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Drug Reactions

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Reaction	Features	Onset and Implicated Drugs	Pathology	Notes
AGEP	Numerous small, nonfollicular, sterile pustules within large areas of edematous erythema; favors face and intertriginous areas, then disseminates; with or without pruritus, burning; high fever; leukocytosis with neutrophilia, eosinophilia; hypocalcemia; must be differentiated from acute pustular psoriasis of the von Zumbusch type; additional skin lesions such as petechiae, purpura, atypical targetlike lesions and vesicles are more frequently observed in AGEP than acute pustular psoriasis	<4 d; β-lactam antibiotics, macrolides, diltiazem, antimalarials	Spongiform pustules in the superficial epidermis; papillary dermal edema with perivascular mixed infiltrate of neutrophils and some eosinophils	Resolves in 1–2 wk with widespread desquamation; may patch test for suspected medication; 90% drug induced, though other causes include enteroviral infection or exposure to mercury; mortality rate of 1%–5%
DRESS/DIHS	Exanthematous eruption with follicular accentuation; prominent facial edema; fever; lymphadenopathy; marked eosinophilia; circulating atypical lymphocytes; visceral involvement (often hepatitis but also myocarditis, nephritis, thyroiditis); with or without arthralgia, arthritis	15–40 d (relatively late onset after drug initiation and long lasting following drug discontinuation); anticonvulsants (aromatic), sulfonamides, allopurinol, minocycline, lamotrigine (especially in combination with valproate), nevirapine, abacavir	Dense, perivascular, lymphocytic infiltrate in the papillary dermis, with the presence of extravasated erythrocytes, eosinophils, and dermal edema	Cutaneous involvement can persist for several weeks to months after discontinuation of drug; treat with slow taper of systemic corticosteroids over weeks to months; onset of visceral involvement may be delayed as much as 80 d including following the taper of corticosteroids; relapses may occur with taper; RegiSCAR group diagnostic scoring system; etiology has been linked with lymphocyte activation, drug metabolic enzyme defects, and human herpesvirus 6 and 7 reactivation; mortality rate 5%–10%; fulminant hepatitis is responsible for the majority of deaths
Drug-induced subacute lupus	Psoriasiform and annular lesions, usually of the upper trunk and extensor surfaces of the arms	2 wk to >3 y; hydrochlorothiazide, calcium channel blockers, terbinafine, NSAIDs, griseofulvin, docetaxel, interferon	Identical to subacute lupus with vacuolar alteration of basal layer, apoptotic keratinocytes, epidermal atrophy, and follicular plugging	Anti-Ro/SS-A and anti-La/SS-B antibodies can be present; resolution of the eruption may or may not occur after discontinuation of the responsible drug

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Drug-induced systemic lupus	Cutaneous involvement is rare but includes malar erythema, photoeruptions, and discoid or erythema multiforme–like lesions; fever, weight loss, pericarditis, and pleuropulmonary inflammation; vasculitis and renal or neurologic involvement are rare	Symptoms usually develop more than a year after the medication was initiated; procainamide, hydralazine, chlorpromazine, isoniazid, methyldopa, propylthiouracil	Nonspecific dermatitis	Antihistone antibodies in up to 95% of cases, but these antibodies are not specific; antibodies against double-stranded DNA typically are absent
Exanthematous/ morbilliform drug eruption	Brightly erythematous macules/papules that often become confluent, measleslike; starts on trunk and upper extremities; favors dependent areas; often pruritic with a low-grade fever; possible eosinophilia	4–14 d; aminopenicillins, sulfonamides, cephalosporins, anticonvulsants, allopurinol	Nonspecific changes with mild superficial perivascular and interstitial lymphocytic infiltrate; eosinophils and interface changes may be present	Most common cutaneous drug reaction; viral infections may enhance risk for developing this drug reaction; treatment involves discontinuing offending drug and supportive therapy with antipruritics and topical corticosteroids; resolves within 2 wk; 0% mortality
FDE	One or few sharply demarcated, annular, edematous, erythematous to violet-brown plaques with central erosion or bulla and peripheral hyperpigmentation or erythema; favors the lips, face, hands, feet, and genitalia; nonpigmenting variant of FDE most common with pseudoephedrine	7–14 d after first exposure; <24 h after reexposure; sulfonamides, NSAIDs, tetracyclines, pseudoephedrine, barbiturates, carbamazepine	Mixed perivascular infiltrate within the superficial and deep dermis as well as necrotic keratinocytes in the epidermis; dermal melanophages often are the only histologic findings in noninflammatory lesions	With reexposure of the causative drug, the lesions recur at exactly the same sites, though there is a refractory period that may last from weeks to months; provocation via patch testing in a previously involved site may be useful in determining the responsible drug
Lichenoid reactions	Photodistributed or generalized small papules, plaques, or exfoliative erythema; may have Wickham striae and nail involvement	Months to years after drug introduction; ACE inhibitors, beta-blockers, calcium channel blockers, NSAIDs, gold	Lichenoid interface changes similar to idiopathic lichen planus, though often with parakeratosis and eosinophils	Can take months to years to resolve following drug withdrawal; treatment with corticosteroids, systemic retinoids, narrowband UVB, and antimalarials may be helpful

