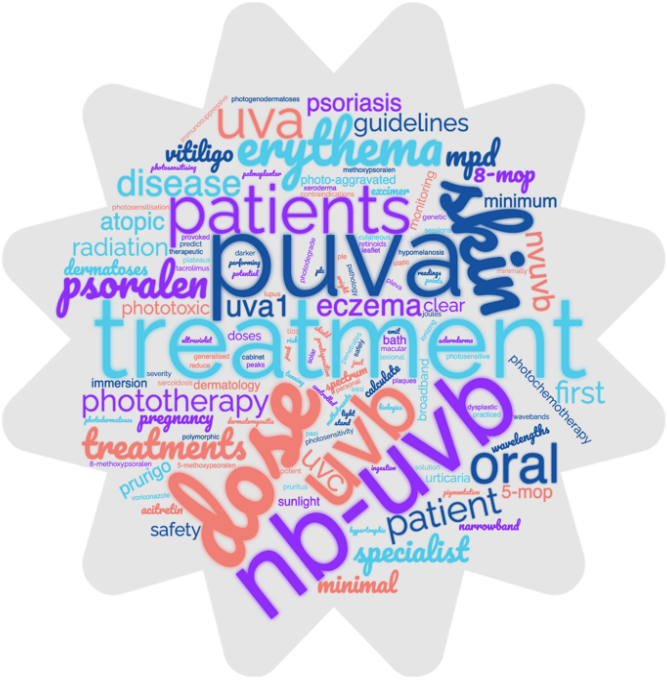
British Photodermatology Group

A Special Interest Society of the British Association of Dermatologists

The Photodermatology Handbook



An Essential Guide

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Aims and Curriculum Competencies

The aim of this handbook is to provide practical advice to complement clinical experience gained during specialty training in photodermatology. However, it may also be helpful for other UK dermatologists and dermatology nurses with a special interest in photodermatology. The 2021 trainee curriculum has highlighted expected competencies that should be achieved in photodermatology by the end of training. By completion of training, trainees should not only feel confident in each of these competencies, but ideally feel confident in setting up a phototherapy unit.

2021 Curriculum Competencies

1. Ability to counsel and select patients appropriately for phototherapy and photochemotherapy.
2. Ability to supervise safe and appropriate delivery of phototherapy and photochemotherapy by allied health professionals (AHPs).
3. Ability to counsel and select patients appropriately for photodynamic therapy.
4. Ability to supervise safe and appropriate delivery of photodynamic therapy by AHPs.
5. Ability to diagnose and manage patients with confirmed or suspected photosensitivity.
6. Ability to refer patients with suspected photosensitivity diseases appropriately to tertiary care.

Resources

There is significant variability in the photodermatology services that training centres offer. Therefore, the ease at which the above competencies will be achieved will vary.

We hope that the below suggestions will be helpful to facilitate achieving these competencies:

1. Attendance at The Photodermatology Course for Trainees – alternates each year between the Photobiology Unit, Dundee and the Photobiology Unit, Department of Environmental Dermatology, St Thomas' Hospital. See bpg.org.uk/courses/ for further information.
2. Attendance at photodermatoses clinics.
3. Understand how phototesting / photopatch testing is performed.
4. Exposure to photodynamic therapy (PDT) service.
5. Complete NHS HEE e-Derm learning modules for phototherapy.
6. Exposure to and experience of phototherapies.

UV Radiation

The ultraviolet radiation spectrum is divided somewhat arbitrarily into 3 main wavebands, typically:

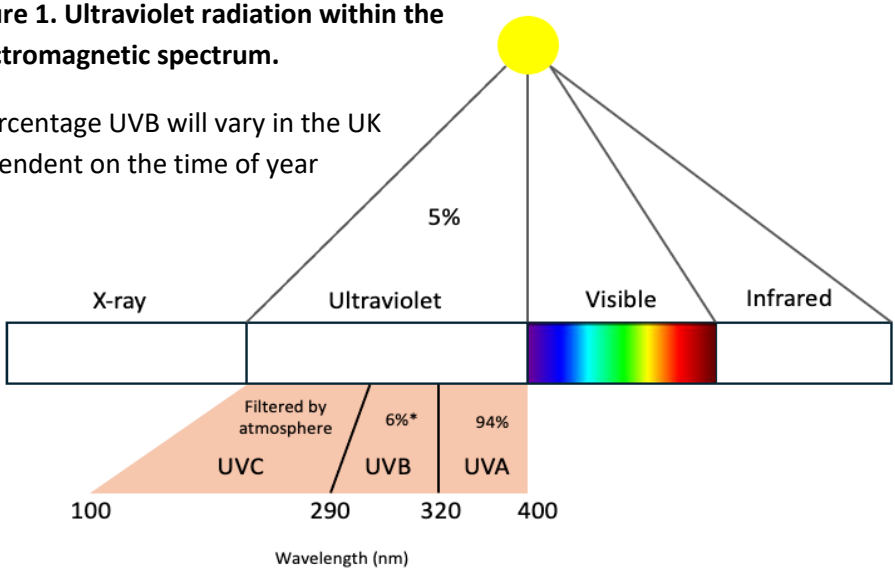
1. UVC (100 – 290 nm)*
2. UVB (290 – 320 nm)
3. UVA (320 – 400 nm)

The exact spectral definitions differ slightly between authorities, for instance the World Health Organisation and the Commission Internationale de l'Eclairage define UV regions as follows: UVA: 315-400 nm, UVB: 280-315 nm, UVC: 100-280 nm.*

*UVC is not present in terrestrial sunlight due to absorption by the ozone layer.

Figure 1. Ultraviolet radiation within the electromagnetic spectrum.

*Percentage UVB will vary in the UK dependent on the time of year



UVC is almost entirely filtered by the Earth's atmosphere, with insignificant quantities reaching the Earth's surface. UVB penetrates into the epidermis and is maximally effective in terms of erythema production, with the minimal erythema dose (MED; i.e. the dose required to cause just perceptible erythema at 24h) being up to 1000 times lower than that for UVA.

What is Phototherapy?

The beneficial effects of sunlight on the skin have been known for thousands of years, with records of heliotherapy being practised in Ancient Greece, Egypt and Rome. Artificial UV sources have been used to treat skin disease since the early 1900s.

1. **UVB:** a relatively safe treatment that can successfully clear psoriasis in 60–70% patients.
    a) **NB-UVB (narrowband UVB):** 311-313 nm
        i. Excludes wavelengths that are not beneficial for treatment, therefore, it presents a lower risk of erythemal episodes and greater efficacy.
        ii. TL01 Philips lamps, which deliver narrowband UVB in UK dermatology units, but historically we also used 'selective broadband' UVB (UV6).
        iii. No significant risk of skin cancer has been reported with use of NB-UVB phototherapy in humans to date.
    b) **308 nm excimer lasers and lamps:** have equal efficacy to NB-UVB and are offered to patients with limited areas of lesional skin. Typically, this is used less on the face as it can cause atypically shaped pigmentation which may be cosmetically unacceptable. Excimer lasers and lamps are currently only available in a limited number of centres within the UK.
    c) **BB-UVB (broadband UVB) sources:** broad spectrum, often including wavelengths <290 nm (UVC). These sources are of historic interest only and you will no longer encounter BB-UVB being used in clinical practice as these sources are no longer available in the UK. BB-UVB has been replaced by NB-UVB, which has been shown to be more effective for psoriasis and is less erythemogenic.
2. **UVA:**
    a) **UVA1:** (340-400nm) available in some specialist departments.
    b) **Broadband UVA**: (i.e. no psoralen) occasionally used for selected conditions such as for desensitisation of photodermatoses, but usually only with specialist advice.

What is Photochemotherapy?

UV radiation is utilised to activate an exogenous chemical which results in the desired therapeutic effect. PUVA (psoralen + UVA) is the primary form of photochemotherapy used in dermatology.

Psoralen forms:

1. Oral 8-methoxypsoralen (8-MOP) or 5-methoxypsoralen (5-MOP)* (whole body or hands/feet): twice per week.
2. Bath / immersion PUVA – typically using topical 8-MOP (whole body or hands/feet): usually twice per week.

Most evidence for efficacy comes from the use of 8-MOP. This is generally prescribed unless it has resulted in significant nausea in the past, in which case 5-MOP is prescribed; although the latter is currently not possible to source* and anti-emetics, such as ondansetron may be required.

There is a significant skin cancer (SCC, and less so BCC and melanoma) risk with exposure to >150-200 PUVA treatments, so typically NB-UVB would be used as first line phototherapy.

Which UV is delivered by commercial sunbeds/ tanning shops?

Sunbeds deliver UVA via fluorescent lamps and frequently emit small amounts of UVB. Sunbeds are only minimally effective for many skin diseases. Upright sunbeds with higher UVB emissions are more effective than 'standard' horizontal sunbeds (when equal exposure times are given) but are generally not recommended for treatment of skin disease.

We do not recommend the use of sunbeds for treatment of skin diseases, as there is good evidence that if they are used regularly before 35-years-of-age, both melanoma and non-melanoma skin cancer risk is increased.

NB-UVB and PUVA indications

The National Institute for Health and Care Excellence (NICE) recommends the use of NB-UVB when skin disease (see list below) is not controlled with topical treatment alone. NB-UVB is usually first line phototherapy, with PUVA being reserved as second line due to safety profile and ease of performing NB-UVB. Failure to respond adequately to NB-UVB does not predict failure to PUVA as the latter penetrates deeper into the skin, therefore, it can be more useful for thicker skin disorders.

NB-UVB

Table 1: Indications for Narrowband UVB

	Treatment	
Indication	**Frequency per week (total no. treatments)**	**Comments**
Psoriasis	3 (24-42)	
Atopic eczema	2-3 (24-42)	
Chronic spontaneous urticaria	2-3 (24-42)	Combine with H1-antihistamines
Palmoplantar dermatoses		Oral PUVA more effective
Mycosis fungoides	2-3 (24-42)	PUVA for thicker plaques
Vitiligo*	2-3	For 6-12 months
Others including: Pruritus, Nodular prurigo, Lichen Planus, Progressive macular hypomelanosis, Pityriasis lichenoides (PLC / PLEVA)	2-3 (24-42)	

Morphoea (localised scleroderma)	UVA1 preferred	
Prophylaxis		
Indication	**Frequency per week (total no. treatments)**	**Comments**
Severe polymorphic light eruption (PLE)**	2-3 (12-21)	Advise that 50% of patients will have rash provoked
Solar urticaria (SU)**	2-3 (12-21)	Combine with H1-antihistamines Avoid in patients who have SU triggered in UVB region. Specialist input required
Erythropoietic protoporphyria**	2-3 (12-21)	Typically, with specialist input
Actinic prurigo**	2-3 (12-21)	Often longer course required
Other photodermatoses**	Seek specialist input and refer to NB-UVB guidelines	

Table 1. Main indications for NB-UVB treatment (list is not fully comprehensive)

UVA1 is more effective for dermal pathology e.g. morphoea, generalised granuloma annulare, sarcoidosis and mastocytosis

If patients wear clothes into the cabinet to protect skin that does not require treatment, then they need to wear the same clothes each time to avoid 'tide marks' burns i.e. accidental skin exposed due to different sleeve/ shorts length.

