideas and attempted suicide. Irritability, anxiety, insomnia and other behavioural disturbances have also been reported and additional adverse effects of IFN- $\alpha$  include mood and personality change. Development of the IFN- $\alpha$ -induced depressive symptoms may arise through depletion of central and peripheral 5-hydroxytryptamine (serotonin, 5-HT) and reduction of tryptophan plasma levels. Psychiatric advice should be obtained if severe symptoms develop.
- **Gastrointestinal (GI) adverse effects** are common and include nausea, anorexia, vomiting and diarrhoea and may result in weight loss. Gingival bleeding and GI haemorrhage have been reported more rarely. Antiemetic medication and adequate hydration may improve nausea, especially during i/v administration. Pancreatitis has been reported rarely.
- **Neurological** (all IFNs but predominantly IFN- $\alpha$ ): headache and dizziness are very common and other neurological effects include impaired concentration, lethargy, sleep disturbance, confusion, paraesthesia, resting and action tremor and involuntary movements. Most of the CNS adverse effects are mild and reversible within a few days to 3 weeks after dose reduction or discontinuation of therapy. Seizures may occur in up to 1% of patients and are reversible on discontinuation of the therapy.
- **Dermatological** (predominantly IFN- $\alpha$  and IFN- $\beta$ ): injection site reactions are common and various rashes have been reported including psoriasiform, eczematous and pemphigus-like eruptions. Seborrhoea, dry skin, pruritus and alopecia may occur.
- **Respiratory** (all IFNs): common flu-like adverse effects include cough, throat irritation and rhinosinusitis. Dyspnoea and pneumonia may occur.
- **Cardiovascular** (all IFNs): cardiovascular adverse effects may include hypertension and hypotension, cardiac failure and rarely, myocardial infarction. Cardiomyopathy has also been reported rarely in patients treated with IFN- $\alpha$ .
- **Hepatic** (all IFNs): adverse effects have included transient increases of liver transaminase or alkaline phosphatase and the development of autoimmune hepatitis.
- **Haematological** (all IFNs): myelosuppression may occur, particularly a reduction in granulocytes, so regular monitoring of the FBC is required throughout therapy.
- **Rhabdomyolysis** and multiorgan failure have been reported shortly after starting high dose IFN.

- **Metabolic adverse effects** include hypertriglyceridaemia and hyperglycaemia. Thyroid function may become abnormal (hypo- or hyperthyroidism).
- Autoimmune abnormalities have been reported including vasculitis, lupus and vitiligo.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category C)

IFNs are contraindicated during pregnancy unless absolutely necessary. Fertility may be impaired by IFN- $\alpha$ , which is known to cause miscarriages in primates. Contraception is recommended for both males and females during treatment. Spontaneous abortions have been reported in females taking IFN- $\beta$  for multiple sclerosis.

#### Lactation

IFNs should be avoided as there are insufficient data regarding safety in lactation.

#### Children

IFN- $\alpha$  has been used safely in children in doses of up to 10 mIU/m<sup>2</sup>. IFN- $\gamma$  has been used in children, but the safety and efficacy in infants under 6 months is not known.

### + Essential patient information

Patients should be advised of the common side-effects of flu-like symptoms and fatigue. Further information can be obtained from [www.macmillan.org.uk](http://www.macmillan.org.uk).

*With acknowledgements to Katharine Acland, author of this chapter in the 1st edition.*

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# Intravenous Immunoglobulin

Francisco Kerdel & Luis Dehesa

## + Classification & mode of action

Immunoglobulin (Ig) preparations derived from human blood are important biological agents. They were first used to treat immune deficiency states in 1952. Intravenous immunoglobulin (IVIg) is purified from the pooled human plasma of 3,000–10,000 healthy donors. Pooling provides the entire array of antibodies normally present in healthy immunocompetent individuals. Since there are large numbers of donors, there is a possibility of diluting rare antibodies that may be present in low concentration.

The manufacturing process is complex and includes important steps such as careful donor selection, screening of plasma samples for infectious agents and the use of modern viral inactivation techniques in order to optimize safety. Standards are set by various regulatory agencies including the FDA, European Medicines Agency and the World Health Organization (WHO).

Various modifications have been applied to the original technique of obtaining purified commercial IVIg by ethanolic fractionation of plasma. Recently, a completely newly engineered purification process combining caprylate precipitation, viral inactivation and double anion exchange chromatography has been developed. This procedure yields a highly purified product in a shorter time and with minimal protein denaturation.

A single donation of whole blood (500 mL) yields approximately 15 mL of plasma proteins, of which only 2–3 mL is highly concentrated pure gammaglobulin. IVIg contains relatively pure concentrate of IgG with a distribution of IgG subclasses corresponding to that of normal serum. The product may also contain variable amounts of albumin, IgA, IgM, IgE, sugars, salts, solvents, detergents and buffers. These may affect the tolerability of IVIg infusions, especially the sugar, salt and/or IgA content. The powder product that has a longer shelf life is dissolved in sucrose. The sucrose content affects the osmotic load of the preparation and can increase the risk of acute renal failure in predisposed individuals.

The exact mechanism of action of IVIg is unclear and may differ in different diseases. Proposed actions include functional blockade of Fc receptors, complement inhibition, enhanced steroid sensitivity, modulation of dendritic cell properties, autoantibody neutralization and inhibition of autoantibody production, modulation of cytokine and cytokine antagonist production, signalling through the inhibitory Fc receptor (Fc gamma RIIB) and inhibition

of keratinocyte apoptosis due to blockade of the death receptor Fas (CD95) by anti-Fas antibodies. In treating any disease, more than one mechanism may operate. It is possible that in diseases that have multiple stages, different mechanisms may play an important role at different stages.

### **+ Indications & dermatological uses**

Human normal immunoglobulin (HNIG) is given i/m as protection against viral infections (hepatitis A, measles and rubella). HNIG is also used as replacement therapy for patients with congenital agammaglobulinaemia/hypogammaglobulinaemia, and for the prophylaxis of infection following bone marrow transplantation and in children with human immunodeficiency virus (HIV) infection.

IVIg is used to treat various autoimmune and infectious diseases, e.g. idiopathic (immune) thrombocytopenic purpura (ITP) and Kawasaki's disease. Other indications include chronic inflammatory demyelinating polyneuropathy (CIDP) and the acute form of the disease, Guillan-Barré syndrome. In dermatology, high dose IVIg has been used with promising results for the treatment of multiple conditions (see below). However, none of these indications have been approved by the FDA.

### **Dermatomyositis**

This is the dermatological condition with the highest level of evidence for treatment with IVIg. Multiple case reports, case series and double-blind, placebo-controlled clinical trials have demonstrated the efficacy of high dose IVIg in patients with dermatomyositis. All severe forms of dermatomyositis and/or polymyositis represent potential indications for the use of IVIg. However, it is not effective as monotherapy and should be used as adjuvant therapy (together with corticosteroids with or without immunosuppressants). IVIg therapy is usually considered as a second-line therapy when steroids have failed or are contraindicated. However, in patients with a severe progressive course, severe myolysis or paralysis, initial treatment with IVIg may be justified. Treatment should be administered for a 6-month period in order to determine efficacy. A total dose of 2 g/kg/mo is generally recommended and should be infused over a period of 2–5 days. Usually, about 3–4 treatment cycles are required at monthly intervals before achieving a significant improvement.

### **Autoimmune blistering diseases**

Adjuvant therapy with IVIg may be considered for all severe, treatment resistant forms of autoimmune blistering disease. Especially good results have been reported for the treatment of pemphigus vulgaris, pemphigus foliaceus, mucous membrane pemphigoid and epidermolysis bullosa acquisita; IVIg may warrant consideration in severe bullous pemphigoid, linear IgA disease and paraneoplastic pemphigus. In all these cases, IVIg therapy should be used as a second-line agent after an adequate trial of systemic steroids and other immunosuppressive agents such as azathioprine or mycophenolate mofetil. As for



dermatomyositis (see above), IVIg appears to have greater efficacy as adjunctive therapy than monotherapy and treatment should therefore be combined with systemic corticosteroids with or without other immunosuppressive agents. IVIg should be administered for a period of 3–6 months in order to assess its efficacy. A total dose of 2 g/kg/mo is generally recommended. It could be infused over a period of 2–5 days or 2–3 days depending on total dose required and the general health of the patient. Slow infusion of 4–5 hours or longer reduces the incidence of infusion related side-effects.

Guidelines for the indications, dosage, frequency of administration and monitoring of IVIg were established by a large panel of experts on blistering diseases from the USA, Canada and Europe, in a consensus statement entitled '*Use of IVIg in autoimmune blistering diseases*'.

### Toxic epidermal necrolysis

Although the early administration of IVIg in toxic epidermal necrolysis (TEN) was reported to reverse the progression of skin disease with a favourable outcome (potentially life-saving) some controversy remains about its effectiveness. Randomized controlled trials are needed to provide a definitive answer. A systematic review and meta-analysis in 2012 found no clear benefit in subjects receiving IVIg versus supportive care alone.

In the treatment of TEN IVIg is usually given as monotherapy and administered as soon as possible after confirmation of the diagnosis. A total dose of 3–4 g/kg is generally recommended and should be infused in divided doses over a period of 3–5 days.

### Systemic vasculitis

Initial treatment usually consists of high dose corticosteroids with or without immunosuppressive agents such as cyclophosphamide. In patients who fail to respond, IVIg may be included as a therapeutic option. Benefit has been reported in Wegener's granulomatosis, Churg–Strauss vasculitis, polyarteritis nodosa, microscopic polyangitis, IgA associated vasculitis and catastrophic antiphospholipid syndrome. Only in Kawasaki's syndrome is the use of IVIg recommended as first-line treatment. However, the early use of IVIg in Wegener's granulomatosis or in haemorrhagic necrotizing vasculitis of the skin may prevent massive tissue destruction. The recommended dose for the treatment of Kawasaki's syndrome in children is 1.6–2 g/kg/cycle (as bolus infusion or given over 2–5 days) in combination with the recommended administration of acetylsalicylic acid.

**Other dermatoses** that have been reported to improve with the use of IVIg include autoimmune chronic urticaria, severe atopic dermatitis, pyoderma gangrenosum, systemic lupus erythematosus (SLE) and other collagen vascular diseases, pretibial myxedema and scleromyxedema. The role of IVIg in the management of these diseases (with the exception of dermatomyositis) awaits clarification by double-blind, placebo-controlled trials. Although relatively safe compared with immunosuppressive agents, the high cost, combined with the logistical issues involved in its administration has limited the use of IVIg in dermatological diseases.

## + Formulations/Presentation

Different preparations of IVIg for i/v administration exist depending on the manufacturer. Lyophilized formulations have to be reconstituted with normal saline, water for injection, or 5% dextrose in water just before treatment to achieve concentrations of 3–12%. Liquid preparations are also available, reducing the time required for reconstitution and limiting the risk of error. Most liquid preparations are available in concentrations of 5% (0.05 g/mL or 1 g/20 mL) or 10% (0.1 g/mL or 1 g/10 mL).

The sugar, sodium, IgA, osmolarity and pH of IVIg vary according to manufacturer and may influence the rate of adverse effects. A highly purified product is now available, marketed under the name Gamunex®.

## + Dosages & suggested regimens

The doses and regimens of high dose IVIg have varied in different studies. A total dosage of **2 g/kg** bodyweight at **monthly intervals** given over **2, 3 or 5 consecutive days** is recommended. The recommended total dose for treatment of TEN is 3–4 g/kg administered on 3–5 consecutive days. The speed of the infusion is carefully monitored and adjusted to reduce the risk of adverse events.

As the half-life of IVIg after i/v infusion is approximately 2–3 weeks, infusions are initially administered at monthly intervals. After 6 months, a gradual increase to 6-week intervals can be considered if there is a satisfactory response. It is usual to prescribe only one treatment cycle of IVIg for TEN and Kawasaki's disease.

## + Baseline investigations & considerations

- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs.
- Hepatitis B and C serology.
- Antinuclear antibody, rheumatoid factor +/- cryoglobulins.
- Quantitative serum immunoglobulins (IgG, IgM, IgA; if IgA is low or absent, measure anti-IgA antibodies).

## + Monitoring

- During infusion, vital signs (BP, heart rate and temperature) should be monitored every 15–30 minutes, particularly during the initial infusion and throughout the first course of therapy.
- Post-infusion, FBC should be measured frequently (daily at first then at least at monthly intervals) for the rare occurrence of Coombs-positive haemolytic

anaemia (reticulocyte count, haptoglobin) and neutropenia. Renal function and LFTs should be checked on day 2 or 3 of treatment.

### + Contraindications

- Previous anaphylaxis or severe systemic response to Ig preparations.
- Rapidly progressive renal failure.
- Selective IgA deficiency with antibodies to IgA is cited by most manufacturers as a contraindication to their product. However, an IgA depleted preparation of IVIg may be used with caution. Selective IgA deficiency occurs in approximately 1 in 700 of the population so IgA should be measured before therapy.
- Recent or imminent live virus vaccination (relative contraindication), as the immune response may be affected.

### + Cautions

- Impaired renal function or concurrent nephrotoxic drug therapy.
- Patients at increased risk of thromboembolism (including obesity, prolonged immobilization, hyperviscosity, cryoglobulinaemia, impaired cardiac function).
- History of SLE, rheumatoid arthritis.
- History of migraine as IVIg may trigger a migraine attack.
- Diabetes mellitus.
- Sepsis.
- Elderly: In patients over 65 years of age the recommended dose should not be exceeded. The infusions should be administered at a very slow rate.

### + Important drug interactions

No drug interactions have been reported to the date with IVIg products.

- **Nephrotoxic drugs** should be used with great caution and in consultation with the treating physician during IVIg therapy. This is emphasized to minimize the risk of causing acute renal failure.
- **Live virus vaccines**, such as measles, mumps and rubella, should not be given for 12 days before or 3 months after IVIg, as the product may contain antibodies which can interact with these vaccines.

### + Adverse effects & their management

With the current careful selection of plasma donors and advances in the manufacturing and purification of IVIg products, the rate of adverse events

associated with IVIg infusion has considerably decreased. Most reactions are mild and self-limiting or easy to treat. Frequently they occur during the first cycle and often during the first few hours of the infusion.

- **Headache, fever, chills, nausea, vomiting, dizziness, flu-like symptoms, arthralgia, migraine, hypotension and urticarial rash** are some of the most common side-effects. These can usually be overcome by reducing the rate of infusion, administering non-steroidal anti-inflammatory drugs (NSAIDs) acetaminophen, corticosteroids and/or antihistamines before beginning the infusion.

The incidence of adverse events is reported by the manufacturers to be in the range of 1–15%, and is usually less than 5%, but may be higher in hypogammaglobulinaemic patients. The management of specific adverse events is shown in Table 1.

- Although rare, severe adverse events can also occur, especially in patients with co-morbidities or risk factors. Therefore, it is important to obtain a complete medical history and to perform a thorough medical evaluation before initiation of IVIg therapy. Adverse events include **aseptic meningitis, acute renal failure, deep venous thrombosis and/or pulmonary embolism, myocardial infarction, stroke and anaphylactic shock**.

**TABLE 1** Adverse effects of IVIg therapy and their management

Minor adverse events	Management
Headache	Paracetamol (acetaminophen)/codeine Slow rate of infusion
Fever, chills, nausea, vomiting, dizziness, flu-like symptoms, arthralgias, sore throat.	Paracetamol Slow rate of infusion
Migraine	Bed rest Consider prophylaxis 2 days prior, during, and 2 days post-therapy with propranolol, or whichever drug has worked in the past, for future infusions
Hypotension/hypertension	Slow rate of infusion
Phlebitis at infusion site	Change infusion site
Transient elevation of serum creatinine	Observe
Transient elevation of liver enzymes	Observe
Transient urticarial eruption	Oral antihistamines
Vesicular hand/foot and generalized eczema	Topical corticosteroids

(continued)

**TABLE 1** (continued)

Severe adverse events (rare)	Management
Aseptic meningitis	Bed rest Paracetamol/codeine/stronger analgesia. For future infusions: pre-medicate with cetirizine, encourage high oral intake of fluids, infuse at a slow rate and the most dilute solution available Check if patient or family has history of migraines
Acute renal failure	Slow rate, low IVIg concentration, sucrose-free preparations Supportive haemodialysis
Anaphylactic shock	Intravenous hydrocortisone + antihistamines, intravenous fluids +/- adrenaline
Deep venous thrombosis (DVT)/ pulmonary embolism (PE)	Stop infusion Specific treatment of DVT or PE Consult vascular surgeon to prevent a future recurrence
Myocardial infarction (MI)	Stop infusion Specific treatment of MI

In practice, when prescribing IVIg, it is important to consider underlying risk factors and choose a brand of IVIg with a suitable composition. For example, in older patients or those with renal dysfunction, use a sugar-free preparation. Despite the absence of comparative data regarding the incidence of side-effects among different IVIg brands, the variable content of sugar, sodium, IgA, pH and osmolarity may influence the occurrence of side-effects. Moreover, the rate of infusion, concentration and total volume infused are important contributing factors.

**+ Use in special situations**

**Pregnancy (FDA Category C)**

There are no animal data regarding the use of IVIg in pregnancy. Manufacturers recommend that IVIg be administered in pregnancy only if clearly needed. IVIg has been safely used in pregnant patients with pemphigus vulgaris with positive outcomes. Benefit has been shown in a number of other conditions in pregnancy, including antiphospholipid syndrome with recurrent spontaneous abortions, ITP and pemphigus gestationis. However, IVIg crosses the placenta and there have been isolated reports of neonatal haemolysis. The potential for transmission of infectious agents remains a concern.

## Lactation

The proteins in IVIg are likely to be excreted in breast milk without having an adverse effect on the breastfed infant. However, there is no information regarding the safety of IVIg during lactation.

## Children

High dose IVIg has been used for non-dermatological diseases in children such as ITP and Kawasaki's syndrome.

### + Essential patient information

Patients should be informed that the product is prepared from human blood or plasma and the transmission of infectious agents (in particular, currently unrecognized ones) cannot be excluded.

*With acknowledgements to Razzaque Ahmed who reviewed this chapter from an international perspective.*

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# Isotretinoin

Alison Layton

## + Classification & mode of action

Oral isotretinoin (13-*cis*-retinoic acid) is a vitamin A derivative, first approved by the USA FDA in 1982 for the treatment of severe, recalcitrant acne. Trace amounts of 13-*cis*-retinoic acid are detectable in normal human plasma suggesting that it is an endogenous retinoid.

Oral isotretinoin monotherapy targets all the major pathogenic processes in acne. It has effects on cell cycle progression, cellular differentiation, cellular survival and apoptosis, which lead to a decrease in sebum production and comedogenesis, thereby reducing surface and ductal *Propionibacterium acnes* and it has additional anti-inflammatory properties. Isotretinoin is the only oral retinoid drug which has a profound effect on sebaceous gland activity, causing sebocyte apoptosis by inducing the expression of neutrophil gelatinase associated lipocalin. Isotretinoin also impairs metabolism of androgens within the sebaceous gland, leading to involution and reduced sebum production. It up-regulates genes encoding differentiation markers, tumour suppressors, serine proteases and innate immune proteins, with more delayed effects on extracellular matrix genes and down-regulates numerous genes involved in lipid metabolism. The drug lacks any direct antimicrobial action against *P. acnes* but makes the microenvironment of the pilosebaceous duct less favourable by inhibition of sebum excretion and reducing the size of the duct. This lowers bacterial levels, which in turn reduces inflammation. Isotretinoin also modifies monocyte chemotaxis, which in part explains its anti-inflammatory effects.

Isotretinoin acts as a pro-drug, as it lacks the ability to bind directly to cellular retinol binding proteins or retinoid nuclear receptors (RAR and RXR) but it has at least five biologically important metabolites that are agonists for these receptors: 4-oxo-isotretinoin, tretinoin, 4-oxo-tretinoin, 9-*cis*-retinoic acid and 4-oxo-9-*cis*-retinoic acid.

## + Indications & dermatological uses

It is recommended that oral isotretinoin is considered in the following situations:

- Severe acne including nodulocystic and conglobate variants and extensive truncal acne.
- Acne with scarring.

- Persistent acne that has failed to respond to adequate antibiotic therapy, including late onset acne (typically females in their 20s and 30s).
- Acne associated with psychosocial disability.

Early onset acne, persistent hyperseborrhoea and a strong family history of acne are relevant factors as these may be associated with more severe or recalcitrant disease.

Oral isotretinoin has unparalleled efficacy in the treatment of acne with the majority of sufferers achieving disease clearance. Relapse rates vary according to patient age, sex, dosage regimens and disease type. It has also been used successfully for the treatment of severe papulopustular rosacea at low dosage and for severe acneiform eruptions induced by epidermal growth factor receptor (EGFR) inhibitors. There are also reports of benefit in hidradenitis suppurativa, cutaneous lupus, pityriasis rubra pilaris, psoriasis, disorders of keratinization (Darier disease, keratoderma), photoageing and in the chemoprevention of non-melanoma skin cancer in naevoid basal cell carcinoma syndrome and xeroderma pigmentosum.

The manufacturers advise that oral isotretinoin should not be used in pre-pubertal children or children under 12 years; however, it has been used in this context without harmful effects and may be warranted for severe disease.

### + Formulations/Presentation

- Soft capsules containing 5 mg, 10 mg, 20 mg or 40 mg isotretinoin, depending on the manufacturers.
- Excipients may include soya bean oil (refined, hydrogenated and partially hydrogenated), gelatine, beeswax and sorbitol (E420). Various colourants are present in the capsule shell.

### + Dosages & suggested regimens

It has been clarified that an isotretinoin dosage of **1 mg/kg/d** achieves a better clearance than 0.5 mg/kg/d over a **4-month period**, but leads to increased mucocutaneous effects that may not be tolerated. The European Directive therefore recommends a **starting dose** of **0.5 mg/kg/d**, with subsequent dose adjustment according to clinical response and side-effects. The use of 0.5 mg/kg or lower dosages at the onset of treatment may reduce the likelihood of an acne flare.

Clinical improvement may not be evident for **6–8 weeks**, with continued improvement over several months and beyond completion of treatment. Early studies suggest that the cumulative dose is important in preventing relapse in patients with severe disease and a **cumulative dose** of **120–150 mg/kg** has been indicated in this context. Severe nodulocystic acne or truncal acne in males may require more prolonged therapy and daily doses above **1 mg/kg**.



Alternative regimens including intermittent (1 week per month) low moderate dose (0.25–0.4 mg/kg/d) have been described in the literature. These may reduce side-effects and the overall cost of therapy but drawbacks include concerns about increased durations of exposure and therefore teratogenic risk in fertile females, as well as possible increased frequency of relapse. This approach is not included in the product license.

If a severe flare occurs, isotretinoin should be stopped or the dose reduced and oral prednisolone/prednisone (0.5–1 mg/kg/d) given, then tapered over 4–6 weeks. Isolated large nodules can be treated with topical or intralesional steroids. Macrocomedones should ideally be treated with cautery or hyfrecation before isotretinoin is considered.

Isotretinoin is fat soluble and should be taken with food (preferably containing some fat) or a glass of milk to maximize bioavailability. A novel hard gelatin capsule, lipid rich formulation is available in the USA that has improved bioavailability when taken without food.

Suggested treatment schedules for unusual forms of acne are listed in Table 1.

**TABLE 1** Suggested treatment schedules for unusual forms of acne

Acne fulminans	Oral prednisolone 0.5–0.1 mg/kg/d for 4–6 weeks Introduce isotretinoin 0.5 mg/kg/d after 3–4 weeks Continue isotretinoin for 6–8 months to reach a cumulative dosage of 120 mg/kg
Pyoderma faciale	Oral prednisolone 0.5–0.1 mg/kg/d for 4–6 weeks Daily application of a very potent topical corticosteroid for 1 week Introduce isotretinoin 0.5 mg/kg/day after 1 week Continue isotretinoin for 4–6 months
Gram-negative folliculitis	Isotretinoin 0.5–1 mg/kg/d for 4–8 months

### Systemic disease

Low starting doses (0.25–0.5 mg/kg/d) and modest increases at 2-monthly intervals if required for a treatment duration of 24 weeks may be considered for patients with underlying medical illnesses such as multiple sclerosis, motor neurone disease or chronic renal failure/dialysis. For those with rare diseases where there is a paucity of information, one suggested regimen is to commence isotretinoin at a dose of 20 mg per week and to increase the dose by 20 mg every subsequent week, so that the patient is taking 20 mg daily by the 7th week. The cycle can then be repeated with a twice daily dose so that by the 14th week patients are taking 20 mg twice a day.

## + Baseline investigations & considerations

The **Pregnancy Prevention Programme (PPP)** for all systemic retinoids includes:

- Pregnancy testing for all females of reproductive age (see below).
- Establishment of effective contraception.
- Counselling regarding teratogenicity for all females.

The following are recommended in all patients:

- FBC (CBC).
- LFTs.
- Fasting lipids.
- Fasting glucose (if family history or known diabetes).
- Document mood/mental health state (see below).

### Special point

Oral isotretinoin is a potent teratogen (see Adverse effects and their management). The European Medicine Control Agency has introduced a PPP to reduce the risk of pregnancy in females of childbearing age who receive oral isotretinoin. A more stringent system (iPLEDGE) has been introduced in the USA.

All females should be carefully counselled about the risk of severe birth deformity associated with oral isotretinoin and provided with a written information brochure provided by the manufacturer of the brand being prescribed.

European guidelines stipulate effective contraception for all sexually active females and the manufacturers specify use of one or preferably two effective contraceptive methods including condoms or a cap plus spermicide. Effective contraception must be started at least 4 weeks before treatment, continued throughout treatment and for at least 4 weeks following cessation. The ultimate choice of specific contraceptive method is a decision made between the patient (and the parent/guardian if relevant) and their consulting physician. Females who are not sexually active may choose to be exempt from the PPP and should sign a disclaimer that they are not at risk of pregnancy and fully aware of the teratogenic risks of treatment (see Appendix 3).

USA recommendations include mandatory simultaneous use of two forms of contraception at least one of which must be highly effective (tubal ligation, partner's vasectomy, intrauterine device or combined hormonal birth control pill/implant/patch).

A negative baseline pregnancy test should ideally be obtained within 2–3 days prior to menstruation and the drug should then be started on the second or third day of the menstrual cycle. Due to irregular menses, this is not always possible, but a negative pregnancy test should be documented prior to starting isotretinoin in this situation. In Europe, no particular form of testing is specified, while the USA licence stipulates that a negative serum or urine pregnancy test with a sensitivity of at least 25 MIU/mL must be performed within the week prior to starting therapy.

USA monitoring requirements stipulate two negative pregnancy tests 30 days apart before starting therapy. Prescriptions for females who are at risk of pregnancy are limited to 30 days and are only valid for 7 days. A negative pregnancy test should be obtained before each repeat prescription and a post-treatment pregnancy test performed 5 weeks after completing therapy to exclude pregnancy.

### + Monitoring

- Pregnancy testing (in females of reproductive age at risk of pregnancy).
- Fasting lipids and LFTs after 1 month; then if normal, at 3 monthly intervals.
- Blood glucose monitoring in patients with diabetes or impaired glucose tolerance.

### + Contraindications

- Pregnancy (see below).
- Lactation.
- Uncontrolled severe hyperlipidaemia.
- Hypersensitivity to retinoids or excipients.

Patients taking isotretinoin should not donate blood during treatment and for at least 1 month after stopping therapy.

### + Cautions

- Liver disease.
- Severe renal impairment (elimination reduced).
- Inflammatory bowel disease (IBD) (see Adverse effects & their management).
- Diabetes.
- Hyperlipidaemia.
- Obesity.
- Alcohol excess.
- Mental health issues (see Adverse effects & their management).

Lower doses or more frequent monitoring may be indicated in these situations.

