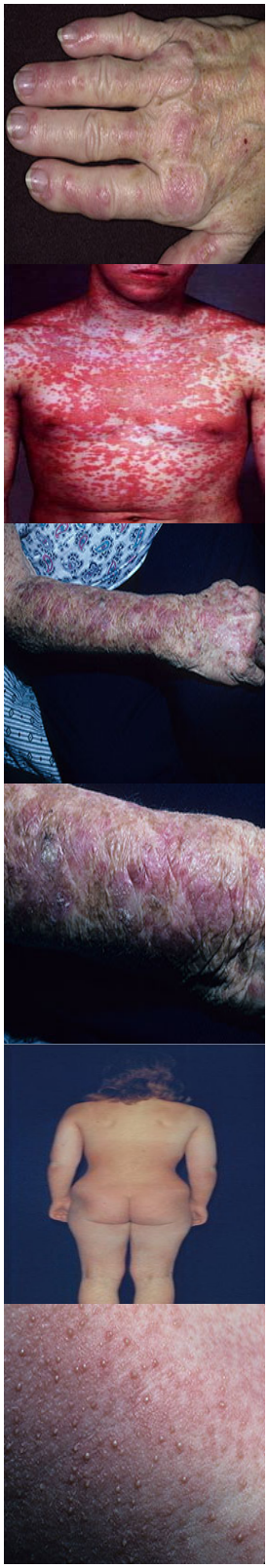
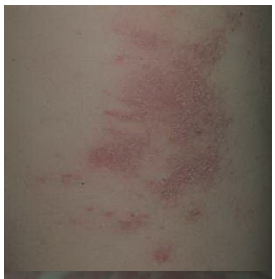
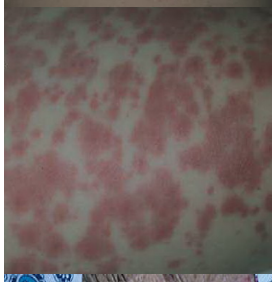
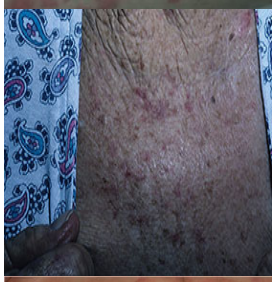
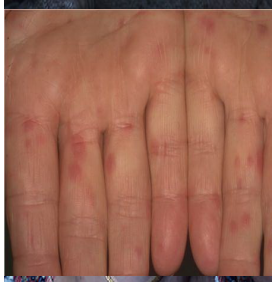
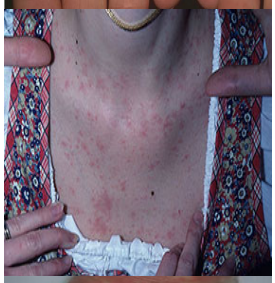


