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# Recognizing photoallergy, phototoxicity, and immune-mediated photodermatoses



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The term *photosensitivity* broadly refers to the skin's sensitivity to sunlight. It often presents as a photodistributed rash, affecting the forehead, cheeks, nape of the neck, upper chest, upper back, and extensor arms, with sparing of the nasolabial fold, upper eyelids, submentum, and postauricular area.[1] Although this definition and clinical presentation are generally accepted, there is a range of photodermatoses with different pathophysiologies. To better understand and treat these photodermatoses, it is important to classify and define them accordingly. In this article, we review the mechanisms and etiologies of selected, more commonly encountered light-mediated skin conditions: phototoxicity, photoallergy, and immune-mediated photodermatoses.

## PHOTOTOXICITY

Phototoxicity occurs when exposure to a phototoxic agent and light cause direct cellular injury and necrosis to the skin. When ultraviolet radiation (UVR) comes in contact with a specific phototoxic agent (classically a drug or its metabolites) cytotoxic compounds such as reactive oxygen species and other inflammatory mediators are generated, damaging cellular lipids, proteins, and DNA with associated cell death.[2] UV A (UVA) radiation is most often responsible for triggering phototoxic reactions, but UV B (UVB) radiation and visible light can also cause phototoxicity.[2] These reactions typically present as an exaggerated sunburn-like reaction in UVR-exposed areas.[2] Biopsy of affected areas shows keratinocyte necrosis, edema, and lymphocytic and neutrophilic infiltrates.[2]

Drug-induced phototoxicity does not require prior sensitization to the offending drug. Systemic medications are more commonly implicated than topical medications are. Classically, the resultant rash develops within minutes to hours after exposure to light. There can be a dose-response gradient between the amount of drug consumed and severity of the skin reaction.[3] Because anyone can theoretically be affected, its overall incidence is high when compared with that of true photoallergic reactions.[2,3] However, the diagnosis of a drug-induced phototoxic dermatitis can be challenging and is often reliant on previously reported data on the suspected agent. In a systematic review looking at 240 eligible studies of drug-induced phototoxicity from oral medications, Kim et al found that most drugs implicated as a phototoxic agent were supported by very-low-quality or low-quality evidence, using the Grading of Recommendations, Assessment, Development, and Evaluation approach.[3] In this systematic review, oral medications with stronger evidence include vemurafenib, nonsteroidal anti-inflammatory drugs, and antibiotics (specifically, fluoroquinolones and tetracycline). The most frequently reported drugs were vemurafenib, voriconazole, doxycycline, hydrochlorothiazide, amiodarone, and chlorpromazine.[3] It is important to recognize patients who are taking phototoxic drugs before administering phototherapy and obtaining a minimal erythemal dose (MED) when appropriate. In a study of 1125 patients treated with oral methoxsalen photochemotherapy (psoralen plus ultraviolet A therapy) for psoriasis, Stern et al found that patients taking phototoxic agents did not develop increased delayed erythema during the initial clearing phase of treatment.[4] After the clearing phase, however, those who were older than 45 years and taking a phototoxic drug had a 2.3 times greater chance of stopping phototherapy than did those not taking a phototoxic drug.[4] Similarly, in a study looking at 880 patients getting narrowband UVB therapy, Harrop et al found that patients taking phototoxic medications were more likely to have grade 2 and grade 3 erythema episodes than were patients not taking such medications.[5]

Phototoxic reactions can also occur in response to phototoxic agents that are applied to the skin. Therapeutically, topical psoralen and aminolevulinic acid are used in dermatology for their phototoxic properties in conjunction with exposure to UVA radiation and visible light, respectively, to treat various dermatologic conditions. Plants containing furocoumarins (botanical phototoxic agents) can induce a phototoxicity after topical exposure, which is known as phytophotodermatitis. Plants from the families Umbelliferae, Rutaceae, and Moraceae, such as celery, bergamot orange and lime, and mulberry, respectively, are known to have high levels of furocoumarins and are known to cause phytophotodermatitis in combination with UVR therapy. A thorough history taking can often be invaluable in diagnosing this condition.[1]

In patients suspected of phototoxic reactions, phototesting is the criterion standard for diagnosis, but it is not widely available. Phototesting is performed by determining the MED by exposing photoprotected areas to increasing increments of UVA and UVB radiation. Reading is performed immediately (for diagnosis of solar urticaria) and at 24 hours. Low MED values at 24 hours would indicate drug-induced phototoxicity.[1] If phototesting is not