### + Important drug interactions

- **Methotrexate** may increase the risk of retinoid hepatotoxicity so careful monitoring is required.
- **Carbamazepine** levels are reduced by concurrent intake of isotretinoin, which may lead to loss of seizure control, so carbamazepine levels need

close monitoring when both drugs are taken. Isotretinoin does not interact with phenytoin.

- **Alcohol:** heavy intake of alcohol has been noted to reduce the efficacy of isotretinoin and may increase the risk of hepatotoxicity.
- **Tetracyclines** should be avoided during isotretinoin therapy as both drugs can cause pseudotumour cerebri (PTC)/benign intracranial hypertension. There are reports of combined treatment resulting in PTC and although this is likely to be idiosyncratic to both drug types, experts advise against their combined use.
- **Vitamin A** intake should not exceed the recommended dietary allowance (4,000–5,000 units/d). Supplements are contraindicated due to the risk of hypervitaminosis/retinoid toxicity.
- **St John's wort** for depression may reduce the effectiveness of hormonal contraception and should be avoided in females who are reliant on this form of birth control.

### + Adverse effects & their management

- **Teratogenicity:** it is established that systemic isotretinoin use in early pregnancy commonly results in fetal abnormalities including craniofacial, cardiac, thymic and CNS problems. Studies of human exposure to isotretinoin demonstrate that about 30% of infants will have major malformations. It is therefore essential that all females are carefully counselled about this risk and that the PPP is followed with adequate contraception before, during and after therapy.
- **Hyperlipidaemia** is common, affecting 30–40% of patients, but drug induced increases in cholesterol or triglycerides do not usually require treatment and are dose related, resolving within 4–8 weeks of stopping therapy. Retinoid induced hyperlipidaemia occurs more frequently in patients with underlying predisposing factors, e.g. obesity, alcohol excess, diabetes, familial hyperlipidaemia and concomitant oral contraceptive use. It may be a predictor of idiopathic hyperlipidaemia in later life. The increased low-density (LDL) cholesterol and decreased high-density (HDL) cholesterol in patients receiving retinoids theoretically increases the possibility of accelerated atherosclerosis and ischaemic heart disease. This is a consideration in patients undergoing long-term therapy or those with pre-existing coronary artery disease.

In the first instance, retinoid induced increased levels of triglycerides and cholesterol can be managed by an appropriate diet and supplementation with fish oil capsules (omega-3 fatty acids). Lipid lowering drugs may be indicated in severe hyperlipidaemia. Triglyceride levels  $>8$  mmol/L may be associated with eruptive xanthomas and acute haemorrhagic pancreatitis. There have been isolated reports of these events in patients receiving isotretinoin, but all have occurred in the context of predisposing underlying medical problems.

- **Psychiatric:** mood changes, depression and suicide have been reported as possible adverse effects of isotretinoin. While acne itself is often associated with anxiety and depression, there is a possibility that in rare cases depression may arise as an idiosyncratic reaction to the drug. Patients with a history of bipolar disorder or family history of psychiatric disorders may be at increased risk. Pre-existing depression and a history of attempted suicide are not contraindications to isotretinoin, but it is important to monitor such patients carefully. The possibility of adverse psychiatric events should be discussed with patients and if relevant, their family. It is sensible to obtain the patient's signature to a statement in their records that they understand and have had the opportunity to discuss and consider these problems.

An enquiry about **psychological symptoms** should be made at each visit. The most commonly described symptoms include fatigue, irritability, poor concentration, tearfulness, apathy and forgetfulness. The following simple screening questions can be asked:

Over the past 2 weeks have you consistently:

- Felt unusually sad or fed up?
- Lost interest in things that used to interest you or gave you pleasure?
- Felt more short tempered, agitated or irritable than previously?

A number of questionnaires to assess depression are available. The PHQ-9 (see Appendix 1) has been validated in adolescents and provides a quick and useful tool to assess depression in this vulnerable age group. If significant depression is identified, then a psychiatric referral is indicated. Increased aggression has been identified in some male patients and the FDA in the USA has advised clinicians to warn potential patients about this side-effect. If there is any doubt, the drug must be stopped.

- **Benign intracranial hypertension** is a rare complication of retinoid therapy. Symptoms include a persistent headache that is unresponsive to simple analgesia, nausea, vomiting and visual disturbance. Patients with these symptoms should be examined for papilloedema and if present they should discontinue the drug immediately and be referred for urgent neurological advice. Mild headache in the absence of other symptoms is common on starting retinoid therapy.
- **Hepatotoxicity:** a transient modest rise in liver transaminases is not unusual but acute hepatitis and jaundice are rare. Abnormalities are most likely to occur in the context of heavy alcohol intake and alcohol consumption should be minimized or stopped during isotretinoin therapy. Elevation of liver enzymes above twice the upper limit of normal should lead to discontinuation of treatment. If the elevation of liver enzymes is less than twice the upper limit of normal, the patient can be managed by more frequent monitoring, e.g. every 2 weeks.
- **Mucocutaneous adverse effects** especially cheilitis and dryness of the skin and mucous membranes affect almost all patients receiving isotretinoin

and are dose related and easily manageable with lip salves and emollients. An increase in epidermal fragility may occur so patients should avoid wax epilation. Due to atrophy of the pilosebaceous apparatus, there is delayed wound healing and it is advised that dermabrasion or laser resurfacing are deferred until at least 6 months after stopping isotretinoin. Facial erythema is also common during treatment and increased sensitivity to sunlight may occur so adequate photo protection is required. Uncommon cutaneous effects include development of pyogenic granulomas, paronychia and diffuse alopecia. Severe skin reactions (erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis) have been reported in patients taking isotretinoin but a causal link is not established.

- **Epistaxis** may occur occasionally due to drying of the nasal mucosa. Petrolatum can relieve dryness and topical antistaphyococcal agents may also be of benefit.
- **Impaired hearing** has very rarely been reported in association with isotretinoin.
- **Ocular adverse effects** include conjunctivitis, dry eyes and decreased tolerance of contact lenses. These may be secondary to meibomian gland dysfunction and can usually be alleviated by eye drops ('artificial tears') and use of spectacles rather than lenses. A decrease in night vision has occasionally been reported and may be persistent, which is an important consideration in those whose employment is dependent on good night vision. Affected individuals should stop isotretinoin and have their serum retinol levels checked, with vitamin A supplements given if required. Pilots should not take isotretinoin and if exposed, can only return to flying after a satisfactory eye examination. Refractive eye surgery should not be undertaken within 6 months of treatment with isotretinoin as this can result in serious sequelae such as corneal ulceration infection and loss of vision.
- **Myalgia and muscle stiffness** occur in a minority of patients, especially those involved in strenuous exercise. Mildly elevated creatine phosphokinase levels have been documented in asymptomatic patients but routine monitoring is not necessary. Patients should be advised to avoid undertaking strenuous exercise or starting fitness training while taking isotretinoin. For keen athletes, a treatment course is best started 'out of season'.
- **Skeletal changes:** children exposed to high doses of isotretinoin are at risk for premature epiphyseal closure, while adults on long-term therapy (>2 years) have an increased tendency to develop hyperostosis and other skeletal changes including calcification of extraspinal tendons and ligaments, especially ankles, pelvis and knees and diffuse idiopathic skeletal hyperostosis (DISH)-like changes in the spine. However, the risk of this is not clearly established. Further investigation with targeted x-rays may be indicated for persistent atypical musculoskeletal pain.
- **Gastrointestinal:** an association between isotretinoin and inflammatory bowel disease (IBD) (ulcerative colitis) has been proposed and this has been the subject of malpractice lawsuits in the USA. However, a recent

population based French case-control study reported that isotretinoin was not associated with any increased risk of ulcerative colitis and was associated with a decreased risk of Crohn's disease. Until clarified, careful counselling and collaboration with GI physicians is advised for patients with IBD prior to commencing therapy. Patients should be advised to stop treatment immediately and seek urgent medical attention if they develop severe GI symptoms.

### **+ Use in special situations**

#### **Pregnancy & pre-conception (FDA Category X)**

Isotretinoin is absolutely contraindicated in pregnancy and females should not become pregnant within at least 1 month of discontinuing treatment (see Special point above). There is no known effect on fertility. There is no evidence of impaired fertility or mutagenic risk in males who receive isotretinoin.

#### **Lactation**

Isotretinoin is excreted in breast milk and should not be taken by females who are breastfeeding.

#### **Children**

Isotretinoin does not have a licence for use in children under the age of 12 years. However, severe nodular acne in early childhood (infantile acne) may merit treatment if unresponsive to conventional therapy. In addition, some patients in the early stages of puberty with marked seborrhoea may fail to respond to conventional therapy and isotretinoin may be required. The risk of scarring from these forms of acne is high if not treated promptly.

### **+ Essential patient information**

Patients should be warned of the possible side-effects and given an up-to-date Patient Information Leaflet as provided by the drug manufacturer. Females should be provided with specific information on teratogenicity and contraception and the requirements of the PPP. Information should be provided on the usual frequency of follow-up visits, monitoring requirements and the contact details of relevant nursing or medical staff should patients or their family have concerns about serious adverse effects.

*With acknowledgements to Gary Peck who reviewed this chapter from an international perspective.*

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# Ivermectin

Francisco Vega-Lopez & Sara Ritchie

## + Classification & mode of action

Ivermectin was developed in the 1970s and is a semi-synthetic derivative of the avermectins (macrocyclic lactones) that are obtained from fermentation products of *Streptomyces avermectinus*. It was initially used in veterinary practice to treat parasitic diseases in small and large vertebrates, and was first reported as a treatment for scabies in humans in 1987.

Ivermectin acts against helminths and arthropods by activating glutamate-gated chloride channels. These receptors are found exclusively in invertebrate nerve and muscle cells and belong to the pentameric cys-loop receptor family of ligand-gated ion channels. Ivermectin binding causes ion channel disruption leading to cell death, and the receptor specificity explains the drug's high efficacy and tolerability in humans. High concentrations of ivermectin can cross the blood-brain barrier and can bind to vertebrate gamma-aminobutyric acid (GABA) type A and glycine receptors. This can cause GABA-mimetic toxicity with hypotension, respiratory failure, coma, and even death.

To ensure human safety, the European Medicines Agency has established an acceptable standard value for fat, liver and kidney tissues from animals; ivermectin is not licensed for use in animals from which milk or milk derived products are used for human consumption.

In Africa, more than 25 million people received ivermectin as treatment for oncocerciasis (river blindness) and lymphatic filariasis (up to 2008). It has subsequently been given as Mass Drug Administration (administration of drugs to whole populations irrespective of disease status) once or twice a year. These parasitic helminth diseases constitute a serious public health burden in tropical regions, hence the importance of programmes to control and eliminate disease and interrupt transmission.

## + Indications & dermatological uses

Ivermectin is unlicensed in the UK. It can be prescribed when indicated and is available by 'special order' manufacturers and specialist-importing companies. The indications for ivermectin in the UK are listed below.

**Onchocerciasis and lymphatic filariasis:** ivermectin is the drug of choice to reduce microfilarial load for prolonged periods of 6–12 months. It has been distributed for more than 25 years in onchocerciasis endemic regions of sub-Saharan Africa, the Arabian peninsula, and Latin America as part of a public health initiative. It has been shown that microfilarial load decreases by 85% within 48 hours of administration and by up to 95% within a few weeks. Ivermectin does not kill the adult *Onchocerca* worms, so treatment needs to be repeated at 6-monthly intervals for several years to kill the microfilaria until the natural death of the adult parasites. There have been a few reports documenting *Onchocerca* resistance to ivermectin.

**Cutaneous larva migrans** (creeping eruption) is caused by migration of animal hookworm larvae in the epidermis and is a self-limiting disease, but if not treated promptly, skin pathology may persist for months. Ivermectin is the drug of choice. Repeated treatments with albendazole (see Azole Anthelmintics) are a good alternative if ivermectin is not available.

**Strongyloidiasis** is caused by a soil transmitted helminth and infected individuals are often asymptomatic. However, severe, disseminated life-threatening disease may occur with immunosuppression. Ivermectin is effective against cutaneous symptoms (larva currens) and systemic disease.

**Scabies:** severe, crusted or resistant scabies is the main indication for ivermectin, particularly in the immunocompromised host. It is also first choice for bed-ridden patients and for institutional out-breaks in prisons, children's homes, hospital wards and homes for the elderly. Efficacy and cure rates of between 85% and 95% have been reported.

**Other uses:** oral ivermectin has been successfully used to treat orbital and nasal myiasis, scalp pediculosis and *Demodex* folliculitis. It is safe and effective against ocular Loa Loa; however, individuals with high parasitic loads are at risk of developing severe neurological reactions after simultaneous treatment with ivermectin and diethylcarbamazine (DEC). Ivermectin has been found to decrease adult survival, fecundity and hatch rate of eggs in *Aedes aegypti* mosquitoes and appears to have similar effects in *Anopheles*, the human malaria vector. Interest has therefore grown regarding its role as a complementary strategy in malaria eradication. Benefit has also been reported in treatment of other soil transmitted helminth infections and gnathostomiasis. An antiviral effect in human immunodeficiency virus (HIV), and cell death in leukaemia cell lines from humans and rodents have also been demonstrated.

## + Formulations/Presentation

- 3 mg tablets and 6 mg scored tablets.
- Tablets should be swallowed whole with water on an empty stomach.
- In the UK, Oral ivermectin is only available on a named patient basis due to its unlicensed status.
- A lotion containing 0.5% ivermectin in 0.5% malathion has been found to be effective in the treatment of head lice in children.
- 1% ivermectin cream is FDA approved for treatment of papulopustular rosacea

### + Dosages & suggested regimens

The dose is **200 µg/kg** bodyweight given in a **single oral dose** (see Table 1). The following regimens are recommended:

- Cutaneous larva migrans: a single dose is usually curative, but if clinical signs and symptoms persist, treatment can be repeated after 3 weeks.
- Strongyloidiasis: treatment given on 2 consecutive days. This 2-day treatment is repeated after 2 weeks in the immunosuppressed.
- Onchocerciasis: single dose every 6–12 months is used as treatment and in Mass Drug Administration (MDA) programmes.

The preferred regimen at the London Hospital for Tropical Diseases is to treat newly diagnosed patients with imported disease as follows: admit patient for first dose, then two further doses at monthly intervals as an outpatient, followed by further doses every 3–6 months.

**TABLE 1** Dosage guidelines for ivermectin

Bodyweight (kg)	Single oral dose (number of 3 mg tablets)
15–24	1 tablet
25–35	2 tablets
36–50	3 tablets
51–65	4 tablets
66–79	5 tablets
≥80	calculate as 200 µg/kg

- Severe scabies (see above): single dose repeated after 1 week.

Additional simultaneous treatment with a topical acaricide should be given on the same days as oral medication. Options include 5% permethrin, 0.5% malathion or 25% benzyl benzoate (avoid in children). All members of the same household require simultaneous treatment. Topical keratolytics and oral antibiotics are indicated for secondarily infected hyperkeratotic lesions.

### + Baseline investigations & considerations

Relevant diagnostic investigations should be performed.

- **Onchocerciasis** is diagnosed on detecting microfilaria in skin snips, positive serology, eosinophilia and ocular manifestations in those with a history of exposure in endemic regions of the world. Patients usually have severe pruritus, which may be accompanied by a papular, lichenified dermatitis. Other findings include nodules (onchocercomata) on trunk and/or limbs

and chronic pigmentary changes (patchy hyper- and hypopigmentation) particularly on the lower limbs. Elimination of *Ascaris* worms can be observed as a secondary effect of treatment with ivermectin.

- **Cutaneous larva migrans** is diagnosed clinically, according to a history of exposure, intense localized pruritus and a distinctive rash comprising an erythematous cutaneous larval track often with a positive 'sign of the loop'. Eosinophilia and Loeffler's syndrome have been described and the diagnosis relies upon a FBC (CBC) with differential white blood cell (WBC) and chest x-rays.
- **Strongyloidiasis** can be reliably diagnosed by an enzyme linked immunosorbent assay (ELISA) serological test and the adult worms can be detected in stools by several methods, though some of these have limitations in detecting the larval stages or particular species. Patients may manifest generalized pruritus, pruritus ani, urticaria and less commonly symptoms of larva currens.
- **Scabies** is usually diagnosed clinically and presents with an intensely pruritic papular eruption with small linear or s-shaped mite tracks (burrows) in the epidermis, which may be more easily visualized with dermoscopy. Vesicopustular and nodular lesions may predominate in children. Microscopic identification of a mite in skin scrapings from a burrow confirms the diagnosis, but is time consuming and not always practical in a busy clinical setting.

### + Monitoring

- No routine blood monitoring is required.
- Treatment response is usually assessed clinically.
- Patients with onchocerciasis are usually followed up every 3–6 months for FBC, skin snips and in some cases repeated serology.

### + Contraindications

- Pregnancy and lactation.
- Young children.

### + Cautions

Severely ill or debilitated individuals and those with neurological disease (due to potential neurotoxicity at high doses).

### + Important drug interactions

Ivermectin is primarily metabolized by cytochrome 450 (CYP450) 3A4, but does not inhibit this enzyme and no drug interactions have been identified.

Simultaneous multidrug treatment with ivermectin, praziquantel and albendazole has been shown to be safe in a study of Ugandan children. When given with DEC for the treatment of lymphatic filiriasis, systemic reactions may be potentiated in heavily infected patients due to death of parasites. Common manifestations include headache, malaise, acute lymphangitis, epididymitis and abscess formation.

### + Adverse effects & their management

Headaches, nausea and vomiting are uncommon. Gastrointestinal symptoms are usually mild and self-resolving.

Ivermectin is usually well-tolerated by patients receiving treatment for scabies, cutaneous larva migrans and strongyloidiasis. In cases of onchocerciasis with heavy microfilaraemia drug reactions can be more severe and similar to those seen in cases treated with DEC (systemic inflammatory and anaphylactoid reactions).

### + Use in special situations

#### **Pregnancy & pre-conception (FDA Category C)**

Ivermectin is contraindicated in pregnancy. Teratogenesis has been widely described in sheep and cows following use of this drug to treat parasitic and ectoparasitic diseases.

#### **Lactation**

Females taking ivermectin should not breastfeed as the drug is excreted in milk.

#### **Children**

It is not recommended for use in children under 5 years of age or weighing less than 15 kg.

### + Essential patient information

The unlicensed nature of this drug should be discussed and females should be advised to avoid pregnancy while taking treatment.

### + Further reading

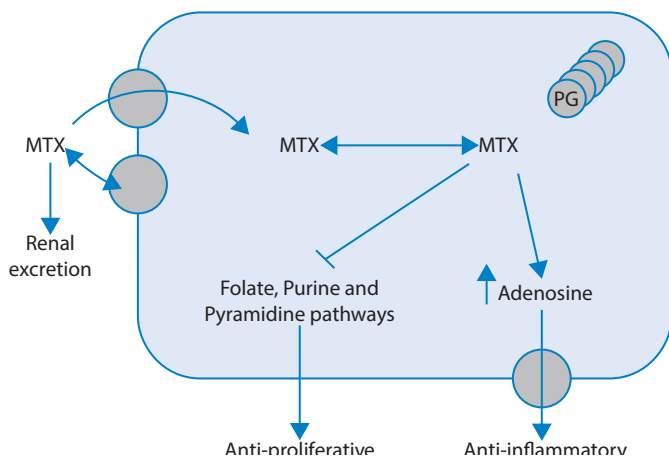
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# Methotrexate

Richard Woolf & Catherine Smith

## + Classification & mode of action

Methotrexate (MTX) is a derivative of folic acid and classified as an antimetabolite cytotoxic agent. It is a pro-drug that is actively transported into cells as MTX-monoglutamate. Following this further glutamic acid residues are added to form biologically active methotrexate polyglutamates (Figure 1) that cannot be transported extracellularly unless hydrolysed back to MTX monoglutamate. This leads to intracellular accumulation of MTX and therapeutic effectiveness with once-weekly administration. Free monoglutamated MTX is rapidly cleared from the serum by renal tubular filtration. In malignant disease, high dose MTX acts as a folate antagonist, competitively inhibiting dihydrofolate reductase, thymidylate synthase and other enzymes involved in *de novo* purine synthesis. At low doses it has anti-inflammatory actions, which are not diminished by concomitant administration of folic acid. These are complex and not clearly understood, but include the release of adenosine that inhibits generation of reactive oxygen species by polymorphs and proliferation of lymphocytes. Adenosine may be responsible for some of the adverse effects of MTX including fatigue and hepatotoxicity.



**FIGURE 1** Methotrexate metabolism in target cell.

Over the past decade there has been a quest to identify genetic markers that reliably predict MTX efficacy and toxicity and it is hoped that in the future these will help to optimize its use.

### + Indications & dermatological uses

- Psoriasis. MTX is licensed for the treatment of severe, uncontrolled psoriasis. It is an effective first-line systemic agent and is considered the gold standard comparator for new interventions for psoriasis, such as biologics. It is a well-established treatment for different variants of psoriasis, including extensive chronic plaque disease, pustular psoriasis, erythrodermic psoriasis and psoriatic arthritis. Published studies suggest that MTX produces a reduction in psoriasis severity of at least 50% in approximately two-thirds of patients. MTX and oral ciclosporin (cyclosporine) have a similar efficacy in the treatment of psoriasis and the choice of agent is influenced by their differing side-effect profiles. Benefit has also been reported in a variety of other inflammatory skin diseases including:
- Atopic dermatitis.
- Lymphoproliferative disorders (lymphomatoid papulosis, mycosis fungoides).
- Bullous pemphigoid.
- Connective tissue disease (recalcitrant cutaneous lupus erythematosus, dermatomyositis, systemic sclerosis and morphoea) and vasculitides.
- Sarcoidosis.
- Lichen planus.

Methotrexate is also licensed in the treatment of rheumatoid arthritis and malignancies (at higher doses), such as leukaemia, non-Hodgkin's lymphoma and certain solid tumours.

### + Formulations/Presentation

- Scored tablets containing 2.5 mg or 10 mg MTX. (NB: Different tablet strengths may be a source of confusion for patients and increase the risk of inadvertent overdose; many dermatologists restrict prescribing to 2.5 mg tablets only to avoid patient error.)
- Parenteral preparations (for i/m, s/c or i/v use): pre-filled syringes containing between 7.5 mg to 30 mg MTX. Usually these are administered by clinical staff; however, with appropriate training patients can self-administer s/c MTX.

### + Dosages & suggested regimens

MTX should be given as a **once weekly single dose**, with or after food, on a specific day of the week, with explicit verbal and written instructions to the



patient. A divided dose regimen (i.e. three 12-hourly doses) should be avoided unless nausea is a significant problem, since the risks of dose error on the part of the patient are greater. Oral administration is convenient and preferable.

**An initial test dose of 5–10 mg** (in normal healthy adults) should be given and FBC (CBC) measured at 1 week. This should detect those that are unduly sensitive to the drug. If the FBC remains stable, the dose can be increased in increments of **2.5 mg** or **5 mg** a week. In the elderly and those with renal impairment the test dose and the dose increments should be reduced to 2.5 mg due to the increased risk of MTX accumulation and toxicity. The **maintenance dose** should be adjusted according to disease response and kept as low as possible. Patients whose weekly dose does not exceed **15 mg/wk** appear to have a very low risk of hepatotoxicity. MTX is a slow acting drug and the complete clinical response for a given dose may take 6–12 weeks to achieve. The **maximum licensed dose** in psoriasis is **30 mg/wk**. However, disease control is usually achieved at a lower dose.

If bioavailability or patient compliance is of concern i/m or s/c administration may be necessary. Although the i/m, s/c and oral routes of administration are considered equipotent, a modest dose reduction is recommended when converting from oral to parenteral administration. Also following a treatment break of several weeks, MTX should be reintroduced at a lower dose (e.g. 5 mg) and then increased as necessary with appropriate monitoring.

### + Baseline investigations & considerations

Baseline liver assessment:

- LFTs including AST and GGT.
- Hepatitis B and C virus.
- Serum PIIINP if available (see Special point).
- Consider liver ultrasound to exclude gross liver pathology.
- Pre-treatment liver biopsy (see Special point): in high risk patients, a liver biopsy is recommended within the first 4–6 months of therapy. Risks of liver biopsy may not be considered justifiable in the elderly, in patients with severe psoriasis where alternative therapies are inappropriate or known to be ineffective and those who may be particularly vulnerable should complications occur (e.g. severe ischaemic heart disease).
- Additional investigations may include: in male patients serum ferritin to exclude haemochromatosis, and in female patients antimitochondrial autoantibodies to exclude primary biliary cirrhosis.

### Special point: Hepatotoxicity

Hepatotoxicity, including liver fibrosis and cirrhosis, is a recognized association with long-term MTX treatment. MTX hepatotoxicity rarely leads to liver failure but is an important cause of treatment withdrawal. The pathogenesis of MTX associated liver fibrosis is not clear and may be multifactorial. Patients on MTX for rheumatoid arthritis appear to be less at risk of liver toxicity. In patients with psoriasis, cumulative MTX (exceeding 1.5 g) and type 2 diabetes mellitus, high

alcohol intake, obesity and viral hepatitis B or C infections are considered risk factors for hepatotoxicity. However, it is unclear if these co-morbidities, often seen in patients with psoriasis, are confounders that in themselves predispose to hepatotoxicity. They should be considered as 'Cautions' when initiating MTX and advice offered on modifiable risk factors before initiating MTX.

Percutaneous liver biopsy is the gold standard for the detection of liver fibrosis/cirrhosis, but its disadvantages include non-diagnostic results due to sampling error and even with ultrasound guidance there is a small risk of serious complications including bleeding and death. Measurement of serial LFTs is unreliable in detecting chronic MTX hepatotoxicity and there is poor correlation with histological change. Newer non-invasive diagnostic tests include measurements of pro-collagen III peptides (type III pro-collagen aminopeptides; PIIINP) and liver fibroelastography (FibroScan®) which utilizes ultrasonography to detect liver fibrosis (see Systemic Therapy & Liver Disease). Serum procollagen III peptide is derived from the synthesis of new type III collagen and degradation of existing collagen fibrils released into the blood during active liver fibrosis. This measurement has a sensitivity and specificity of 74% and 79% respectively, so if normal, it is unlikely that significant liver fibrosis is present. Factors associated with false-positive PIIINP results are young age, smoking, non-steroidal anti-inflammatory drugs (NSAIDs) and joint involvement/arthritis. Serial PIIINP measurement has been adopted by some UK centres to replace/guide routine liver biopsy. With the emergence of non-invasive diagnostic tests, the risks associated with liver biopsy must be balanced against the risks of MTX induced liver fibrosis. However, at present, guidelines for the use of liver biopsy at baseline and during MTX monitoring vary between countries and specialties. Stratification of patients into those with low or high risk of MTX hepatotoxicity may be helpful. High risk patients include those with a history of diabetes, obesity, abnormal LFT results, excessive alcohol intake and/or chronic liver disease. The PIIINP assay can also be used to identify high risk patients (a pre-treatment PIIINP of  $>8.0$  mg/L; during treatment at least three PIIINP results  $>4.2$  mg/L or two consecutive results  $>8.0$  mg/L within a 12-month period). The American Academy of Dermatology guidelines on the use of MTX in psoriasis for high risk patients recommend a liver biopsy near the beginning of therapy, and at each additional 1.0–1.5 g cumulative dose (provided all other investigations are normal). For low risk patients a baseline liver biopsy is not routinely recommended, with a biopsy considered after 3.5–4.0 g cumulative dose, and at each additional 1.5 g. In the UK it has been suggested that pre-treatment liver biopsy is not routinely necessary. If in doubt, specialist hepatological advice should be sought.

