Drug Eruptions

Roman Bronfenbrener, MD, and Courtney Ensslin, MD

Drug Eruption	Common medications	Time course	Clinical features	Laboratory values	Pathology	Treatment	Notes
Morbilliform drug rash	Antibiotics, anticonvulsants	Onset after several days or up to two weeks after drug initiation; resolves within two weeks	Generalized eruption of brightly erythematous macules that often become confluent; start proximally and proceed distally in a symmetric distribution; favors dependent areas; lesions may become slightly palpable and annular plaques or "target" lesions may be present; often pruritic with a low-grade fever; mucous membranes spared	Possible eosinophilia	Nonspecific changes; mild superficial perivascular and interstitial lymphocytic infiltrate, with or without eosinophils	Discontinue the offending agent; supportive treatment with antipruritics, antihistamines, and topical corticosteroids	Most common cutaneous drug reaction; Ampicillin or amoxicillin given during Epstein-Barr Virus infection can cause identical rash in 100% of children that is not allergic in nature
Acute Generalized Exanthemous Pustulosis (AGEP)	Beta-lactam antibiotics, calcium channel blockers, macrolides, anti-malarials	Sudden onset; within an average of 10 days after initiation of medication and lasts for 1-2 weeks	High-fever; diffuse edematous erythema studded with numerous non-follicular, minute, sterile pustules; lesions begin on the face or intertriginous areas and then disseminate; may have pruritus and/or burning; resolves with widespread superficial desquamation; may have + Nikolsky sign	Marked leukocytosis with neutrophilia; mild to moderate eosinophilia; transient renal dysfunction; hypocalcemia	Superficial epidermal spongiosis and pustules; edema of the papillary dermis; rich perivascular mixed infiltrate of neutrophils and some eosinophils	Discontinue offending agent; topical and/or systemic steroids; antihistamines; antipyretics	May patch test for suspected medication; mortality rate of 1-5%; main differential is pustular psoriasis, elucidated by history and other evidence of psoriasis; AGEP can also be caused by radiocontrast material and mercury
Drug reaction with eosinophilia and systemic symptoms (DRESS)/ Drug-induced hypersensitivity syndrome (DIHS)	Anticonvulsants, sulfonamides, Allopurinol, Minocycline, dapsone, nevirapine, abacavir	Relatively late-onset; begins >3weeks after drug initiation; long-lasting, lasts >2 weeks after drug discontinuation	Fever; lymphadenopathy; morbilliform eruption that becomes edematous with follicular accentuation; facial edema; often involves vesicles, tense bullae, pustules, erythroderma and purpura; may have associated arthralgias and arthritis; internal organ involvement (most commonly hepatitis, but also myocarditis, interstitial pneumonitis, interstitial nephritis, thyroiditis and eosinophilic meningitis or encephalitis)	Marked hypereosinophilia; atypical lymphocytosis; may involve elevated liver enzymes, evidence of thyroid or cardiac dysfunction	Mild to dense lymphocytic infiltrate in the superficial dermis with eosinophils present; dermal edema	Discontinue offending drug; topical and/or systemic corticosteroids with slow taper over weeks to months. Avoid cross-reacting medications.	Mortality rate 5-10%; due to alteration in drug processing with sensitivity to toxic metabolites such as hydroxylamines and arene oxides coupled with HHV-6 reactivation; Long term risk of autoimmune connective tissue disease and endocrinopathies