****When using desensitisation phototherapy for the photosensitivity disorders (photodermatoses), close specialist monitoring is required and at baseline a decision will need to be made as to whether photo-exposed sites only or whole-body treatment will be undertaken. This will depend on the individual case and situation and is typically decided with patient discussion and specialist input.**

Note: Treatment of photosensitivity disorders with NB-UVB requires close specialist monitoring**.**

***Vitiligo**, key points**:** (see specific vitiligo guidelines: Eleftheriadou V, *et al*. BJD. 2022; 186(1):18-29)

- NB-UVB may be combined with topical calcineurin inhibitors/ potent topical steroids (ointments can block UV absorption so do not apply first).
- Discuss at the start of treatment the intended treatment duration.
- Inform patients that their disease may appear to worsen before improvement is seen.
- In darker skin types, higher treatment doses may be required.
- In rapidly progressive disease, consider combining NB-UVB with oral steroids (see specific vitiligo guidelines).

An improvement is not usually seen until after the first 2-3 weeks of NB-UVB treatments, and patients may then steadily improve. Atopic dermatitis patients will often flare in the first 2-3 weeks and will require topical treatment optimisation during phototherapy.

Table 1 provides a guide for the indications and frequencies of NB-UVB phototherapy. Please note that these are approximations and will vary between treatment centres and should be individualised for patients.

The minimum interval between NB-UVB exposures is 24 hours but ideally should be 48 hours. Minimal erythema dose (MED) is the lowest UV dose required to elicit just perceptible erythema of the skin (more detail below). Testing is performed at baseline and read at 24 hours.

If improvement is ongoing despite completing the number of recommended total treatments, phototherapy sessions can continue until the patient is clear or almost clear. However, if improvement plateaus, there is little value in continuing treatment unless there are exceptional circumstances.

PUVA

Can be given first line in certain diseases including:

- Localised psoriasis/eczema to hands /feet
- Thicker plaque stage mycosis fungoides
- Thicker plaques of psoriasis
- Adult pityriasis rubra pilaris
- Granuloma annulare (limited evidence of efficacy)
- Hypertrophic lichen planus (LP) / thick nodular prurigo

Refer to the PUVA guidelines for further indications (Ling TC, *et al*. BJD. 2016;174(1):24-55).

Peak psoralen levels are achieved 2 hours following oral 8-MOP ingestion, which is the time-point at which UVA irradiation is undertaken in most centres. Occasionally, if 5-MOP is used, irradiation could be undertaken 3 hours after oral ingestion, at peak levels of 5-MOP, although many centres keep to 2 hours.

PUVA treatment is twice-weekly (minimum of 72 hours between treatments), typically for 6-15 weeks. The minimum phototoxic dose (MPD) is performed at baseline and read at 72-96 hours (discussed in more detail below).

NB-UVB, PUVA and UVA1 contraindications / cautions

Absolute

1. **Photogenodermatoses** (Xeroderma Pigmentosum, Cockayne syndrome, Trichothiodystrophy, Bloom syndrome and Rothmund Thomson syndrome).
2. Disorders with a **genetic predisposition to skin cancers** (Gorlin syndrome and albinism).
3. History of, or current specific **immunosuppressive treatments** (including azathioprine, ciclosporin, oral tacrolimus, voriconazole). Phototherapy can be safely combined with methotrexate, acitretin and biologics in specific instances, although would not be routinely used in combination with systemic immunosuppressants or immunomodulators.
4. **Medically unfit** and unable to stand safely (UVA1 bed may be appropriate).

Relative

1. **Photosensitising drugs** (particularly relevant to NB-UVB and UVA1 phototherapy) e.g. quinine, calcium channel blockers, NSAIDs, thiazides, prochlorperazine, chlorpromazine, doxycycline. MED testing can be performed whilst taking these medications to determine photosensitivity and adjust the dose prescribed. Be wary about photosensitising drugs prescribed during a course of phototherapy, as there may be an increased risk of erythemal episodes during the phototherapy course - a drug history needs to be gathered before each phototherapy exposure.
2. **Personal history of skin cancers** (particularly melanoma in the past or current melanoma / non-melanoma skin cancer).
3. **Family history of skin cancers** at young age.
4. **Hereditary dysplastic naevus syndrome**
5. **Photo-aggravated dermatoses** e.g. lupus erythematosus (LE) (can occasionally use very low dose UVA1 phototherapy but only with specialist

input), dermatomyositis, Darier's disease and transient acantholytic dermatoses, pityriasis rubra pilaris (can use PUVA), active herpes simplex, erythrodermic or pustular psoriasis, and atopic dermatitis (the minority of patients with atopic dermatitis have photo-aggravated disease and although phototherapy can still sometimes be effectively used in this setting, we would urge careful review and consideration of specialist input and if appropriate, phototesting in order to rule out the development of chronic actinic dermatitis in this patient cohort, certainly a baseline MED would be required as a minimum).

6. Previous exposure to **arsenic or ionizing radiation**.
7. **Past excessive exposure** to natural sunlight, sunbeds or phototherapy, especially if signs of photodamage/actinic keratoses.

Special groups

Pregnancy

1. NB-UVB: safe in pregnancy and breastfeeding. High cumulative doses can photodegrade folic acid. Consider monitoring of folate levels and supplementation (including if childbearing age/ trying to conceive). Provide facial shielding to reduce risk of melasma.
2. PUVA: contraindicated in pregnancy and breastfeeding.

Children

1. NB-UVB: no specific minimum age but need to comply with safety measures and be left alone, therefore generally > 6 years old.
2. PUVA is rarely used in older children (especially with higher skin types) with specialist input. NB-UVB is always preferable and should be used first before PUVA is considered.

Treatment Protocols

Please note that these will vary between centres and should be used only as a guide as protocols should be individualised when required. Commonly used UK protocols:

1. NHS Scotland Photonet: https://www.nn.nhs.scot/photonet/professionals-area/standards-and-protocols/
2. St John's Institute of Dermatology, London: http://www.phototherapysupport.net/st-johns-phototherapy-guidelines/

NB-UVB

- Provide a patient information leaflet.
- Document indication for NB-UVB.
- Record severity before and after (ideally objective assessment e.g. PASI (psoriasis), EASI (eczema)).

- **Minimal erythema dose (MED)** is the lowest UV dose required to elicit just perceptible erythema of the skin. It is used to guide the starting dose of UV. Using uninvolved skin of the upper back is recommended. A small (often handheld) device can be used for this if available.

- MEDs should be performed when patients are taking their usual medications and repeated during the treatment course if new medications are commenced.

- MED testing results are read after 24h (if formal MED testing cannot be performed then a small area test dose can be done).

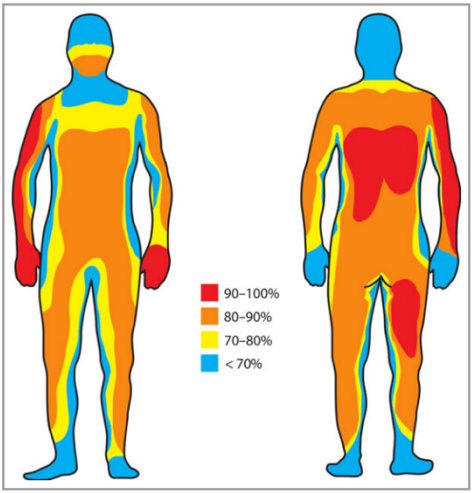


Figure 2. Variation in UV dose delivery to different body sites. Dose delivery within cabinets is not uniform and varies with body site and position. Approximately 70% of the prescribed dose reaches the forearm, hence the initial starting dose of 0.7 MEDs (Moseley H *et al*. BJD. 2015; 173(2):333-50).

- MED testing should be performed on all skin phototypes.
- Common starting dose: 70% of MED for UVB. This is determined by the nursing team. If no erythema occurs, the dose is increased by 20%. Dose escalation depends on response.
- Patients prone to cold sores should have sunscreen applied to their lips. If frequent cold sores, then prophylactic oral aciclovir may be advised throughout the phototherapy course. Those with rosacea should wear a visor.

- All patients should wear goggles unless in exceptional circumstances such as eyelid involvement where they can reliably keep their eyes closed during treatment.
- Men should wear a sock to cover the genitals.
- Burning usually does not occur with progressive increases due to cutaneous hyperplasia and increased melanin (tanning).
- Ideally aim for a 12-month interval between the start of UVB courses and do not organise routine follow-up following completion of the course as remission time is variable. This will depend on individual patient situations and local phototherapy service arrangements.

Oral PUVA

The dose of UVA delivered is determined by the minimum phototoxic dose (MPD). The MPD is the minimal dose of UVA required to cause barely perceptible erythema after ingestion of a standard oral psoralen dose (typically 2 hours after 8-MOP ingestion). The erythema assessment time-point (MPD reading) is typically undertaken at 96 hours after the UVA irradiation of psoralen-sensitised skin.

The purposes of MPD assessment prior to PUVA are:

1. As a bioassay to ensure there is a phototoxic response. This indicates there is sufficient psoralen in the skin.
2. To ensure a safe starting dose of PUVA.

MPD-based regimes are more efficient in treating psoriasis than those based on skin phototype and help to ensure that patients are not under- or over-treated in terms of PUVA doses (Macfarlane L, *et al*. Photodermatol Photoimmunol Photomed. 2015; 31(4):224-6).

Oral psoralen is available in two forms: 8-methoxypsoralen (8-MOP; 10mg tablets) and 5-methoxypsoralen (5-MOP; 20mg tablets). 8-MOP is the standard psoralen used and has a larger evidence base for its use, but 5-MOP may cause less nausea. If converting from 8- to 5-MOP, the same number of tablets should be used (i.e. 5-MOP is double the dose). However, as mentioned, 5-MOP is not available in the UK at the time of writing and we do not know whether this will become available again in future, so currently all oral PUVA in the UK is with 8-MOP.

- Explain potential side effects and consent patients prior to treatment.
- Document indication for PUVA.

- There are various methods to calculate the number of tablets required by the patient. One method used by many centres is to use the patients' height and weight to calculate body surface area (figure 3). Both are unlicensed but routinely used.