Other baseline investigations:

- FBC, red cell folate.
- Serum electrolytes and renal function.
- Urinalysis (including glucose).
- Glomerular filtration rate (GFR) or creatinine clearance in patients over the age of 60 years, with a raised serum creatinine level or a history to suggest potential renal impairment.

- Chest x-ray: useful in the event of pulmonary symptoms developing and also to exclude foci of old tuberculosis that may become reactivated as a result of the immunosuppressive effect of MTX therapy.
- Pregnancy test (urine/serum) in females of childbearing age.
- HIV testing.
- Assessment of disease severity (e.g. Psoriasis Area and Severity Index [PASI], Body Surface Area [BSA], Physician's Global Assessment [PGA]) and health-related quality of life (e.g. Dermatology Life Quality Index [DLQI], see Appendix 4).

### + Monitoring

- FBC, serum electrolytes, renal function and LFTs:
  - Weekly for 2 weeks after each dose increase.
  - 8–12 weekly once dose stabilized.
- Red cell folate if MCV increases.
- Serum PIIINP at 3-monthly intervals (if available).
- Liver biopsy: in low risk patients should be considered after 3.5–4.0 g cumulative dose of MTX, and at each additional 1.5 g. In high risk patients a liver biopsy is recommended at each additional 1.0–1.5 g cumulative dose of MTX. This is provided all other investigations are normal (see Special point).
- Assessment of disease severity (as above) to monitor MTX efficacy.

### + Contraindications

- Severe haematological abnormality – severe anaemia, leukopenia or thrombocytopenia.
- Severe liver disease (fibrosis or cirrhosis).
- Severe renal insufficiency (eGFR <20 mL/min).
- Pregnancy or breastfeeding.
- Hypersensitivity to MTX.
- Active peptic ulcer disease.
- Severe and/or active infectious disease.
- Immunodeficiency.
- Significantly reduced lung function.

### + Cautions

- Renal impairment, i.e. GFR <50 mL/min: since MTX is renally excreted, toxic levels may rapidly accumulate in the presence of renal impairment increasing the risk of myelosuppression. This is particularly liable to occur in the elderly during episodes of dehydration, or as a result of concomitant drug administration, e.g. NSAIDs.

- Pre-existing liver disease or current excessive alcohol intake may predispose to hepatotoxic effects of MTX.
- Serious infection including HIV infection.
- Gastritis or ulcerative colitis.
- History of malignancy.

### + Important drug interactions

- **Cyclosporin, leflunamide, azathioprine and sulfasalazine**; concomitant use with nephrotoxic, myelotoxic or hepatotoxic drugs is not recommended.
- **NSAIDs, penicillin, colchicine and probenecid** may reduce MTX elimination, leading to increased MTX toxicity. Where NSAIDs are considered essential, the lower starting dose of 2.5 mg MTX is indicated with monitoring of renal function after 1 week and at further weekly intervals after dose increases or changes in NSAID therapy. Ideally, NSAIDs should not be taken on a sporadic basis, as the effects on MTX levels can be difficult to predict.
- **Retinoids** may increase the risk of MTX hepatotoxicity.
- **Tetracyclines and chloramphenicol** displace protein-bound MTX, increasing serum concentrations that may lead to increased MTX toxicity.
- **Trimethoprim, sulphonamides and phenytoin** are folate antagonists and may increase MTX toxicity.
- **Radiotherapy**: radiation recall (burns) may occur at sites of prior irradiation.
- **Live vaccines** are contraindicated on theoretical grounds in patients taking MTX.
- **St John's wort** may increase the risk of toxicity.

### + Adverse effects & their management

- **Folic acid deficiency** may arise in patients on MTX and is often identified by a rise in mean corpuscular volume (MCV). This may be exacerbated by concomitant medications that have antifolate activity (see Important drug interactions). If suspected, patients should receive folic acid supplementation for the duration of MTX therapy. Some physicians recommend routine folic acid supplementation to reduce the gastrointestinal or hepatic adverse effects of MTX. Different folic acid dosing regimens have been proposed including 1–5 mg daily, 1–5 mg daily except for days of MTX and 2.5–5 mg once weekly 24 hours following MTX dose. There is no convincing evidence that concomitant folic acid administration reduces MTX efficacy, irrespective of dosing regimen. It is essential that the regimen for folic acid replacement is clearly explained to the patient to avoid confusion with MTX and overdosage of the latter. If the MCV continues to rise (>106 fL) despite folic acid supplementation and other causes are excluded (B12 deficiency or alcohol excess), MTX should be discontinued.

- **Gastrointestinal:** nausea/vomiting affects about 10% of patients, usually occurring 12 hours after ingestion and persisting up to 3 days after therapy. Possible (although unproven) solutions include reducing the dose, adding folic acid, taking MTX with food, administering MTX i/m, s/c and dividing the once weekly dose into three doses, given at 12-hourly intervals (see Dosages and suggested regimens). Malaise, fatigue, dizziness and headache may occur.
- **Myelosuppression** may affect up to 20% of patients on long-term therapy for psoriasis, manifesting as leukopenia, thrombocytopenia, anaemia or pancytopenia. Myelosuppression is the most common cause of death due to MTX in psoriasis patients; 22 (85%) of the 26 fatalities associated with MTX therapy for psoriasis reported to the Committee on Safety of Medicines (UK) between 1969 and 1995 were related to myelosuppression. The risk is increased in those with renal impairment, especially in the elderly, those taking concomitant drugs that reduce MTX excretion, and in folate deficiency (see above). MTX should be discontinued if severe leukopenia, thrombocytopenia or anaemia occur.
- **Hepatotoxicity:** MTX has been associated with both acute and chronic hepatotoxicity (see Special point). Acute elevation in serum aminotransferase concentrations frequently occur 1–3 days after a dose of the drug. These changes are usually transient, asymptomatic and do not appear to be predictive of subsequent chronic hepatotoxicity. Chronic hepatotoxicity may manifest as fibrosis or cirrhosis. Studies in patients with psoriasis treated with MTX have reported widely varying rates of ‘any stage’ of liver fibrosis (5.7–71.8%), which may relate to sample size and inconsistency in histopathological classification. In psoriasis the degree of liver fibrosis appears to be relatively benign with few patients on long-term MTX progressing to cirrhosis. In addition, the aetiopathogenesis of MTX associated hepatotoxicity is not fully understood and is likely confounded by co-morbidities. Withdrawal of MTX in patients who develop MTX induced cirrhosis may lead to improvement in liver histology and even in those who continue treatment, progression of cirrhosis leading to liver failure is not inevitable.

If transaminases (ALT, AST) rise above three times the upper limit of normal, then MTX should be discontinued. For mild rises in liver tests, a minor dose reduction may be considered with close monitoring of LFTs to ensure normalization. Referral to a hepatologist and liver biopsy should be considered if there is persistent elevation of liver enzymes or PIIINP (at least three PIIINP results >4.2 mg/L or two consecutive results >8.0 mg/L within a 12-month period).

- **Pulmonary toxicity** appears to be more common in patients given MTX for rheumatoid disease and is an idiosyncratic adverse effect. If respiratory symptoms develop, such as a dry persistent cough, MTX should be stopped until MTX induced pulmonary toxicity has been excluded.
- **Carcinogenicity:** the risk of carcinogenicity with MTX appears to be low when compared with other immunosuppressive agents used for psoriasis, such as ciclosporin.
- **MTX overdose:** expert advice should be sought in the event of MTX overdose. Clinical manifestations of acute toxicity include myelosuppression, mucosal

ulceration (particularly oral ulcers) and rarely acute skin ulceration. This latter complication is occasionally seen in patients with active extensive psoriasis if the dose of MTX is increased too rapidly. Toxicity can also be precipitated by factors that interfere with either the renal excretion of the drug, such as dehydration, or drug interactions. Folinic acid (calcium leucovorin) is a fully reduced folate coenzyme that can bypass the metabolic effects of MTX. A source of folinic acid should be identified by the prescribing physician for use in the event of overdose. It should be given without delay, ideally within 4 hours of MTX administration, as its efficacy reduces with time. An initial dose of 20 mg of folinic acid should be given i/v or i/m, followed by measurement of serum MTX levels if available. Further doses of folinic acid can be titrated accordingly. If MTX levels cannot be measured, 20 mg of folinic acid should continue to be given every 6 hours until the blood count has normalized and mucosae healed.

- **MTX osteopathy** is a poorly recognized complication of low dose MTX and is characterized by a triad of severe pain, osteoporosis and compression fractures, mostly affecting the distal tibia.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category X)

MTX is strictly contraindicated during pregnancy as it is both an abortifacient and teratogen. It is advised that MTX therapy should be stopped at 3 months before conception by both males and females. However, the necessity of this precaution in males taking low dose MTX has recently been questioned. In the event of an unplanned pregnancy expert advice should be sought.

#### Lactation

MTX is contraindicated in lactation as it is excreted in breast milk.

#### Children

MTX may be used under specialist supervision for children (2–18 years old) with severe psoriasis requiring second-line therapy, although it is not licensed for psoriasis in this age group. It is also gaining popularity as a treatment for severe atopic dermatitis. MTX is given as a once weekly dose, usually initiated at 0.2 mg/kg, which can be increased to 0.4 mg/kg (max. 25 mg) as guided by clinical response. The lowest possible dose required to maintain disease control should be prescribed. The safety profile is relatively favourable in terms of known long-term oncogenic risk. Normal serum PIIINP levels are much higher in children and are therefore of little value in monitoring for hepatotoxicity.

*With acknowledgements to Jonathan Barker, author of this chapter in the 1st edition, and Jean Ayer who reviewed this chapter from an international perspective.*

### + Essential patient information

- The patient must understand and is able to comply with regular blood test monitoring.
- The patient should seek urgent medical attention if they develop symptoms of serious infection including fever, sore throat, breathlessness or unexplained bleeding or bruising.
- Clear prescribing information is essential, especially when folic acid is co-prescribed with MTX, to avoid confusion between these drugs.
- Patients who have not had chickenpox and come into contact with either chickenpox or shingles should seek urgent medical advice.
- Patient should inform their doctor/pharmacist that they are taking MTX before starting any new medication.
- To help improve the safety of MTX prescribing a 'MTX treatment booklet' is recommended for patients to keep a record of any dose changes and the results of monitoring investigations.

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# Mycophenolate Mofetil

Joey L. Chong & Jane Setterfield

## + Classification & mode of action

Mycophenolate mofetil (MMF) is a lymphocyte selective immunosuppressive agent. It inhibits *de novo* purine synthesis via its active metabolite, mycophenolic acid, a potent selective and reversible inhibitor of inosine monophosphate dehydrogenase. Lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can use salvage pathways. MMF thereby prevents the proliferation of T-cells, lymphocytes and the formation of antibodies by B-cells. It may also inhibit leukocyte recruitment to inflammatory sites.

MMF is used for the prophylaxis of acute organ transplant rejection and like several other immunosuppressive agents developed for this use, it has been found to be an effective treatment for various inflammatory dermatoses. The appeal of MMF in dermatology is related to both its potential steroid-sparing effects and its relative lack of toxicity.

## + Indications & dermatological uses

MMF is licensed for use in combination with prednisolone or ciclosporin (cyclosporine) for the prevention of acute kidney, heart and liver transplant rejection.

It has been demonstrated to be of benefit in the treatment of many inflammatory skin diseases, but its use is unlicensed due to lack of large randomized controlled clinical trials. It may be used either as a monotherapy or as a steroid-sparing agent and is generally well-tolerated with a relative lack of toxicity compared with other immunosuppressive drugs. Examples include:

- Autoimmune blistering diseases: bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullosa acquisita, paraneoplastic pemphigus, pemphigus foliaceus and pemphigus vulgaris.
- Dermatitis: actinic dermatitis, atopic dermatitis and psoriasis.
- Connective tissue disorders: dermatomyositis, lupus erythematosus, scleroderma.



- Vasculitides: pyoderma gangrenosum, Churg–Strauss syndrome, hypocomplementaemic urticarial vasculitis, microscopic polyangiitis, Wegener’s granulomatosis.
- Graft-versus-host disease: acute and chronic variants.
- Granulomatous dermatoses including cutaneous Crohn’s disease and sarcoidosis.
- Others: lichen planus, relapsing idiopathic nodular panniculitis.

### + Formulations/Presentation

- 250 mg capsules and 500 mg tablets of MMF.
- Oral suspension (1 g/5 mL) and 500 mg vials of MMF for i/v injection.
- Mycophenolic acid 180 mg and 360 mg delayed release tablets.

In patients who are unable to tolerate the gastrointestinal side-effects of MMF, mycophenolic acid delayed release tablets may be an alternative. Mycophenolic acid 720 mg is approximately equivalent to 1 g of MMF, but unnecessary switching should be avoided due to pharmacokinetic differences.

### + Dosages & suggested regimens

The usual **starting dose** of MMF in dermatological disease is **500 mg bd**. If there is no improvement after 1 month, doses are typically increased in 500 mg increments. The usual **maintenance dose** is **1 g bd**, increased to a **maximum** of **1.5 g bd** if required. These are the doses commonly used in transplant recipients, and for therapeutic effectiveness in skin diseases, similar dosages are usually required.

Dose adjustment is required for patients with renal insufficiency. In those with a glomerular filtration rate (GFR) of less than 25 mL/min, the maximum dosage is 1 g twice a day.

### + Baseline investigations & considerations

- FBC (CBC) and differential WBC.
- Urea, electrolytes and creatinine.
- LFTs.
- Hepatitis B & C serology.
- HIV testing s.
- Chest x-ray.
- Pregnancy testing and effective contraception for females of childbearing age.
- Thorough examination of skin to exclude malignancy and clinical examination to detect lymphadenopathy, breast lumps or organomegaly.
- Ensure up-to-date cervical screening.

MMF may be used with caution in patients with HIV and hepatitis B and C virus infection, under close collaboration with other specialist medical practitioners. The immunosuppressant action of MMF can reactivate hepatitis B and C as well as worsen the immunosuppressive status of patients with HIV.

Flu and pneumococcal vaccination are recommended for people who are on immunosuppressant medication. Ideally these inactive vaccines should be administered at least 2 weeks before therapy is started.

Varicella zoster virus (VZV) vaccine (live attenuated) should be given to the non-immune several weeks before starting MMF if treatment can safely be delayed.

### + Monitoring

FBC, urea, electrolytes and creatinine and LFTs should be monitored weekly for 4 weeks, then twice a month for 2 months and then monthly for the first year. Thereafter, most clinicians would advise monitoring every 3 months provided the patient has been stabilized on MMF.

It is recommended to stop or withhold treatment and contact initiating specialist in the following situations:

- Total white cell count  $<4 \times 10^9/L$ .
- Neutrophil count  $<2 \times 10^9/L$ .
- Platelet count  $<150 \times 10^9/L$ .
- Aspartate or alanine aminotransferase  $>2 \times$  the upper normal limit.
- Hypogammaglobulinaemia.

### + Contraindications

- Hypersensitivity to MMF or mycophenolic acid.
- Pregnancy and lactation (see below).
- Rare inherited deficiencies of the enzyme hypoxanthine-guanine phosphoribosyl-transferase, such as Lesch–Nyhan and Kelley–Seegmiller syndrome, as it exacerbates the underlying abnormality of uric acid metabolism.

### + Cautions

- Peptic ulcer disease (active or past history) and serious gastrointestinal (GI) disease, due to risk of GI haemorrhage, ulceration and perforation associated with MMF therapy.
- HIV and hepatitis B or C (see above).

### + Important drug interactions

Patients should be advised to check with pharmacists and treating physicians before taking any prescribed or over-the-counter medication while on MMF.

- **Antacids** with magnesium and aluminium hydroxides: may impair MMF absorption.
- **Cholestyramine and bile acid sequestrants**: may reduce the enterohepatic circulation and efficacy of MMF.
- **Rifampicin**: may decrease MMF efficacy.
- **Broad-spectrum antibiotics** such as ciprofloxacin and amoxicillin plus clavulanic acid: may reduce the efficacy of MMF due to alteration of GI flora and reduced enterohepatic drug recirculation.
- **Azathioprine**: also inhibits purine metabolism with potential enhanced toxicity.
- **Aciclovir (acyclovir), valaciclovir (valacyclovir) and related antiviral drugs**: may increase mycophenolic acid plasma concentration as they compete for renal tubular secretion so closer monitoring of blood counts is needed.
- **Hormonal contraceptive efficacy** may be reduced: see specific manufacturer's recommendations.

### + Adverse effects & their management

MMF is generally well-tolerated with fewer nephrotoxic, hepatotoxic and neurotoxic side-effects than other immunosuppressive agents.

- **Gastrointestinal**: the most commonly reported side-effects are GI and are dose dependent, occurring in up to 20% of patients at doses of 2 g daily. They include diarrhoea, nausea, vomiting, abdominal pain, anal tenderness, and constipation. These are usually mild and rarely severe enough to result in discontinuation of therapy. Diarrhoea and nausea may be reduced by increasing the dose frequency of MMF. Serious adverse effects include GI haemorrhage, perforation and peptic ulceration.
- **Myelosuppression**: these are mostly anaemia and neutropenia and are usually mild, dose related, and reversible with discontinuation of therapy or dose reduction. Abnormal neutrophil morphology may occur with a left shift phenotype in the absence of infection.
- **Urinary**: these include dysuria, urgency, frequency, and sterile pyuria, as well as haematuria and urinary tract infection.
- **Infection**: the risk of common and opportunistic infections is increased, especially at high doses. This includes herpes simplex, herpes zoster and staphylococcal skin infections in patients with atopic dermatitis and tuberculosis, atypical mycobacterial infections and lower respiratory tract infection/pneumonia.
- **Carcinogenicity**: animal studies have shown an increase in lymphoma; use of MMF in transplant recipients is associated with an increased risk of malignancy, especially lymphoma and lymphoproliferative disorders and non-melanoma skin cancer. These are generally considered to be related

to the duration and intensity of immunosuppression rather than a MMF specific effect. However, MMF may also impair UVB-induced DNA damage repair and apoptosis by immunosuppression independent mechanisms. There have been few reports of malignancy in dermatology patients. Rare cases of primary CNS lymphoma and Epstein–Barr virus (EBV) related B-cell lymphoma of the CNS have also been reported in non-transplant patients.

## + Use in special situations

### Pregnancy (FDA Category D)

MMF should be avoided in pregnancy as an increased rate of first trimester fetal loss and congenital malformations including cleft lip and palate, anomalies of the distal limbs, heart, oesophagus and kidney have been reported. Animal studies have shown reproductive toxicity at doses equivalent to and less than clinical doses.

Females of childbearing age should have effective contraception prior to commencing MMF therapy, during therapy and for 6 weeks following discontinuation of therapy. MMF should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their physician immediately should pregnancy occur, due to the risk of teratogenicity.

### Lactation

Mothers who are taking MMF should not breastfeed. Animal studies have shown that MMF is excreted in milk and although it is not known whether this applies to humans, breastfeeding should be discontinued because of the potential risk to the infant.

### Children

MMF is licensed for use in children of 2 years and above after renal transplantation, at dosages of 600 mg/m<sup>2</sup> twice daily (maximum 2 g daily). There are sparse data of the use of MMF in infants under 2 years. There are very few reports of its use for skin disease in children. Treatment is not appropriate in children with a body surface area less than 1.25 m<sup>2</sup>.

### Elderly

Elderly patients (>65 years) may generally be at increased risk of adverse reactions due to immunosuppression, especially infection and possibly GI disease.

## + Essential patient information

- Patients should be fully informed of the indications for therapy and the unlicensed use of the drug.
- The need for close monitoring with blood tests especially during the initiation phase of treatment should be emphasized.

- Patients should be informed of the increased risk of common and unusual infections and the need to seek urgent medical attention if they become unwell with a high fever.
- The small increased risk of skin cancer must be discussed and the potential risk of lymphoma.
- Females of childbearing age should be given advice on the teratogenic risk in pregnancy and effective contraception advised before treatment is commenced.

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# Potassium Iodide

Genevieve Osborne

## + Classification & mode of action

Iodine is an essential dietary mineral, required for the biosynthesis of tri-iodothyronine and thyroxine by the thyroid gland. Deficiency of iodine leads to 'endemic goitre', intellectual and developmental disabilities, which can be prevented by the routine addition of iodine to dietary salt in the form of potassium iodide (KI) or potassium iodate ( $\text{KIO}_3$ ). KI was first isolated in seaweed in the 19th century, and thereafter it was used to treat both thyroid disorders and various dermatological and infective diseases. Its use then dwindled until the 1970s when reports appeared of its benefit in treating the neutrophilic dermatoses, erythema nodosum and nodular vasculitis.

KI is well-absorbed orally and distributed selectively into the thyroid gland. It also distributes to a minor extent into the salivary glands, breast, choroid plexus and gastric mucosa. It readily crosses the placenta and is distributed into milk, and is excreted mainly in urine, with lesser amounts via the faeces, saliva and sweat.

The exact mechanism of action of KI in inflammatory dermatological diseases is not understood, but is thought to be immunomodulatory. KI appears to be most effective in conditions where neutrophils predominate, and it has been speculated that it suppresses the ability of the neutrophils to generate toxic oxygen intermediates and inhibits neutrophilic chemotaxis. The antifungal mode of action of KI has not yet been established. Activation of macrophages may be involved. KI does not have any direct antimicrobial action on *Sporothrix schenckii*. The spontaneous healing and the variability of the clinical presentation of sporotrichosis support the idea that KI acts by altering the immune response of the host in this infection.

## + Indications & dermatological uses

KI is a thyroid-blocking agent and is licensed for the treatment of thyrotoxicosis. It is used to protect the thyroid during therapy with radioactive iodine and may also be given pre-operatively before partial thyroidectomy. It is also used as emergency protection of the thyroid following accidental exposure to radiation. Solutions of KI are used as expectorants to reduce the stickiness of mucus in

chest complaints. It is not licensed for use in any dermatological disease. Although benefit has been reported in several dermatoses, the level of evidence for these is limited to small open studies or case reports. These indications include:

- Fungal infections, specifically cutaneous and lymphocutaneous sporotrichosis and cutaneous cryptococcosis. These probably account for the main use of KI worldwide, given its low cost compared with systemic antifungal medication. Benefit has also been reported in other subcutaneous mycoses such as phycomycosis, human pythiosis, *Nocardia brasiliensis*, cutaneous cryptococcosis and rhinoentomophthoromycosis (rhinophycomycosis).
- Panniculitis: erythema nodosum, erythema induratum (nodular vasculitis).
- Neutrophilic dermatoses: Sweet's syndrome, pyoderma gangrenosum.
- Miscellaneous: erythema multiforme, Behçet's syndrome, disseminated granuloma annulare, Wegener's granulomatosis.

### + Formulations/Presentation

- 65 mg and 130 mg tablets.
- Aqueous solution in various concentrations, including saturated solution of KI (1000 mg KI/ml)
- Supplements containing much lower doses of KI (e.g. 150 µg) can be obtained from health food shops.

### + Dosages & suggested regimens

- Tablets have a bitter taste and should be swallowed whole with plenty of water. Aqueous KI solution may be diluted with water, juice or milk and drunk with a straw to limit dental staining. The daily dose may be divided to reduce gastrointestinal (GI) side-effects. For inflammatory dermatoses, a typical dose is **300 mg tds for 2–4 weeks**. Remissions have been reported within 2 weeks. Higher doses are used for fungal infections, **600–2400 mg tds**. Children typically take one-third to one-half of the adult dose.

### + Baseline investigations & considerations/Monitoring

Baseline monitoring includes:

- Urea, electrolytes and creatinine.
- Thyroid function; thyroid autoantibodies.

During treatment:

- Thyroid function should be checked every 2 months.
- KI is a source of potassium ions so serum potassium should be monitored if given with drugs known to cause hyperkalaemia.

### + Contraindications

- Impaired renal function.
- Iodine induced goitre.
- Hyperkalaemia.
- Iodine hypersensitivity.
- Pregnancy.
- Lactation.
- Hypocomplementaemic vasculitis, dermatitis herpetiformis.
- Tuberculosis.

### + Cautions

- Drugs that cause hyperkalaemia (see below).
- Previous thyroid disease and/or positive thyroid autoantibodies (multinodular goitre, Grave's disease, autoimmune thyroiditis) increase the risk of hypothyroidism as there is dysfunctional thyroid autoregulation.
- KI should be used with caution in patients with Addison's disease, cardiac disease, myotonia congenita or renal impairment.
- Acne may be aggravated.

### + Important drug interactions

- Drugs that cause **hyperkalaemia**, including spironolactone, potassium-sparing diuretics, angiotensin converting enzyme inhibitors and ciclosporin (cyclosporine).
- **Iodine containing drugs**, e.g. amiodarone and thyroid inhibiting drugs (lithium, possibly sulphonamides) as they may cause hypothyroidism.

### + Adverse effects & their management

- **Gastrointestinal adverse effects** are common and usually mild to moderate. They include nausea, vomiting, diarrhoea and epigastric pain. They are often dose related and can be limited by slow and small dose increments. Rarely, small bowel ulceration.
- **Thyroid dysfunction**: occurs due to loss of normal thyroid gland autoregulation. Hypothyroidism is more likely the longer KI is taken and when there is pre-existing thyroid disease; it arises due to inhibition of thyroid hormone production by an excessive iodine supply (Wolff–Chaikoff effect). This and is usually reversible. Thyrotoxicosis may also occur when taking KI if there are pre-existing functional thyroid foci, e.g. multinodular goitre (Jod–Basedow effect).
- **Metabolic**: hyperkalaemia and metabolic acidosis may cause confusion, arrhythmias, weakness, paraesthesia.



- **Iodism/KI poisoning** usually occurs at high doses or after prolonged use and may cause oral ulceration and soreness, lacrimation, sialorrhoea, rhinorrhoea and blurred vision. The side-effects usually resolve within a few days of discontinuing KI.
- **Hypersensitivity:** angioedema, urticaria, bronchospasm, pulmonary oedema, headache, fever, arthralgia and vasculitis can occur.
- **Dermatological (iododerma):** pustular, cystic and acneiform reactions can result. Ulcerating nodules and plaques appear more common where there is co-existing systemic disease. Immunobullous diseases (dermatitis herpetiformis and bullous pemphigoid) may be exacerbated.

### + Use in special situations

#### Pregnancy (FDA Category D)

KI should not be used in pregnancy (unless benefits outweigh risks) as it crosses the placenta and will cause fetal goitre and hypothyroidism.

#### Lactation

KI is contraindicated as it is excreted in breast milk.

### + Essential patient information

Patients should be instructed to discontinue treatment and seek urgent medical attention if they develop features of iodism, hyperkalaemia, shortness of breath, severe abdominal pain or dark stool.

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# Propranolol

Susannah Baron & Brid O'Donnell

## + Classification & mode of action

Propranolol was the first successful beta-adrenoceptor antagonist (beta-blocker) to be used medically following its discovery by James Black in 1962. It is a non-selective beta-blocker and has been widely used in cardiovascular medicine to treat hypertension, angina and tachyarrhythmias. In 2008, reports of its successful use in infantile haemangiomas emerged and propranolol is currently used to treat haemangiomas that are either causing, or are likely to cause, clinically significant impairment of function or lesions that could lead to significant permanent disfigurement if untreated. Haemangiomas of infancy are vascular tumours that undergo a proliferative phase followed by stabilization and eventual spontaneous involution. The therapeutic effectiveness of propranolol in this indication may relate to peripheral vasoconstrictive actions and the reduced expression of pro-angiogenic factors.

## + Indications & dermatological uses

Propranolol is licensed for use in cardiovascular disease, essential tremor and migraine prophylaxis. Its use in the treatment of infantile haemangiomas has been on an off-label basis until recently. In 2014, The FDA and EMA granted marketing authorisation for a new oral solution of propranolol, Hemangiol® for proliferating infantile haemangiomas. Its cost is considerably greater than other oral solutions.