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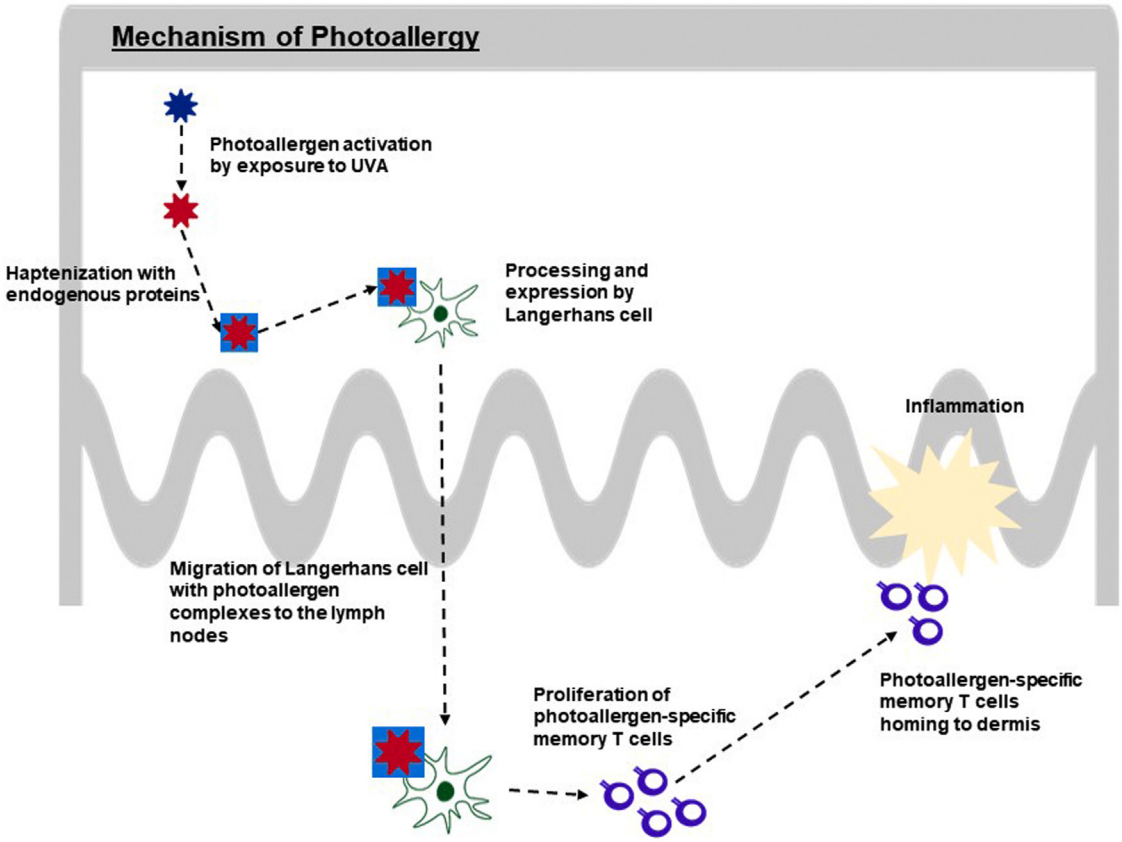


**FIG 1.** Schematic depicting mechanism of photoallergy.

**TABLE I.** List of common photoallergens by class of medications

| Class of medication | Systemic agents | Topical agents |
|---|---|---|
| Antibiotics | Dapsone, doxycycline, isoniazid, quinolones, tetracycline | Bithionol, chlorhexidine, dibromosalicylanilide, fenticlor, hexachlorophene, tetrachlorosalicylanilide |
| Other anti-infective agents | Efavirenz, griseofulvin | Acyclovir, bromochlorosalicylanilide, buclosamide, thiobischlorophenol |
| Psychotropic drugs | Amitriptyline, chlordiazepoxide, chlorpromazine, clomipramine, citalopram, flupentixol, fluphenazine, fluvoxamine, perazine, paroxetine, perphenazine, sertraline, thioridazine, trifluoperazine | |
| Cardiovascular drugs | Amiodarone, captopril, diltiazem, enalapril, fenofibrate, hydrochlorothiazide, methyldopa, ramipril, quinidine, simvastatin, valsartan | |
| Chemotherapeutic agents | Tegafur, vandetanib | |
| NSAIDs | Aceclofenac, benzydamine, celecoxib, diclofenac, ketoprofen, piroxicam, suprofen, tiaprofenic acid | Benzydamine, diclofenac, ketoprofen, piroxicam |
| UV filters | | Avobenzone, cinnamates, dibenzoylmethanes, mexenone, ecamsule, octocrylene, oxybenzone, PABA, salicylates, sulisobenzone |
| Others | Quinine, sulfonamides, sulfonylureas | Chlorpromazine, dibucaine, fenofibrate, hydrocortisone, sulfonamides |

Data from Lim et al,[1] Bylaite et al,[7] Greenspoon et al,[8] and Onoue et al.[9]
*NSAID*, Nonsteroidal anti-inflammatory drug; *PABA*, *p*-aminobenzoic acid.

available, challenge-rechallenge testing, during which resolution of the cutaneous reaction occurs with withdrawal of the suspected agent and recurrence occurs with its reintroduction, can be confirmatory of a phototoxic reaction.