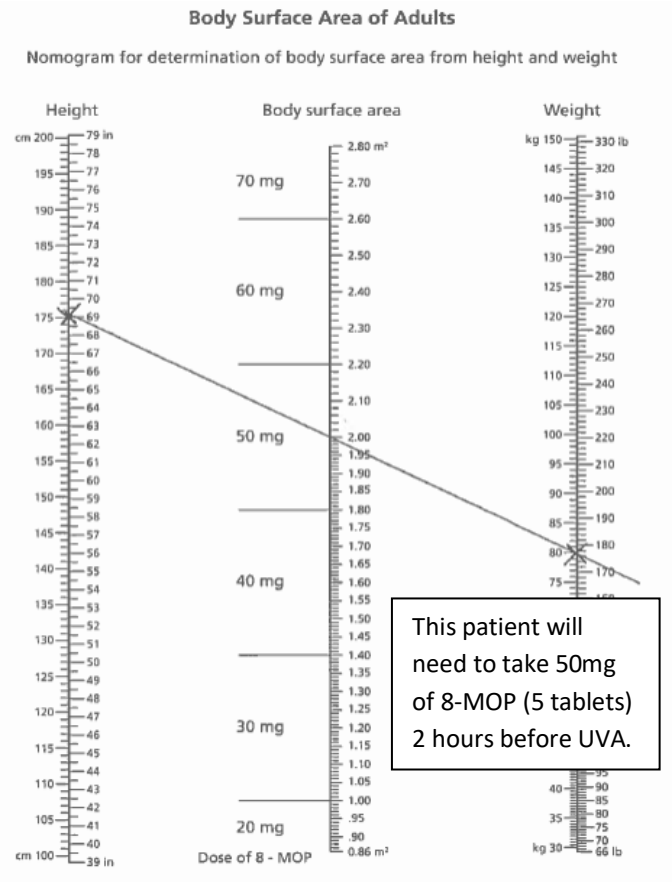


Figure 3. Dose of 8-MOP (10mg) psoralen tablets required can be calculated by drawing a straight line between the patient's height and weight (double the dose for 5-MOP (20mg); but the number of tablets given remains the same; i.e. 50mg 8-MOP (5 tablets) is equivalent dose to 100mg 5-MOP (5 tablets)).

- Psoralen tablets are taken exactly 2 hours prior to treatment (with light/moderate meal) with the same dose taken before each treatment.
- Patients should be advised to maintain a consistent diet (particularly the meal psoralen is taken with) during treatment course and avoid excess coffee consumption in the morning.
- Ensure that patients inform staff if they start a new medication/ herbal remedy during treatment, as this may induce photosensitisation (e.g. St John's wort).
- If a patient is receiving co-treatment with a retinoid (e.g. acitretin), this should be started two weeks before starting PUVA and continued. The MPD (or MED in the case of retinoid-NB-UVB) should be undertaken whilst the patient is on a steady state dose of the oral retinoid.
- Face shield and goggles must be worn unless otherwise indicated.
- MPD determined (reading occurs at 96 hours +/- 6 hours):
    - Initial irradiation dose is 70% of MPD when measured on the forearm.
    - Dose is increased in increments. If no erythema, increase at 40% increments, reducing to 20% increments according to erythema response. Increase by no more than 20% increments if atopic eczema, polymorphic light eruption (PLE), solar urticaria (SU) or if taking oral retinoids.

Bath / Immersion PUVA

- Dosing: 30ml of 1.2% 8-MOP lotion in 140L of water, final concentration 2.6mg/L.
- Patient bathes for 15 mins in this solution, waits for 30 mins, and then enters UVA cabinet (dose determined by MPD).
- Increase dose in 20-40% increments.
- No washing of skin is required following irradiation.
- Erythema peaks at 3-5 days.

Key facts to be aware when prescribing PUVA

1. **Eyes:** Patients' eyes are sensitive to UVA following psoralen ingestion. Goggles and/or a visor must be worn during treatment and advice should be given about wearing UVA-filtered glasses during daylight hours when outside, even on cloudy days for at least 12 hours. This reduces risk of cataracts. For high risk patients (pre-existing cataracts, atopic eczema and children), advise wearing glasses for 24 hours. The nurses should check that the patient's sunglasses provide adequate protection (minimum of UV400).
2. **Nausea**: consider an antiemetic such as ondansetron (4-8mg two hours before the psoralen is taken) in the first instance. If necessary, convert from 8-MOP to 5-MOP (no change in the number of tablets taken) but note the doses are different. 8-MOP is 10mg tablets and 5-MOP is 20mg tablets. However, switching to 5-MOP is not possible at the time of writing due to lack of availability of 5-MOP.
3. **"Retinoid PUVA":** retinoid (e.g. acitretin) + systemic PUVA may be an option for recalcitrant disease. Retinoids can also be combined with NB-UVB.
4. **Skin cancer:** a well-recognized side-effect of PUVA following high (>150-200) treatment number exposures.

   The risk of squamous cell carcinoma (SCC) increases in a dose-dependent manner. Additional risk factors include UVB therapy, MTX, ciclosporin and X-ray radiation/arsenic (see PUVA guidelines). Risk of melanoma and BCC is also increased, albeit to a lesser extent than for SCC, following high treatment numbers of oral PUVA.

   In general, limit each patient to a maximum of 5 courses of PUVA over their lifetime (150-200 treatments), and no more than one course per year. Always discuss with a consultant if you wish to consider exceeding this number of courses, as usually an alternative treatment approach is desirable. Indeed, consider alternative treatments once approaching 100

PUVA treatments. Patients who have received >150–200 PUVA treatments should be offered an annual skin examination to ensure no premalignant or malignant skin lesions have developed.

5. **Localised PUVA treatment:** PUVA with undiluted psoralen can treat limited areas of skin (e.g. vitiligo) – applied neat (e.g. puvasoralen 1.2%) as an emulsion or paint (if fissuring/erosions, a diluted form may be required to prevent stinging). Psoralen gel (methoxsalen 0.005%) is a milder alternative.
6. **PUVA pain**: severe skin pain (characterised as a burning sensation) can occur rarely (~4%). In very rare cases this can persist for several months. If this develops, further PUVA is contraindicated as it is likely to recur.
7. **Pre-treatment liver function tests**: not routinely required unless there is a history/ suspicion of liver disease.

UVA1

A longer wavelength of UV radiation (340 – 400 nm) and therefore, penetrates the dermis deeper than UVB. UVA1 phototherapy is not equivalent to that used in tanning salons (also emits UVA2 wavelengths and some UVB). UVA1 phototherapy is only available through limited specialist centres and is not widely accessible to all. In most situations, an effective phototherapy alternative will be available if UVA1 is not accessible.

Dosing is categorised into low (10 to 29 J/cm^2), medium (30 to 59 J/cm^2), and high (>60 J/cm^2) dose regimens. MED should be performed prior to initiating treatment.

Indications:

1. Morphoea (scleroderma)
2. Urticaria Pigmentosa
3. Cutaneous T cell lymphoma
4. Atopic dermatitis

Contraindications:

As per contraindications for UVB. In addition, avoid UVA1 in patients with UVA-sensitive photodermatoses and with drug-induced photosensitivity.

Protocol:

- MED test required before use (often no response but will identify if a patient has an unexpected photosensitivity).
- Delivered 3-5 times per week for approximately 12 weeks (may be >50 treatments in some clinical situations).

Excimer Laser / Lamp

Used for targeted phototherapy and emits UV wavelength at 308nm (within the UVB spectrum). Uses a hand-held wand device to direct the UV at specific sites.

Currently very few centres have access to excimer lamps and the evidence base for its use is more limited than for other modalities.

Indications:

1. Vitiligo
2. Localised psoriasis
3. Localised mycosis fungoides
4. Lichen simplex/ Nodular prurigo
5. Alopecia areata

Higher fluences may allow excimer to penetrate more deeply into the dermis than conventional NB-UVB. The treatment of smaller areas may allow higher dose (supra erythemal) treatments to be used than with traditional NB-UVB light sources. The duration and number of treatments is usually shorter than a total body course of NB-UVB.

Dose: 2-3 MEDs as starting dose.

Contraindications: as per UVB.

Caution: with use on the face, as hyperpigmentation response to a localised area can be more marked than if the whole face is treated.

Protocol: Dose increases by 20-40% increments during treatment course.

Troubleshooting during On-Calls

1. **Erythroderma post-phototherapy**
   a) Review urgently and perform observations. Consider inpatient admission and ensure fluid balance is maintained.
   b) Topical corticosteroids and copious emollients should be applied to the skin. Systemic corticosteroid may be indicated if severe erythema. Phototherapy course should be suspended.

2. **Erythema / burning post-treatment**
   a) Following UVB, erythema usually develops within 3-5 hours, peaks between 12-24 hours and resolves by 72 hours. Following PUVA, erythema usually peaks by 72-96 hours.
   b) Erythema is graded. Most centres will have an erythema protocol (example below (table 2), although local protocols may differ).

Grade	Description	Management
E0	No erythema	None.
E1	Faint erythema – pink asymptomatic	Repeat previous dose and reduce subsequent increments to 10%. Consider if area can be covered e.g. use of visor if area is clear.
E2	Marked erythema – red	Localised: cover for remaining treatments. Generalised: omit treatment until settled, then repeat previous dose and reduce subsequent increments to 10%. Encourage use of emollients.
E3	Fiery erythema with oedema	Omit treatment until the erythema has settled and the patient has been reviewed by a doctor. On resolution,

		treat with 50% of previous dose and subsequent 10% increments. Prescribe topical/oral steroids, emollients and analgesia.
E4	Intense erythema, oedema with blistering	Arrange urgent review by a doctor. Manage as for E3 grade but stop phototherapy.

Table 2: Erythema grading and example management protocol.

c) Always review the individual situation as to why the episode has occurred – did the patient start any photosensitising drugs or change current drug doses? Any application, for example, of fragrances? Was there human error in the dose delivered?

d) Ensure that there are no new medications or UV exposure from another source that could be contributing, such as additional natural sunlight or sunbed exposure.

3. **Pruritus**

Continue regular emollient use during a course of NB-UVB to prevent and alleviate skin dryness and pruritus (avoid use 2 hours prior to NB-UVB as may reduce UV penetration). Avoid emollients containing SPF.

4. **Provocation of polymorphic light eruption (PLE) flare**

Apply a potent corticosteroid, reduce UVB dose and escalate cautiously. May need to miss the next treatment until the reaction has settled. An oral steroid course or single dose on the same day as treatment can be offered if PLE is severe.

5. **Flare of disease (eczema and psoriasis)**
   a) Determine if this is truly a disease flare versus UV-induced erythema.
   b) Ensure topical therapy is optimised and slow phototherapy dose escalation.
   c) If flare is severe, UV dose may require reduction or treatment withheld.
   d) Generally, flaring is more common in eczema and oral steroid cover can be useful in this situation.