## + Formulations/Presentation

Oral solutions of propranolol (which are of relevance for infants) are available in several concentrations ranging from 1mg/ml-10mg/ml. Hemangiol® contains propranolol hydrochloride 4.28mg/ml, equivalent to propranolol 3.75mg/ml.

## + Dosages & suggested regimens

As yet, there are no nationally agreed guidelines, and practice may vary in different centres of expertise.

The following regimen for off-label use of propranolol oral solution is suggested:

**Initiation of treatment** should take place in a hospital setting. Infants <3 months old should be admitted and those ≥3 months treated as a day case. Treatment may require the guidance of a paediatric cardiologist.

Propranolol should be administered within 1 hour of the last feed or immediately before feeding.

**Starting doses** of **1 mg/kg/d** are given with close monitoring (see below) and increased after 24 hours to a maintenance dose of **2 mg/kg/d**. The daily dosage is taken as three divided doses at least 6 hours apart.

Some clinicians delay increasing propranolol to 2 mg/kg/d until the second week of treatment. Other experts advocate a **high initial test dose** of **1 mg/kg** of propranolol (this is a higher dose than will be given on discharge) for infants ≥3 months old.

Occasionally higher doses are required, these can be increased on a monthly basis according to the infant's weight. The dose should not be increased by more than 0.5 mg/kg/d without cardiovascular monitoring (BP and heart rate).

The recommended starting dose of Hemangiol® is **1mg/kg/day** in two doses at least 9 hours apart, increased to **2mg/kg/day** for the second week and then **3mg/kg/day** as a maintenance dose. It is specified for initiation in infants aged from 5 weeks to 5 months and for a 6-month period.

The child should be reviewed within **6–8 weeks** of starting treatment, then every **3–4 months**. The growth period of infantile haemangiomas may vary considerably, so the age at which treatment can be stopped is highly variable, and treatment may be required beyond the age of 1 year. Some physicians taper propranolol over a 4-week period at the end of treatment (e.g. half the dose for 2 weeks, then half again for 2 weeks then stop). Haemangiol® may be stopped without dose decreases.

### + Baseline investigations & considerations

- A thorough clinical history and full examination especially cardio-respiratory system with heart rate, BP and pulse oximetry (SpO<sub>2</sub>).
- Document family history of arrhythmias or maternal connective tissue disease.
- Clinical photography.
- Echocardiogram and ECG in selected patients (see Table 1).
- Capillary blood glucose.
- Referrals to ENT team for suspected airway haemangioma and Ophthalmology team for peri-ocular haemangioma.

### + Monitoring

- Observations at initiation of treatment.
- Heart rate and BP every 30–60 minutes for 4 hours after each dose and before the next dose.
- Capillary blood glucose at 2 and 4 hours after each dose and before the next dose.

- For infants weighing less than 3.5 kg or with co-morbidities, it may be appropriate to continue monitoring for 4 hours or longer at the initiation of the treatment and when the dose is doubled.

**TABLE 1** Investigations for children receiving propranolol

Investigation	Required for
Echocardiogram and ECG	Large haemangiomas (>10 cm in diameter) >5 cutaneous haemangiomas or known liver haemangioma History, symptoms or signs of cardiovascular disease, i.e. heart murmurs, tachypnoea, dyspnoea, tachycardia, poor weight gain, difficulties feeding, repeated respiratory infections, cyanosis, enlarged liver, excessive sweating, fatigue, clubbing of the fingers PHACES
ECG	If the HR is below normal for age: newborns (<1 month old), <70/min infants (1–12 months old), <80/min children (>12 months old), <70/min
FBC (CBC)/urea and electrolytes/ glucose/LFTs/TFTs	Liver haemangiomas, PHACES, Large haemangiomas, Bleeding haemangiomas, Failure to thrive
Abdominal ultrasound	>10 cutaneous haemangiomas, Very large haemangiomas Lumbosacral segmental haemangiomas, Failure to thrive
MRI brain and neck	PHACES
MRI spine	Plaque haemangioma in lumbosacral area/perineum crossing the midline or perianal haemangioma extending into gluteal cleft

ECG: electrocardiogram; FBC (CBC): full blood count; HR: heart rate; LFT: liver function test; MRI: magnetic resonance imaging; PHACES: plaque/segmental haemangiomas of the head syndrome; TFT: thyroid function test.

### + Contraindications

Asthma, uncontrolled heart failure, bradycardia, hypotension, atrioventricular (AV) block, sick sinus syndrome, severe peripheral arterial disease, phaeochromocytoma.

### + Cautions

- Hepatic and renal impairment, portal hypertension, diabetes mellitus, bronchospasm, heart disease.

Referral for additional specialist advice is recommended for suspected airway haemangiomas (otolaryngeal referral) and for periocular haemangiomas and plaque/segmental haemangiomas of the head syndrome (PHACES) (ophthalmological referral).

### + Important drug interactions

- **Lidocaine containing medications:** care should be taken with topical agents containing lidocaine, including teething gels (Bonjela, Dentinox and Calgel), as concurrent use of propranolol increases the risk of lidocaine toxicity.
- **Salbutamol** or any other **selective beta-2-agonists:** if bronchodilatation is needed, ipratropium bromide (Atrovent) should be used.
- **Cardiac medication** may increase the risk of bradycardia and hypotension. Expert advice and closer monitoring is required.
- **Corticosteroids** may increase the risk of hypoglycaemia due to adrenal suppression.
- **Bile acid sequestrants (colestyramine, colestipol)** may decrease propranolol levels up to 50%

### + Adverse effects & their management

- **Common:** cold hands and feet, peripheral vasoconstriction, gastrointestinal disturbance (diarrhoea or constipation), decreased appetite, agitation, sleep disturbance, sweating.
- **Rare:** bradycardia, hypotension and high output cardiac failure. Bronchospasm may occur. Propranolol should be temporarily discontinued during episodes of viral induced wheeze or chest infection.
- **Propranolol** should be discontinued during intercurrent illness associated with **restricted oral intake** and if the infant is undergoing procedures requiring fasting, due to the increased risk of hypoglycaemia.

*With acknowledgements to Ilona Frieden who reviewed this chapter from an international perspective.*

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# Psoralens

Gillian Murphy & Veronika Dvorakova

## + Classification & mode of action

Psoralens are naturally occurring furocoumarins that are found in several plant species. They appear to have a protective role against microbes, and inhibit germination of seeds. These aromatic molecules strongly absorb certain ultraviolet (UV) wavelengths (220–400 nm) and act as photosensitizers when administered orally or topically. Synthetic psoralens have been used therapeutically in dermatology since the 1970s in conjunction with UVA in psoralen-UVA photochemotherapy (PUVA). Three psoralens are in use in dermatology: 8-methoxypsoralen (8-MOP; Methoxsalen), 5-methoxypsoralen (5-MOP; Bergapten) and 4,5,8-trimethylpsoralen (TMP).

Photochemical reactions involve the interaction of light or UV radiation with a specific molecule or chromophore, which absorbs this radiation to induce a photochemical reaction. The precise molecular structure of a chromophore determines the wavelength of radiation absorbed, while the degree of tissue penetration by such radiation regulates the depth at which the photochemical reaction occurs. In PUVA, the chromophore is psoralen, which is distributed throughout the skin by diffusion from dermal blood vessels or transdermally following topical application. Since UVA readily penetrates the skin to the region of the papillary dermis, the therapeutic effects of PUVA are maximal in epidermal and superficial dermal skin pathologies.

Psoralens intercalate between DNA strands, favouring thymidine rich portions of genome. Subsequent absorption of UVA leads to their photoreaction with DNA, binding to both sides of the double-stranded helix (bifunctional adducts) to produce interstrand cross-links that prevent DNA replication. PUVA also induces reactive oxygen species formation, which leads to cell membrane damage by lipid peroxidation. Skin infiltrating lymphocytes are suppressed by PUVA, which may explain its therapeutic effects in cutaneous T-cell lymphoma as well as inflammatory skin diseases. PUVA induces pigmentation by enhanced proliferation of melanocytes, increased formation and melanization of melanocytes and transfer of melanosomes to keratinocytes.

## + Indications & dermatological uses

Psoralens are unlicensed drugs in the UK and Ireland. 8-methoxypsoralen is approved for dermatological diseases by the USA FDA. The main uses of PUVA therapy are as listed below

## Psoriasis

PUVA is effective in clearing guttate, plaque and palmoplantar psoriasis, but thick plaques may be slow to respond. The overall efficacy is good with approximately 60–70% of patients achieving a 75% reduction from baseline Psoriasis Area and Severity Index (PASI 75) and disease remission may last several months. Maintenance PUVA should be avoided in order to minimize cumulative skin damage and carcinogenesis.

## Idiopathic vitiligo

PUVA is usually reserved for patients with deeply pigmented skin (types V or VI). Widespread small lesions, central body involvement and disease of recent onset responds best, while acral vitiligo and bony areas generally respond poorly. Progress should be documented with clinical photographs (at approximately 4-monthly intervals) and treatment discontinued once improvement has ceased. In sunny parts of the world, application of topical psoralen creams and use of natural sunlight in low doses is widely practised. Narrow band UVB therapy has now superseded PUVA as the treatment of choice for vitiligo, as it has similar efficacy, but induces a better quality of skin repigmentation.

## Cutaneous T-cell lymphoma (CTCL)

PUVA is an effective treatment for early stage CTCL, and achieves high rates of clearance and prolonged disease free intervals, although the long-term course of the disease may be unchanged. It is also a useful adjunctive therapy for late stage disease through reducing tumour burden in the skin and improving quality of life for patients. Extracorporeal photophoresis involves the removal of circulating white blood cells, their irradiation with UVA in conjunction with 8-methoxypsoralen followed by reinfusion into the patient. It is used in the treatment of advanced CTCL in persons who have not been responsive to other forms of treatment.

Other unapproved dermatological conditions that are commonly treated with PUVA include:

- Atopic dermatitis (atopic eczema); this is more difficult to treat compared with psoriasis and a higher number of treatments is often required.
- Photodermatoses (polymorphic light eruption, solar urticaria, chronic actinic dermatitis): the mechanism by which phototherapy induces tolerance to sunlight might involve hyperpigmentation and thickening of stratum corneum as well as modulation of cutaneous immune response.
- Other dermatoses: PUVA is also used with variable effect in other dermatoses such as lichen planus, generalized granuloma annulare, chronic graft-versus-host disease, urticaria pigmentosa and nodular prurigo.



## + Formulations/Presentation

Two oral psoralens are currently available:

- 8-MOP (Methoxsalen) is available in two different 10 mg capsule formulations:
  - Oxсорalen-Ultra® soft gelatin capsules taken 1.5–2 hours prior to UVA exposure for psoriasis treatment.
  - Puvasoralen® hard gelatin capsules taken 2 hours prior to UVA exposure for psoriasis and 2–4 hours prior to UVA in vitiligo treatment. If nausea occurs the dose may be divided and extended to 4 hours before treatment in both diseases.

These formulations should not be used interchangeably as the bioavailability and photosensitization time course is significantly greater/earlier for soft gelatin capsules.

A variety of other generic and branded topical formulations are available globally.

- Oxсорalen® lotion 1%: used topically prior to UVA for treatment of vitiligo (USA only).
- 1.2% 8-MOP lotion for dilution in bathwater to a final concentration of 2.6 mg/L for immersion (bath- or hand/foot-PUVA).
- 5-MOP (Bergapten) is available in 20 mg capsules taken 3 hours before UVA.

TMP (tripsoralen/trioxsalen) manufacturing has now been largely discontinued. It is still used in Scandinavia for bath-PUVA and is available as a 5% solution in ethanol (5 mg TMP in 100 mL ethanol) for dilution in water and immersion.

## + Dosages & suggested regimens

8-MOP capsules should be taken at a specified time before UVA exposure (see above). The timing of psoralen ingestion should be exact and the dosage based on bodyweight (Table 1). The usual dosage is **0.6 mg/kg** bodyweight, which can be decreased to 0.4 mg/kg if necessary to relieve nausea or other side-effects. Ideally, food should be avoided 1 hour before and after dosing, but it is usually necessary to take with a light meal to avoid nausea. In this case, the type and amount of food should be kept constant for the patient to avoid variations in drug bioavailability.

In standard PUVA regimens, the initial UVA exposure should preferably be determined on the basis of prior measurement of the minimal phototoxic dose (MPD) rather than skin type as this allows more accurate and higher UVA doses during the initial treatment phase. PUVA erythema peaks at 48–96 hours and as a compromise MPDs are usually measured at 72 hours. PUVA treatments are usually given **twice weekly** for psoriasis, and increases in UVA dose calculated as a percentage of previous exposures, or rarely by intermittent MPD testing. Treatment regimens vary for other dermatoses: smaller incremental doses of UVA are used in the management of atopic eczema and CTCL, while low doses of UVA are used in the prophylaxis of polymorphic light eruption.

**TABLE 1** Standard dosages of 8-methoxypsoralen for psoralen combined with ultraviolet A (PUVA) treatment of psoriasis

Patient's weight (kg)	(lb)	(mg)
<30	<66	10
30–50	66–110	20
51–65	111–145	30
66–80	146–175	40
81–90	176–200	50
91–115	201–250	60
>115	>250	70

When adding an oral retinoid to patients already receiving PUVA therapy, the UVA dosage needs to be reduced by about **50%**. It is best to recheck the MPD to minimize the risk of burning as the effects of retinoids vary between individuals.

5-MOP is administered at a dose of **1.2 mg/kg** and its slower absorption leads to less nausea.

**Retinoid with UVA (RePUVA):** RePUVA therapy involves combination of a systemic retinoid with PUVA. It reduces the number of treatments needed for disease clearance by about one-third, and the total UVA dose often by more than half compared with conventional PUVA. The 'synergistic' action accelerates desquamation of psoriatic plaques, reduces inflammatory infiltrate and retinoids also provide chemoprevention against non-melanoma skin cancer development. Treatment is initiated with oral retinoid approximately 10–14 days before starting PUVA. The starting dose ranges from 0.1 to 1 mg/kg as retinoids are variably tolerated by the individual; most people tolerate 0.3–0.5 mg/kg.

Acitretin is currently the conventionally used oral retinoid, but isotretinoin can be used instead if prolonged risk of teratogenicity is unacceptable.[]

**Eye and skin protection:** Patients should avoid sun exposure for at least 8 hours after psoralen ingestion. Eye protection with special protective goggles is mandatory during UVA exposure and UVA absorbing wrap-around sunglasses should be worn throughout daylight after psoralen ingestion. The sunglasses should be marked UV400 (blocking all wavelengths below 400 nm). In view of the high risk of PUVA induced genital skin cancer in males, genital protection with a UV opaque garment is strongly recommended. Facial skin, if unaffected, should also be covered during treatment, usually by means of a visor.

**Topical PUVA (bath, immersion or paint):** UVA is administered immediately after immersion for bath PUVA therapy, while an interval of 15–30 minutes should be allowed between application of psoralen paint and UVA exposure. It is preferable to oral PUVA in patients with hepatic dysfunction, gastrointestinal disease where absorption is impaired (e.g. after ileostomy), cataracts or those unable to comply with eye protection, to permit shorter irradiation times and where drug interactions are anticipated. Bath PUVA and oral PUVA appear to have similar efficacy in the treatment of psoriasis.

### Special point

MPD testing should be repeated if patients are changed from oral to bath PUVA, as bath 8-MOP therapy is approximately 5–10 times more photosensitizing than the oral form. Severe burning may therefore result if the UVA dose is not reduced during conversion from oral to bath PUVA.

## + Baseline investigations & considerations

- FBC (CBC).
- Renal profile.
- LFTs.
- Antinuclear antibodies.
- Ophthalmological investigation for patients at increased risk of cataracts.

## + Monitoring

- FBC, renal profile and LFTs should be repeated 6–12 months after initiation of therapy.
- During and particularly after protracted PUVA therapy (more than 150 treatments) patients should undergo regular full skin examination for pre-cancerous and cancerous lesions, as well as receiving advice on self-examination for new or changing skin lesions.

## + Contraindications & cautions

The absolute and relative contraindications for PUVA are listed below according to guidelines from the British Photodermatology Group and the American Academy of Dermatology:

### Absolute contraindications (British Photodermatology Group Guidelines)

- Xeroderma pigmentosum.
- Gorlin's syndrome.
- Hereditary dysplastic naevus syndrome.

- Systemic lupus erythematosus.
- Dermatomyositis.
- Trichothiodystrophy.
- Bloom's syndrome.
- Cockayne's syndrome.
- Previous malignant melanoma.

### Relative contraindications

- Major:
  - Age <10 years.
  - Previous or current non-melanoma skin cancer.
  - Previous exposure to arsenic or ionizing radiation.
  - Current pre-malignant skin lesions.
  - Concomitant immunosuppressive therapy.
  - Pregnancy.
  - Porphyria.
- Minor:
  - Age <16 years.
  - Cataracts.
  - Bullous pemphigoid.
  - Pemphigus.
  - Previous or concomitant treatment with methotrexate.
  - Significant hepatic impairment.
  - Previous internal malignancy.

As oral psoralens are metabolized in the liver, it is sensible to avoid their use in severe liver disease, although they may be used in mild impairment. Sporadic reports of hepatitis associated with PUVA treatment have been published. In severe impairment the use of topical psoralens is recommended (bath or lotion) because serum levels are low compared with oral therapy.

Renal excretion is the main route of elimination of psoralen metabolites; thus oral PUVA can be used in patients with stable renal impairment in a reduced dose, but preferably combined with MPD measurement prior to treatment, to reduce the risk of burning. Bath PUVA is preferable in such circumstances.

### Contraindications (American Academy of Dermatology Guidelines)

- Lupus erythematosus.
- Porphyria.
- Xeroderma pigmentosum.

### Cautions

- Patients with skin type I and II who tend to burn easily.
- History of arsenic intake.
- Previous treatment with ionizing radiation.
- History of melanoma.
- History of multiple non-melanoma skin cancers.
- Any medical condition causing intolerance of heat or prolonged standing.

- Severe liver disease.
- Pregnancy and nursing.
- Previous treatment with ciclosporin (cyclosporine) or methotrexate.

### + Important drug interactions

- **Photosensitizing** concurrent drug treatment should be noted, and if started after the onset of PUVA, MPD testing should be undertaken with appropriate UVA dosing to prevent excessive phototoxic reactions. These include retinoids, non-steroidal anti-inflammatory drugs (NSAIDs), fluoroquinolone and tetracycline antibiotics, thiazide diuretics, griseofulvin, phenothiazines and sulphonamides. Other interactions include:
- **Coumarin** anticoagulants may be displaced from binding sites by psoralens.
- **Anticonvulsant** therapy can result in low serum concentrations of oral psoralens as a result of the induction of hepatic enzymes.
- Hepatic **cytochrome 450** (CYP450) 1A2 is inhibited by systemic PUVA and metabolism of theophylline and other CYP1A2 substrates may be affected (including tricyclic antidepressants and propranolol).

### + Adverse effects & their management

#### Acute adverse effects

- **Nausea** is a relatively common side-effect of oral psoralens and is usually reduced by taking psoralens with food. A light low fat meal is recommended as high fat diets can cause a significant decrease in psoralen absorption. Rescheduling UVA treatment for later in the day or taking the dose of psoralen in divided portions over a 30-minute period may help. Severe nausea can be treated with a prescription anti-nausea medication or if intractable, the psoralen dose may be reduced by 10 mg and UVA dose increased proportionately. Nausea is less frequent with 5-MOP therapy because of slower absorption.
- **Erythema and burning** may occur due to pronounced sensitivity to psoralen or excessive UVA dosing. Early recognition and prompt treatment with emollients, topical corticosteroids and oral NSAIDs may be helpful. If not too severe, once the erythema has resolved PUVA might be restarted at a lower UVA dose, using smaller increments.
- **Pruritus** may be either localized or generalized, and usually occurs in patients receiving oral psoralens. It may rarely be severe and persistent and treatment with topical and systemic steroids, emollients and antihistamines is often unsatisfactory. The itch has a prickling quality and may persist for weeks to months before eventually resolving. If PUVA is required thereafter, oral 5-MOP should be used. Generally, however, further PUVA should be avoided.
- **Anaphylaxis** is an extremely rare event.

## Chronic adverse effects

- **Cutaneous photocarcinogenesis** and **photoageing** are the most significant long-term complications of PUVA. A significant increase in squamous cell carcinoma (SCC) is noted in patients exposed to more than 150 treatments and there is also an associated increase in basal cell carcinoma. An increased rate of melanoma has been reported with high cumulative doses of PUVA, but there may be a latent period of many years and the relationship remains to be clarified. Ciclosporin should be avoided in those with a history of PUVA treatment as this increases the risk of **SCC development**.
- **PUVA lentigines** (stellate hyperpigmented macules) may develop in fair-skinned individuals, particularly after a high cumulative number of PUVA treatments. Other skin changes related to high exposure include poikiloderma.
- **Cataracts**: the induction of cataracts is a theoretical risk but is virtually unheard of in practice. The use of UVA protective goggles in the UVA cabinet and the wearing of UV protective glasses on treatment days prevents this potential side-effect, which dissipates after 24 hours. Protective glasses are not needed after bath PUVA.

## + Use in special situations

### Pregnancy (FDA Category C)

Small studies did not reveal a higher rate of congenital malformations, although there was an increase in low birthweight babies born to females who received PUVA during pregnancy.

### Lactation

There is a minor risk of transmission of psoralen in breast milk, with the consequent slight possibility of induction of photosensitization in infants. PUVA in all forms is therefore contraindicated during lactation.

### Children

Oral psoralens should not be used routinely in children under the age of 12 years due to long-term risk of carcinogenicity. Treatment can be undertaken in special circumstances with great caution.

## + Essential patient information

Prior to starting PUVA it is recommended that written patient consent is obtained. This should supplement careful verbal explanation and helps to document that the patient has been informed of potential risks of treatment.

*With acknowledgements to Daniel Creamer and John Hawk, authors of this chapter in the 1st edition.*

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# Rituximab

Melissa Saber & Richard W. Groves

## + Classification & mode of action

Rituximab is a chimeric, murine–human monoclonal antibody of immunoglobulin (Ig) G1 subclass directed against the B-lymphocyte specific antigen CD20 expressed only by pre-B and mature B-cells. These include early B-cells in the bone marrow, autoantigen specific B-cells, memory B-cells and mature B-cells. Haematopoietic stem cells and plasma cells lack the CD20 antigen and are therefore not affected by rituximab treatment. The precursor cells maintain their ability to regenerate the B-lymphocyte population and Ig levels generally tend not to decrease significantly since plasma cells are unaffected. CD20 is thought to regulate cell cycle initiation and differentiation of the B-cell lineage and possibly functions as a calcium channel. Interestingly, rituximab seems predominantly to affect autoantigen specific B-cells in comparison to memory B-cells directed against microbial antigens, which seem to be protected by their privileged location in bone marrow and solid organs. The fragment antigen-binding (Fab) domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector cells that mediate B-cell lysis. Three mechanisms of B-cell depletion have been proposed including complement dependent cytotoxicity, antibody dependent cell-mediated cytotoxicity and induction of apoptosis. Thus, rituximab results in a rapid and sustained depletion of circulating and tissue-based B-cells, which can be maintained for at least 6–12 months. Recent data suggest that rituximab may also affect T-cell function and might modulate autoreactive T cells and production of T-cell cytokines.

The half-life of the monoclonal antibody in the peripheral circulation is approximately 8 days. It is thought that non-specific degradation of rituximab occurs in the liver, followed by renal excretion.

## + Indications & dermatological uses

Rituximab has been widely used in the treatment of B-cell malignancies with use in over a million patients. The licensed indications in the UK are:

- B-cell haematological malignancies: CD20 positive non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia.
- Severe active rheumatoid arthritis.
- It is also approved by the FDA for the treatment of Wegener's granulomatosis and microscopic polyangiitis.



Rituximab has also been reported to be of benefit in the treatment of several autoimmune diseases such as idiopathic thrombocytopenic purpura, haemolytic anaemia, connective tissue diseases (systemic lupus erythematosus [SLE], dermatomyositis, Sjögren syndrome) and systemic vasculitis. Its main use within dermatology has been in the treatment of immunobullous skin disorders, which is off label.

Patients suffering from immunobullous skin diseases who have failed conventional immunosuppressive therapy (systemic corticosteroid with other immunosuppressive agents) or have developed intolerable side-effects from these drugs may benefit from rituximab. The most common disease that has been treated is pemphigus vulgaris, and high response rates have been reported, mostly when used in conjunction with concurrent immunosuppressive medication. There have also been several case reports and studies reporting effectiveness in pemphigus foliaceus, paraneoplastic pemphigus, mucous membrane pemphigoid, epidermolysis bullosa acquisita and bullous pemphigoid.

Other dermatoses that have been reported to respond to rituximab include atopic dermatitis, chronic graft-versus-host disease, cutaneous lupus, cryoglobulinaemia and cutaneous B-cell lymphoma.

### + Formulations/Presentation

Rituximab is given by i/v infusion and is available as follows:

- Vials of 10 mL containing 100 mg of rituximab (packs of 2 vials).
- Vials of 50 mL containing 500 mg of rituximab (pack of 1 vial).

### + Dosages & suggested regimens

The licensed dosing regimens in the UK for rituximab are as follows:

- **Weekly infusions** of 375 mg/m<sup>2</sup> for 4–8 consecutive weeks, as a single agent or in combination with chemotherapy (NHL regimen).
- **Two infusions** of 1000 mg given 2 weeks apart (rheumatoid arthritis regimen).

In the initial reports of immunobullous disease treatment, the NHL regimen was used, but the rheumatoid arthritis regimen is generally favoured nowadays.

Rituximab should be administered under close supervision in a setting with full resuscitation facilities. Since transient hypotension may occur during infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout infusion with rituximab. Treatment with paracetamol (acetaminophen) and H<sub>1</sub>-antihistamines is recommended before and throughout each infusion to reduce the risk of infusion reactions. **Pre-medication** with corticosteroids may also be considered in order to reduce the frequency and severity of infusion related reactions. Patients should receive 100 mg i/v methylprednisolone to be completed 30 minutes prior to each infusion.

Patients with pre-existing cardiac conditions such as angina and arrhythmias or patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab.

For the **first infusion**, rituximab should be administered at an initial rate of **50 mg/h**. If hypersensitivity or infusion related events do not occur, this can be increased in 50 mg/h increments every 30 minutes, to a **maximum of 400 mg/h**. If hypersensitivity or an infusion related event develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at half of the previous rate upon improvement of the patient's symptoms.

Subsequent infusions of rituximab can be administered at an initial rate of **100 mg/h**, and increased by 100 mg/h increments at 30-minute intervals, to a maximum of **400 mg/h** as tolerated. No dose adjustment is required in elderly patients (aged >65 years).

The **onset** of therapeutic effects in autoimmune bullous dermatoses is usually **2–3 months** after initiation, though responses as late as 12 months after initiation of treatment have been reported. If disease relapses, further courses of rituximab can be safely administered without an increased risk of adverse effects. The manufacturers advise avoiding readministration within 4 months of the last infusion.

Adjuvant systemic immunosuppressive drugs can be continued with concomitant use of rituximab but dose reduction should be considered to decrease the risk of infections and other adverse effects related to immunosuppression.

Treatment of cutaneous B-cell lymphoma with intralesional injections of rituximab is also reported to be effective.

### + Baseline investigations & considerations

- FBC (CBC) and lymphocyte subsets including B-lymphocyte count.
- Urea, electrolytes and creatinine.
- LFTs.
- Ig levels.
- Hepatitis B and C serology.
- (HIV) testing.
- Pregnancy test.

These investigations should be repeated before each subsequent course of rituximab. Immunization status should be assessed before initiation of rituximab and consideration given to vaccination if appropriate.

### + Monitoring

- FBC and lymphocyte subsets (B-cell count).
- Ig levels.
- Urea, electrolytes and creatinine.
- LFTs.