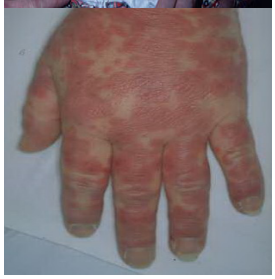


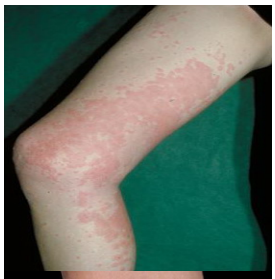


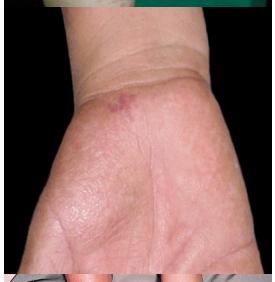


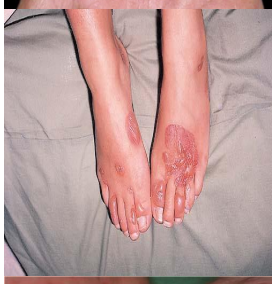


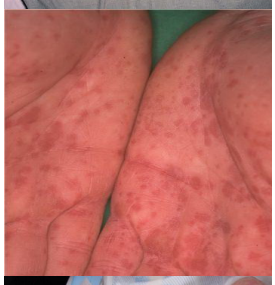


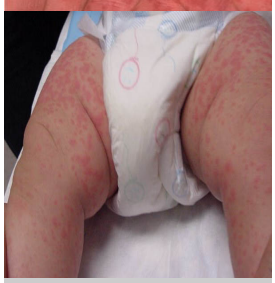


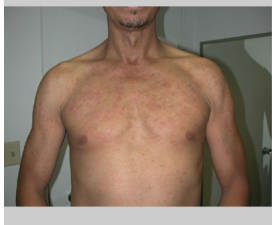


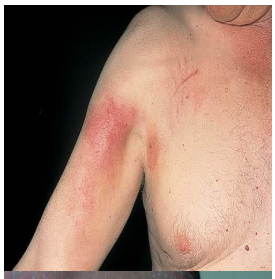
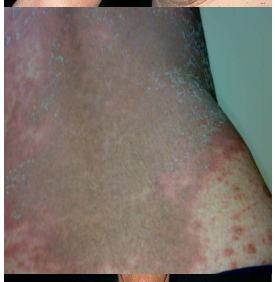
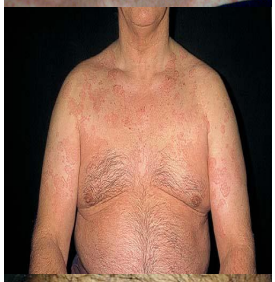
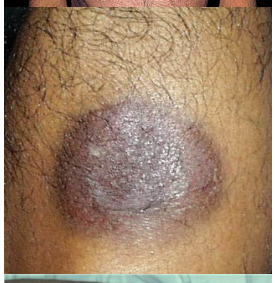
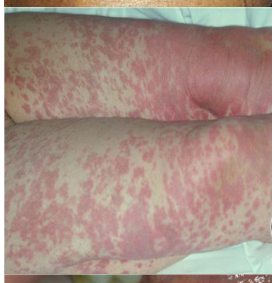
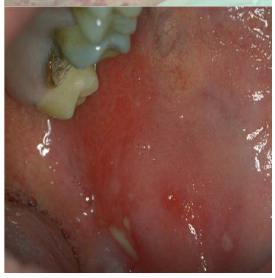


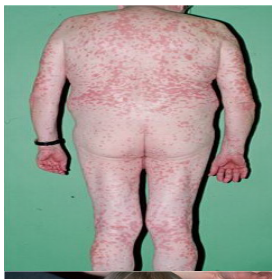
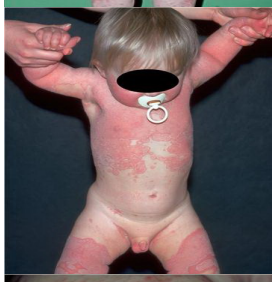
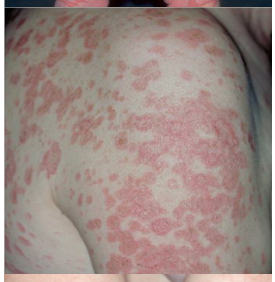
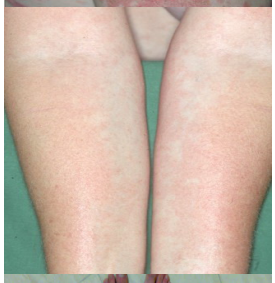
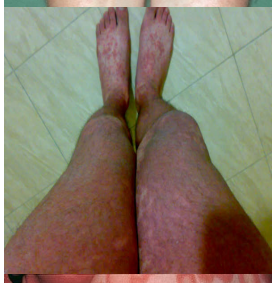
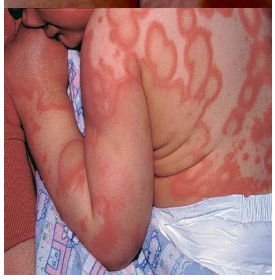