6. **Cold sores (HSV reactivation)**
   If the patient has a history of cold sores, give prophylactic aciclovir prior to and during the treatment course, lip photoprotection, and consider facial shielding**.** If a cold sore develops during treatment, oral aciclovir can be prescribed, and the area should be shielded.

7. **Naevi**
   Benign naevi do not require covering during phototherapy.

8. **Poor or plateaued treatment response**
   a) Consider the cause and whether the skin can be further optimised for phototherapy (NB-UVB, UVA, UVA1 or PUVA). For example, thick scaly psoriasis plaques may require descaling.
   b) If the skin cannot be optimised further, there may be little value in continuing treatment and consideration of alternative approaches may be required. Examples being, switch from NB-UVB to PUVA or adding in a systemic retinoid and continuing the NB-UVB or PUVA, or consideration of other therapies, such as methotrexate or biologics (avoid ciclosporin and azathioprine if a patient has had significant NB-UVB, UVA, UVA1 or PUVA therapy).

9. **Skin continues to improve but is not clear by the final treatment**
   Discuss with the patient if they would like to continue with a few further treatments with the aim of clearing the skin. Longer courses are more often required for eczema than psoriasis. Please note, there is no evidence that 100% clearance leads to a longer remission than 'almost clear' following UVB (Watson N, *et al*. J Eur Acad Dermato Venereol. 2021; 35(11): 2250-8).

10. **Persistent PUVA pain requiring treatment**
    a) Refer to the information above.
    b) Topical steroids/ anaesthetics or oral analgesia/ steroids have little value.
    c) Neuropathic agents such as topical capsaicin or gabapentin could be trialled.
    d) Stop PUVA and avoid further PUVA in future as symptoms will likely recur.

11. **Eye damage**
    a) Acute (photokeratitis and photo-conjunctivitis) and chronic (pterygium and cataract formation) eye damage can occur. If these are suspected, refer to ophthalmology.
    b) UV protective goggles should be used during NB-UVB, UVA, UVA1 or PUVA treatments, unless eyelid skin is involved (in which case patients should keep their eyes closed throughout treatment and please discuss with patient and senior staff). Refer to the information above regarding eye protection during PUVA treatment course.

12. **New photosensitising drug commenced during phototherapy course**
    Enquire about the indication for the drug and the intended duration. With this information assess risk of proceeding with phototherapy.

Management options will include:

1. If short drug course: generally, withhold NB-UVB phototherapy until photosensitising drug is stopped (e.g. five-day course of doxycycline, and for 2-3 days after stopping to allow drug to clear).
2. If drug likely to be continued for duration of phototherapy:
   a) If early in the NB-UVB phototherapy course, it is often appropriate to go back a few doses and continue the course (particularly if drug is of low photosensitisation risk) or to repeat the MED on the drug.
   b) If later in the course, repeat MED and adjust exposure doses based on this, but continue phototherapy course. Pay attention to dose increments, which may need reducing to avoid erythemal episodes during the course.
3. For PUVA: if MPD has been performed, further drug photosensitisation is unlikely to be problematic due to the psoralen photosensitisation, which typically is well in excess of other drug photosensitisers the patient is taking. However, a cautious approach, such as avoiding further PUVA dose increments for 2-3 treatments after introduction of a photosensitising drug, is advised. Be aware of drug interactions with oral psoralen, including theophylline, caffeine and warfarin.

Photonet has further advice on managing this:
www.nn.nhs.scot/photonet/wp-content/uploads/sites/26/2022/10/NSD610-008.07-PNMCN-Photosensitising-Drugs-Phototherapy-Guidance-Final.pdf

Other Tips

1. To improve NB-UVB response with children or if foot/ankle involvement, use a box to raise their height.
2. Underwear/genital protection: men should wear a sock to cover the genitals, and dark coloured underwear should be worn unless there is genital skin involvement.
3. Chemical peels: avoid phototherapy until skin completely healed following peel.
4. Topical retinoids: avoid application during phototherapy.
5. Fragrances: avoid application during phototherapy.
6. Haircuts: avoid during phototherapy course.

Setting up a Photodermatology Unit

If you require advice on setting up a new photodermatology/photodiagnostic unit in your centre, please contact the British Photodermatology Group (BPG). Any consultant members will be happy to advise, as photodiagnostic tertiary services are only available in a few centres in the UK.

What is more likely is that you may need to set up a phototherapy service, and again the BPG are happy to offer advice on this. The British Association of Dermatologists (BAD) has a set of audit criteria to monitor standards within phototherapy units. These cover: referral and patient assessment, patient information and consent, staff training and education, clinical management and monitoring, equipment and facilities, clinical governance and audit, discharge protocol and skin cancer surveillance. This guidance can be found in the Service Guidance and Standards for Phototherapy Units document:

https://cdn.bad.org.uk/uploads/2021/12/29200202/Phototherapy-Service-Guidance-and-Standards-20193.pdf

All equipment should undergo annual servicing and checks with your local medical physics team.

Additional relevant information can be found at the NHS Scotland Photonet website:

https://www.photonet.scot.nhs.uk/professionals-area/standards-and-protocols/

Photoprotection

Sunscreen is an important component of photoprotection, however other strategies such as sun-avoidance, shade from trees, clothing and hats should be emphasised. It is important to educate the public about factors which impact on the overall Ultraviolet Radiation (UVR) exposure, as discussed below.

Sun-avoidance/ behavioural change

UltraViolet Index (UVI) – is the measure of UVR from the sun at a particular time and location. This is usually reported by various media outlets, mobile apps and websites. The higher the UVI, the greater the harmful effects of UVR. It is highly recommended to use protective measures when UVI is high to protect against the harmful effects of UVR.

UVR is attenuated when it passes through the earth's atmosphere (absorption by atmospheric gases etc). The shorter the distance, the greater the amount of UVR. Since the length of the distance is inversely proportional to the elevation of the sun, UVR is highest at noon. Avoiding sun exposure for 4 hours around this time can reduce UVR exposure by 60%.

Other factors which impact UVR levels are:

- Seasonal variations (for example, there is no UVB in the UK during Winter).
- Proximity to the **equator.**
- Higher **altitude.**
- **Reflection from other surfaces** (snow > sand > water).
- Dense **cloud**: 90% of UVR can penetrate through thin clouds.
- Staying in the **shade:** be aware of scattered radiation and penetration through shade-providing material (between the tree leaves, weaves of clothes, etc).

UVB is effectively absorbed by **window glass,** but UVA and visible light can easily penetrate through glass (please note, laminated front windscreen glass in vehicles does not allow UVA penetration, although it will pass through window glass of car doors etc). Plastic blinds and self-adhesive window films (DermaGard, GlassGard) can provide adequate protection and are helpful in the management of photodermatoses.

Clothing

Use of protective clothing is highly recommended to protect against harmful effects of UVR. The degree of protection achieved by a particular garment is determined by the Ultraviolet Protection Factor (UPF)**.** Like the Sun Protection Factor (SPF) in sunscreens, the higher the UPF, the greater the protection. The UPF of a garment is dependent on multiple factors, however, the **weave** of the garment is the most important factor. This can be assessed by holding the garment up to the light. UVR transmission is lower in tightly versus loosely woven and un-stretched versus stretched fabric clothes (e.g. Lycra, elastane), which therefore have a high UPF. Certain materials, such as cotton, go through shrinkage and relaxation after **washing**, leading to a reduction in the spaces between weaves, increasing the UPF. Laundry detergents with **UV absorbers** are also commercially available which can enhance the UPF of a garment.

The colour and weight of the garment are also important factors. Dark coloured and heavier garments absorb more UVR, thus have higher UPF as compared to light coloured and lightweight garments of similar weave.

Trees

Shade from trees depends on various factors including the density of foliage, the height of the tree's canopy above the ground, season, solar zenith, density of cloud and the angle of the sun. The protection factor of trees is from SPF 2 to 20. The sparse canopy of a gum tree gives an SPF of 2-6, the denser canopy of an Australian pine tree (Casaurina) gives an SPF of 3-20. Unexpectedly, the

protection factor is not significantly affected by changes in foliage with the seasons.

Sunscreens

Sunscreens are topical agents which protect the skin against the harmful effects of UVR. They should be used in conjunction with the above strategies. There are two types of sunscreens based on the ingredients: chemical/organic and physical/in-organic.

UVR is typically absorbed by the organic ingredients of **chemical sunscreens,** thus attenuating the effect of UVR. Different organic molecules absorb different UVR wavelengths; hence a mixture of different molecules is used in sunscreens. PABA derivatives, methoxycinnamate ester and salicylate ester derivatives mainly absorb UVB, whereas benzophenone and dibenzoylmethane derivatives are effective UVA filters. Newer improved chemical sunscreens, such as Mexoryl and Tinosorb, protect further across the UV range and are becoming increasingly available. Absorption of UVR may lead to photochemical reactions resulting in phototoxicity or photo allergy.

Physical sunscreens physically block the penetration of UVR. In contrast to common belief, they act primarily by absorbing UVR but also reflect/scatter longer wavelength UVA and visible light. These are inorganic substances which provide broad-spectrum protection and do not cause photosensitivity. Titanium dioxide and zinc oxide are the most popular and widely used agents, with iron oxide being increasingly used. Their efficacy in the UV spectrum, particularly the UVB and UVA2 regions, is lower than that of chemical sunscreens, hence a high concentration and larger particle size (200nm) is required to attain photoprotection. However, higher concentrations can give a cosmetically undesirable whitish tint to the skin. Nanosized particles (10-50 nm) are now available which are much more cosmetically acceptable and rub

in easily, however the visible light reflection effectiveness decreases with small particle size.

Sunscreens specially designed for sensitive skin contain physical substances (photochemically inert), and pigments are added to make them more cosmetically acceptable (e.g. Dundee cream). These sunscreens are devoid of organic sunscreen chemicals (which can cause photochemical reactions), are fragrance-free and contain fewer preservatives.

Good broad-spectrum protection against UVA and UVB is important for almost all photosensitive patients, and for individuals at risk of skin cancer. The non-tinted La Roche Posay Anthelios SPF50+ is now available for clinicians to prescribe for patients with photosensitivity diagnoses and a set of diseases which predispose to skin cancer.

Some patients with solar urticaria or chronic actinic dermatitis, and all patients with erythropoietic protoporphyria require visible light photoprotection and sunscreens are available which protect against short wavelength (blue/violet) visible light. A recent study evaluating La Roche Posay Anthelios Mineral One sunscreen has demonstrated superior photoprotection to Dundee creams, in the short visible part of the spectrum.