These should be checked 1 month after the last infusion, then every 3 months.

In pemphigus, serum desmoglein 1 and desmoglein 3 antibody levels should be measured by indirect immunofluorescence and/or enzyme linked immunosorbent assay (ELISA) before, 1 month after the last infusion, then every following 3 months, as they reflect disease activity and can predict relapse. In the majority of patients with pemphigus vulgaris the level of these autoantibodies parallels disease activity and decrease 3–10 months after treatment with rituximab. Rarely, clinical improvement occurs in the absence of a significant fall in antibody titre.

Circulating B-lymphocyte levels usually recover before disease activity relapses, but in some patients relapse may occur despite persisting B-cell depletion.

### + Contraindications

- Hypersensitivity to rituximab or to murine proteins.
- Progressive multifocal leukoencephalopathy (PML).
- Live virus vaccines.
- Severe active infection including active hepatitis B disease.
- Severely immunocompromised patients.

### + Cautions

- Severe heart failure (New York Heart Association Class IV) or severe uncontrolled cardiac disease.
- Patients with positive hepatitis B serology but no active disease should be referred to a hepatologist for assessment prior to starting rituximab, for advice on further management and monitoring.

### + Important drug interactions

There are limited data on drug interactions with rituximab. It is unlikely that rituximab affects the pharmacokinetics of drugs that are used in combination with it.

- Concomitant use of other **immunosuppressive** or **immunomodulatory** drugs can enhance the degree of immunosuppression and increases the risk of severe infections.
- Patients may be immunized with **non-live vaccines** during treatment with rituximab. However, the vaccine response may be attenuated.

### + Adverse effects & their management

Rituximab is generally well-tolerated.

- **Infusion reactions** are usually mild to moderate and occur within 30–120 minutes of infusion. They can present with fever, chills, headache, weakness, hypotension, nausea, dizziness, cough, pruritus and urticaria. The majority of reactions occur during the first infusion of rituximab and are less frequent with subsequent infusions. The symptoms are reversible when the infusion is discontinued and can usually be prevented by use of pre-treatment with antihistamines, corticosteroids and paracetamol. When infusion reactions happen, treatment should be discontinued. If symptoms resolve, the infusion can be restarted at a reduced rate (half of the flow rate). **More severe** (occasionally fatal) infusion reactions have been reported rarely with acute respiratory distress syndrome, myocardial infarction (MI), ventricular fibrillation, cardiogenic shock and/or anaphylaxis. Stop the infusion immediately and start appropriate supportive management.
- **Infections** may occur due to immunosuppressive effects. The most common are respiratory tract infections, urinary tract infections and nasopharyngitis. Serious infections and fatal outcomes have been reported in patients treated for autoimmune bullous diseases with rituximab. In other indications, severe opportunistic, bacterial and viral infections such as pneumonias, pyelonephritis, skin infections, sepsis and systemic varicella zoster virus infections have been fatal. Reactivation of hepatitis B may occur (see Cautions), leading to fulminant hepatitis.

Skin disease severity and concomitant immunosuppressant therapy affect the risk of severe infections. It is therefore advisable to try to reduce other immunosuppressive drugs to the minimal effective dose. Data from patients with primary cutaneous B-cell lymphoma suggest that the risk of infection is less frequent when rituximab is used as a monotherapy.

- **Progressive multifocal leukoencephalopathy (PML)** due to reactivation of latent JC virus has been reported in at least 50 patients treated with rituximab for lymphoproliferative disorders, rheumatoid arthritis or SLE. Most cases were diagnosed within 12 months of treatment. Confusion, disorientation, motor weakness, diplopia, altered speech, dysphagia and ataxia should raise suspicion for PML. Discontinuation of rituximab and urgent neurological evaluation is advised.
- **Hypogammaglobulinaemia** has been reported in rare cases of children treated with rituximab for pemphigus vulgaris and bullous pemphigoid as well as in adults. Hypogammaglobulinaemia may be associated with severe infections in patients treated with rituximab.
- **Leukopenia, neutropenia and thrombocytopenia** have been reported in about 10% of patients. Closer monitoring of blood counts is indicated in such cases. Late neutropenia may occur up to 6 months after therapy. The mechanism of these reactions is unclear.
- **Cardiac adverse effects** such as angina, arrhythmia, heart failure and MI have been reported, so close monitoring is required in patients with history of cardiac disease.
- **Other severe adverse effects** include tumour lysis syndrome and renal failure in patients with NHL.

- **Severe mucocutaneous reactions** (lichenoid dermatitis, paraneoplastic pemphigus, Stevens–Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis) have been reported. In these situations immediate cessation of treatment is required.

It is not clear if there is an increased risk of **malignancy** relating to the immunosuppressant actions of rituximab.

### + Use in special situations

#### Pregnancy (FDA Category C)

IgG is known to cross the placental barrier and transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons rituximab should not be used in pregnancy.

Females of childbearing potential should use effective contraceptive methods during treatment and for 12 months following the last infusion.

#### Lactation

Maternal IgG is excreted in human milk and mothers should not breastfeed while receiving rituximab and for 12 months following the last infusion.

#### Children

There are limited safety data for the use of rituximab in children, but uncontrolled studies have shown effectiveness in idiopathic nephrotic syndrome and severe rheumatic diseases. Transient and persistent hypogammaglobulinaemia have been reported in rare cases of children with immunobullous diseases (see above).

### + Essential patient information

- Patients should be advised to seek prompt medical attention if they develop signs or symptoms of infection.
- Patients should be informed of the potential risk of PML, though the magnitude of risk is unclear for patients with immunobullous disease.

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# Sulfapyridine & Sulfamethoxy-pyridazine

Eirini Mereki & Catherine Hardman

## + Classification & mode of action

The sulfonamide (sulphonamide) antibacterial drugs, **sulfapyridine (SP)** and **sulfamethoxypyridazine (SMP)** are structurally related to para-aminobenzoic acid (PABA). Their antibacterial effects are related to competitive inhibition of the bacterial enzyme dihydropteroate synthase, which plays a key role in converting PABA to dihydrofolic acid (a precursor of folic acid). Folic acid is required for the biogenesis of DNA and RNA synthesis in both bacteria and in mammals.

Sulfonamides do not affect human cells by this mechanism, as they require pre-formed folic acid. Enzyme inhibition is reversible, so sulfonamides have bacteriostatic rather than bactericidal activity. They are rarely used as antibiotics nowadays due to adverse effects and bacterial resistance.

SP was introduced in 1938 as M&B (May and Baker) 693 and was one of the first generation of sulfonamide antibiotics before being followed by several other related drugs. Shortly afterwards their effectiveness in treating non-infective skin disorders was recognized. The current main use of SP and SMP is in inflammatory skin conditions mediated by activated neutrophils. They impair neutrophil cytotoxicity by inhibiting myeloperoxidase activity and preventing the formation of activated oxygen species, leading to anti-inflammatory actions. It is thought the inhibitory effects on neutrophil function are similar to those of dapsone (see Dapsone). They may also affect the protein moiety of glycosaminoglycans leading to a reduction in tissue viscosity, oedema and vesicle formation.

Sulfonamides are slowly and incompletely absorbed from the gastrointestinal (GI) tract and do not undergo first-pass metabolism. They are protein bound to variable degrees in the circulation and unbound sulfonamide diffuses throughout the body especially to sites of inflammation. Sulfonamides are metabolized to inactive compounds by hydroxylation and acetylation in the liver, the latter varying with acetylator phenotype. Parent drugs and their metabolites undergo renal excretion and some sulfonamides are actively reabsorbed in the renal tubule. SP has a half-life of about 6–14 hours depending on acetylator status and SMP is longer acting, with a half-life of 22 hours.

## + Indications & dermatological uses

The produce licence for SP and SMP has lapsed and they are now only available on a named patient basis. The main use for these drugs is in the treatment of immunobullous diseases:

- Dermatitis herpetiformis.
- Linear IgA disease, chronic bullous dermatosis of childhood.
- Cicatricial (mucous membrane) pemphigoid.

Dapsone is usually the treatment of choice for these conditions, but should be used with caution in elderly patients, when its haemolytic effects may be poorly tolerated especially in those with underlying cardiorespiratory disease (see Dapsone). In such patients, SP or SMP are preferred options. Combination therapy with two or three agents (dapsone, SMP and SP) is occasionally used in patients with treatment resistant disease. It also reduces the risk of renal toxicity from crystalluria (see Adverse effects & their management).

Other rarer uses of SP and SMP include pustular disorders such as subcorneal pustular dermatosis, pyoderma gangrenosum, pustular psoriasis and cystic or conglobate acne. There have also been reports of benefit in acrodermatitis continua, erythema elevatum diutinum and angiitis as well as leukocytoclastic vasculitis.

The pro-drug sulfasalazine, which is licensed for the treatment of inflammatory bowel disease, is broken down in the colon to form 5-aminosalicylic acid and SP.

## + Formulations/Presentation

- SP is available as 250 mg capsules under the brand name 'Concord 693'. It is manufactured by Archemides Pharma UK Ltd.
- SMP is currently available as 500 mg tablets by HAUPT Pharma. It is manufactured as an unlicensed product in Germany and imported by IDIS.

Both drugs should be protected from exposure to light.

## + Dosages & suggested regimens

SP and SMP are used as second-line agents when treatment with dapsone has failed or is contraindicated. They may be used in combination or with low dose corticosteroid if monotherapy does not adequately control the disease.

In the treatment of adults with dermatitis herpetiformis (Table 1) a typical **starting dose** of SP is **500 mg twice a day**, increasing if needed up to **3 g daily** and according to dose related side-effects. In most patients the rash is controlled within this dose range. The clinical response should be assessed within 2 weeks and dosage adjusted as necessary. The **maintenance dose** should be the **lowest**



dose that prevents disease breakthrough. This may require frequent adjustment because of irregular absorption. With longer-term use, drug requirements should fall as dietary measures become effective. With a strict gluten-free diet, drug requirements usually diminish after an average of 8 months, but it usually takes 2 years of a strict gluten-free diet before drug discontinuation is possible. A partial gluten-free diet usually requires ongoing drug therapy.

**SMP** has a longer half-life, and the usual starting dose is **500 mg once daily**, increasing as above according to disease response up to a maximum daily dose of 1.5 g.

Lower doses are used in the treatment of other pustular and immunobullous diseases.

Both drugs should be taken with plenty of water and a high fluid intake is recommended.

**TABLE 1** Dosage schedule for the treatment of dermatitis herpetiformis

Dosage/day	Sulfapyridine	Sulfamethoxypyridazine
Initial dose	1 g	500 mg
If good disease control reduce to*:	0.5 g	500 mg on alternate days
If disease not controlled, incrementally increase dose to:	3 g	1 g
Maximum dose	4.5 g	1.5 g

\*If control is maintained, reduce the dose further at 2–3 day intervals until breakthrough occurs. Maintain at the dose required to prevent breakthrough.

### + Baseline investigations & considerations

- FBC (CBC).
- Reticulocyte count.
- Urea and electrolytes.
- LFTs.
- Glucose-6-phosphate dehydrogenase (G6PD) level in patients from ethnic groups at risk of deficiency (see Dapsone).
- Urinalysis.

### + Monitoring

- FBC and urinalysis at monthly intervals for the first 3 months and then every 3–6 months.
- Urea and electrolytes and LFTs: in the absence of specific advice a similar monitoring schedule is reasonable, i.e. monthly for the first 3 months, then every 3–6 months.

### + Contraindications

- Pregnancy & lactation (see below).
- Hypersensitivity to sulfonamides\*.
- Infants (<1 year).
- Acute porphyrias.
- G6PD deficiency.
- Pre-existing anaemia or history of haemolytic anaemia.
- Interstitial lung disease (SMP).

\*The sulfonamide chemical moiety is present in a range of other non-antimicrobial drugs including certain diuretics, sulfonyleureas and cyclo-oxygenase 2 inhibitors. However, the reactive arylamine group present in sulfonamide antibiotics that is a cause of drug hypersensitivity is absent in other non-antimicrobial sulfonamides, and the latter do not routinely need to be avoided in patients with a history of hypersensitivity to sulfonamide antimicrobials.

### + Cautions

Extra caution should be taken when SP/SMP is prescribed in the following:

- Liver dysfunction: use lower dose.
- Renal impairment: use lower dose.
- Blood dyscrasias: requires closer monitoring.

### + Important drug interactions

SP and SMP bind to plasma proteins and may displace other protein bound drugs, resulting in increased free levels of the displaced drug with potential toxicity. Drugs affected include:

- **Ciclosporin** (cyclosporine).
- **Clozapine** (increased risk of agranulocytosis).
- **Coumarin anticoagulants** (warfarin).
- **Methotrexate**.
- **Phenytoin**.
- **Procaine** (amino ester) local anaesthetics.
- **Sulfonyleurea oral hypoglycaemic agents**.
- **Non-steroidal anti-inflammatory drugs** (NSAIDs): sulfonamides may be displaced from the binding sites by highly acidic drugs such as NSAIDs, increasing the risk of toxicity.
- **Zidovudine**: hepatic metabolism and clearance may be inhibited by SP.
- **Live typhoid vaccine**: sulfonamides possess bacterial activity against *Salmonella typhi* and may thus interfere with the immunological response to live typhoid vaccine. Allow 24 hours or more to elapse between the last dose of the antibiotic and live typhoid vaccine. SP is also an inhibitor of cytochrome P450 2C9 and this may also contribute to interactions.

## + Adverse effects & their management

Adverse effects are uncommon with the low doses used in dermatology. Sulfonamides undergo hepatic metabolism to inactive compounds and slow acetylators appear to be at greater risk of severe adverse drug reactions. The adverse effect profile of SP and SMP are similar.

- **Haematological:** adverse effects include blood dyscrasias (leukopenia, agranulocytosis and aplastic anaemia), methaemoglobinaemia and sulphaemaglobinaemia. These can usually be prevented by careful FBC monitoring and early drug withdrawal. Haemolysis particularly affects those with G6PD deficiency, but can occur with normal G6PD levels. Macrocytosis may also occur without folate deficiency.
- **Dermatological:** urticarial/immediate type hypersensitivity reactions and delayed type hypersensitivity reactions may occur. The latter include **severe cutaneous adverse drug reactions** (Stevens–Johnson syndrome/toxic epidermal necrolysis and hypersensitivity vasculitis). Appearance of any of these necessitates immediate drug withdrawal. Milder adverse effects include uncomplicated exanthems and fixed drug eruptions. Desensitization may be considered in special situations in patients with milder rashes. It has been successfully reported in patients with cystic fibrosis and human immunodeficiency virus (HIV) who require antimicrobial sulfonamide therapy. Photosensitivity has been reported with various sulfonamides, but is rarely a clinical problem with SP and SMP.
- **Gastrointestinal:** nausea and vomiting, stomatitis (SP >SMP) and abdominal pain are usually mild and may be helped by dose reduction. Nausea and vomiting often settle as treatment continues, so immediate change of drug dosage may not be needed. Enteric coated formulations may help if available.
- **Hepatotoxicity:** this ranges from mildly abnormal LFTs to severe hypersensitivity hepatitis with jaundice, fever and rash. Abnormalities usually occur within the first month of treatment, but later reactions have been described so continued monitoring is important. Pancreatitis has also been reported as an idiosyncratic reaction with SP.
- **Renal and urinary:** crystalluria and nephrolithiasis are commoner with rapidly excreted sulfonamides (SP >SMP) and relate to a reduction in drug solubility in the acidic pH of the urinary tract. They may be asymptomatic or cause renal colic, haematuria, chronic or even acute renal failure. A daily fluid intake of 2.5–3.5 L is recommended to maintain high urinary output. Other measures that reduce crystal precipitation include alkalinization of the urine and using triple sulfonamide combinations. Nephritis and albuminuria have also been rarely reported.
- **Endocrine:** goitre and thyroid dysfunction have been reported with SP.
- **Neurological:** fever, headaches, dizziness and drowsiness may respond to dose reduction. Paraesthesiae and motor neuropathy have rarely been reported.
- **Respiratory adverse effects** that have been reported specifically with SMP include pneumonitis, alveolitis and obliterative bronchiolitis. These

are potentially serious complications and usually present with progressive breathlessness and cough. Chest radiographs show diffuse interstitial shadowing and a restrictive pattern is seen on lung function tests (reduced FEV<sub>1</sub> and FVC). A peripheral eosinophilia has been found in a minority of cases and an underlying vasculitis has been implicated. Most cases have occurred during prolonged drug administration. The condition generally responds to drug withdrawal and oral corticosteroid therapy but rare fatalities have occurred.

- **Hypersensitivity myocarditis** is one of the most serious adverse effects, and presents with cardiac failure.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category C)

SP has been shown to cause oligospermia and infertility in males. Sulfonamides can cross the placenta and are relatively contraindicated in pregnancy, especially in the last trimester due to potential neonatal toxicity.

#### Lactation

SMP is contraindicated. The use of SP is controversial: it is excreted into breast milk at a concentration of 30–60% of that in maternal serum. Infants with G6PD deficiency may develop haemolytic anaemia. Kernicterus is theoretically possible but breastfeeding, according to the manufacturers, does not pose a significant risk for the healthy full-term neonate. However, its use should be avoided in pre-term, stressed, or ill infants.

#### Children

Both drugs have been used safely in a limited number of children, especially for chronic bullous disease of childhood (childhood linear IgA disease) (Table 2). The usual recommendation is to use half the adult dose for SP or 15–60 mg/kg/d. For SMP dosing is weight dependent as below (based on manufacturer's advice for Lederkyn®, the previous available formulation of SMP).

**TABLE 2** Sulfamethoxypyridazine dosing in children

Age in years (approx weight)	Initial SMP dose/day	Maintenance SMP dose/day
1–3 (9 kg)	250 mg	125 mg
4–6 (18 kg)	500 mg	250 mg
6–10 (27 kg)	750 mg	375 mg

### **+ Essential patient information**

- Patients should be advised to maintain a high fluid intake during treatment to reduce the risk of crystalluria.
- Patients should report immediately any signs of bone marrow suppression (bleeding, bruising, etc) or new rashes.
- Due to the possible risk of photosensitivity, patients taking sulfonamide drugs should be advised to avoid excessive sun exposure.

*With acknowledgements to Jonathan Leonard, author of this chapter in the 1st edition.*

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# Thalidomide

Elaine Agius & Robert P.E. Sarkany

## + Classification & mode of action

Thalidomide (alpha-thalimido-glutaramide) is a derivative of glutamic acid and was first introduced in 1957 as a non-barbiturate sedative hypnotic. However, it was withdrawn several years later when an association with severe congenital abnormalities became clear. Thalidomide is a potent teratogen, and up to 12,000 newborn infants were affected, particularly with phocomelias. Interest in thalidomide and its analogues has re-emerged in recent years as it has significant anti-inflammatory, immunomodulatory and anticancer effects. It was approved by the USA FDA for the treatment of erythema nodosum leprosum in 1998, then later by the FDA and European Medicines Agency for the treatment of multiple myeloma. Thalidomide has orphan drug status. This provides the incentive for a company to produce a drug for a rare medical condition where a profit motive would otherwise be lacking. In the USA thalidomide is prescribed under a mandatory registry, the System for Thalidomide Education and Prescribing Safety (STEPS) and in Europe, it is dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

Thalidomide has complex immunomodulatory effects which are not fully understood. It has a direct suppressive effect on tumour necrosis factor (TNF)-alpha synthesis, and reduces production of other cytokines such as interleukin (IL)-6 and IL-12 and free radicals that may cause oxidative DNA damage. It also activates apoptotic pathways and inhibits angiogenesis. New analogues of thalidomide, lenolidamide and pomalidomide with greater anti-TNF activity and reduced toxicity have been licensed for use in oncology.

## + Indications & dermatological uses

Thalidomide is only licensed in Europe for the treatment of multiple myeloma. It is widely used to treat leprosy reactions (erythema nodosum leprosum) and licensed for this indication in the USA. It has also been reported to be of benefit in a range of inflammatory skin diseases including:

- Actinic prurigo.
- Cutaneous lupus erythematosus.
- Erythema nodosum leprosum.
- Nodular prurigo.
- Pyoderma gangrenosum.
- Severe aphthous stomatitis and Behçet's syndrome.
- Graft-versus-host disease.

- Cutaneous sarcoidosis.
- Erythema multiforme.
- Kaposi's sarcoma.
- Lichen planus.
- Uraemic pruritus.
- Systemic mastocytosis.

### + Formulations/Presentation

Thalidomide is available in 50 mg hard capsules.

### + Dosages & suggested regimens

The onset of action is slow, and therapeutic effects may take several months except in cases of resistant oral ulceration, where a more rapid response is typical. Dosing for dermatological conditions is usually in the range of **50–150 mg per day** taken at **bedtime**. It is advisable to **initiate treatment** at a **low dose** for the first 3 months and titrate the dose upwards if tolerated. Slow relapse usually occurs over a period of months following drug withdrawal, though long-term remission after discontinuation has been reported in subacute cutaneous lupus erythematosus.

### + Baseline investigations & considerations

Disease severity should be documented with clinical score if available and dermatology life quality index (DLQI) and a full medical history taken to assess history and risk factors for cardiac disease, thromboses and neuropathy, in addition to the following:

- FBC (CBC).
- Urea, electrolytes and creatinine.
- LFTs.
- Thyroid function tests (TFTs).
- Coagulation screen (INR, activated partial thromboplastin time [APTT] and derived fibrinogen).
- Nerve conduction studies.
- Pulse rate, BP and weight.
- Contraception and pregnancy prevention programme (including pregnancy test) (Table 1).
- Prescription authorization form (Thalidomide Pharmion Pregnancy Prevention Programme).
- Immunization with live vaccines (4 weeks) and inactive vaccines (2 weeks) prior to commencing treatment. Patient may have flu vaccine while taking thalidomide.

**TABLE 1** Contraception and pregnancy prevention programme for thalidomide

<b>FEMALE PATIENTS OF CHILDBEARING POTENTIAL</b>	
<p><b>Counselling:</b> ensure the patient understands the teratogenic risk and the absolute requirement for a reliable form of contraception without interruption for 4 weeks before starting, throughout the entire duration of treatment and for 4 weeks after stopping</p> <p>Assess capability to comply with effective contraceptive measures and explain the need to consult rapidly if there is a risk of pregnancy</p> <p>Explain the need to commence the treatment as soon as thalidomide is dispensed following a negative pregnancy test</p> <p>Explain the need and check that the patient agrees to undergo pregnancy testing every 4 weeks</p>	
<p><b>Contraception:</b> one effective method of contraception for 4 weeks before therapy: ovulation inhibitory progesterone-only pills, e.g. desogestrel NOT a combined OCP since this increases the risk of thromboembolism</p>	
<p><b>Pregnancy testing:</b> should be carried out once the patient has been on effective contraception for at least 4 weeks, and on the same day that the prescription is issued</p>	
<p><b>Prescribing and dispensing:</b> prescriptions must be limited to 4 weeks of treatment</p> <p>Pregnancy test, writing of prescription and dispensing of thalidomide should be carried out all on the same day</p> <p>The prescription is only valid for 7 days from the date it is written</p>	
<p><b>Treatment initiation form</b> (Thalidomide Pharmion Pregnancy Prevention Programme Women of Childbearing Potential) signed by patient</p>	
<b>FEMALE PATIENTS OF NONCHILDBEARING POTENTIAL</b>	
Check that patient is either post-hysterectomy or 1 year post-menopause	
Thalidomide Pharmion Pregnancy Prevention Programme Women of Non-Childbearing Potential Treatment Initiation form signed by patient	
<b>MALE PATIENTS</b>	
<p>Check that the patient understands the need for the use of a condom if engaged in sexual activity with either a pregnant woman or a woman of childbearing potential who is not using effective contraception</p> <p>This applies during the treatment period and for 1 week after stopping</p>	
<p><b>Treatment initiation form</b> (Thalidomide Pharmion Pregnancy Prevention Programme Male) signed by patient</p>	



### + Monitoring

- FBC (CBC), urea, electrolytes and creatinine and LFTs monthly for first 3 months then every 3 months thereafter.
- TFTs: repeat every 3 months.
- Nerve conduction studies: repeat every 6 months.
- Pulse rate, BP: repeat every 3 months.
- Pregnancy test: repeat every 4 weeks through treatment and 4 weeks after discontinuing.

### + Contraindications

- Hypersensitivity to thalidomide.
- Pregnancy.
- Females of childbearing potential unless all the conditions of the Pregnancy Prevention Programme are met.
- Patients unable to fully adhere to required contraceptive measures.

### + Cautions

- Patients with risk factors for myocardial infarction (MI), bradycardia, atrioventricular (AV) block or cardiac failure.
- Existing peripheral neuropathy (may be aggravated).
- History or risk factors for thromboembolism, including smoking, hypertension and hyperlipidaemia.
- The elderly are more susceptible to the adverse effects of thalidomide, so lower dosages should be considered.
- Renal or hepatic insufficiency.
- Anaemia and/or cytopenias.

### + Important drug interactions

There is evidence that thalidomide requires cytochrome P450 (CYP450) catalysed biotransformation to exert its pharmacological activity and that the CYP2C subfamily may be primarily involved. The potential for clinically relevant interactions with medicinal products appears to be low. Special precautions should be taken with:

- **Beta-blockers** or **anticholinesterase** agents (e.g. neostigmine), due to increased risk of bradycardia.
- **Sedatives** such as anxiolytics, hypnotics, antipsychotics, antihistamines, opiate derivatives, barbiturates and alcohol, due to thalidomide's sedative effect.
- Drugs known to be associated with **peripheral neuropathy** (e.g. vincristine and bortezomib).

- **Oral contraceptive pills and hormone replacement therapy**, due to increased risk of venous thromboembolic disease.
- **Erythropoiesis** stimulating agents, due to a higher risk of thromboembolic reactions.
- **Live vaccines** since thalidomide is an immunosuppressant.

### + Adverse effects & their management

- **Teratogenicity**: the risk of intrauterine death or severe birth defects, particularly phocomelia, is extremely high. Thalidomide must not be used at any time during pregnancy.
- **Venous and arterial thromboembolic events**: an increased risk of venous thromboembolism (such as deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (MI and cerebrovascular events) has been reported in patients treated with thalidomide, especially during the first 5 months of therapy. Although the majority of data are associated with its use in patients with malignant disease (multiple myeloma), there have been isolated cases reported in a non-cancer setting. Patients should be advised to seek urgent attention if they develop shortness of breath or limb pain/swelling.
- **Cardiac**: drug induced bradycardia and AV block, may present with orthostatic hypotension, syncope and signs of cardiac failure. BP and pulse should be monitored regularly.
- **Neurological**: peripheral neuropathy is a very common, potentially severe effect as it may be irreversible. It generally occurs following long-term use and the risk appears related to cumulative dosage and duration of therapy. However, reports following relatively short-term use also exist, and symptoms may also develop some time after treatment has been stopped. The typical presentation is with symmetrical painful distal paraesthesias. The risk may vary with disease and is higher in nodular prurigo and Behçet's disease. It may also be greater in females and the elderly. All patients require careful monitoring for symptoms of neuropathy including pain, tingling, numbness, abnormal co-ordination or weakness. Expert neurological assessment should be sought if these symptoms develop.
- **Sedative**: somnolence/drowsiness is an expected effect, so medication should be taken before bed. Patients should be advised about possible impairment of mental or physical abilities for hazardous tasks such as driving or operating machinery.
- **Haematological**: neutropenia, lymphopenia, thrombocytopenia and anaemia may occur. If white blood cell count (WBC) is  $<3.5 \times 10^9/L$ , neutrophils  $<2.0 \times 10^9/L$ , lymphocytes  $<0.5 \times 10^9/L$ , platelets  $<150 \times 10^9/L$ , then withhold drug until discussed with a haematologist.
- **Hepatitis**: biochemical evidence of hepatocellular, cholestatic and mixed abnormalities may occur, usually within the first 2 months of therapy. Most reactions resolve with dose reduction or drug discontinuation.

