Photosensitivity and Other Reactions to Sunlight

Chapter 64 | Part 2: Cardinal Manifestations and Presentation of Diseases

KEY CLINICAL POINTS

1. Photosensitivity requires a chromophore (e.g., DNA, proteins, lipids) to absorb photon energy and transfer it to structures or oxygen.
2. UV-B (290–320 nm) is the primary driver of erythema; UV-A (320–400 nm) penetrates deeper and causes photoaging.
3. Fitzpatrick skin types (I–VI) determine susceptibility based on melanin type (Eumelanin vs. Pheomelanin).
4. Polymorphous Light Eruption (PMLE) is the most common photosensitivity disease, often characterized by pruritic erythematous papules.
5. Merkel Cell Carcinoma (MCC) is a neuroendocrine carcinoma associated with MCPyV and high mortality in metastatic cases.
6. Phototoxic reactions are nonimmunologic; photoallergic reactions are immunologic.
7. Immune suppression from UVR involves Langerhans cell depletion and urocanic acid isomerization.
8. Vitamin D synthesis occurs via UV-B photolysis of 7-dehydrocholesterol; sunscreens do not significantly reduce these levels.
9. NMSC (BCC, SCC) are directly linked to sun exposure; melanoma's link is less direct but significant in childhood.
10. Drug-induced photosensitivity can be categorized as phototoxic or photodermatitis based on the timing of the reaction.

DEFINITION & CLASSIFICATION

- **Definition (Harrison's 22e):** Photosensitivity is a reaction where a photon-absorbing chemical (chromophore) present in the skin absorbs incident energy, becomes excited, and transfers the absorbed energy to various structures or to molecular oxygen.
- **Diagnostic Requirements:**
  - Careful history to define duration of signs/symptoms.
  - Time between exposure and symptoms.
  - Visible changes in skin.
  - Age of onset (e.g., EPP begins in infancy; PCT in 4th–5th decades).
- **Solar Radiation Dynamics:**
  - UV-B (290–320 nm): Most efficient at producing erythema (sunburn spectrum).
  - UV-A (320–400 nm): ~1000-fold less efficient at erythema but penetrates to dermis → causes photoaging of structural/matrix proteins.
  - Absorption Spectrum: Range of wavelengths a molecule absorbs.

  - Action Spectrum: Range of wavelengths that evoke a specific response.
- **Skin Anatomy & Chromophores:**
  - Epidermis (stratified squamous) and Dermis (collagen, elastin) both susceptible to damage.
  - Stratum corneum is major UV-B absorber; <10% of UV-B reaches dermis.
  - Endogenous chromophores: Nucleic acids, proteins, lipids, 7-dehydrocholesterol.
  - Porphyrins: Trace amounts normally; increased in porphyrias. Used in photodynamic therapy (PDT) for BCCs and SCCs.
- **Melanin & Pigmentation:**
  - Synthesis: Tyrosine derivatives in melanocytes → transferred to keratinocytes.
  - Mechanism: Increased tyrosinase activity via MC1R (melanocortin-1 receptor).
  - Eumelanin: Brown/black; high MC1R activity; better shielding.
  - Pheomelanin: Red; low MC1R activity; weaker shielding → higher melanoma risk due to ROS amplification.
  - Regulation: Controlled by p53; absence of functional p53 attenuates tanning.
- **Fitzpatrick Classification (Table 64-1):**
  - Type I: Always burn, never tan.
  - Type II: Always burn, sometimes tan.
  - Type III: Sometimes burn, sometimes tan.
  - Type IV: Sometimes burn, always tan.
  - Type V: Never burn, sometimes tan.
  - Type VI: Never burn, always tan.

Classification of Photosensitivity Diseases (Table 64-2)

- **Genetic:** Congenital erythropoietic porphyria (CEP), Erythropoietic protoporphyria (EPP), X-linked protoprophyria (XLP), Porphyria cutanea tarda (PCT) —familial, Variegate porphyria (VP), Hepatoerythropoietic porphyria (HEP), Albinism, Xeroderma pigmentosum, Rothmund-Thomson syndrome, Bloom syndrome, Cockayne syndrome, Kindler syndrome, Phenylketonuria.
- **Phototoxic:** Includes reactions to internal drugs and external agents (drugs, plants, food).
- **Photoaggravated:** Lupus erythematosus (Systemic, Subacute cutaneous, Discoid), Dermatomyositis, Herpes simplex, Lichen planus actinicus, Acne vulgaris (aestivale).
- **Other:** Pseudoporphyria.

EPIDEMIOLOGY

- **General Trends:**
  - High geographic variation based on skin phototype and UVR intensity.
  - NMSC incidence increasing 2–3% per year due to detection/outdoor activity.
  - Risk of NMSC: ~15% lifetime risk for fair-skinned individuals.
- **Non-Melanoma Skin Cancer (NMSC):**
  - 80% develop on face, neck, hands.
  - Risk factors: Male sex, childhood sun exposure, older age, fair skin, low latitude.
- **Merkel Cell Carcinoma (MCC):**
  - Incidence: ~1 in 100,000.
  - Profile: Neuroendocrine; predominantly fair-skinned males in 6th–8th decades.