Sun protection factor (SPF) is "the ratio of minimum erythema dose (MED) in unprotected skin to MED in protected (via sunscreen) skin". SPF15 means the MED of skin has been increased by 15-fold, for example if the MED dose is 15 mJ/cm^2 in unprotected skin, after the application of SPF15 it will increase to 225 mJ/cm^2. SPF is a measure of protection against UVB but heavily depends on thickness of application, with most patients applying sunscreens much more thinly than in lab testing.

The '**Boots Star rating system**' indicates protection against UVA. It is important to choose a sunscreen which has high enough SPF and a good star rating. The

rating ranges from 1 to 5 stars; 4- and 5-star ratings indicate that the product has balanced UVB and UVA protection, and lower star ratings indicate lower UVA protection proportional to the stated SPF.

Other UVA ratings include: (i) the UVA seal (the word UVA inside a circle), which indicates that a sunscreen has a UVA protection value of at least ⅓ of the SPF (ii) the PA system, where PA+ offers lowest and PA++++ is highest UVA protection. Sunscreens from the USA will state "broad spectrum" if there is UVA protection.

If using a high factor sunscreen without broad spectrum cover, i.e. without 5 star/ good UVA protection (labelled as broad-spectrum in the USA), although the risk of burning is reduced, high doses of UVA1 can increase the risk of skin cancer and ageing.

Photoprotection by sunscreens theoretically sounds very simple, but real-life application is quite different from the lab-based, highly controlled environment. When the products are tested for SPF, strict application and UVR procedures are followed such as, 2mg/cm^2 of product being applied by a trained technician before standardised UV exposure. In real life settings:

- Application is 0.5-0.8mg/cm^2 (0.5g is approximately equivalent to 1 adult fingertip unit). Since the SPF decreases exponentially with thickness of sunscreen film, in real life an SPF 50 sunscreen provides an SPF in the range 2.7 - 4.8 i.e. absorbs 60-80% of incident UVB.
- Uniform and even application of product is usually not achieved. Certain areas of the body (e.g. back) are difficult to reach. The upper eyelids, ears, post-auricular areas, and back are mostly missed.
- Products can rub and wash off (swimming, sweating etc).

Advise patients that sunscreen should be:

1. Applied 15-20 minutes before sun exposure and evenly over all the sun exposed areas. According to a BAD report, on average individuals miss 10% surface area of the face when applying sunscreen.

2. Reapplied 15-20 minutes after sun exposure. If staying outdoors, application should be repeated every 6-8 hours, and more frequently if there is swimming, rubbing, or excessive sweating (by 8 hours on average the sunscreen protection has decreased by approximately 45% in holiday-type situations).

3. Combined with behaviour change and protective clothing.

It is important to advise patients that there is no such thing as a sunblock, only relative sunscreen protection.

It is also important to emphasise that the actual level of protection achieved with a sunscreen when used in a real-life situation equates to significantly less than the level of protection stated on the bottle (though the level of protection of 60-80% (see above) is reasonable, and few patients will know what the SPF number on the sunscreen means).

It is important that patients and doctors are aware that most people who sunbathe use sunscreens to enable them to stay outside sunbathing for longer. If they are used in this manner, sunscreens do not reduce the dose of UV absorbed by the skin.

Vitamin D deficiency

There is little evidence to support sunscreens blocking vitamin D production when used in real-life concentrations. However, other photoprotective behaviours such as covering skin and shade seeking will increase the risk of vitamin D deficiency, particularly in those with photosensitive skin disorders that adhere strictly to photoprotection advice. Vitamin D deficient patients should be advised to take supplementation and be given dietary advice.

Phototesting

This is a method to objectively measure a patient's sensitivity to UV which can be performed with a variety of equipment, including:

1. **Irradiation monochromator**: measures MEDs (minimal erythema doses) at specific wavelengths (often with narrow bandwidths) to identify photosensitivity. This is usually read 24 hours later.
2. **Provocation testing**: repeated low doses of UVA, UVB or solar simulated radiation with the aim of inducing the skin disorder.
3. **Photopatch testing**: duplicate patch tests (including sunscreens) applied to the patients back. One is irradiated with broadband UVA after 48 hours and the other remains covered (non-irradiated). These will both be read at standardised time points including 72 and 96 hours after application (24 and 48 hours after one set of patches are irradiated).

A guide of expected phototesting results for common photodermatoses is given in table 3.

The Irradiation Monochromator

A xenon arc lamp, which can deliver continuous emissions.

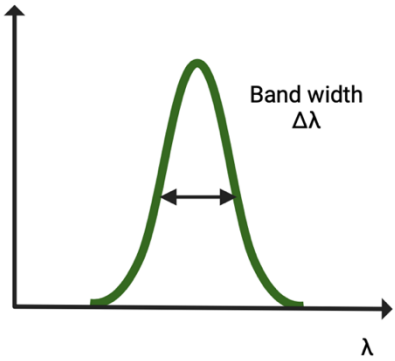


Figure 4: The monochromator bandwidth - the range of emitted wavelength, measured at half maximal intensity (i.e. the full width measured halfway up the peak of the graph). The smaller the bandwidth, the more specific the wavelength being delivered, but the longer it will take to deliver the dose.

It can deliver a range of wavelengths (UVC to visible light) to a small area of skin via a flexible handheld (liquid-filled) light guide. The exact bandwidth can be manipulated by the user.

Photoprovocation

The aim of photoprovocation is to artificially induce the photosensitivity disorder to aid diagnosis (clinically or biopsy can subsequently be performed). Patients attend daily for up to 4-5 days and receive repeated exposures to UVA or UVB to small areas of skin marked on the back or forearm. Surrounding skin is covered to prevent UV exposure.

Photopatch testing

Chemicals including sunscreens can be chemically altered by UV, and as a result patients may be allergic to the activated (UV irradiated) form of the compound, but not to the non-irradiated form. Photopatch testing therefore investigates this by comparing irradiated and non-irradiated patch tests.

Sunscreen products are therefore applied in duplicate to a patient's upper back. After 24-48 hours, one set of patches are removed and irradiated with broadband UVA using a dose below the patient's MED (typically 5J/cm^2). The second set of patches are removed at 24-48 hours (these have not been irradiated), and both sets of patches are read at 72 and 96 hours (from patch application) (Gonçalo M, *et al*. Contact Dermatitis. 2013;68(4):239-43; Bruynzeel DP, *et al*. J Eur Acad Dermatol Venereol. 2004;18(6):679-82).

Condition	Monochromator test	Provocation
Polymorphic light eruption (PLE)	Not required if typical history Normal in two-thirds	Can be useful if history is in doubt, and to find which wavelengths induce
Solar urticaria (SU)	UVA and visible light > UVB Read immediately (rarely can take up to 2 hours)	Used occasionally if monochromator test is negative and a larger area of skin is to be tested
Actinic prurigo	UVB and UVA > visible light Abnormal in two-thirds	Yes
Drug-induced photosensitivity	Usually, UVA alone or predominantly	Yes, with UVA – may not be required unless diagnostic doubt, where provocation site biopsy may be useful
Chronic actinic dermatitis	UVB and UVA > visible light	Usually not required
Hydroa vacciniforme	UVA > UVB and visible light	Yes, with UVA
Photo-aggravated atopic dermatitis	Usually normal If active or sub-clinical eczema, may be aggravated by phototesting	Can be helpful if diagnosis is uncertain (often UVA) and biopsy required Please note, eczema will also be in covered sites and may be photo-aggravated by UV provocation testing

Table 3: Guide to phototesting results for photodermatoses

Photosensitivity skin disorders (photodermatoses)

Broadly categorised into the following categories:

1. **Immunological (previously known as idiopathic)**
   a) Polymorphic light eruption (PLE)
   b) Juvenile spring eruption (JSE)
   c) Actinic prurigo (AP)
   d) Chronic actinic dermatitis (CAD)
   e) Solar urticaria (SU)
   f) Hydroa vacciniforme (HV)
2. **Photogenodermatoses**
3. **Metabolic**
4. **Drug- or chemical-induced photosensitivity**
5. **Photo-aggravated skin diseases**

Detailed discussion of these disorders is beyond the scope of this handbook. We will briefly discuss immunological photodermatoses as these are relatively common presentations in photodermatology clinics.

Polymorphic light eruption (PLE)

- Affects 18% of the UK population.
- Spring/summer onset.
- PLE usually appears hours - days after sun exposure, but the very first episode of the year can take more than 24 hours to develop.
- The rash is polymorphic i.e. can be papules, vesicles or plaques.
- Mainly on the sun exposed areas (be aware – clothing/ fabric with a loose weave may not be fully protective as UVR, especially UVA, can penetrate).
- Face and back of the hands are often spared due to “hardening” from regular low-level exposure.

- Episodes are usually worse in spring (first sun exposure of the year) and gradually improve as the patient's skin thickens with repeated exposure (hardening).
- Depending on the severity, rash resolves within days - 2 weeks if subsequent sun exposure is avoided.
- Causative wavelength UVA > UVB - provocation test can be performed to determine sensitivity in some patients. However, phototesting responses are frequently normal in PLE (see table 3).
- Perform ENA and ANA to rule out lupus erythematosus.

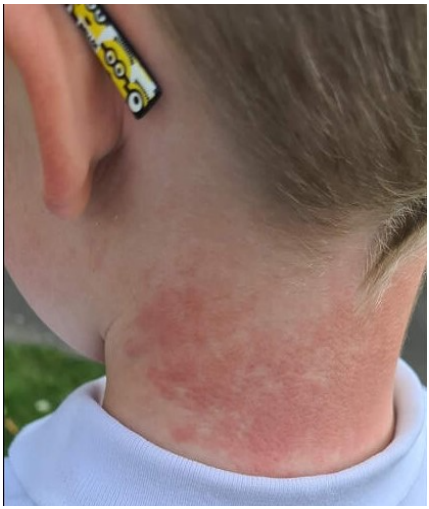


Figure 5. Polymorphic light eruption in a child.

- Treatment: sun avoidance and appropriate use of sunscreens (see previous section). Topical corticosteroids may help if given early. Patients can be given a short course of prednisolone (e.g. 20mg once daily) in case of flares during holidays. Natural hardening or a prophylactic course of NB-UVB to achieve hardening prior to summer or sunny holidays can be helpful, however, requires natural top-up exposure to keep hardening going as this will otherwise be lost over 4-6 weeks. NB-UVB phototherapy

provokes PLE in >50% but usually with topical corticosteroid use, and reduction of NB-UVB dose increments, patients can get through the 3 times per week for five-weeks course.

Solar urticaria (SU)

- Rare
- Perennial immediate onset photosensitivity.
- Well-defined burning/itching erythema with or without wheals.
- Develops minutes after exposure - typically within 10 minutes and often resolved by 30 minutes - 2 hours. Flare often develops beyond the irradiation site initially.