## PHOTOALLERGY

*Photosensitizers* is a term that covers phototoxic agents and photoallergens. Phototoxic agents (eg, psoralens) induce direct tissue damage in the presence of the action spectrum. In

**TABLE II.** Immune-mediated photodermatoses and additional features

| Immune-mediated photodermatosis | Population affected | Time of onset after sun exposure | Clinical features | Histologic features | Phototesting | Proposed pathophysiology |
|---|---|---|---|---|---|---|
| PMLE/JSE | Children and adults; female predominance | Minutes to hours, rarely days after exposure | The most common photodermatosis, most commonly presenting in spring and summer, with immunologic tolerance (hardening) as the season progresses; presents as papules, plaques, and vesicles in sun-exposed skin; JSE is a clinical variant found in children that predominantly affects the ears | Spongiosis, focal edema, with occasional vesiculation and prominent lymphocytic infiltrate with occasional eosinophils and neutrophils | Tends to demonstrate normal MED | Reduced level of photoimmunosuppression leading to enhanced immune response to neoantigens in the skin caused by sun exposure, resulting in a delayed type IV hypersensitivity reaction |
| Hydroa vacciniforme | Children; male predominance | Hours to a few days after exposure | Summer months; discrete erythematous macules that evolve into vesicles and umbilicated papules with crusts and pits and heals with varioliform scarring | Intraepidermal multilocular vesicles with hemorrhage and inflammation; epidermal and dermal necrosis and mononuclear cell infiltrate can be seen in late lesions | Often demonstrates decreased MED for UVA | Pathophysiology is unknown but thought to be associated EBV infection |
| Actinic prurigo | Children; with female predominance, primarily affecting indigenous tribes of North, Central, and South America | Persistent and chronic; exacerbated in the summer months | Associated with HLADRB1*0407; presents with flat, shiny, and polygonal papules coalescing into lichenified plaques on sun-exposed face and extremities; associated with cheilitis, conjunctivitis, and photophobia; leonine facies can develop in chronic and severe disease | Nonspecific; hyperkeratosis, spongiosis, with significant perivascular lymphocytic infiltrate and papillary dermal edema | May be positive for UVA or normal | Autoantigens exposed by UV radiation resulting in delayed type IV hypersensitivity reaction in genetically susceptible individuals |
| Solar urticaria | Adults; rarely in children | Within minutes of sun exposure | Presents as urticarial papules and plaques that resolve <24 hours after withdrawal of sun exposure; can be associated with angioedema and constitutional symptoms such as headache, dizziness, nausea, and wheezing | Similar to urticaria, with mild dermal edema with sparse perivascular infiltrate with neutrophils, lymphocytes, and eosinophils | Positive for immediate urticarial plaques with UVB, UVA, and visible light | IgE-mediated, immediate type I hypersensitivity reaction to endogenous photoallergen |
| CAD | Adults aged >50 years; male predominance; in United States, it is more common in FST types IV and V | Persistent and chronic with flaring in summertime | Can be associated with contact allergy or photocontact allergy to *Compositae oleoresins* (airborne plant allergen); presents as confluent eczematous and lichenified plaques on sun-exposed scalp, face, neck, trunk, and extremities, often with sparing of skin creases and sun-protected skin; consider HIV infection in younger individuals with CAD | Nonspecific spongiosis and acanthosis of the epidermis, with lymphohistiocytic infiltrate; papillary dermal fibrosis in chronic cases | Can demonstrate decreased MED for UVA, UVB, and/or visible light | Similar to PMLE, with reduced level of photoimmunosuppression leading to enhanced immune response to neoantigens in the skin caused by sun exposure, resulting in a delayed type IV hypersensitivity reaction |

Data from Lim et al[1] and Bylaite et al.[7]
*CAD*, Chronic actinic dermatitis; *FST*, Fitzpatrick skin type.