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN	Antibiotics Anticonvulsants (aromatic) Allopurinol NSAIDs Lamotrigine	Occurs 7-21 days after drug introduction; epidermal regrowth in 3 weeks	High fever and flu-like symptoms may precede skin eruption by 1-3 days; initial lesions are dusky-red macules on the face and trunk that spread quickly; may desquamate or form atypical targets with purpuric centers that coalesce, become gray, form bullae, and slough off; necrolytic epidermis resembles "wet cigarette paper"; several mucosal surfaces involved; moderate to severe skin pain; + Nikolsky and Asboe–Hansen sign; may have internal involvement (most frequently hepatitis and renal dysfunction)	May see elevation of BUN, creatinine, LFTs, leukopenia, eosinophilia	Early stage lesions: apoptotic keratinocytes in the basal and suprabasal layers of the epidermis; late stage lesions: subepidermal blister with overlying necrosis of the entire epidermis, mild to dense lymphocytic infiltrate	Immediate discontinuation of the causative drug; rapid initiation of supportive care ideally in burn unit (nutritional support, fluid and electrolyte repletion, wound care); Medical treatments controversial but include high-dose IVIG; high-dose systemic steroids, etanercept, infliximab, cyclosporine.	Mortality rate predicted by SCORTEN; Increased incidence in HIV/AIDS; SJS is <10% BSA involved, SJS/TEN overlap is 10-30% BSA, and TEN is >30% BSA involved
Fixed Drug eruption	Sulfonamides NSAIDs Tetracyclines Pseudoephedrine, Barbiturates, Carbamazepine	Begins 1-2 weeks after first exposure, <48 hours after re-exposure	One or few round, sharply demarcated, erythematous to violet-brown plaques, up to several centimeter in diameter; often edematous with a bulla, or central erosion and peripheral hyperpigmentation or erythema; predilection for oral and genital mucosa, face, hands, feet; as lesions heal, they leave behind a post-inflammatory brown pigmentation	None	Mixed infiltrate within the superficial and deep dermis that involves lymphocytes, eosinophils and sometimes neutrophils; necrotic keratinocytes may be present within the epidermis; subepidermal vesicle formation; marked pigment incontinence; evidence of prior episodes includes papillary dermis fibrosis and deep perivascular pigment incontinence; a normal stratum corneum (suggesting an acute process) and chronic dermal changes (from prior episodes) is a pathognomonic finding.	Discontinue the offending medication; Topical steroids if symptomatic	Re-exposure to medication results in recurrence of lesions at the exact same sites; however, there is a presumed "refractory period" which may last from weeks to months. With each recurrence, additional sites of involvement may appear. Non-pigmenting FDE most common with pseudoephedrine
Urticaria	Antibiotics NSAIDs Monoclonal antibodies Contrast media	Develops within minutes to hours and resolves within 24 hours	Transient erythematous and edematous papules and plaques with central pallor (wheals/hives); associated with pruritus; lesions can appear anywhere on the body, and vary in size and number; may have associated angioedema; respiratory compromise and hypotension can be fatal in severe reactions	None	Upper dermal edema with a sparse, perivascular inflammatory infiltrate of lymphocytes, eosinophils and some neutrophils	Withdrawal of the causative agent; H1 antihistamines; epinephrine and systemic steroids for anaphylactic response	May use immunoassays and skin prick tests to confirm diagnosis; NSAIDs, ACE inhibitors, ARBs can cause angioedema without wheals