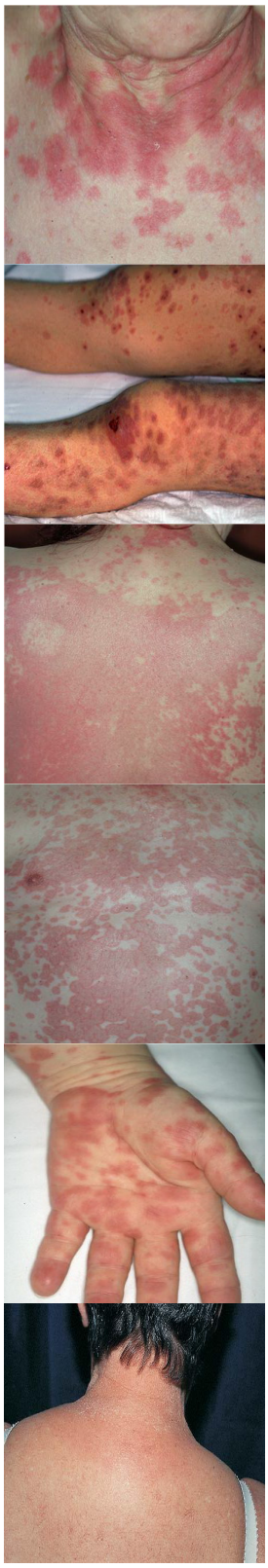


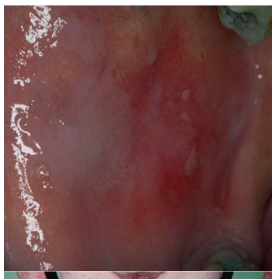
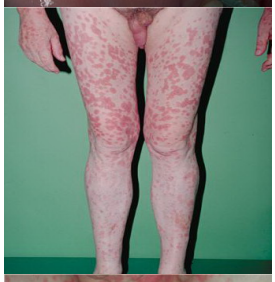
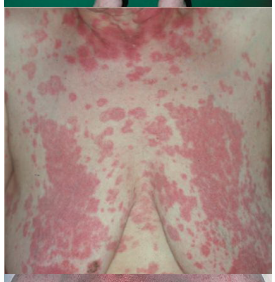
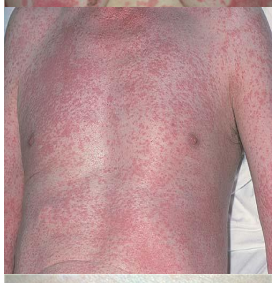
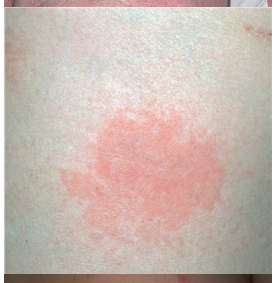
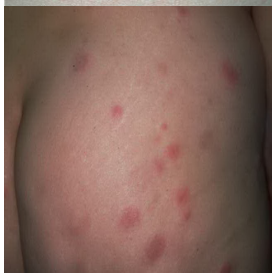