Closer monitoring is indicated in patients with pre-existing liver disease or concomitant use of hepatotoxic medication.

- **Cutaneous:** severe adverse effects include angioedema, Stevens–Johnson syndrome and toxic epidermal necrolysis. Immediate discontinuation is indicated.
- **Gastrointestinal:** these include dry mouth and constipation.
- **Endocrine:** thyroid abnormalities have been reported rarely. Common side-effects of thalidomide (bradycardia, oedema, weight gain) may be indistinguishable from the symptoms of hypothyroidism, so biochemical monitoring is recommended.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category X)

- Thalidomide is absolutely contraindicated due to the high risk of teratogenicity.
- Thalidomide is excreted in semen; males are advised not to father children during treatment or for 1 month after the last dose.

#### Lactation

The safety of thalidomide in lactation is not established. Mothers taking thalidomide should not breastfeed.

#### Children

Thalidomide has been used successfully in children, particularly in actinic prurigo. It should only be considered if clinically necessary and after alternative treatments have failed.

### + Essential patient information

- Patients should be informed of the reasons for treatment and whether the drug is being used for a licensed indication or not.
- It should be explained that the onset of action is slow and that benefit may not appear until after 2–3 months' treatment.
- All patients must be aware of the extremely high risk of teratogenicity with thalidomide used in pregnancy or around conception by both males and females.
- Patients must clearly understand the need for regular monitoring in order to minimize the risk of adverse effects and are able to comply with this.
- Patients should be advised that they are at increased risk of thromboembolic events and should seek urgent medical attention if they develop the following symptoms and signs: calf pain, chest pain, shortness of breath, haemoptysis.
- Patients should be told about common adverse effects including sedation and peripheral neuropathy.

- It must be explained that medication must not be shared with anyone and that the patient should not donate blood/semen.

*With acknowledgements to Alex Harris, author of this chapter in the 1st edition.*

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# Tumour Necrosis Factor Antagonists

Leena Chularojanamontri & Christopher E.M. Griffiths

## + Classification & mode of action

The tumour necrosis factor (TNF) family is a group of 19 cytokines that can produce inflammation, apoptosis, proliferation and angiogenesis. The best known members of the TNF family are TNF- $\alpha$  and TNF- $\beta$ .

TNF- $\alpha$  is often simply referred to as 'tumour necrosis factor'. At a low concentration in tissues, TNF- $\alpha$  has beneficial effects such as prevention of infections, although it can lead to excess inflammation and organ injury at high concentrations. As the name implies, TNF- $\alpha$  has antitumour properties and plays a key role in induction of apoptosis as well as transduction of cell survival signals. Pro-caspase-8 is a key regulator of TNF- $\alpha$  induced apoptosis, while nuclear factor kappa B (NF- $\kappa$ B) is the major factor in TNF- $\alpha$  induced survival signals. The role of TNF- $\alpha$  in the regulation of the apoptosis and proliferation cascade indicates its potential for the treatment of malignancy.

TNF- $\beta$  or lymphotoxin is derived from T lymphocytes and has a 50% amino acid sequence homology, and binds to the same receptor as TNF- $\alpha$ . Its biological significance is unclear. TNF- $\alpha$  is a key pro-inflammatory cytokine that plays a central role in the pathogenesis of psoriasis, psoriatic arthritis and many dermatological diseases. It is released as soluble (sTNF) and membrane-bound forms (transmembrane TNF; tmTNF). sTNF and tmTNF bind to distinct receptors: TNF receptor 1 (TNFR1, p55) and TNF receptor 2 (TNFR2, p75) leading to activation of NF- $\kappa$ B, inflammation and cell apoptosis, respectively. TNF may also drive keratinocyte proliferation in psoriasis.

The anti-TNF agents/TNF antagonists currently used in dermatology can be divided into two groups: monoclonal antibodies (adalimumab and infliximab) and soluble TNF receptors (etanercept). Although all three drugs inhibit TNF- $\alpha$ , their structures and pharmacodynamic and pharmacokinetic profiles are different.

**Adalimumab** is a fully human monoclonal immunoglobulin (Ig)G1 antibody specific for TNF- $\alpha$ . It acts by blocking TNF interaction with the p55 and p75 cell surface TNF receptors.

**Infliximab** is a chimeric IgG1 human–murine monoclonal antibody (~25% mouse derived protein). It binds and neutralizes both soluble and membrane-bound TNF- $\alpha$ , but not TNF- $\beta$ .

**Etanercept** is a soluble TNF receptor protein consisting of the extracellular portions of human TNFR2 (p75) linked to the Fc domain of human IgG1.

Recently, new TNF antagonists such as golimumab and certolimumab-pegol have been approved for rheumatological diseases. Golimumab, like adalimumab, is a fully human IgG1 antibody licensed for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Certolizumab-pegol is a humanized anti-TNF Fab' fragment conjugated to a polyethylene glycol to prolong serum half-life, which facilitates once-monthly dosing. It is approved for the treatment of rheumatoid arthritis. As these two Adalimumab and infliximab bind to both sTNF and tmTNF, whereas etanercept binds primarily to sTNF and TNF- $\beta$ . All three biological agents act by: (i) blocking TNF receptor mediated mechanisms and (ii) inducing tmTNF (reverse-signalling) events. In addition, adalimumab and infliximab can fix complement, thereby leading to antibody dependent cytotoxicity and can trigger T-cell apoptosis, whereas etanercept lacks these actions. Thus, adalimumab and infliximab seem to have a greater propensity to cause lymphocyte apoptosis compared with etanercept.

## + Indications & dermatological uses

TNF antagonists are approved for the management of psoriasis and are also indicated for psoriatic arthritis.

The Psoriasis Area and Severity Index (PASI) is a widely used measure of the clinical severity of psoriasis whereas the Dermatology Life Quality Index (DLQI) (see Appendix 4) is a validated tool used to evaluate the impact of skin disease on quality of life. In the UK, patient eligibility for treatment with TNF antagonists is dictated by the National Institute for Health and Care Excellence (NICE) eligibility criteria, which include:

- Chronic plaque psoriasis of at least 6 months' duration.
- Documented failure to respond to and/or unsuitability for other conventional systemic treatments.
- A PASI of  $\geq 10$ , and a DLQI of  $> 10$  for adalimumab and etanercept; and a PASI of  $\geq 20$  and a DLQI of  $> 18$  for infliximab.
- Both PASI and DLQI are calculated before and during treatment.

The definition of treatment response is either:

- PASI 50: a 50% or greater reduction from baseline PASI or % body surface area where PASI is not applicable, and at least a 5 point reduction in DLQI.
- PASI 75: a 75% reduction from baseline PASI.

TNF antagonists should be discontinued if patients do not achieve these response criteria. According to NICE guidelines, the time point for reviewing whether to continue therapy is at 16 weeks for adalimumab, and 12 weeks and 10 weeks for etanercept and infliximab, respectively.

These three TNF antagonists are also approved for the treatment of other inflammatory diseases:

- Adalimumab for ankylosing spondylitis, Crohn's disease and rheumatoid arthritis.
- Infliximab for ankylosing spondylitis, Crohn's disease, rheumatoid arthritis and ulcerative colitis.
- Etanercept for ankylosing spondylitis and rheumatoid arthritis.

There are several skin diseases that have been successfully treated off-label with TNF antagonists (Table 1).

**TABLE 1** Off-label uses of tumour necrosis factor (TNF) antagonists in skin diseases

Skin diseases	Off-label uses
Granulomatous diseases: sarcoidosis granuloma annulare necrobiosis lipoidica diabetorum	adalimumab, infliximab infliximab, etanercept infliximab, etanercept
Neutrophilic dermatosis: pyoderma gangrenosum Sweet's syndrome subcorneal pustular dermatosis	adalimumab, infliximab infliximab, etanercept adalimumab, infliximab
Autoimmune blistering diseases: bullous pemphigoid pemphigus vulgaris mucous membrane pemphigoid	infliximab, etanercept infliximab etanercept
Autoimmune connective tissue diseases: lupus erythematosus scleroderma dermatomyositis Behçet's disease	infliximab, etanercept infliximab, etanercept infliximab, etanercept adalimumab, infliximab, etanercept
Acute and chronic graft-versus-host disease:	infliximab, etanercept
Other inflammatory dermatoses: pityriasis rubra pilaris SAPHO syndrome multicentric reticulohistiocytosis toxic epidermal necrolysis erythema annulare centrifugum Hailey–Hailey disease hidradenitis suppurativa vasculitis	infliximab infliximab, etanercept adalimumab, infliximab infliximab etanercept etanercept adalimumab, infliximab adalimumab, infliximab, etanercept

### Special point: Tuberculosis

It is estimated that nearly one-third of the world's population is infected with tuberculosis (TB). While most cases are in developing countries, there has been a rise in the number of TB case in the UK and USA in recent years. Immigration, human immunodeficiency virus (HIV) infection and the rise in multidrug resistant TB are contributory factors.

Asymptomatic latent TB infection may be reactivated upon immunosuppression and this is an important risk with anti-TNF therapy as TNF- $\alpha$  plays a central role in the phagocytic activity of macrophages.

Post-marketing surveillance has indicated an increased risk of TB associated with the monoclonal antibodies (infliximab and adalimumab) compared with the soluble receptor, etanercept. The risk of reactivation of latent TB has been estimated to be 12-fold greater with infliximab than etanercept, and all anti-TNF agents may increase the proportion of newly acquired cases of TB that progress to active disease.

There is a high rate of atypical clinical presentations of TB with these agents. Extrapulmonary disease occurs in >50% of cases and disseminated/miliary TB may be found. Careful screening for TB prior to starting therapy and ongoing vigilance for newly acquired disease is therefore essential.

There are few data available on off-label uses of adalimumab as it is relatively new compared with infliximab and etanercept. However, the efficacy of adalimumab is expected to be more like that of infliximab than etanercept due to a similar mechanism of action. Etanercept appears to be ineffective or at best moderately effective in hidradenitis suppurativa, pyoderma gangrenosum, sarcoidosis, Crohn's disease and Wegener's vasculitis, whereas infliximab appears to be effective.

### + Formulations/Presentation

- Adalimumab: a single-use, sterile, preservative-free solution of 40 mg adalimumab in a pre-filled autoinjector pen device or a pre-filled glass syringe for s/c administration.
- Infliximab: a freeze-dried powder in 100 mg vials for reconstitution with sterile water for i/v infusion over a period of 2 hours; the drug should be infused within 3 hours after reconstitution or within 24 hours if refrigerated.
- Etanercept: preservative-free, lyophilized powder in 10 mg and 25 mg vials for reconstitution with 1 mL of sterile water for subcutaneous administration, pre-filled syringe with 25 mg or 50 mg etanercept and 50 mg pre-filled autoinjector pen.
- All the drugs should be stored at 2–8°C and reconstituted prior to injection.

### + Dosages & suggested regimens

Adalimumab is administered s/c at an **initial dose of 80 mg** once, then, after 1 week, **40 mg s/c** every **2 weeks** for **maintenance therapy**. Maximal disease



response is achieved after **12–16 weeks**. Approximately 50% of patients achieve a PASI 75 response at week 12 with this regimen.

Etanercept is administered s/c at a dose of **25 mg twice weekly** or **50 mg once weekly** throughout treatment. Studies have shown that 48%, 38% and 34% of patients treated with etanercept 50 mg twice weekly, 50 mg once weekly and 25 mg twice weekly achieved PASI 75 at week 12. In two separate randomized controlled trials 71% and 60% of patients taking 50 mg twice weekly and 50 mg once weekly, respectively, achieved PASI 75 at week 24. Thus the USA FDA has approved a dosage of 50 mg once or twice a week for the first 3 months, whereas NICE did not consider the twice weekly 50 mg dosage to be cost-effective and does not endorse this regimen. Infliximab is given as a 5 mg/kg i/v infusion repeated after 2 and 6 weeks, then every 8 weeks thereafter.

**Continuous treatment** with anti-TNF agents provides better disease control than interrupted therapy, and there may be some loss of efficacy if treatment is reintroduced after a drug holiday. Loss of efficacy correlates with development of antibodies to TNF antagonists. Co-administration of **low dose methotrexate** (5–7.5 mg once weekly) can reduce the incidence of formation of antibodies to infliximab and sustain efficacy. In rheumatology, methotrexate is routinely co-administered with anti-TNF therapy in the treatment of rheumatoid arthritis, and infliximab is also used with methotrexate for psoriatic arthritis. Withdrawal of anti-TNF therapy usually leads to a slow relapse of disease with no evidence of rebound.

**Switching** between biologics may be considered in patients who have experienced poor results or adverse effects. Many patients have demonstrated a good response to a second anti-TNF agent, but no firm conclusions on sequential use are currently available.

### + Baseline investigations & considerations

- FBC (CBC).
- LFTs.
- Urea, electrolytes and creatinine.
- Urinalysis.
- Pregnancy test.
- Hepatitis B virus, hepatitis C virus, HIV.
- Chest x-ray.
- TB evaluation should be carried out on all patients; this includes a detailed medical assessment of past history of TB and possible exposure to those with active infection.

The tuberculin skin test (TST) or Mantoux test is routinely used as a screening test for latent TB infection in asymptomatic individuals. However, it has several limitations including the need for repeated clinic visits at 48 and 72 hours, a lack of specificity for *Mycobacterium tuberculosis* in those who have received TB immunization (false positive) and attenuated responses in patients receiving immunosuppressant therapy (false negative). Interferon-gamma release assays (IGRAs) are a new generation of laboratory tests based on the measurement of interferon-gamma (IFN- $\gamma$ ) release from sensitized T cells in response to

*M. tuberculosis* specific antigens using enzyme linked immunosorbent (ELISA) techniques. IGRAs may be the future gold standard in TB screening and have reported sensitivities and specificities of 89% and 98%, respectively.

A TST or IGRA should be performed at baseline according to local guidelines. The TST remains a useful test, but IGRA is recommended if the TST is ambiguous and particularly when the patient is receiving immunosuppressive therapy.

### + Monitoring

FBC, LFTs, creatinine, urinalysis, and pregnancy tests should be performed at weeks 4 and 12 and thereafter every 3 months for adalimumab and etanercept. Infliximab requires monitoring at weeks 2, 6 and prior to each infusion.

Further TB testing may be required according to clinical signs and risks.

NB: The response to IGRAs may be reduced in patients taking anti-TNF therapy, so their usefulness is limited once patients have commenced therapy.

### + Contraindications

- Serious infection (e.g. hepatitis B virus infection).
- Active TB.
- Congestive heart failure (NYHA grade III or IV), due to a risk of exacerbation.
- NYHA class I or II heart failure with ejection fraction < 50% by echocardiography.
- Hypersensitivity to any component of the formulation.
- Pregnancy or breastfeeding.
- History of demyelinating disease/multiple sclerosis.

### + Cautions

- Family history of multiple sclerosis or other demyelinating disease.
- Live vaccines.
- Psoralen with ultraviolet A (PUVA) >200 treatments (especially if followed by ciclosporin [cyclosporine]).
- Malignancies or lymphoproliferative disorders.
- Hepatobiliary disorders.
- Hepatitis C.

In addition the following should be noted:

TNF antagonists should be avoided in patients with a history of multiple sclerosis or other types of **demyelinating disease** because of reports of either new onset or exacerbation of pre-existing multiple sclerosis.

**Hepatitis virus:** patients who are chronic carriers of hepatitis B should not be treated with TNF antagonists due to the risk of viral reactivation. TNF antagonists can be used in patients with hepatitis C infection with appropriate

evaluation and monitoring during therapy. The best studied of these drugs in the setting of hepatitis C infection is etanercept.

**Vaccines:** patients should not receive vaccinations with live or live attenuated organisms within the 2 weeks prior to starting therapy, during and for 6 months after discontinuation. Patients should avoid contact with children who have received the live polio vaccine for up to 4–6 weeks after the vaccination. Pneumococcal and influenza vaccinations are safe and are recommended.

**Malignancies:** it should be noted that patients with psoriasis have a higher risk of lymphoma compared with the general population. Moreover, they are also at an increased risk of developing skin cancer due to previous sun exposure, and UV phototherapy, particularly PUVA. Therefore, patients with prior PUVA therapy and intensive use of immunosuppressive drugs should be evaluated for skin cancer before and during TNF antagonist therapy.

**Asymptomatic latent TB** may be reactivated by anti-TNF therapy and a respiratory physician should be consulted for advice on therapy that must be commenced prior to anti-TNF therapy. Patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with anti-TNF agents.

### + Important drug interactions

- Increased immunosuppression is more likely to occur when TNF antagonists are combined with other **immunosuppressive** drugs such as ciclosporin.

### + Adverse effects & their management

- **Adalimumab.** The commonest side-effects reported are injection site reactions, viral, candidal and bacterial infections, dizziness, headaches, vertigo, gastrointestinal upset, musculoskeletal pain, rash, asthenia and malaise. Injection site reactions (erythema, itching, pain, swelling and haemorrhage) occur in 15% of patients but generally do not result in discontinuation of therapy.
- **Etanercept.** The commonest side-effects are injection site reactions, allergic reaction, headache and upper respiratory tract infection. Injection site reactions are common but usually diminish with ongoing therapy and do not relate to antibody development.
- **Infliximab.** Infusion reactions are defined as any adverse events occurring during or within 1 hour after completion of the infusion. These reactions are mild to moderate symptoms such as flushing, pruritus, chills, headache, and urticaria. Mild to moderate reactions occur in 3–22% of patients with psoriasis. Severe infusion reactions include anaphylactic reactions and serum sickness-like reactions are rare. If mild to moderate infusion reactions occur, treatment can usually be continued by decreasing the infusion rate or temporarily stopping the infusion. Pre-treatment with oral antihistamines,

paracetamol (acetaminophen) and/or glucocorticosteroids should be considered for the future infusions. Serious infusion reactions seem to occur more frequently with intermittent rather than continuous therapy. The commonest side-effects are upper respiratory tract infection, headache, elevated liver enzymes and infection. Elevation of liver enzymes is generally transient and asymptomatic. Treatment can be continued in the majority of cases with close monitoring. The following guidelines can be used with respect to the elevation of aminotransferase:

- Continue treatment if values <3 times of normal upper limit.
- Treat with caution if values 3–5 times of normal upper limit.
- Stop treatment if values >5 times of normal upper limit.

Other rare but important adverse effects of TNF antagonists include the following:

- **Demyelinating disorders** have been reported with all three TNF antagonists; the risk appears small and partial or full recovery has occurred on discontinuation.
- **Malignancy** has been reported in association with anti-TNF therapy including solid tumours, non-Hodgkin's lymphoma and malignant melanoma: however, as many patients have been exposed to other immunosuppressant therapies in the past, it is difficult to determine the true risk of malignancy with TNF antagonists alone.
- **Congestive heart failure** is a contraindication to anti-TNF therapy, but reports of it occurring *de novo* with anti-TNF therapy are rare.
- **Drug induced lupus** has been reported in association with anti-TNF therapy; treatment should be discontinued if symptoms develop, but can be continued in asymptomatic patients who develop positive antinuclear antibodies (ANA).
- **Paradoxical worsening** or new onset of **psoriasis**: has been reported in patients given anti-TNF therapy for non-dermatological indications, and rarely, for psoriasis.

## + Use in special situations

### Pregnancy & pre-conception (FDA Category B)

Anti-TNF agents cross the placenta and both infliximab and etanercept have been detected in the serum of infants born to mothers who received these agents. Although the majority of cases of antenatal exposure have resulted in birth of normal infants, there is inadequate safety data to recommend their use, and females who receive anti-TNF agents should use effective contraception. If pregnancy occurs, temporary withdrawal of treatment should be considered. The manufacturers advise that females who have received anti-TNF therapy should avoid pregnancy for variable time periods following cessation, notably 6 months with infliximab.

Limited data suggest that TNF antagonists can affect sperm motility but the clinical relevance is unclear at present.

### Lactation

Breastfeeding should be avoided in patients receiving TNF antagonist therapy although limited evidence indicates that if present in breast milk, levels will be extremely low.

### Children

Longer-term safety data are lacking. However, etanercept is licensed for the treatment of severe chronic plaque psoriasis in children aged 8 years and older if their disease is unresponsive to conventional systemic therapy or phototherapy or they are intolerant of treatment. The dosing schedule is 0.8 mg/kg up to a maximum dose of 50 mg once weekly by s/c injection.

### + Essential patient information

- Patients should be informed of the risks and benefits.
- Patients should be monitored for early signs and symptoms of infection throughout treatment.
- All patients should be fully assessed for active and latent TB before starting therapy.
- All patients should be assessed for current and past history of malignancy and/or any future risk of malignancy before starting and throughout treatment.
- Patients should not receive live or live attenuated vaccination within 2 weeks before, during and for 6 months after discontinuation.
- Patients at risk for hepatitis B infection should be screened for hepatitis B prior to starting TNF antagonist therapy.
- Pneumococcal vaccine and annual influenza vaccine are recommended while patients are on therapy.
- Agents should be discontinued at least four half-lives prior to major surgery (2 weeks for etanercept, 4–6 weeks for infliximab, 6–8 weeks for adalimumab).
- Where a TNF antagonist therapy is used outside its indication, written consent should be obtained from the patient.

*With acknowledgements to Nicholas Blickenstaff who reviewed this chapter from an international perspective.*

### + Further reading

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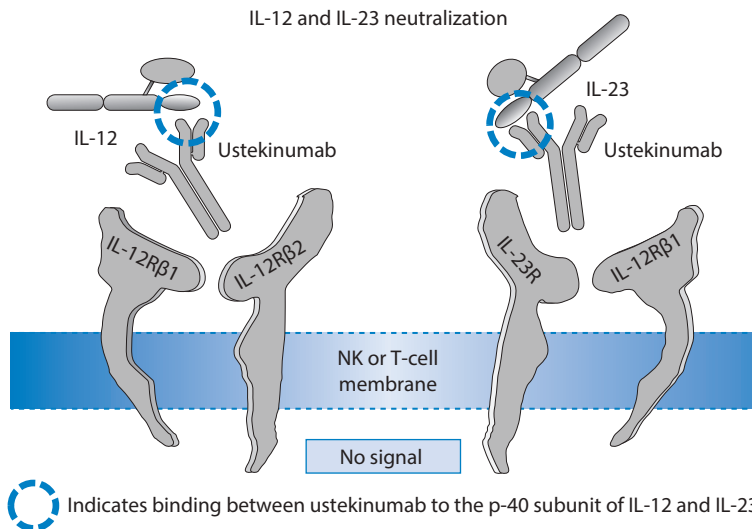
# Ustekinumab

Rose Mak

## + Classification & mode of action

Ustekinumab is the first licensed biological therapy inhibiting the action of interleukin (IL)-12 and IL-23 for use in the treatment of moderate to severe psoriasis. It is a fully human monoclonal antibody that binds with high affinity and specificity to the p-40 subunit common to IL-12 and IL-23, thereby preventing their binding to cell surface receptors and blocking their ability to activate T-lymphocyte subsets (Figure 1). IL-12 and IL-23 are heterodimeric cytokines derived from activated dendritic cells. IL-12 activates Th1 lymphocytes (that produce tumour necrosis factor [TNF] and interferon-gamma) while IL-23 stimulates survival and proliferation of Th17 lymphocytes that appear to play a key role in the pathogenesis of psoriasis.

The longer half-life of ustekinumab (21 days) compared with TNF antagonists allows extended intervals between dosing for maintenance therapy.



**FIGURE 1** Mode of action of ustekinumab, which binds to the p-40 subunit common to both IL-12 and IL-23, thereby inhibiting their binding to cell surface receptors and subsequent activation of T-lymphocyte subsets (reproduced with kind permission of Janssen Pharmaceuticals).

## + Indications & dermatological uses

Ustekinumab is licensed for the treatment of adults with moderate to severe plaque psoriasis or active psoriatic arthritis. In the UK patient eligibility for treatment is determined by the National Institute for Health and Care Excellence (NICE) criteria which include chronic plaque psoriasis of  $\geq 6$  months' duration; documented failure to and/or unsuitability for other standard systemic treatments including ciclosporin (cyclosporine), methotrexate and psoralen with ultraviolet A (PUVA); with a Psoriasis Area and Severity Index (PASI) of  $\geq 10$  and a Dermatology Life Quality Index (DLQI) of  $> 10$ .

The 2009 British Association of Dermatologists' (BAD) guidelines for biological interventions for psoriasis recommended that TNF antagonists were the first-line intervention for patients fulfilling criteria for treatment with biological therapy, with use of ustekinumab reserved for patients who had failed TNF antagonist therapy or where these agents are contraindicated. This reflected the limited (1 year) safety data for ustekinumab available at this time.

Ustekinumab may be beneficial in the treatment of palmoplantar psoriasis but more data are needed to further evaluate its use in this condition.

## + Formulations/Presentation

- Ustekinumab 45 mg solution in a 0.5 mL pre-filled syringe for s/c injection.
- The solution is clear to slightly opalescent, colourless to light yellow.
- The pre-filled syringe should be kept in the outer carton in order to protect from light.
- Ustekinumab should be stored in a refrigerator (2–8°C).

Prior to injection, the pre-filled syringe should be taken out of the refrigerator and be left to stand in room temperature for about 30 minutes. This allows the solution to come to a comfortable temperature for injection (room temperature). Injection into areas of psoriasis should be avoided.

## + Dosages & suggested regimens

- Patients  $\leq 100$  kg: **45 mg** administered s/c at weeks 0 and 4, then every 12 weeks.
- Patients  $> 100$  kg: **90 mg** administered subcutaneously at weeks 0 and 4, then every 12 weeks.

It is recommended that treatment should be discontinued if there is inadequate clinical response after **28 weeks**. In practice, the onset of action is usually evident within 2 weeks and a 75% reduction in PASI (PASI 75) occurs in over 60% of patients at 16 weeks with sustained efficacy at 12 months. After withdrawal, there is a slow relapse with no rebound and the efficacy on retreatment does not appear to be reduced.



Pharmacokinetic data have shown that in patients weighing more than 100 kg there is a 55% greater clearance and a 37% greater volume of distribution. Clinical trials also showed a reduced efficacy in patients >100 kg using a standard 45 mg dosage, and this is the rationale for the use of higher (90 mg) dosage in these individuals. Consideration of the higher dose may be useful in patients weighing 90–100 kg who have failed to respond to the standard dose regimen.

In the treatment of psoriatic arthritis, ustekinumab is licensed both as monotherapy and in combination with methotrexate.

### + Baseline investigations & considerations

- FBC (CBC).
- LFTs.
- Serum creatinine.
- Urinalysis.
- Pregnancy test.
- Hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), screening for tuberculosis (TB) including chest x-ray.
- Body weight.

### + Monitoring

FBC, LFTs, serum creatinine, urinalysis, pregnancy test and bodyweight should be performed at weeks 4 and 12 and every 3 months thereafter. Further testing may be required according to clinical signs and risks.

### Use in kidney disease

There are no available pharmacokinetic data on the use of ustekinumab in patients with renal or hepatic impairment. Theoretically the kidneys only play a relevant role in the catabolism and elimination of protein therapeutics when the molecular size is below the cut off for glomerular filtration of ~60 kDa (examples include interleukin-10, growth hormone, erythropoietin and anakinra). Ustekinumab is a human IgG1 monoclonal antibody and like other biological therapies, has a molecular weight of ~150 kDa, so its clearance is unlikely to be affected by renal impairment. Limited case reports on the use of other antibody mediated therapy such as cetuximab and rituximab suggest that these agents are safe in renal impairment with no dose reductions required. The FDA advised that renal impairment was unlikely to alter the pharmacokinetics of monoclonal antibodies, and therefore renal impairment studies were not required in the development program of this group of compounds (including ustekinumab).