Roman Bronfenbrener, MD, is a 2nd year derm resident or PGY-3 at SUNY - Stony Brook

Courtney Ensslin, MD, is a MS-4 at SUNY - Stony Brook University Medical School

Drug Eruptions (cont.)

Roman Bronfenbrener, MD, and Courtney Ensslin, MD

Drug Eruption	Common medications	Time course	Clinical features	Laboratory values	Pathology	Treatment	Notes
Serum Sickness Like Reaction (SSLR)	Cefaclor, penicillins, sulfonamides, minocycline, NSAIDs, bupropion, phenytoin	Occurs 1-3 weeks after drug exposure	Fever, arthralgias, urticarial or morbilliform rash and lymphadenopathy. Urticarial plaques favoring Wallace's lines are seen in *TRUE* serum sickness, not SSLR	Absence of hypocomplementemia, vasculitis and renal disease (in comparison to true serum sickness)	No vasculitis; superficial and deep dermal insterstitial and/or perivascular lymphocytic infilitrate; dermal edema may be seen	Withdrawl of causative agent; antihistamines or oral steroids to speed resolution	More common in children; not due to immune complex deposition as in Serum Sickness
Acneiform reactions	Corticosteroids, androgens, hydantoins, lithium, oral contraceptives, iodides/bromides, EGFR inhibitors	Varies depending on offending agent	Monomorphous papules and/or pustules on the face and upper trunk; no comedones	None	Follicular neutrophilic pustules	Withdrawl of causative agent; topical acne regimens and oral antibiotics	Incidence is increasing with the introduction of EGFR inhibitors, approximately 80% of patients treated with these anticancer agents develop papulopustular rash, which portends a better prognosis.
Vasculitic reactions	Penicillins, NSAIDs, sulfonamides, cephalosporins	Occurs 7-21 days after drug intiation and less than 3 days following rechallenge	Palpable purpura on the lower extremities; may also involve pustules, ulcers, blisters, urticaria-like lesions, and digital necrosis; internal involvement includes GI bleeding, arthritis, nephritis, peripheral neuropathy; systemic symptoms are rare	Must rule out cutaneous involvement of a systemic vasculitis; consider CBC, CMP, UA, Complement, ANA, ANCA, cryoglobulins, RF as directed by history	Transmural infiltration of vessel walls by leukocytes (early stage: neutrophils, late stage: mononuclear cells) with leukocytoclasia; fibrinoid necrosis of the damaged vessel walls, resulting in extravasation of erythrocytes; direct immunofluorescence (DIF) reveals deposition of C3, IgM, IgA and/or IgG within the vessel walls in a granular pattern	Discontinue medication; supportive care; oral corticosteriods may benefit those with systemic symptoms	ANCA-positive vasculitis has been associated with propylthiouracil, hydralazine, and minocycline; polyarteritis nodosa has been observed following hepatitis B vaccination; drugs are the cause of 10-15% of cutaneous small-vessel vasculitides
Lichenoid reactions	ACE inhibitors, beta-blockers, calcium channel blockers, antimalarials, diuretics, NSAIDs, gold salts	Occurs several months to years after drug introduction and take months to years to resolve	Photodistributed or generalized plaques, small papules, or exfoliative erythema, +/- Wickham's striae; oral involvement is uncommon; may affect nails	None	Lichenoid inflammation along the dermoepidermal junction, necrosis of keratinocytes, and a dermal lymphocytic infiltrate (very similar to idiopathic lichen planus). Parakeratosis with eosinophils/plasma cells can be seen in drug induced LP	Withdrawal of the suspected drug; symptomatic treatment with antipruritics; lichen planus therapies such as corticosteroids, systemic retinoids, narrowband UVB, PUVA, topical calcineurin inhibitors, and antimalarials may be helpful	Hepatitis B vaccination may trigger a lichenoid eruption
Photoallergic	Thiazide diuretics, sulfonamide antibiotics, sulfonylureas, phenothiazines; sunscreens	Sensitization on first exposure; upon re-exposure, cutaneous eruption occurs quickly; course may be chronic (months to years)	Pruritus; eczematous or lichenoid lesions; limited to sun-exposed areas	None	Epidermal spongiosis, dermal lymphohistiocytic infiltrate	Withdrawal of offending agent; photoprotection; topical steroids	Cell-mediated hypersensitivity reaction to an allergen produced by the effect of UVA light on a drug; phototesting may be useful; when photoallergic reaction persists for months to years it is known as chronic actinic dermatitis
Phototoxic	Tetracyclines, NSAIDs, fluoroquinolones, amiodarone, psoralens, phenothiazine	Onset within hours to days of exposure	Erythema, vesicles and bullae limited to sun-exposed sites; appears similar to an exaggerated sunburn; heals with desquamation and residual hyperpigmentation; photo-onycholysis	Normal plasma porphryins (in pseudoporphyria)	Necrotic keratinocytes, edema, mild dermal lymphocytic infiltrate, vasodilation	Dose reduction or withdrawal of offending agent; photoprotection	Can occur in anyone who reaches the clinical threshold for phototoxicity and has sufficient UV light exposure, resulting in reactive oxygen species that damage the skin; studies show decreased reactivity in higher fitzpatrick skin type

Boards' Fodder

In addition to this issue's Boards' Fodder, don't forget to download the new Board's Fodder online exclusive from **www.aad.org/DIR**, *where a new chart is published each quarter. The latest online Boards' Fodder is Cutaneous Manifestations of HIV Infection by Monika Kaniszewska, MD, MS and Kelly Park, MD, MSL.*

To view, download, or print every Boards' Fodder ever published, both in print and online, check out the complete archives at **www.aad.org/BFarchives**.

References

1. Bolognia JL, Jorizzo JL, Schaffer JV, editors. Bolognia Textbook of Dermatology. 3rd ed. Spain: Mosby Elsevier publishing; 2012: chapters 20-21.
2. James WD, Berger TG, Elston DM, eds. Andrews' Diseases of the Skin: Clinical Dermatology. 11th ed. Philadelphia, Pa: Saunders Elsevier; 2011: chapter 6.
3. Balagula Y, Garbe C, Myskowski PL et al. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. International Journal of Dermatology 2001; 50: 129-146.