– Survival Rates:
– Local disease: ~50% at 5 years.
– Nodal disease: ~35% at 5 years.
– Metastatic disease: ~15% at 5 years.
– Pathogenesis: Linked to Merkel cell polyoma virus (MCPyV).
– MCPyV-negative cases: High levels of UV-induced signature mutations (C → T, CC → TT) and p53 inactivation.
– Treatment: Metastatic MCC successfully treated with PD-1/PD-L1 inhibitors.

ETIOLOGY & PATHOPHYSIOLOGY

- **Carcinogenesis Mechanisms:**
  – UV-B is a complete carcinogen (initiator and promoter).
  – Mutation Accumulation: Transition from precancerous clones to cancer requires additional mutations in genes like CDKN2A.
  – SCC vs. BCC Differentiation:
  – SCC: High mutation rates in NOTCH1 (~60% of SCCs) and p53.
  – BCC: Distinct profile; inactivating mutations in *patched* or activating mutations in *smoothened* → activation of sonic hedgehog pathway.
  – Signaling Pathways: Wnt/β-catenin and Hedgehog pathways are critical for hair follicle development and skin cancer.
- **Photoimmunology & Immunosuppression:**
  – Local Suppression: UV-B depletes epidermal Langerhans cells → reduced allergic sensitization to contact allergens (e.g., dinitrochlorobenzene).
  – Systemic Suppression: High doses of UVR; involves T-cells, B-cells, and cytokines (TNF-α, IL-4, IL-10).
  – Molecular Drivers:
  – DNA & Urocanic acid: Urocanic acid trans-isomer → UV-induced trans-cis isomerization → immunosuppression.
  – DAMPs: From necrotic keratinocytes → Type I interferon response via Toll-like receptor signaling.
  – Clinical Impact: Chronic sun exposure leads to higher NMSC risk due to T-cell suppression of antitumor responses.

CLINICAL FEATURES

- **Diagnostic Clues:**
  – Age of onset (e.g., EPP in infancy vs. PCT in 4th–5th decades).
  – Timing: Time between exposure and symptom development.
  – Location: Areas protected from sun (scalp, eyelids) may be spared; exposed areas show photoaging.
- **Polymorphous Light Eruption (PMLE):**
  – Prevalence: More common in women.
  – Juvenile variant: Known as juvenile spring eruption.
  – Clinical Presentation: Pruritic erythemated papules/plaques on trunk and forearms; face less affected.
  – "Hardening": Symptoms may subside with continued exposure.
- **Other Conditions:**

- Actinic prurigo, Hydroa vacciniforme, Sunburn, Acne vulgaris (aestivale).
- Role of genetics: Xeroderma pigmentosum (DNA repair defect), Porphyrias (heme synthesis defects).

DIFFERENTIAL DIAGNOSIS

- **Classification of Photosensitivity:**
  - Phototoxic (nonimmunologic, e.g., fluoroquinolones).
  - Photoallergic (immunologic, e.g., chlorpromazine, piroxicam).
  - Systemic conditions: SLE, Dermatomyositis.
  - Genetic disorders: Porphyrias, Xeroderma pigmentosum.

DIAGNOSTIC APPROACH

1. **Initial Presentation:** Patient presents with photosensitivity.

2. **Laboratory Screening:**

a. ANA Test → If Positive → Diagnosis: Systemic Lupus Erythematosus (SLE).

b. Plasma Porphyrin → If High → Diagnosis: Porphyria (further differentiated as Lupus erythematosus or Porphyria cutanea tarda).

3. **History of Exposure to Photosensitizing Drug:**

a. If "Chronic drug" → Diagnosis: Drug photosensitivity.

b. If "Rash drug" → Determine timing:

i. Immediate → Diagnosis: Phototoxic (e.g., acetone, chemicals).

ii. Delayed → Diagnosis: Photodermatitis (e.g., sulfonamides, tetracyclines).

iii. Unrelated → Other considerations.

4. **Specific Testing for "Rash drug":**

a. Perform Photo Patch Test.

b. If Positive → Diagnosis: Phototoxic or Photodermatitis.

c. If Negative → Diagnosis: Polymorphism/Systemic Lupus Erythematatus.

MANAGEMENT & TREATMENT

1. **Photoprotection:**

a. Use high-SPF broad-spectrum sunscreens.

b. Use protective clothing and sun avoidance.

2. **Drug Management:**

a. Identify and remove offending agents (e.g., fluoroquinolones, sulfonamides).

b. For acute flares of PMLE: Topical or systemic glucocorticoids.