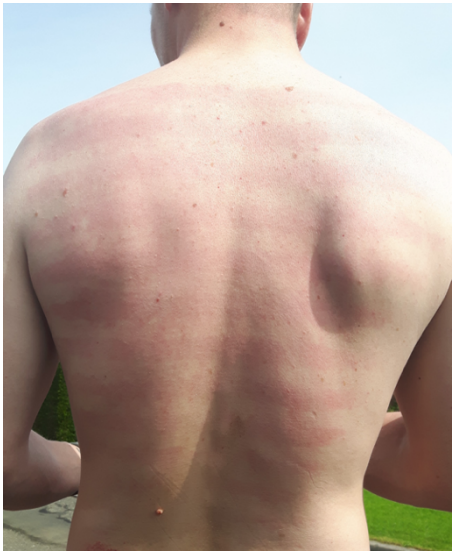


Figure 6. Solar urticaria: marked UVA/visible light sensitivity – the lighter stripes of his T-shirt were not protective, whereas the darker stripes were.

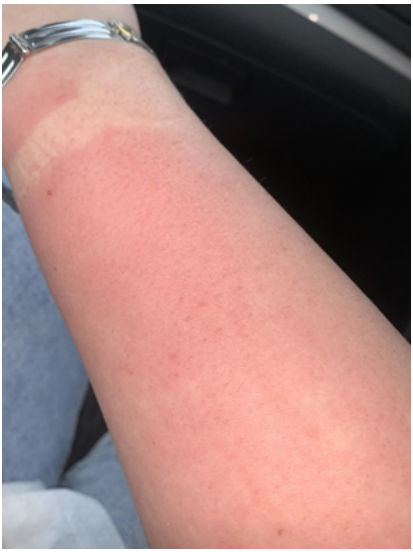


Figure 7. Solar urticaria: the patient's watch strap provided UVA and visible light protection.

- Causative wavelengths may be UVA, visible light (often blue/green) and/or UVB.
- Commonest inducing wavelengths are UVA (through windows, through clothes) and visible light.
- Generalised urticaria with circulatory collapse is possible with large area exposure.
- Monochromator test positive – UVA (mostly), UVB and visible. Test is read immediately (peak 10 minutes). Can be used to define the minimal urticarial dose (MUD) at each positive wavelength.
- Condition is often chronic and treatment includes photoprotection (including clothing and mineral-based sunscreens such as Dundee cream / Anthelios Mineral One, antihistamines (helpful in 35-50%: non-sedating, higher doses, including adding in H2 blockers) and montelukast. Failing these measures, second line approaches can include anti-IgE therapy with omalizumab, or immunosuppression e.g. methotrexate or ciclosporin. Phototherapy desensitisation may be possible e.g. NB-UVB if the patient is sensitive to long UVA/visible light and not to UVB, in which case this could be trialled prior to immunosuppressants or omalizumab.

Chronic actinic dermatitis (CAD)

- Rare, acquired photosensitivity disorder.
- Historically elderly Caucasian men, but is increasingly reported in younger patients, typically atopic, higher skin phototypes and female.
- Erythema on sun exposed sites, usually becoming eczematous, with cut-off at collars and cuffs. In severe cases rash can be widespread (erythrodermic).
- Rash can be perennial, usually with spring and summer worsening.
- Causative wavelengths UVB and/or UVA > visible light.
- Monochromator phototesting abnormal - UVB and UVA > visible light.
- If isolated UVA abnormality, consider the possibility of drug sensitivity.

- Consider patch testing +/- photopatch testing as ≥75% of patients with CAD will have contact allergies to common allergens such as fragrances, Compositae/Asteraceae plants, rubber additives or colophony and can develop sensitivity to sunscreens.
- Management: sun avoidance and protection. Topical and systemic treatments as per eczema.
- PUVA is useful as an effective immune suppressant treatment even in some cases where the CAD action spectrum reaches into the UVA. It is generally used when other systemic immunosuppressants are contraindicated, stopped due to adverse effects, or are ineffective.
- **UVB phototherapy is strictly contraindicated in CAD and must be avoided**. Since CAD is a disorder characterised by exquisitely severe UVB sensitivity, UVB phototherapy frequently induces erythrodermic eczema in CAD patients.

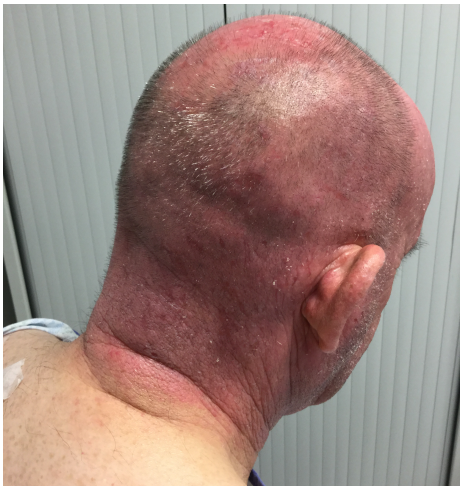


Figure 8. Chronic actinic dermatitis: chronic photoexposed site dermatitis, with collar line cut-off evident.

Actinic prurigo

- Rare in the UK.
- Strong genetic HLA association – in the UK with HLA-DR4, in particular the subtype DRB1*0407.
- Commonly presents before puberty (can be late onset).
- Itchy papules, nodules, plaques and excoriations on the sun exposed areas, particularly face, dorsal nose, arms, buttocks and legs. May be associated with cheilitis and conjunctivitis.
- Heals with scarring secondary to excoriation.
- Often two phases: an acute oedematous phase followed by a chronic pruritic eczematous phase and can be confused with photo-aggravated atopic or other dermatitis.
- Covered skin is often affected, which can delay the diagnosis as the patient may not consider light as a possible cause.
- Causative wavelengths: UVB and UVA.
- Monochromator phototesting shows abnormal sensitivity, often to UVB and UVA.
- Management: sun protection and sun avoidance, emollients, topical steroids, NB-UVB desensitisation and immunosuppression (although poor evidence due to rarity of disease).

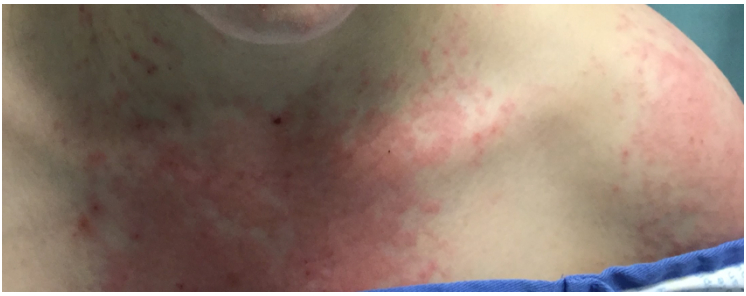


Figure 9. Actinic prurigo: photo-exposed site papular chronic eczematous changes. Initially diagnosed as photo-aggravated atopic dermatitis but phototesting was abnormal and HLA-DRB1*0407 positive, confirming the diagnosis of actinic prurigo.

Hydroa Vacciniforme

- It is important that this rare diagnosis is not missed.
- Classical HV in Caucasians typically occurs in an otherwise well child.
- Childhood disease (1–7 years, 12-16 years) – most improve and even resolve in teenage years, but it can persist.
- Typically presents in spring/summer 15 minutes – few hours after sun exposure (direct sun exposure or through glass window).
- In an acute inflammatory episode, the patient develops intensely pruritic vesicles (may be haemorrhagic) and papules on a background of erythema and oedema within 12-24 hours after exposure.
- Affects sun exposed areas: often face (ears) and dorsum of hands.
- Heals with vacciniform scars.
- Subungual haemorrhage, cartilage destruction (ears and nose), corneal opacification has also been reported in rare severe cases.
- May have associated fever and malaise.
- HV is always caused by and associated with chronic active systemic Epstein Barr virus (EBV) infection and is classified as one of the EBV-related lymphoproliferative disorders. It can progress to leukaemia, lymphoma or haemophagocytic lymphohistiocytosis (HLH), or fully resolve over time. It is less common for this progression to malignant or other dangerous diseases to occur in Caucasian patients and more common in Asian, Hispanic and Afro-Caribbean patients.
- **Features that may prompt suspicion of lymphoproliferative disease are systemic features, severe disease, an unwell child and Asian/Hispanic background.**
- Photo-provocation, usually with UVA, may induce the eruption and biopsy of a provoked site is typically diagnostic. Monochromator phototesting shows UVA sensitivity.
- **Diagnosis is made with appropriate clinical features in association with very high EBV viral load in blood. The EBV viral load in blood must be raised to make the diagnosis. EBV antibody serology testing is of no value for making the diagnosis.**

- ANA, ENA and porphyria screen should be undertaken to exclude other causes of photosensitivity.

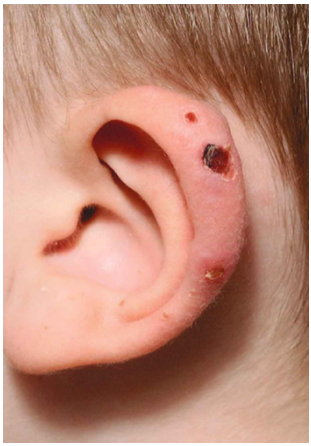


Figure 10. Hydroa vacciniforme: haemorrhagic scarring lesions on the photo-exposed site of the helix of the ear in a young Caucasian boy with classical HV, who was otherwise well.

- Management of classical HV includes sun avoidance and photoprotection, topical/oral steroids during an acute eruption, and cautious springtime desensitisation with NB-UVB. Topical calcineurin inhibitors, such as tacrolimus (Protopic) may also be beneficial.
- Oral prednisolone, B-carotene, omega-3 fish oil, hydroxychloroquine, azathioprine and ciclosporin have been reported as treatment in some case reports. However, use of long-term systemic immunosuppression in the context of chronic active high viral load EBV infection is contraindicated, therefore ciclosporin and azathioprine are no longer part of the treatment.

Juvenile spring eruption

- Mainly affects young boys (short haircut, exposing ears).
- Recurrent papular and blistering eruption on the pinna of ears a few hours to days after sun exposure.
- Resolves spontaneously without scarring.
- Possible variant of PLE and may co-exist with classical PLE.
- Diagnosis is clinical, however, lupus erythematosus and porphyria should be excluded.
- Monochromator tests are usually normal.
- Management: photoprotection (advise on hair growth to cover the outer pinnae).
- Natural hardening (NB-UVB desensitisation is rarely required).