contrast, photoallergens undergo activation by UV therapy, typically UVA therapy, and covalently bond with endogenous proteins in a process called haptenization.[2] Once haptenization occurs, these photoallergens are subsequently processed by Langerhans cells in the epidermis, resulting in increased production of IL-1β and increased production of TNF-α by epidermal keratinocytes, promoting the migration of Langerhans cells expressing MHC II–photoallergen complexes to the lymph nodes. In the lymph nodes, these Langerhans cells present their MHC II–photoallergen complexes to naive T cells to produce mature photoallergen-specific memory T cells.[2] This results in the development of a cell-mediated response following subsequent exposures (Fig 1). The mechanism of photoallergy parallels that of allergic contact dermatitis, but with the requirement of light-induced activation. Therefore, photoallergy classically presents as an eczematous eruption on photoexposed skin. Nonetheless, phototoxicity and photoallergy can often be clinically difficult to distinguish. Biopsy of the involved skin demonstrates acute spongiotic dermatitis with superficial perivascular lymphocytic inflammation.[2]

Given the more selective conditions required to produce a photoallergic reaction, photoallergy is far less common than phototoxicity. Because sensitization is necessary, photoallergy does not occur after the first exposure. Subsequent exposures typically induce a delayed response occurring from hours to several days after exposure.[2] Both topical and systemic agents have been implicated in photoallergy. Topically, nonsteroidal anti-inflammatory drugs and sunscreens have been the main causes of photoallergic contact dermatitis since the 1980s.[6] The most common photoallergen in sunscreens is oxybenzone. Systemically, the implicated classes of medications include antibiotics, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, and psychotropic drugs (Table I).[1,7-9]

Photopatch testing can identify patient-specific photoallergens. On day 1, determination of the MED to UVB and UVA therapy is performed, and the suspected photoallergens are placed in duplicate onto a patient's back, after which the sites are covered. On day 2, reading of the MEDs is done. On the same day, 1 set of photoallergens will then be exposed to UVA radiation. The UVA radiation dose used is 10 J/cm$^2$, or for those with decreased a MED to UVA radiation, 50% of the MED for UVA. The sites will then be covered again, and reading is done on day 3.[1,2,6] A positive read on nonirradiated skin suggests an allergic contact dermatitis in response to that specific allergen, whereas a positive read on irradiated skin together with a negative read on nonirradiated skin suggests a photoallergic process.[2] Although photopatch testing can be an invaluable tool in identifying photoallergens, it is not widely available and the testing process is not standardized. In a survey of American Contact Dermatitis Society members, less than 50% of the 112 respondents performed photopatch testing.[6] Additionally, among those who did perform photopatch testing, duration of patch placement, determination of the MED before photopatch testing, use of UV light (dose and UVA vs UVB), and the specific photopatch series used varied greatly, suggesting a further need for improved guidelines for phototesting.[6]

## IMMUNE-MEDIATED PHOTODERMATOSES

Immune-mediated photodermatoses are a group of disorders caused by altered skin immunity when the skin is exposed to sunlight. Clinically, they have diverse presentations but tend to worsen in the spring or summer owing to the increased intensity of sunlight.[1,7] Immune-mediated photodermatoses include polymorphous light eruption (PMLE)/juvenile spring eruption, hydroa vacciniforme, actinic prurigo, solar urticaria, and chronic actinic dermatitis.

These disorders can affect patients of all ages and all skin types, although age and racial differences can be appreciated in the distribution of photodermatoses.[10] PMLE is the most common photodermatosis in both adults and children.[10] In a large retrospective chart review study involving 4 academic institutes, Hamel et al found that PMLE was more common in Black patients, whereas photoallergic contact dermatitis, phototoxic drug eruptions, phytophotodermatitis, porphyrias, and solar urticaria were more commonly found in White patients.[10]

To differentiate between various immune-mediated photodermatoses, a thorough patient history, including the age of onset, seasonality, onset and duration of episodes, and family history of similar findings, along with a detailed skin examination and when appropriate, skin biopsies and additional testing, can be invaluable in determining the diagnosis.[1,7] Phototesting by irradiating uninvolved skin with increasing doses of UVA, UVB, and/or visible monochromatic or broad-spectrum radiation can help diagnose chronic actinic dermatitis and solar urticaria, but the results can often be normal in PMLE.[1] Additional information regarding the features of each individual immune-mediated photodermatosis can be found in Table II.

## CONCLUSION

Phototoxicity, photoallergy, and immune-mediated photodermatoses can all cause photosensitivity. There is clinical overlap between these conditions; therefore, a thorough patient history, family history, and medication list should be obtained, and a physical examination looking closely at morphology and distribution of skin findings should be performed.[1] Phototesting, photopatch testing, and biopsy can also be helpful. Photoprotection with a broad-spectrum, tinted UV filter with a high sun protection factor is the mainstay of treatment. In cases of phototoxicity and photoallergy, removal of exposure to the precipitating agent should be done if possible. It is important to recognize these disorders, refer the patient for pertinent diagnostic testing, and treat the disorder appropriately for better patient outcomes.

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