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Reaction	Features	Onset and Implicated Drugs	Pathology	Notes
SJS/TEN[a]	Dusky red macules on trunk and face initially; can desquamate, form bullae; mucosal surfaces (ocular, oral, genital, respiratory, or GI mucosal surfaces) involved; prodromal high fever and flulike symptoms; common internal involvement (hepatitis, renal dysfunction); leukopenia; eosinophilia; elevated BUN, creatinine, LFTs	7–21 d; sulfonamides, anticonvulsants (aromatic), allopurinol, NSAIDs, lamotrigine	Early lesions with apoptotic keratinocytes scattered in the basal and immediate suprabasal layers of the epidermis; later stages show subepidermal blisters with overlying confluent necrosis of the entire epidermis and a sparse lymphocytic perivascular infiltrate	Controversial treatment options include high-dose intravenous immunoglobulin, systemic corticosteroids, etanercept, infliximab, cyclosporine; increased incidence in HIV; mortality predicted by SCORTEN; mortality rate 5%–30%; major causes of morbidity and mortality include hypovolemia, electrolyte imbalance, renal insufficiency, and sepsis

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; DIHS, drug-induced hypersensitivity syndrome; RegiSCAR, European Registry of Severe Cutaneous Adverse Reactions; NSAID, nonsteroidal anti-inflammatory drug; SS-A, Sjögren syndrome antigen A; SS-B, Sjögren syndrome antigen B; FDE, fixed drug eruption; ACE, angiotensin-converting enzyme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; BSA, body surface area; GI, gastrointestinal; BUN, serum urea nitrogen; LFT, liver function test; HIV, human immunodeficiency virus; SCORTEN, score of TEN.

[a]SJS, <10% BSA; SJS/TEN, 10%–30% BSA; TEN, >30% BSA.

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Practice Questions

1. RegiSCAR is a scoring method used for what drug reaction?

a. RegiSCAR is a diagnostic scoring method for DRESS/DIHS
b. RegiSCAR is a diagnostic scoring method for FDE
c. RegiSCAR is a diagnostic scoring method for SJS
d. RegiSCAR predicts mortality rate for AGEP
e. RegiSCAR predicts mortality rate for SJS

2. DRESS/DIHS is associated with what mortality rate?

a. 0%
b. 1%–5%
c. 5%–10%
d. 5%–30%
e. 10%–40%

3. Unlike other drug eruptions that typically develop 1 to 2 weeks after drug initiation, which drug eruption has a relatively late onset, often 3 weeks after drug initiation?

a. AGEP
b. DRESS/DIHS
c. exanthematous/morbilliform drug eruption
d. FDE
e. SJS

4. A patient develops a morbilliform eruption 14 days after starting an anticonvulsant. What additional finding(s) make DRESS/DIHS more likely than a common morbilliform drug rash?

a. hypocalcemia
b. lymphadenopathy
c. prominent facial edema
d. A and C
e. B and C

5. Which drug is commonly implicated in the nonpigmenting variant of FDE?

a. barbiturates
b. carbamazepine
c. NSAIDs
d. pseudoephedrine
e. sulfonamides

Fact sheets and practice questions will be posted monthly.

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