Drug/chemical-induced photosensitivity

- Systemic drugs can cause phototoxic or more rarely photoallergic reactions. The vast majority will be phototoxic in nature.
- Detailed drug history (new/over the counter systemic and topical medications, topical cosmetics including sunscreens) should be taken in patients with suspected photosensitivity.
- Monochromator phototesting typically reveals UVA sensitivity either alone or disproportionately more than UVB, in systemic drug photosensitivity.
- Consider photopatch testing for suspected photocontact allergy to topical agents – particularly sunscreen chemicals and less often, topical nonsteroidal anti-inflammatories (NSAIDs).
- Photopatch testing is not useful for suspected systemic drug photosensitivity as it is unreliable and can lead to misleading false positive and false negative results.

Drug-induced phototoxicity

- Minutes - hours after drug intake and sun exposure.
- Limited to sun exposed areas (lightly woven clothing and window glass are not protective).
- Can present as exaggerated sunburn, vesicles, bullae, photo-onycholysis and pigmentary changes.
- Usually reversible on stopping drug. Time to resolution depends on the drug and its elimination e.g. 24-48 hours for fluoroquinolones, 3-6 months for thiazides and 6-12 months for quinine or amiodarone.

Drug-induced photoallergy

- Initial sensitisation required.
- Applies mainly to topical photoallergens (sunscreen chemicals and NSAIDs).
- Once sensitised, the reaction occurs 24-72 hours after application of the drug/chemical and sun exposure.
- Presents as an eczematous pruritic rash, which may spread to non-exposed areas.

Photo-aggravated atopic dermatitis

- This describes a poorly understood subtype of atopic dermatitis that is worsened or provoked with UV radiation exposure.
- The prevalence is estimated at 1.4-16% of patients with atopic dermatitis.
- Patients may report worsening of eczema over the summer months, photo-distributed eczema, flaring during sunny holidays or following sun exposure, phototherapy or photopatch testing.
- Most patients give a history of childhood-onset atopic dermatitis and photo-aggravation developing later in adulthood.
- Diagnosis: monochromator phototesting is typically normal. UV provocation testing usually with UVA. Biopsy if diagnosis is uncertain.

- It is important to distinguish this diagnosis from CAD.
- Management: as for atopic dermatitis (phototherapy can be effective in a carefully selected population with specialist input) and photoprotection advice.

Porphyria

A group of disorders caused by an interruption of the haem synthesis pathway due to a genetic or acquired deficiency of enzymes.

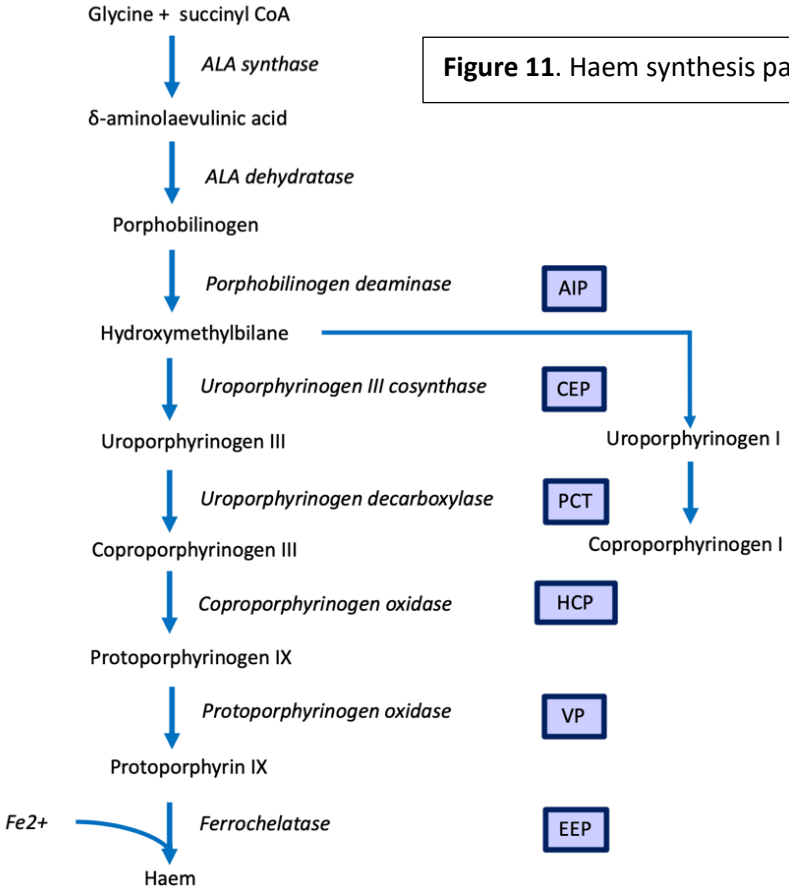


Figure 11. Haem synthesis pathway

Enzyme substrates i.e. porphyrins, accumulate. Porphyrin is derived from the Greek word “porphuros” meaning purple and reflects the colour of the urine when porphyrins are in excess. Porphyrins are photosensitive tetracyclic molecules, and when they accumulate in the skin they cause phototoxic reactions when exposed to light.

Haem synthesis is an eight-step process, which occurs in all nucleated mammalian cells (predominantly in hepatocytes and erythrocytes) in the presence of a substrate and enzyme (figure 11). Deficiency of an enzyme at any given stage results in the accumulation of the relevant substrate. Clinical presentation of a specific porphyria depends on the relevant substrate accumulation.

Porphyrias can be classified depending on the organ where the primary enzyme defect occurs:

- **Erythropoietic:**
    - Congenital Erythropoietic Protoporphyria (CEP)
    - Erythropoietic Protoporphyria (EPP) and X-linked Erythropoietic Protoporphyria (XLP)
- **Hepatic:**
    - Porphyria Cutanea Tarda (PCT)
    - Variegate Porphyria (VP)

Alternatively, they can be classified by clinical phenotype:

- **Acute:**
    - Acute Intermittent Porphyria (AIP)
- **Mixed Acute and Cutaneous:**
    - Hereditary Coproporphyria (HCP)
    - Variegate Porphyria (VP)

- **Cutaneous:**
    - Porphyria Cutanea Tarda (PCT)
    - Congenital Erythropoietic Porphyria (CEP)
    - Erythropoietic Protoporphyria (EPP) and X-linked Erythropoietic Protoporphyria (XLP)

Detailed discussion of all the porphyrias is beyond the scope of this handbook, however, we will discuss porphyrias with cutaneous manifestations below.

Porphyrias with cutaneous manifestations

- Porphyria Cutanea Tarda (PCT)
- Erythropoietic Protoporphyria (EPP) and X-linked Erythropoietic Porphyria (XLP)
- Variegate Porphyria (VP)
- Hereditary Coproporphyria (HCP)
- Congenital Erythropoietic Protoporphyria (CEP)

Porphyria Cutanea Tarda (PCT)

- Most common porphyria, usually >40-years-old, males more than females.
- "Acquired" or "sporadic" (Type I) is the most common type of PCT.
- Uroporphyrinogen decarboxylase enzyme activity is inhibited, leading to accumulation of uroporphyrins in the liver, which diffuse through the body and as they are water-soluble, they are excreted in the urine, which appears dark and fluoresces crimson red when illuminated with Wood's light.
- Risk factors: alcohol, hepatitis C, HIV, haemochromatosis and oral oestrogens.
- Type II and Type III (25%) are due to an inherited mutation in uroporphyrinogen decarboxylase.

- Clinical features include increased fragility on light-exposed skin, (particularly the backs of the hands, forearms, face and scalp), blisters and erosions. Atrophic scars, milia and mottled hyper- or hypopigmentation can occur with chronicity.
- In severe cases, patches of scarring alopecia following resolution of bullae on the scalp, hypertrichosis, sclerodermatous change and photo-induced onycholysis can be seen.
- Mostly patients are unaware of photosensitivity as the skin changes are chronic and the photosensitivity occurs perennially, often with no seasonal variation (patients are abnormally sensitive to visible light rather than UVR).

Investigations

1. Urine and blood porphyria screening: a peak at 615-620 nm on plasma spectrometry is diagnostic along with a high urine porphyrin concentration (predominantly uroporphyrin and hepta-carboxylic acid porphyrins). Urine porphyrin concentration can be used to monitor treatment response.

2. If urine porphyrins are positive, stool porphyrins should be analysed to confirm a PCT diagnosis. Detection of isocoproporphyrin in the faeces is important to differentiate between PCT and HCP (patients with VP/HCP can have the PCT urine pattern). Stool porphyrin analysis can also be used to make the diagnosis in cases where urine analysis is not available, such as patients with renal failure on haemodialysis.

3. Skin biopsy is not required for diagnosis. However, histopathology will show subepidermal blistering with characteristics “festooning” of dermal papillae in bullae and PAS staining of the basement membrane.

As 75% of PCT cases are acquired, further investigations should be done to establish the cause as patients invariably have liver disease and iron overload, as it is this that in turns inhibits uroporphyrin decarboxylase in acquired PCT. The cause of the liver disease should be investigated and is most often multifactorial, such as alcohol excess, hepatitis C and/or haemochromatosis. Patients with PCT are at higher risk of developing hepatocellular carcinoma, so vigilance and screening is advised.

Management:

1. Treat underlying cause if present (viral hepatitis with antiviral medications, venesection or iron chelation therapy for iron overload). If no cause is identified, consider genetic testing for familial PCT.
2. Avoid alcohol and oestrogen containing medications.
3. Sun protection – shade, hats, clothing and physical sunscreens (Dundee cream / Anthelios Mineral One to reduce visible light exposure).
4. Low-dose antimalarials and venesection if chloroquine fails or when haemochromatosis is diagnosed.

Erythropoietic Protoporphyria (EPP) and X-linked Erythropoietic Porphyria (XLP)

- Caused by deficiency of ferrochelatase due to ferrochelatase gene mutations (EPP) or gain of function in erythroid ALA synthase-2 (XLP), leading to accumulation of protoporphyrin IX. EPP and XLP are clinically indistinguishable.
- EPP is autosomal dominant or recessive, usually the latter, and this also requires a low expression ferrochelatase allele, present in about 10% of the general population. XLP is X-linked dominant and as such is more common in males.
- Presents in childhood: first sign could be an inconsolable crying baby when exposed to sunlight or near windows.

- If presents in adulthood, other acquired causes of ferrochelatase deficiency (sideroblastic anaemia) and an underlying myeloproliferative disease should be considered.
- Typical presentation includes immediate pain, tingling, discomfort or burning sensation (sometimes swelling) within minutes of exposure to sunlight, which may be relieved by cold water.
- Lack of physical signs can make the diagnosis difficult and delayed. Over the years patients develop subtle pitted scarring and waxy skin thickening, such as over the knuckles and nasal bridge.
- A normocytic normochromic or microcytic anaemia may be seen in EPP/XLP patients, as ferrochelatase is required for the final step of haem synthesis. Be very wary of treating any microcytic blood film with iron, as in EPP this is usually not indicative of iron deficiency. Suggest checking iron studies and only treat cautiously with iron if marked iron deficiency, as this may otherwise exacerbate EPP symptoms and biochemistry. There is some evidence that iron is beneficial in reducing protoporphyrin IX in XLP.
- Gallstones, of pigment type, are more common in patients with EPP/XLP.
- Up to 5% of EPP/XLP patients develop hepatocellular failure, therefore liver monitoring is recommended along with 6-monthly to yearly blood protoporphyrin measurements.