In addition, data from approximately 2000 ustekinumab-treated psoriasis patients in the PHOENIX 1 and PHOENIX 2 phase three trials showed that the creatinine clearance did not substantially alter the clearance of ustekinumab.

### + Contraindications

- Hypersensitivity to ustekinumab.
- Significant active infection.
- Pregnancy or breastfeeding.

### + Cautions

- Due to the potential of biological therapies in increasing the risk of infections and reactivating latent infections, ustekinumab should be used with caution in patients with chronic infection or history of recurrent infection, especially TB.
- Consider possible increased risk of malignancy.
- Provide age-appropriate immunizations prior to initiating therapy.
- Use caution in patients genetically deficient in IL-12, IL-23.

### + Important drug interactions

No drug interactions have been reported thus far. *In vitro*, ustekinumab has no effect on cytochrome P450 (CYP450) activities.

- **Live vaccines** should not be given concurrently with ustekinumab, and should be withheld for at least 15 weeks after the last dose of ustekinumab; medication can resume at least 2 weeks after live vaccinations.
- The safety and efficacy of ustekinumab in combination with other **immunosuppressants** including biologics, or phototherapy have not been evaluated.

### + Adverse effects & their management

- The most **common adverse reactions** (>5%) are nasopharyngitis, headache and upper respiratory tract infection. These are usually mild and treatment can be continued.
- **Injection site reactions** are less common than with TNF antagonists, possibly due to the infrequency of injections. They do not appear to be correlated with the presence of neutralizing antibodies (that may reduce treatment efficacy).
- **Hypersensitivity reactions** are usually mild and include rashes and urticaria (<1 in 10 patients). Serious hypersensitivity reactions (anaphylaxis angioedema) and Bell's palsy are rare (<1 in 1000 patients). The needle cover on the pre-filled syringe contains **natural rubber latex** and may cause allergic reactions in individuals with latex allergy.
- **Infections and reactivation of latent infections:** serious bacterial, fungal and viral infections such as herpes zoster and viral hepatitis have been observed in patients receiving ustekinumab. If a patient develops a serious infection,

ustekinumab should be withheld until the infection has resolved. Baseline screening prior to commencing ustekinumab includes a careful evaluation for TB and anti-TB therapy should be considered prior to initiating ustekinumab in patients with past history of latent or active TB. Patients should continue to be closely monitored for symptoms and signs of active TB during and after ustekinumab treatment (see Tumour Necrosis Factor Antagonists).

As ustekinumab is a newer therapy than TNF antagonists, it is important that prescribers are vigilant to the possibility of unknown or long-term adverse events. Serious infections, infections requiring antibiotics, malignancies and major adverse cardiac events have been evaluated as adverse events of special interest and have been found to remain stable for up to 5 years of treatment. Biologics registries have been established in several European countries and should provide increasingly robust data on the safety and efficacy of these agents. Prescribers are strongly encouraged to enroll their patients into these registries.

### **+ Use in special situations**

#### **Pregnancy & pre-conception (FDA Category B)**

The effect of ustekinumab on human fertility has not been evaluated but no adverse effect on male fertility has been observed in animal studies.

Pregnancy should be avoided. Use of effective contraception during treatment and for at least 15 weeks post-treatment is recommended. The 2009 BAD guidelines recommended that biologic agents should be avoided and/or stopped in advance in females who are planning a pregnancy, and biologic agents should be avoided so the fetus is drug free during the critical developmental period of the first 12 weeks.

#### **Lactation**

It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown low level excretion of ustekinumab in milk, but it is unknown if ustekinumab is absorbed systemically after ingestion. It is advised that breastfeeding be discontinued during treatment and for 15 weeks after treatment.

#### **Children**

Ustekinumab is currently unlicensed for patients under the age of 18 years old and experience in younger patients is limited to case reports.

#### **Elderly**

No overall significant differences in efficacy or safety of ustekinumab have been observed in patients aged 65 years old or over compared with younger patients. However, due to declining immune function and the increased risk of infections in the elderly population, caution is advised when treating this age group with biologic drugs including ustekinumab.

## + Essential patient information

- Patients should be informed of the risks and benefits of therapy through detailed discussion supplemented with written information.
- As ustekinumab is newer than other biologic therapies, the available safety data are of shorter duration than TNF antagonists.
- Information on the risks of infections and guidance on vaccinations should be provided and females of childbearing potential should be advised to avoid pregnancy.

*With acknowledgements to Nicholas Blickenstaff who reviewed this chapter from an international perspective.*

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# Vismodegib

Faisal R. Ali & John T. Lear

## + Classification & mode of action

Vismodegib is the first in a new class of orally active anticancer drugs that inhibit the hedgehog (Hh) signalling pathway by binding to smoothened transmembrane protein (Smo) and blocking induction of Hh target genes. Many of these genes are involved in cell proliferation, survival and differentiation. Recent development of Smo inhibitors has led to the current investigation of several drugs as therapy for a range of tumours.

The Hh signalling pathway plays a key role in the morphogenesis of the epidermis and its appendages during embryogenesis and for self-renewal of the skin and hair follicles throughout life. Mutations in *PTCH1*, the human homolog of the *Drosophila* gene 'patched', which is a negative regulator of the Hh pathway, have been found in both hereditary basal cell naevus syndrome (Gorlin syndrome) and the majority of sporadic basal cell carcinomas (BCCs). These result in an unregulated proliferation of basal keratinocytes and the formation of tumours.

Vismodegib is absorbed after oral administration and slowly eliminated by a combination of metabolism by cytochrome 450 (CYP450) 2C9 and CYP3A4/5 and hepatic excretion of the parent drug. Only a small fraction is excreted renally. Its terminal half-life after administration of a single dose is approximately 12 days.

## + Indications & dermatological uses

Vismodegib was approved by the USA FDA in 2012 and by the UK MHRA in 2013 and is licensed for the treatment of adults with advanced BCC in the following contexts:

- Symptomatic metastatic BCC.
- Locally advanced BCC inappropriate for surgery or radiotherapy.

Short-term studies (median duration of 6 months) have found that approximately 40% of patients with locally advanced BCC had a clinical response (reduction in tumour diameter of >30%) and that there was clearance of the tumour in 20% of patients.

In patients with metastatic BCC, approximately one-third showed evidence of a clinical response.

## + Formulations/Presentation

- Hard capsules containing 150 mg vismodegib (Erivedge®).

## + Dosages & suggested regimens

One capsule (**150 mg**) **once daily**. Capsules should be swallowed whole and taken with water +/- food.

Tumour response should be gauged through serial measurements of tumour diameter and the documentation of the presence of ulceration. Therapy should be continued until disease progression or unacceptable side-effect profile. The benefit gained and side-effect profile associated with continued treatment should be regularly evaluated in each individual patient.

Adverse effects are common (see Adverse effects & their management, below) and given its long half-life, interval dosing is being investigated as a means to improve tolerability, though there are no formal guidelines for this. The manufacturers advise that treatment may be interrupted for up to 4 weeks if adverse effects are not tolerated.

Some BCCs continue to grow despite treatment (primary resistance) with vismodegib and in other cases, there may be regrowth of the BCC after an initial clinical response (acquired resistance). These may reflect mutations in Smo which confer drug resistance, for example by decreased drug binding.

Vismodegib is not a curative treatment and in patients who respond, BCCs have been found to recur within 3 months of stopping treatment. There is interest in using this drug as neoadjuvant therapy, shrinking large primary tumours prior to complex reconstructive surgery, but further studies are needed to investigate this role.

## + Baseline investigations & considerations

For females of childbearing potential, pregnancy testing within 7 days before starting vismodegib treatment and commencement of the manufacturer's Pregnancy Prevention Programme (PPP) are imperative. The plan includes using two forms of contraception prior to and during treatment and 24 months after the last dose, including one highly effective method and a barrier contraceptive, limiting prescriptions to 1 month's duration and having monthly pregnancy testing during treatment.

For males (including those with vasectomy) having sexual intercourse with females of childbearing potential, counselling should be given of the need for barrier contraception with spermicide throughout treatment and for at least 2 months after the last dose.

FBC, renal function and LFTs should be checked.

### + Monitoring

No specific recommendations currently exist. Intermittent monitoring of routine blood parameters (FBC, LFTs, urea and electrolytes) may be advisable. Females of childbearing potential should be part of the PPP, including monthly pregnancy testing.

### + Contraindications

- Hypersensitivity to the active substance/excipients.
- Pregnancy or breastfeeding.
- Females of childbearing potential who do not comply with the PPP.

### + Cautions

Hepatic and renal impairment safety is not established. The manufacturers advise close monitoring in patients with severe renal impairment and moderate–severe hepatic impairment.

### + Important drug interactions

- **Antacids, proton pump inhibitors** and **H<sub>2</sub>-receptor antagonists** may reduce the solubility and bioavailability of vismodegib.
- **CYP450 inducers** (rifampicin, carbamazepine, phenytoin, St John's wort [*Hypericum perforatum*]) may reduce the effectiveness of vismodegib.
- Vismodegib is a substrate for the efflux transporter P-glycoprotein and the metabolizing enzymes **CYP2C9** and **CYP3A4**.
- **P-glycoprotein inhibitors** (e.g. macrolide antibiotics, verapamil, ciclosporin [cyclosporine]), **CYP2C9** inhibitors (amiodarone, fluconazole or miconazole) and **CYP3A4** inhibitors (including antiretroviral drugs, clarithromycin and azole antifungal drugs) may increase systemic exposure to vismodegib and the risk of adverse effects.

### + Adverse effects & their management

Adverse effects are frequent and may be severe, leading to treatment withdrawal.

- The most common side-effects of vismodegib are: **muscle cramps** (72%), **alopecia** (64%) and **taste disturbance** (55%), including both abnormal taste and loss of taste.
- Other frequent side-effects include: weight loss, fatigue, nausea, diarrhoea, decreased appetite, constipation, arthralgia and vomiting.

- **Hepatitis** with elevated transaminase and/or alkaline phosphatase levels has been noted.
- **Rebound** of BCCs in hereditary basal cell naevus syndrome has been described on discontinuing therapy.
- **Squamous neoplasms** have been reported to develop during treatment with vismodegib including keratoacanthomas and moderate to highly differentiated squamous cell carcinomas.

### + Use in special situations

#### Pregnancy & pre-conception (FDA Category D)

Animal studies have shown irreversible loss of fertility after treatment with vismodegib. Females taking vismodegib may become amenorrhoeic. Fertility preservation strategies should be discussed with individuals who may wish to have children after completing therapy.

Vismodegib is excreted in semen and male patients must use a condom when having sex with a female of childbearing potential during treatment and for 2 months after the last dose.

Smo inhibitors including vismodegib are potent teratogens, causing severe birth defects and embryofetal death. They are absolutely contraindicated during pregnancy. In reality, the majority of female recipients will be beyond an age of childbearing potential. However, for females with childbearing potential, stringent precautions apply including a strict PPP. The manufacturers advise that pregnancy must be avoided for 24 months after the final dose.

#### Lactation

Mothers must not breastfeed while taking vismodegib and for 24 months after the final dose.

#### Children

Animal studies indicate a potential risk of short stature and tooth deformities in infants and children and vismodegib should not be given to those under the age of 18 years. This may be of relevance in hereditary basal cell naevus syndrome where BCCs may first appear in early childhood.

#### Elderly

In clinical trials of vismodegib approximately 40% of patients have been over the age of 65 years and vismodegib did not differ in terms of safety or efficacy in this age group compared with younger patients.

### + Essential patient information

- Patients and their carers should be advised that this treatment is for symptomatic relief rather than curative; BCCs will likely recur if treatment is discontinued.



- Patients and their carers should be advised of common adverse effects as detailed above.
- Females of childbearing potential must comply with the manufacturer's PPP during treatment and at least 24 months following the final dose.
- Males (including those post-vasectomy) should use barrier contraception with spermicide and must not donate semen while taking treatment and for 2 months after the final dose.
- Patients should not donate blood or blood products while taking vismodegib and for at least 24 months after the final dose.
- Patients must inform their healthcare team should they or their partner become pregnant while taking vismodegib, plan to become pregnant or plan to breastfeed.

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# Systemic Therapy in Children

Susannah Baron

## + Principles of treatment

Prescribing systemic therapies in children poses several challenges, not least because many drugs are not licensed for use in the paediatric population. While most children tolerate systemic medication well, neonates are at special risk of adverse drug reactions due to their immature liver and renal function. Reliable information on prescribing for children can be found in the British National Formulary for Children (BNFC).

## + Use of unlicensed & off-label medicines

When a pharmaceutical produce is granted market authorisation ('product license'), the terms of its use are clearly specified in the Summary of Product Characteristics: dose, regimen, route of administration, patient population etc. Use of the product outside these terms is said to be 'off-label'. Much prescribing in children is off-label, as the pharmaceutical companies do not usually have sufficient data at the time marketing authorisation is granted. There is little incentive to do so unless the drug is principally for use in children.

Off-label prescribing in children, should as far as possible be supported by evidence of safety and efficacy. The use of the product outside the terms of its license should be discussed with the child and their parents. Examples include the use of ciclosporin in childhood psoriasis and azathioprine in atopic eczema. The term 'unlicensed' refers to a product that does not have a license at all and is a less common scenario. Such treatment will usually be initiated and maintained in secondary or tertiary care. Secondary formulations of a product (e.g. dilution or re-formulation) are also considered unlicensed.

### **+ Prescription, formulation & administration of drugs in children**

When choosing the best preparation for children, use one that is acceptable to them and that fits in with their daily routine. Some flexibility should be allowed in children to avoid waking them during the night so their night time dose may be given at their bedtime.

For young children liquid preparations are frequently prescribed. Branded oral liquid preparations that do not contain fructose, glucose or sucrose are described as 'sugar free' and should be prescribed whenever possible to prevent dental caries.

Some drugs are only available in solid dosage which can pose administration problems for parents. It is important for parents to obtain the correct advice from the dispensing pharmacist on crushing the tablets or emptying the capsules into a suitable vehicle for administration.

Liquid preparations can be available in different strengths so it is imperative when writing prescriptions to write clearly the drug dosage rather than the amount to be given. Confusion can occur with oral solutions, e.g. methotrexate and propranolol that are formulated in different strengths. This should be discussed with the pharmacist and the parents and the same strength formulation dispensed each time to avoid over- or under-dosage.

### **+ Specific drugs**

It is recommended that all drugs and dosages are checked in the BNFC or other pharmaceutical database.

#### **Acitretin (see Acitretin)**

- Licensed for use in children in exceptional circumstances, e.g. severe ichthyosis.
- Child 1 month–12 years: 0.5 mg/kg once daily with food or milk (occasionally up to 1 mg/kg daily) to maximum of 35 mg daily.
- Child 12–18 years: for Darier's disease 10 mg daily, for other conditions up to 25–30 mg daily for 2–4 weeks then adjusted for response. Dosage may be increased up to 75 mg for short periods in severe ichthyosis.
- Caution: growth should be monitored to detect premature epiphyseal closure. Concomitant use of keratolytics should be avoided.

Acitretin is insoluble in water and light sensitive. A suspension may be formulated from capsule contents for neonates and infants but care must be taken that the suspension is dispensed in a dark bottle and not exposed to light.

**Acne antibiotics (see Acne Antibiotics)**

- Indications: infantile and childhood acne.
- In children <12 years: oral erythromycin is first-line treatment with oral trimethoprim for resistant acne.
- In children >12 years: oral tetracyclines are the first-line systemic treatment.

**Alitretinoin (see Alitretinoin)**

Not recommended for use in children under the age of 18 years.

**Antibiotics commonly used for skin infections (see Antibiotics commonly used for skin infections)**

Indications: impetigo/infected atopic eczema (atopic dermatitis).

Impetigo is common in young children and can be caused by *Staphylococcus aureus* and beta-haemolytic streptococci. These bacteria may also be implicated in infected flares of atopic eczema (atopic dermatitis). Flucloxacillin is the treatment of choice for staphylococcal infections, with erythromycin an alternative for penicillin-allergic children. Virulent and resistant community-onset staphylococcal disease has emerged worldwide associated with Panton–Valentine leukocidin (PVL) cytotoxin. In the UK it is present in the majority of community-associated methicillin-resistant *S. aureus* (MRSA). Clindamycin alone or in combination with rifampicin may be used for PVL-positive *S. aureus* skin infections in children. Advice should be sought from local microbiologists.

**Antifungals (see Antifungals)**

Oral azole antifungals (particularly itraconazole) and terbinafine are increasingly being used in preference to griseofulvin as they have a broader spectrum of activity and shorter treatment duration. Remember that immunocompromised children are at particular risk of fungal infections. Table 1 provides detailed information regarding age, formulation, appropriate dosages and licensing information.

**TABLE 1** Formulation and licensing information for oral antifungals in children

Generic Name	Formulation	Information
Fluconazole	Capsules 50 mg, 150 mg, 200 mg Oral suspension 50 mg/5 mL, 200 mg/5 mL	Unlicensed for superficial fungal infections in children
Itraconazole	Capsules 100 mg Oral liquid sugar free 10 mg/mL	Unlicensed in children under 12 years
Griseofulvin	Tablets 125 mg, 500 mg Oral suspension 125 mg/5 mL	Licensed in children
Terbinafine	Tablets 250 mg	Unlicensed in children

**Tinea capitis** is predominantly a complaint of pre-adolescent children; infants are affected less commonly. Oral therapy is usually required in order to eradicate the organism, alleviating disease symptoms quickly and safely and to reduce transmission to others. The choice of drug will vary according to the causative organism but as fungal culture may take up to 1 month it is reasonable to start therapy immediately. Although griseofulvin is the only drug licensed for the treatment of tinea capitis in children in the UK, newer antifungal agents are gaining popularity, due to their greater cost-effectiveness and safety. In the UK *Trichophyton tonsurans* is reported to account for 50–90% of dermatophyte scalp isolates, whereas in Europe *Microsporum canis* remains the most commonly involved organism.

Griseofulvin is more effective against *Microsporum* species than *Trichophyton* species, and the latter may require prolonged therapy. The suspension is more palatable for children, but has become expensive and may be difficult to source.

Terbinafine has much higher efficacy against *Trichophyton* species than *Microsporum* species, and may be considered the treatment of choice for *T. tonsurans* infection. A granule formulation which can be sprinkled over food is licensed for use in children over 4 years in the USA.

Itraconazole is active against both *Microsporum* and *Trichophyton* species and is widely used in many European countries. It is not licensed in children under the age of 12 years in the UK. A liquid formulation exists.

UK guidelines suggest the use of griseofulvin or terbinafine as first-line therapy, dependent on the organism suspected/isolated, with itraconazole used as second-line therapy.

Fluconazole is licensed for use in the treatment of candidiasis in children of all ages and exists in an orange flavoured liquid formulation. The antifungal medications and dosage regimens suggested for use in children are outlined in Table 2.

**Onychomycosis** is less common in children than in adults. The dominant causative agents in this age group are *T. rubrum*, *T. mentagrophytes* and *Candida* species. Griseofulvin is no longer recommended for paediatric onychomycosis due to long treatment duration and lack of efficacy. Daily terbinafine and daily or pulsed itraconazole have been shown to be well-tolerated in paediatric populations, with faster response and higher cure rates than in adults due to the faster growth of the nail plate in children.

**Pityriasis versicolor** may affect older children and usually responds to topical therapy. If required it may be treated with oral itraconazole or fluconazole.

Widespread or intractable superficial candidiasis may require systemic therapy. Fluconazole is licensed for use in mucosal and invasive *Candida* infection in children of all ages. As stated above, itraconazole is not licensed for use in children under 12 years.

### Antihistamines (see Antihistamines)

Indications: urticaria, pruritus in atopic eczema, allergic rhinitis. If possible prescribe sugar- and colour-free oral solutions. In practice, higher doses of oral antihistamines than licensed dosages or those recommended in BNFC are often used in chronic urticaria in children, as in adults.

**TABLE 2** Oral antifungal medication and dosage regimens for children

Generic Name	Indication	Oral dose 12–18 years	Oral dose <12 years
Fluconazole	Oropharyngeal candidiasis	50 mg daily for 7–14 days up to 100 mg daily	<2 weeks: 3–6 mg/kg on day 1 then 3 mg/kg every 72 hours 2–4 weeks: 3–6 mg/kg on day 1 then 3 mg/kg every 48 hours 1 month–12 years: 3–6 mg/kg on day 1 then 3 mg/kg for 7–14 days (max 100 mg)
	Tinea corporis, tinea cruris, tinea pedis, tinea manuum		1 month–18 years: 3 mg/kg (max 50 mg) daily for 2–4 weeks (maximum duration 6 weeks)
	Tinea capitis		1–18 years: 6 mg/kg (maximum 300 mg) daily for 2–4 weeks
Itraconazole	Oropharyngeal candidiasis	100 mg once daily for 15 days	1 month–12 years: 3–5 mg/kg once daily (maximum 100 mg daily)
	Tinea corporis, tinea cruris, tinea pedis, tinea manuum	Either 100 mg once daily for 15 days in tinea corporis and tinea cruris, and 30 days for tinea pedis and tinea manuum, or 200 mg twice daily for 7 days	1 month–12 years: 3–5 mg/kg (maximum 100 mg) daily for 15 days for tinea corporis and cruris and 30 days for tinea pedis and manuum
	Onychomycosis	>50 kg 200 mg/d pulsed for 1 week out of 4; 2–4 pulses may be needed	Pulsed dosing at 3–5 mg/kg 1 week out of 4; 2–4 pulses may be needed
	Tinea capitis		1–18 years: 3–5 mg/kg (maximum 200 mg) daily for 2–6 weeks
Griseofulvin	Tinea capitis	>50 kg: 1 g/d (single or divided dose) for 6–8 weeks	>50 kg: 15–20 mg/kg/d (single or divided dose) for 6–8 weeks
Terbinafine	Tinea capitis	>40 kg: 250 mg/d for 2–4 weeks	<20 kg: 62.5 mg/d for 2–4 weeks 20–40 kg: 125 mg/d for 2–4 weeks >40 kg: 250 mg/d for 2–4 weeks
	Onychomycosis	Above dose for 6 weeks for fingernails and 12 weeks for toenails	Above dose for 6 weeks for fingernails and 12 weeks for toenails

### **Antivirals (see Antivirals for HerpesViruses)**

Indication: eczema herpeticum, an acute disseminated herpes simplex virus (HSV) infection in children with atopic eczema. It is often associated with systemic symptoms and should be treated with oral antiviral medication.

Aciclovir (acyclovir) is active against HSV. Tablets and suspension are not licensed in children.

- Tablets, 200 mg, 400 mg, 800 mg.
- Dispersible tablets, 200 mg, 400 mg, 800 mg.
- Suspension, 200 mg/5 mL, 400 mg/5 mL.
- Child 1 month–2 years: 100 mg 5 times daily for 5 days.
- Child 2–18 years: 200 mg 5 times daily for 5 days.

### **Antimalarials (see Antimalarials)**

Hydroxycloiquine is occasionally used for severe photodermatoses in childhood at a dosage of 5–6.5 mg/kg (max 400 mg) once daily.

### **Biologics (see Tumour Necrosis Factor Antagonists)**

The only biologic currently licensed for severe plaque psoriasis in children (aged 6 years and older) is etanercept. It is administered as a s/c injection of 800 µg/kg (max 50 mg) once weekly for up to 24 weeks.

### **Corticosteroids (see Corticosteroids)**

Prednisolone has predominantly glucocorticoid activity and is the corticosteroid most commonly used orally in children with severe atopic dermatitis. There are concerns regarding their potential to suppress growth due to the suppressive action of glucocorticoids on the hypothalamic–pituitary–adrenal axis. This suppression is greatest and most prolonged when the drugs are given at night and least when given in a single dose in the morning.

Normal growth is allowed by 5 mg prednisolone/d for a child with 1 m<sup>2</sup> surface area. Alternate day dosing may reduce growth suppression but can have reduced therapeutic effectiveness against the disease being treated.

Courses of oral corticosteroids for skin diseases in children are usually prednisolone 1–2 mg/kg in total and should be intermittent and short (5–7 days). Prolonged courses increase susceptibility to infections and severity of infections. Clinical presentations of infections may also be atypical or exacerbated.

### **Isotretinoin (see Isotretinoin)**

Although unlicensed in children under 12 years old, isotretinoin has been safely used in infantile acne and in younger children. Capsule contents are light sensitive and insoluble in water. The author recommends mixing with a fatty food such as peanut butter on toast in the dark! Severe infantile acne should be managed by those with special expertise in paediatric dermatology.

- 1 month–2 years: 200 µg/kg daily.
- Child 2–12 years: 200–500 µg/kg increased if necessary to 1 mg/kg.
- Child 12–18 years: 500 µg/kg daily increased if necessary to 1 mg/kg.

## Immunosuppressive therapy

Before beginning systemic immunosuppressive medications in children, it should be established if the child has had chickenpox. If in doubt the varicella zoster virus (VZV) serology should be checked. Children who are not immune to VZV are at risk of severe chickenpox when taking immunosuppressive therapy, including prolonged corticosteroids. If exposed to chickenpox, advice should be sought from the local microbiology department regarding post-exposure treatment. If confirmed to have chickenpox infection or shingles the child will need urgent specialist care and treatment.

Immunizations with live vaccines such as polio and rubella should be avoided while children are taking systemic immunosuppressive drugs as the immunizations may not be effective.

Most immunosuppressive agents are not licensed for use in the treatment of skin disease in children including ciclosporin (not licensed under 16 years), methotrexate and mycophenolate mofetil.

## Special point: vitamin D supplementation

Children may have asymptomatic vitamin D deficiency. Furthermore, studies have suggested that there may be an inverse relationship between the severity of atopic dermatitis and vitamin D levels, with vitamin D supplementation leading to a decrease in severity of disease. Therefore, in children with difficult and severe eczema nutritional intake of vitamin D should be discussed with the parents and levels checked if appropriate.

Simple nutritional vitamin D deficiency can be prevented by oral supplementation with ergocalciferol (calciferol, vitamin D<sub>2</sub>) or colecalciferol (vitamin D<sub>3</sub>) daily, using multivitamin drops or preparations of vitamin A and D.

*With acknowledgements to Chin Gan and David Atherton, authors of this chapter in the 1st edition.*

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# Systemic Therapy & Liver Disease

Rachel Westbrook & Mark Thursz

## + Assessment of liver function

The prevalence of liver disease is increasing in the UK and worldwide and assessment of hepatic function is essential before commencing any potentially hepatotoxic drug. Pre-existing liver disease can be identified in the majority of cases with a brief clinical history, examination and routine liver function tests (LFTs) as below. Any abnormality requires further investigation to assess the underlying cause and the extent of liver damage (fibrosis). This will allow an informed decision to be made regarding the safety of a particular drug.

- **Clinical history:** alcohol consumption, illicit drug use, medication and family history of liver disease.
- **Clinical examination:** stigmata of chronic liver disease (jaundice, spider naevi, hepatomegaly, splenomegaly or ascites).
- **Liver function tests:**
  - Aminotransferases: the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are present in hepatocytes and leak into the blood when there is hepatocyte damage/inflammation.
  - Alkaline phosphatase (ALP): elevations in ALP occur due to cholestasis (i.e. failure of bile secretion or drainage) secondary to intra- or extrahepatic causes. A raised ALP without gamma-glutamyl transferase (GGT) should raise suspicion of bone disease. ALP levels are raised in pregnancy due to production of the placental isoenzyme and the normal range is higher in children.
  - GGT: elevations in GGT occur in diseases of the liver and biliary system. Causes include excessive alcohol consumption, cholestasis (intra- or extrahepatic) and medication.
  - Bilirubin: bilirubin is produced from the breakdown of erythrocytes in the liver and reticuloendothelial system. Bilirubin is conjugated with glucuronic acid in the liver and excreted in the bile. Rises in unconjugated bilirubin are derived from extrahepatic erythrocyte breakdown, i.e. haemolysis or defects in conjugation, e.g. Gilbert's syndrome. A rise in conjugated bilirubin indicates hepatic disease and can be due to hepatocyte damage, cholestasis or synthetic liver failure.