3. **Vitamin D Maintenance:**

a. Supplementation is preferred to sun exposure for Vitamin D deficiency.

b. Note: Sunscreens do not significantly reduce Vitamin D levels; they are not a justification for increased cancer risk.

4. **Special Populations (Organ Transplant):**

a. Monitor closely and use rigorous photoprotection.

b. Note: mTOR inhibitors (sirolimus, everolimus) may reduce NMSC risk compared to calcineurin inhibitors (cyclosporine, tacrolimus).

PROGNOSIS & COMPLICATIONS

- **Skin Cancer Survival:**
  - Melanoma: Risk linked to childhood exposure; can occur in non-sun-exposed skin.
  - MCC: 50% survival (local), 35% (nodal), 15% (metastatic).
- **Complications of Photosensitivity:**
  - Chronic sun exposure → Photoaging, Actinic keratosis, NMSC (BCC, SCC, MCC).
  - Systemic issues: SLE exacerbation by UVR.

SPECIAL POPULATIONS

- **Organ Transplant Recipients:**
  - >50% develop BCCs and SCCs due to immunosuppression.
  - Risk correlates with duration/degree of immunosuppression.
  - Calcinerin inhibitors (cyclosporine, tacrolimus) may suppress p53-dependent senescence pathways.
- **Systemic Lupus Erythematosus (SLE):**
  - UVR-induced DNA damage may promote autoantibody formation.
  - Clinical forms: Systemic, Subacute cutaneous, Discoid.

KEY PEARLS & HIGH-YIELD POINTS

- **Phototoxic vs. Photoallergic:** Phototoxic is nonimmunologic; Photoallergic is immunologic.
- **Urocanic Acid:** Key mediator of UV-induced immunosuppression via trans-to-cis isomerization.
- **Vitamin D:** Sunscreen use does not significantly impact Vitamin D levels; supplementation is the preferred method for deficiency.
- **Merkel Cell Carcinoma:** High suspicion in fair-skinned patients with head/neck lesions; associated with MCPyV.
- **Drug Identification:** Fluoroquinolones and Sulfonamides are common culprits for drug-induced photosensitivity (Table 64-3, Table 64-4).
- **Sunscreen Ingredients (Table 64-5):** Includes PABA (15%), Avobenzone, Cinoxate (3%), etc.

REFERENCE TABLES

TABLE 64-1

Skin Type and Sunburn Sensitivity (Fitzpatrick Classification) TYPE I II III IV V VI

TYPE	DESCRIPTION
I	Always burn, never tan
III	Sometimes burn, sometimes tan
V	Never burn, sometimes tan

TABLE 64-2

Classification of Photosensitivity Diseases TYPE Genetic

TYPE	DISEASE
Genetic	Congenital erythropoietic porphyria (CEP)
	Erythropoietic protoporphyria (EPP) X-linked protoprophyria (XLP)
	Porphyria cutanea tarda (PCT) —familial
	Variegate porphyria (VP)
	Hepatoerythropoietic porphyria (HEP)
	Albinism
	Xeroderma pigmentosum
	Rothmund-Thomson syndrome
	Bloom syndrome
	Cockayne syndrome
	Kindler syndrome
	Phenylketonuria
Phototoxic	
Internal	Drugs
External	Drugs, plants, food
Neoplastic and degenerative	Photoaging
	Actinic keratosis
	Melanoma and nonmelanoma skin cancer
Photoaggravated	Lupus erythematosus
	Systemic
	Subacute cutaneous
	Discoid
	Dermatomyositis
	Herpes simplex

TYPE	DISEASE
	Lichen planus actinicus
	Acne vulgaris (aestivale) Pseudoporphyria

TABLE 64-4

Drugs That May Cause a Photoallergic Reaction DRUG 6-Methylcoumarin Aminobenzoic acid and esters Bithionol...

DRUG	TOPICAL	SYSTEMIC
6-Methylcoumarin	+	
	+	
Bithionol	+	
Diclofenac		+
Halogenated salicylanilides	+	
	+	
Musk ambrette	+	
Promethazine		+
Sulfonylureas		+

TABLE 64-3

Drugs That May Cause a Phototoxic Reaction DRUG Amiodarone Dacarbazine Fluoroquinolones 5-Fluorouracil Furosemide...

DRUG	TOPICAL	SYSTEMIC
Amiodarone		+
Fluoroquinolones		+
	+	
Furosemide		+
Phenothiazines		+
	+	
Retinoids	+/−	+
Sulfonylureas		+
Thiazides		+

TABLE 64-5

FDA Category I Monographed Sunscreen Active Ingredients INGREDIENTS p -Aminobenzoic acid (PABA) Avobenzone Cinoxate...

INGREDIENTS	MAXIMUM CONCENTRATION, %
p-Aminobenzoic acid (PABA)	15
Cinoxate	3
Ecamsule	15
Meradimate	5
Octinoxate	7.5
Oxybenzone (benzophenone-3)	6
Ensulizole	4
Titanium dioxide	25
Zinc oxide	25