Investigations:

1. Blood porphyrin screening: increased erythrocyte free protoporphyrin concentration alongside a peak at ~630 nm on plasma spectrometry is diagnostic (plasma porphyrins are usually raised but may be normal in milder cases). Urinary porphyrins are normal. Please note, protoporphyrin can also accumulate in iron deficiency, lead poisoning and anaemia of chronic disease.
2. Increased faecal protoporphyrin concentrations in 60% patients (not diagnostically sensitive).

Management:

1. Photoprotection (behavioural change – shade, hats, clothing and reflectant sunscreens such as Dundee creams/Anthelios Mineral One, window film (which is of limited use as patients are sensitive to visible light, but it may offer some protection for home-use if tinted)).
2. Afamelanotide (note: not currently available to prescribe in the UK (limited availability in Scotland) at the time of writing).
3. NB-UVB
4. Be aware of vitamin D deficiency due to chronic sun avoidance, treat accordingly.
5. Six-monthly to yearly blood protoporphyrins and liver function tests are recommended for early detection of hepatocellular failure. Viral hepatitis and alcohol will exacerbate this.
6. Regular fibroscans (consider yearly).

Variegate Porphyria (VP)

- Autosomal dominant inherited (variable penetrance).
- Deficiency of protoporphyrinogen oxidase resulting in accumulation of photosensitive coproporphyrinogen and protoporphyrinogen.
- Clinically indistinguishable from PCT but up to 17% develop acute neurovisceral attacks. The only difference clinically in the skin is that skin disease in VP develops in the teens (not in mid-life as PCT does) and skin changes associated with VP are usually less severe than in PCT.
- Acute attacks are three times more common in women and most often occur between 20-40-years-old.
- Acute attack severity varies from mild abdominal pain, vomiting and constipation, through to very severe attacks, with bulbar palsy and respiratory paralysis.

Investigations:

1. Urine and blood porphyrin screen:
   a) Urine: increased level of coproporphyrin and sometimes, similar to PCT, increased levels of hepta-carboxylic acid porphyrins, hence urine alone is not enough for the diagnosis of VP. Plasma and faecal porphyrin analysis is recommended to confirm a diagnosis.
   b) During acute attacks, urinary porphobilinogen levels are raised and fall to normal within weeks of attack resolution.
2. Plasma spectrofluorimetry peak ~626 nm is strongly suggestive of VP.

Management:

1. Avoidance of triggers (crash-dieting, oestrogen-containing contraceptive pills, medication triggers, recreational drugs etc).
   SAFE drug list can be found via http://porphyria.org.uk/safe-drug-list/ and https://www.wmic.wales.nhs.uk/specialist-services/drugs-in-porphyria/
2. Photoprotection (to include Dundee cream/Anthelios Mineral One)
3. Genetic testing for patient and relatives.

Congenital Erythropoietic Protoporphyria (CEP)

- Autosomal recessive disease
- Deficient functioning of the uroporphyrinogen III co-synthase enzyme.
- Life-threatening, with multi-organ involvement: skin, eyes (keratoconjunctivitis, cataracts, corneal ulcers, scars, cicatricial ectropion, pterygium formation, etc) bone marrow (haemolytic anaemia, bone marrow hyperplasia), teeth (brown stained) and spleen.
- Severe photosensitivity leading to photo-mutilation (erosion of the terminal phalanges, onycholysis and destructive changes affecting the pinnae and nose) and hypertrichosis.
- Diagnosis is usually established in early childhood due to characteristic clinical features including brown amniotic fluid, red urine (turns brown in natural light), brown teeth and severe photosensitivity (blistering on exposed areas).

- Late onset CEP (usually 3rd decade onwards) is also recognised: clinically resembles PCT, caused by mild gene mutations (inherited) or secondary to bone marrow myelodysplasia (acquired).

Investigations

1. Send blood, urine and stool samples for porphyria screen. Urine and red blood cells show high levels of type I uro- and copro-porphyrins. Faeces show dominance of type I coproporphyrin.
2. Similar to PCT, plasma spectrofluorimetry peak is seen at 615–620 nm.

Hereditary Coproporphyria (HCP)

- Rare autosomal dominant, acute porphyria due to deficiency of coproporphyrinogen oxidase.
- Although it has been said that HCP can cause cutaneous manifestations similar to PCT/VP (skin fragility, bullae formation at sun exposed sites), it is not clear that this is the case, and if it does occur it is rare.

Investigations

1. Blood, urine and faecal samples are needed to make the diagnosis. Urine can be similar to PCT (high levels of uro- and hepta- carboxylic acid porphyrin concentrations). Faecal porphyrin analysis is needed to differentiate PCT/HCP – HCP shows increased faecal coproporphyrin (type III isomer).
2. Plasma spectrofluorimetry peak is seen at 615–620 nm.

Key points for all porphyria investigations

Sample collection:

1. Porphyrins are highly photosensitive molecules and care should be taken to prevent photo-contamination of all samples: wrap in an opaque material such as tinfoil to avoid exposure to light during collection, transportation and storage.

2. Inform the biochemistry laboratory to expect the samples ahead of time as these may require forwarding externally for analysis and the laboratory should have protocols in place for storage and transportation. Samples should be sent without delay to preserve the porphyrins for analysis.
3. Blood samples: collected in EDTA-containing test tubes and wrapped in tinfoil.
4. Urine samples: 20ml of fresh random urine (preferably early morning sample), collected in a universal bottle and protected from light as above. 24-hour urine collection is not needed.
5. Stool analysis: 5-10gm of fresh faeces is required. Samples are to be protected from light.

Even though visible light sensitivity is a well-established feature of the cutaneous porphyrias, phototesting is not necessary in making a diagnosis and biochemical porphyrin analysis is key.

Photogenodermatoses

Xeroderma Pigmentosum (XP)

- Rare autosomal recessive disorder with 100% penetrance.
- Caused by a mutation in one of eight genes that are involved in the repair of UV-induced DNA damage.
- Classified based on the gene that is affected (XP-A to XP-G and XP-variant (XP-V)).

Clinical manifestations:

- Photosensitivity (exaggerated and prolonged sunburning), extensive freckling (generally before 2-years-old), lentigines and hypopigmented macules, skin cancer within the first decade and ocular disease (can cause a variety of ocular features, including scarring).

- 50% of patients do not experience exaggerated sunburn. These patients generally develop skin cancers at a younger age.
- Progressive neurodegenerative disease can occur causing intellectual impairment, hearing loss, ataxia and speech delay. There is an increased risk of nervous system malignancy (such as glioblastoma). Some of the XP complementation groups and XP-V patients do not seem to develop neurodegenerative disease.

Investigations:

1. Genetic testing should be performed if clinically suspected: skin and blood samples should be sent to the national XP service at Guys and St Thomas' NHS Foundation Trust, London: (https://www.guysandstthomas.nhs.uk/health-information/xeroderma-pigmentosum-xp/genetic-testing-xp)
2. Skin fibroblast culture (4mm punch biopsy) taken from an unexposed area of the skin should be sent for functional DNA repair studies in fibroblasts (sent to University of Sussex): http://www.sussex.ac.uk/lifesci/lehmannlab/diagnosticservice

A multidisciplinary team approach is taken to diagnosis and management. Focus is on early diagnosis, photoprotection, regular skin and eye examinations, screening for neurological disease, management of skin cancers and vitamin D supplementation.

Cockayne Syndrome

- Rare autosomal recessive disorder of DNA repair.
- Two groups: CSA (ERCC8 gene) and CSB (80% of patients, ERCC6 gene).
- Multisystem disease, causing progressive dementia and physical manifestations: cutaneous photosensitivity, postnatal growth failure,

microcephaly, prognathism, enophthalmos, dental caries, cataracts, characteristic facies with thin nose, large ears and premature ageing.
- There is no increased risk of skin cancer.
- Patients should avoid metronidazole due to the increased risk of liver failure.
- Diagnosis: with fibroblast culture and genetic testing (as above).
- Death usually occurs by 10-years-of-age.

Trichothiodystrophy

- Rare autosomal recessive disorder of DNA repair.
- Many genes implicated (if XP gene involvement, photosensitivity is typically a feature).
- Clinical manifestations: complicated maternal pregnancy, truncal ichthyosis, brittle and fragile hair (tiger tail pattern on polarised microscopy), hypotrichosis of scalp/eyebrows/eyelashes, extreme and prolonged sunburn in some patients (there are two groups of patients genetically, one group suffer XP-type photosensitivity, the other group are not photosensitive), bony abnormalities (particularly hip), developmental delay and short stature and susceptible to infections.
- Diagnosis: with fibroblast culture and genetic testing (as above).
- Death is most commonly caused by infections.

Bloom Syndrome

- Rare, autosomal recessive disorder due to mutations in the BLM gene (RECQL3 on chromosome 15) causing chromosomal instability.
- Most common in Eastern Europeans of Jewish (Ashkenazi) descent.
- Clinical manifestations: small stature, early development of cancers (particularly haematological), increased risk of infections due to immunodeficiency.

- Photosensitivity was previously thought to be a feature of Bloom's syndrome, however, a recent study has found that acute photosensitivity is not a feature (unpublished data at the time of writing).
- Diagnosis: clinical features and confirmed with detecting increased sister chromatid exchanges on standard karyotype.
- Management: photoprotection, malignancy surveillance, optimising nutrition and treating infections.

Rothmund Thomson Syndrome

- Rare, autosomal recessive. Two-thirds of cases are due to a mutation in the RECQL4 helicase gene.
- Two types: if normal hair and teeth, this is type 2.
- Clinical manifestations:
  - Facial erythema in the first year, which changes to poikilodermatous, atrophic and telangiectatic skin, which spreads to the extremities.
  - Photosensitivity in some patients, sparse hair and dental abnormalities.
  - Juvenile cataracts, small stature with saddle nose and frontal bossing and other skeletal abnormalities (including osteosarcomas).
  - Usually patients are of normal intelligence, although intellectual impairment can occur.
- Diagnosis is with genetic testing (although negative testing for RECQL4 does not exclude Rothmund Thomson Syndrome).
- Management: multidisciplinary approach, usually symptomatic and supportive.

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