- Serum albumin: albumin is synthesized in the liver and thus a falling albumin level may indicate synthetic liver failure; i.e. cirrhosis.
- Prothrombin time (PT): this is a marker of hepatic synthetic function due to the short half-life of prothrombin. The PT may be prolonged in acute liver injury and chronic liver disease (cirrhosis).
- **Ultrasound scan:** this non-invasive, safe and inexpensive investigation should be undertaken in all patients with suspected liver disease. It allows identification of parenchymal disease, biliary obstruction, portal hypertension, vascular pathology and liver lesions.

If abnormalities of liver function are detected, specialist advice from a hepatologist is essential prior to commencing a potentially hepatotoxic drug to ensure the appropriate choice and dose of drug and adequate monitoring.

### + Prescribing in patients with liver disease

Prescribing systemic dermatological treatment in patients with pre-existing liver disease can present challenges as many of these drugs commonly cause liver damage. The following factors should be considered:

- Is there an alternative, effective non-hepatotoxic drug?
- How severe is the underlying liver disease? Does the patient have hepatic fibrosis/cirrhosis?
- Could the liver disease be treated/controlled prior to drug therapy?
- What is the effect of the drug on liver function? Does the drug have the potential to worsen pre-existing liver disease? Is it a dose dependent or idiosyncratic effect?
- What is the effect of liver disease on drug metabolism and dosage?
- How will the effect of the drug on liver function be monitored?

### + Monitoring

More than 900 drugs have been reported to cause liver injury with manifestations ranging from asymptomatic elevations in liver enzymes to fulminant hepatic failure resulting in death or requiring liver transplantation. Drug induced liver injury (DILI) is the most commonly cited reason for withdrawal of an approved drug. Thus any prescriber must be vigilant in identifying DILI, as early drug discontinuation can limit its severity. Hepatitic reactions (hepatocyte inflammation) are usually associated with a rise in transaminases and cholestatic drug reactions are usually associated with a rise in ALP and GGT levels, though biochemical features often overlap.

As a general guide, patients commenced on a drug with an established risk of idiosyncratic DILI, should undergo monitoring of LFTs every 4 weeks for 3 months and then 3 monthly thereafter. If the LFTs rise to more than 2–3 times the upper limit of normal then the drug should be discontinued and LFTs closely monitored to document resolution.

Re-exposure to a drug implicated in DILI is not advisable, even at a reduced dose as it may lead to a rapid and more severe relapse of DILI. In special circumstances, a rechallenge may be warranted with close monitoring of LFTs if the drug is considered essential.

## + Specific drugs

### Antibiotics (see Antibiotics)

**Flucloxacillin** is reported to cause severe hepatotoxicity in approximately 1 in 13,000 patients. This risk is increased at higher doses and for treatment longer than 14 days. Liver dysfunction can occur any time between 1 week and 2 months after commencing therapy and up to 6 weeks after stopping. Deranged LFTs typically show a mixed cholestatic and hepatitic profile, with cholestasis and a mixed inflammatory infiltrate on histology. The course of cholestatic hepatitis from flucloxacillin is often prolonged with persistently abnormal LFTs for over 6 months in 10–30% of cases. These are associated with loss of smaller bile ducts and peri-portal inflammation which may progress to biliary cirrhosis and liver failure.

**Tetracyclines** may also be hepatotoxic, causing jaundice and acute fatty infiltration. Minocycline is associated with two distinct forms of liver injury; an acute hepatitis-like syndrome typically arising within 1–3 months of commencing therapy and chronic hepatitis usually with autoimmune features which follows long-term therapy. In both forms hypersensitivity features may be present with rash, fever and eosinophilia. The liver injury is usually self-limiting with prompt drug discontinuation, but if treatment is continued inadvertently, progressive liver fibrosis and cirrhosis may develop.

**Sulphonamides** have been known to produce liver damage since their development as antimicrobial agents. Most cases occur within 2–4 weeks although the onset may be delayed several months. Hepatocellular injury with marked increases in transaminases is often accompanied by hypersensitivity features (rash and eosinophilia). Recovery may take several months.

### Antifungals (see Antifungals)

**Ketoconazole**: this is the most hepatotoxic oral azole antifungal drug, due to its extensive metabolism within the liver. Mild asymptomatic and transient elevations (<2 times upper limit of normal) of transaminases have been estimated to occur in up to 20% of patients, with clinically apparent hepatotoxicity incidence in approximately 1 in 2000 and 1 in 15,000 users. The presentation is usually with acute hepatitis any time between 1 and 6 months after starting the drug. Recovery is usual within 3 months of drug discontinuation of the drug, but acute fulminant hepatic failure requiring transplantation has been reported.

**Itraconazole**: this has been reported to cause asymptomatic rises in LFTs in 1–5% of patients. Biochemically the abnormalities are typically cholestatic but hepatitic or mixed pictures can occur. LFTs generally return to normal within 3 months of discontinuing treatment. Reports of serious hepatotoxicity are extremely rare.

**Fluconazole:** transient mild to moderate elevations of serum aminotransferases occur in up to 5% of patients treated with fluconazole. The severity of liver injury ranges from transient asymptomatic enzyme elevations in the majority to clinically apparent hepatitis and acute fatal liver failure in a very small number of cases. The liver injury is typically hepatocellular, occurs within the first few weeks of therapy and can be associated with a rash, fever and eosinophilia. Complete resolution can take up to 4 months following drug withdrawal.

With all the azoles, there are little data regarding cross-reactivity and extreme caution should be applied when exposing patients who have had hepatotoxicity to other agents in the same class.

**Terbinafine:** this has very rarely been associated with liver dysfunction. Liver injury usually arises within the first 6 weeks of therapy. In a surveillance study including over 25,000 patients there were only two reports of symptomatic cholestatic liver injury. Asymptomatic elevations in hepatic enzymes were recorded in less than 0.5% and in all cases, these normalized within 3–6 months of discontinuation.

### **Azathioprine (see Azathioprine)**

Azathioprine (AZA) therapy has been associated with several forms of hepatotoxicity. Mild transient and asymptomatic rises in serum aminotransferase levels are common during the first 3 months of therapy and resolve rapidly with dose reduction or discontinuation. Acute cholestatic injury may occur within the first year of therapy, and longer-term AZA may cause chronic hepatic damage with nodular regenerative hyperplasia and portal hypertension. Baseline and regular assessment of liver function is therefore required throughout treatment.

### **Corticosteroids (see Corticosteroids)**

Corticosteroids can have major effects on the liver, particularly with long-term or high dose therapy. Particular caution is needed in patients with pre-existing liver disease.

Corticosteroid therapy can cause steatohepatitis, especially when given in high doses for prolonged periods. Biochemical features include elevated transaminases and liver histology demonstrates steatosis, hepatocyte ballooning and an inflammatory infiltrate. These findings are usually reversible on dose reduction or discontinuation. Pre-existing non-alcoholic steatohepatitis (NASH) may be aggravated due to a combination of weight gain, insulin resistance and altered lipid metabolism. Prolonged therapy increases the risk of fibrosis and cirrhosis. Dose minimization and alternative drugs should be considered, with monitoring for liver fibrosis in those on long-term treatment.

In patients who are hepatitis B virus (HBV) core antibody positive, high dose steroids (e.g. prednisolone 60 mg daily or higher) can cause reactivation of viral infection, resulting in an acute hepatitis and acute liver failure. Such patients should be given prophylactic antiviral therapy with lamivudine 100 mg once daily prior to commencing steroids. In patients with chronic HBV (i.e. HBV surface antigen positive) oral corticosteroids are not contraindicated but advice should be sought from a hepatologist as these drugs may increase the viral

load (Table 1). Abnormal LFTs do not usually develop during treatment due to immunosuppressive effects, but on drug withdrawal an acute hepatitis may occur, which may aggravate underlying liver damage and on rare instances, precipitate acute liver failure.

**TABLE 1** Hepatitis B virus (HBV) blood tests and their interpretation

Test	Interpretation of positive result
Hepatitis B surface antigen (HBsAg)	Acute or chronic infection with HBV
Hepatitis B surface antibody	Successful response to HBV vaccine or recovery from acute HBV infection
Hepatitis B core antibody (HBcAb)	Past or present infection depending on above test results

In patients with hepatitis C virus (HCV) infection, corticosteroid therapy can lead to a rise in hepatitis C viral load, which may ultimately accelerate the progression to hepatic fibrosis so close collaboration with a hepatologist is advised to ensure appropriate monitoring.

### Dapsone (see Dapsone)

Dapsone can cause an acute hepatitis and cholestatic jaundice. The onset is usually sudden and associated with fever and a rash followed by jaundice, and it occurs within a few days or weeks of starting treatment. Eosinophilia is commonly seen. In rare instances dapsone DILI has led to acute liver failure; however, most cases resolve within 2–4 weeks of drug discontinuation.

### Methotrexate (see Methotrexate)

Short-term low to moderate dose treatment with methotrexate causes mild, self-limiting elevation in the serum transaminases in about 15–50% of patients. About 5% of patients develop more significantly elevated liver enzymes that usually normalize rapidly with dose reduction or drug discontinuation. Folic acid supplementation has been shown to be protective against this effect and is routinely prescribed in conjunction with methotrexate.

Long-term methotrexate therapy is associated with development of dose dependent hepatic fibrosis and this drug is therefore contraindicated in those with underlying chronic liver disease, apart from in exceptional circumstances. The risk and rate of progression to fibrosis or cirrhosis is increased in patients with a heavy alcohol intake, those with diabetes, obesity, renal failure, age >60 years and concomitant use of other potentially hepatotoxic drugs. These factors are therefore considered to be relative contraindications to methotrexate therapy. Nowadays, a pre-treatment liver biopsy to assess the degree of fibrosis is only recommended in patients who are suspected clinically, biochemically or radiologically to be at risk of, or to have underlying liver disease. If fibrosis is confirmed then methotrexate is best avoided and an alternative therapy considered.

Significant fibrosis can occur in the context of entirely normal LFTs, which are therefore unreliable in isolation for drug monitoring. A significant fibrosis risk is associated with a cumulative dose of methotrexate exceeding 2.5 g. Historically, due to the dose dependent development of hepatic fibrosis, guidelines have recommended liver biopsy prior to commencement of therapy and after a cumulative dose of 1, 3 and 8 grams. While liver biopsy remains the gold standard for assessment of fibrosis, it carries a significant risk of morbidity and is subject to sampling error.

Monitoring the blood level of the aminoterminal peptide of type III pro-collagen (PIIINP) (a serological marker of hepatic fibrosis), has reduced the need for routine liver biopsies. Patients with a persistently normal PIIINP levels (measured 3 monthly) are very unlikely to have significant liver damage and thus liver biopsies can be restricted to those with raised PIIINP levels.

Over the last decade other additional non-invasive methods to assess hepatic fibrosis have become widely available. Transient elastography (FibroScan®) is a rapid, immediate, cheap, non-invasive, reproducible and validated test that uses ultrasound to measure liver stiffness gauged in kilopascals (kPa) as a marker of fibrosis. It may help limit the need for biopsies, with the latter being reserved for patients whose score is suggestive of moderate fibrosis (i.e. >7.1 kPa) or where clinical suspicion/concern exists. At present a combination of transient elastography in conjunction with PIIINP is likely to provide the ideal method for monitoring of hepatic fibrosis and guiding the need for liver biopsy in patients with psoriasis on methotrexate. The sensitivity and specificity of combining these non-invasive markers of fibrosis need to be validated in future studies.

Long-term, low dose methotrexate therapy has also been implicated in rare instances to cause reactivation of HBV in patients who are HBV core antibody positive. However, the majority of the patients were also receiving concomitant corticosteroids (see Corticosteroids). These cases have however, led to recommendations that patients being commenced on methotrexate should be tested for HBV surface antigen and HBV core antibody and, if positive, consideration given to prophylaxis with antiviral agents.

### **Retinoids (see Acitretin and Isotretinoin)**

**Acitretin.** Mild abnormalities in LFTs occur in up to one-third of patients taking acitretin; however, only 1–5% of patients have abnormalities greater than three times the upper limit of normal and require drug discontinuation. Clinically apparent liver injury due to acitretin is rare, but several cases have been reported. The time of onset is wide, ranging from 1 week to 9 months after commencing therapy. The biochemical profile is typically of raised transaminases but cholestatic hepatitis has been reported and may be accompanied by rash, fever and eosinophilia. The vast majority of cases resolve on drug discontinuation.

**Isotretinoin.** Modest increases in serum aminotransferases occur in up to 15% of patients taking isotretinoin, but fewer than 1% of patients have abnormalities greater than three times the upper limit of normal. Clinically apparent liver injury is exceedingly rare and acute liver injury with signs of hypersensitivity seen with acitretin has not been reported. The serum aminotransferase elevation

is self-limiting and often resolves without drug discontinuation. Isotretinoin is contraindicated in patients with severely impaired liver function.

### + Summary

In summary, the majority of systemic dermatological medications are safe. In those known to be hepatotoxic, LFTs should be checked prior to commencement and referral to a hepatologist for further investigations if abnormalities detected. In patients with chronic liver disease the majority of drugs can be used, but specific consideration should be given to dosing and monitoring. Systemic drugs that are recognized to cause hepatotoxicity require LFT monitoring, with cessation of the offending drug if LFTs become greater than 2–3 times the upper limit of normal.

*With acknowledgements to Jo Puleston and Julian Teare, authors of this chapter in the 1st edition.*

### + Further reading

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# Systemic Therapy & Kidney Disease

Phil Mason

Many drugs and their metabolites are renally excreted and accumulate in patients with chronic kidney disease (CKD), which may lead to increased toxicity and side-effects. Kidney function decreases with age so otherwise healthy elderly patients may have unrecognized CKD. It is therefore important to identify such patients in order to modify dose or dosing frequency. This has become easier with nearly universal reporting of an estimated glomerular filtration rate (eGFR) alongside the creatinine measurement.

Other renal factors may be relevant, in particular heavy proteinuria, hypoalbuminaemia and marked salt and water retention, which may change drug pharmacokinetics (and pharmacodynamics). However, these rarely have a significant effect on drug dosing.

## + Identification of patients with impaired renal function

Table 1 indicates the prevalence of different degrees of CKD. Renal function declines with age so that, for example, approximately 25% of men and approximately 50% of women over the age of 75 years have an eGFR of less than 60 mL/min (CKD3). Although most of these will not progress to more severe CKD (especially in the absence of proteinuria), the reduced GFR will affect drug elimination.

**TABLE 1** Prevalence of different stages of chronic kidney disease

Stage	GFR (mL/min/1.73 m <sup>2</sup> )	Prevalence in USA
1	>90	3.3%
2	60–89	3.0%
3	30–59	4.3%
4	15–29	0.2%
5	<15 (or dialysis/transplant)	0.1%

GFR: glomerular filtration rate.

Although data are from the USA, the prevalence is similar in other developed countries. (from K/DOQI-NHANES III study)

Precise measurement of the actual GFR using either radioactive isotopes or iothexol is time consuming, expensive and neither practical nor necessary in clinical practice. A creatinine clearance is a reliable surrogate of actual GFR but requires an accurately collected 24-hour urine sample and blood creatinine, making it unsuitable as a routine measurement. However, the GFR may be estimated by a variety of formulae based on the serum creatinine, which is dependent on renal function but also on muscle mass and dietary meat intake, and can be affected by concurrent medication (Table 2). The method of estimating renal function reported by all laboratories now uses the formula developed by the Modification of Diet in Renal Disease Study Group (MDRD), which estimates the GFR based on the patient's age, sex, racial background and creatinine (Table 3). It generally underestimates GFR when renal function is near normal (>50 mL/min) but these patients tend not to need dose modification.

It should be remembered that any estimate of GFR is only valid for stable patients without an acute illness.

**TABLE 2** Factors affecting creatinine levels

GFR
Muscle mass
Dietary meat intake
Hydration status
Drugs – direct, e.g. trimethoprim, cimetidine (interfere with renal tubular secretion of creatinine) NB: creatinine increased but GFR unaltered
Drugs – indirect, e.g. diuretics, which affect hydration status
Drugs which do affect GFR, e.g. NSAIDs or via interstitial nephritis, e.g. PPIs

GFR: glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor.

**TABLE 3** Formulae for calculating estimates of kidney function: the Cockcroft–Gault formula estimates a calculated creatinine clearance and the Modification of Diet in Renal Disease (MDRD) estimates GFR

Cockcroft–Gault	$\text{CrCl} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 1.23 \text{♂} (1.04 \text{♀})}{\text{creatinine } (\mu\text{mol/L})}$
MDRD	$\text{eGFR} = 32788 \times (\text{creatinine, } \mu\text{mol/L})^{-1.154} \times \text{age}^{-0.203}$ [× 1.212 if black] [× 0.742 if female]

GFR: glomerular filtration rate.

### + Dosages for patients with CKD

Drug dose modification is rarely required until the eGFR falls below 60 mL/min (CKD3) and most renally excreted drugs only need adjustment below 30 mL/min (CKD4 and 5). Many drug Summary of Product Characteristics (SPCs) and the British National Formulary (BNF) recommend dose modifications based on the Cockcroft–Gault formula but the eGFR is a reasonable surrogate for this.

Before prescribing any drug in patients with CKD, the dosage should be checked in the BNF. *The Renal Drug Handbook* provides comprehensive dose recommendation for virtually all available drugs and also indicates whether they are removed by different dialysis modalities. Pharmacists and renal units are also available for advice.

### + Nephrotoxic drugs

Some drugs have predictable dose related effects on kidney function (but often of variable magnitude in different patients). These include, for example, the calcineurin inhibitors tacrolimus and ciclosporin (cyclosporine), non-steroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides. Other drugs may have idiosyncratic effects, for instance drugs causing acute interstitial nephritis. Currently proton pump inhibitors are the commonest culprits, but others include antibiotics, mesalazine, allopurinol and diuretics. However, it is important to remember these reactions are actually very rare.

### + Drugs commonly used in dermatology

This is not an exhaustive list, and for patients with CKD it is important that the correct dose of every prescribed drug be checked.

- **Hydroxychloroquine and chloroquine:** these drugs and their metabolites are renally excreted so dose reduction is required and consideration should be given to limiting the duration of treatment. They also increase levels of ciclosporin.
- **Mepacrine:** no dose reduction is necessary but renal function should be monitored as idiosyncratic renal failure may develop.
- **Antibiotics:** most antibiotics do not need dose reduction but tetracycline should be avoided, although doxycycline, minocycline and lymecycline are safe. The macrolides are safe, but erythromycin doses need to be reduced in dialysis patients and those with CKD5. They also inhibit cytochrome P450 (CYP450) 3A4 and increase calcineurin inhibitor levels.
- **Retinoids:** isotretinoin and acitretin are safe above a GFR of 10–15 mL/min but at lower levels (and for patients on dialysis) the situation is unclear and careful titration with monitoring is advised. They are reported to cause glomerulonephritis and vasculitis, but this is very rare.
- **Antiproliferative drugs:** azathioprine and mycophenolate do not need dose reduction but cyclophosphamide and especially methotrexate do. Methotrexate is best avoided with eGFR <20 mL/min.

- **Biologics:** in general, no dose modifications are necessary but the SPCs usually advise caution.
- **Triazole antifungals:** no dose reduction is required in CKD but they are potent CYP3A4 inhibitors and so drug interactions are common.
- **Calcineurin inhibitors** (tacrolimus and ciclosporin) There is no doubt that these drugs are nephrotoxic. Patients with non-renal solid organ transplants have a high incidence of developing CKD4–5 (6–21%) at 5 years post-transplant, with an estimated overall incidence of renal failure requiring dialysis or transplantation of 1–1.5% per annum. Renal impairment is also a recognized complication of their use in psoriasis. Higher levels are associated with a higher incidence of CKD and, although some dermatological data suggest that monitoring levels is not necessary, especially when used at doses of 5 mg/kg or less, some patients will have high levels even at these doses and a proportion of these will develop CKD. Monitoring of levels should be considered especially in those at risk, soon after commencement and regular creatinine measurements should be made for the duration of treatment. It is important to warn the patient of potential interactions with drugs (so that anyone prescribing is aware that the patient is on this drug) foods and over-the-counter preparations (e.g. grapefruit juice, St. John's wort), which may increase drug levels. Any decline in renal function should be investigated by referral to a nephrologist and a biopsy will usually be performed to determine the cause.

### + Drug prescription in dialysis & transplant patients

Dialysis patients should be considered to have an eGFR <10%, but it should also be determined if the drug is removed by dialysis, and some drugs are best administered at the end of a dialysis session. It is best to liaise with the renal team involved before prescribing for this group of patients.

Transplant patients often have a degree of CKD but the main concern is drug interactions that may affect levels of immunosuppressive drugs. Again, it is best to liaise with the transplant team or transplant pharmacists.

*With acknowledgements to Ruth Tarzi and Andrew Palmer, authors of this chapter in the 1st edition.*

### + Further reading

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# Appendix 1

## Patient Health Questionnaire for Depression (PHQ-9)

**Over the last two weeks, how often have you been bothered by any of the following problems?**

Little interest or pleasure in doing things?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Feeling down, depressed, or hopeless?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Trouble falling or staying asleep, or sleeping too much?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Feeling tired or having little energy?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Poor appetite or overeating?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Feeling bad about yourself – or that you are a failure or have let yourself or your family down?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Trouble concentrating on things, such as reading the newspaper or watching television?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3
Thoughts that you would be better off dead, or of hurting yourself in some way?	Not at all 0 Several days 1 More than half the days 2 Nearly every day 3

0 – not at all; 1 – several days; 2 – more than half the days; 3 – nearly every day.

The total score is then added. Minimum score = 0; maximum score = 27.

Depression Severity: 0–4 none, 5–9 mild, 10–14 moderate, 15–19 moderately severe, 20–27 severe.

# Appendix 2

## Reading Chart for Use With Antimalarials

Use the texts below to test each eye separately with glasses when appropriate. Record the smallest text that can be read at a distance most comfortable to the patient.

### N.5

He moved forward a few steps: the house was so dark behind him, the world so dim and uncertain in front of him, that for a moment his heart failed him. He might have to search the whole garden for the dog.

### N.6

The camp stood where, until quite lately, had been pasture and ploughland; the farm house still stood in fold of the hill and had served us for battalion offices; ivy still supported part of what had once been the walls of a fruit garden.

### N.8

And another image came to me of an arctic hut and a trapper alone with his furs and oil lamp and log fire; the remains of supper on the table, a few books.

# Appendix 3

## Example of Consent Form to Opt Out of the Mandatory Pregnancy Prevention Programme

I have received the information about the risks of having an affected baby if I should become pregnant while taking isotretinoin.

I am aware that this risk to a pregnancy persists throughout the duration of the treatment with isotretinoin and during the month after finishing treatment.

I believe that I am not pregnant at this moment.

I believe that I am not at risk of becoming pregnant during the course of treatment with isotretinoin or in the month following treatment.

I have discussed with ..... (name of doctor or nurse) the risks to a pregnancy during treatment with isotretinoin and accept these risks if I take isotretinoin.

I am prepared to take isotretinoin without taking/using contraception at the same time.

If I become pregnant while taking isotretinoin or in the month after treatment, I will inform ..... and seek advice from .....

Signed: \_\_\_\_\_ Date: \_\_\_\_\_

Print Name: \_\_\_\_\_

Witnessed: \_\_\_\_\_

Declaration: \_\_\_\_\_



# Appendix 4

## Dermatology Life Quality Index (DLQI)

Hospital No:.....

Date:.....

Name:.....

Score:.....

Address:.....

Diagnosis:.....

The aim of this questionnaire is to measure how much your skin problem has affected your life **OVER THE LAST WEEK**. Please tick ☐ one box for each question.

- |    |  |  |                                       |
|----|--|--|---------------------------------------|
| 1. | Over the last week, how <b>itchy, sore, painful or stinging</b> has your skin been?  | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> |                                       |
| 2. | Over the last week, how <b>embarrassed or self conscious</b> have you been because of your skin?                                   | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> |                                       |
| 3. | Over the last week, how much has your skin interfered with you going <b>shopping</b> or looking after your <b>home or garden</b> ? | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 4. | Over the last week, how much has your skin influenced the <b>clothes</b> you wear?   | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 5. | Over the last week, how much has your skin affected any <b>social or leisure</b> activities?                                       | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
| 6. | Over the last week, how much has your skin made it difficult for you to do any <b>sport</b> ?                                      | Very much <input type="checkbox"/><br>A lot <input type="checkbox"/><br>A little <input type="checkbox"/><br>Not at all <input type="checkbox"/> | Not relevant <input type="checkbox"/> |

Cont...

- |     |   |            |                          |                                       |
|-----|---|------------|--------------------------|---------------------------------------|
| 7.  | Over the last week, has your skin prevented you from <b>working</b> or <b>studying</b> ?  | Yes        | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
|     |   | No         | <input type="checkbox"/> |                                       |
|     | If "No", over the last week how much has your skin been a problem at <b>work</b> or <b>studying</b> ?   | A lot      | <input type="checkbox"/> |                                       |
|     |   | A little   | <input type="checkbox"/> |                                       |
|     |   | Not at all | <input type="checkbox"/> |                                       |
|     |   |            | <input type="checkbox"/> |                                       |
| 8.  | Over the last week, how much has your skin created problems with your <b>partner</b> or any of your <b>close friends</b> or <b>relatives</b> ?      | Very much  | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
|     |   | A lot      | <input type="checkbox"/> |                                       |
|     |   | A little   | <input type="checkbox"/> |                                       |
|     |   | Not at all | <input type="checkbox"/> |                                       |
| 9.  | Over the last week, how much has your skin caused any <b>sexual difficulties</b> ?  | Very much  | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
|     |   | A lot      | <input type="checkbox"/> |                                       |
|     |   | A little   | <input type="checkbox"/> |                                       |
|     |   | Not at all | <input type="checkbox"/> |                                       |
| 10. | Over the last week, how much of a problem has the <b>treatment</b> for your skin been, for example by making your home messy, or by taking up time? | Very much  | <input type="checkbox"/> | Not relevant <input type="checkbox"/> |
|     |   | A lot      | <input type="checkbox"/> |                                       |
|     |   | A little   | <input type="checkbox"/> |                                       |
|     |   | Not at all | <input type="checkbox"/> |                                       |

**Please check you have answered EVERY question. Thank you.**

© AY Finlay, GK Khan, April 1992

For permission to use the DLQI, contact [dermqol@cf.ac.uk](mailto:dermqol@cf.ac.uk).

More information at [www.dermatology.org.uk](http://www.dermatology.org.uk).

Scoring: 0 – not at all; 1 – a little; 2 – a lot; 3 – very much. Minimum score = 0; maximum score = 30.

Score Analysis: 0–1 = no effect at all on patient's life; 2–5 = small effect on patient's life; 6–10 = moderate effect on patient's life; 11–20 = very large effect on patient's life; 21–30 = extremely large effect on patient's life.















The **Handbook of Systemic Drug Treatment in Dermatology** helps prescribers and patients make rational decisions about drug treatment while considering known risks and potential unwanted effects.

Presented in a concise and reader-friendly format, this valuable reference is of practical use for dermatologists at all stages in their careers as well as specialist nurse practitioners and family practitioners who share the care of patients being administered systemic dermatological therapy. It can also be helpful to those in allied specialties such as rheumatology, gastroenterology, and ophthalmology.

This second edition includes new drugs as well as information on new guidelines for prescribing and monitoring established drugs.

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