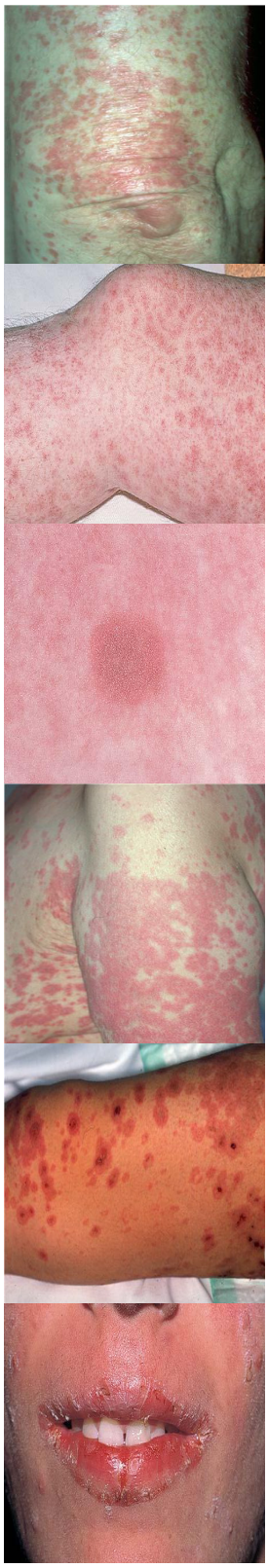


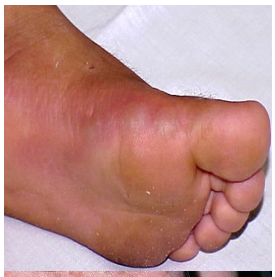
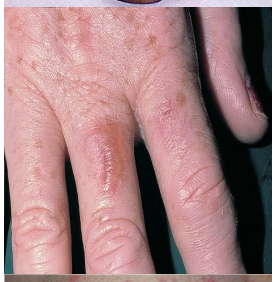
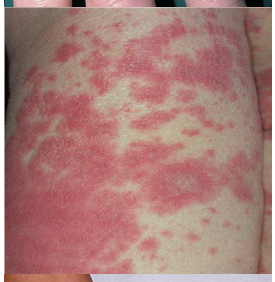
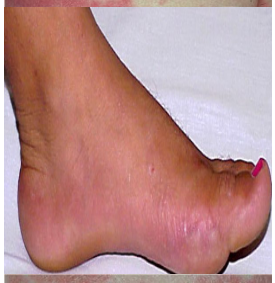
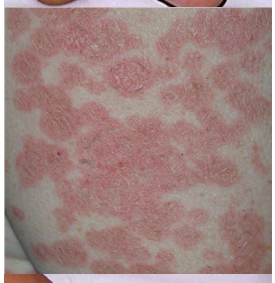
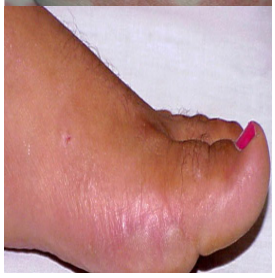







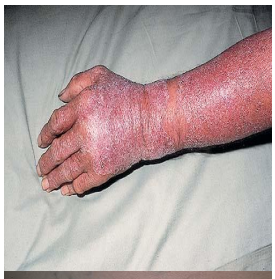
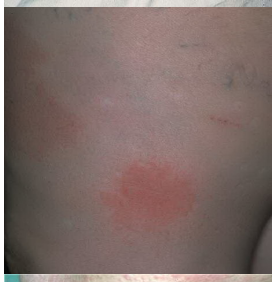
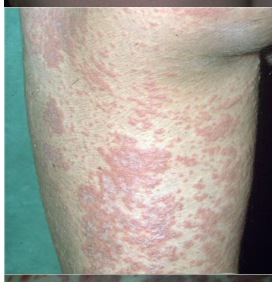
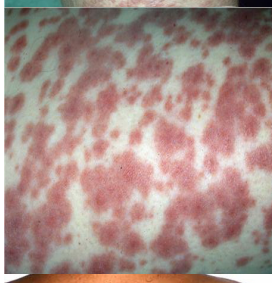
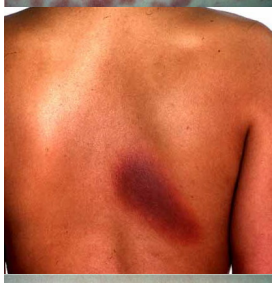
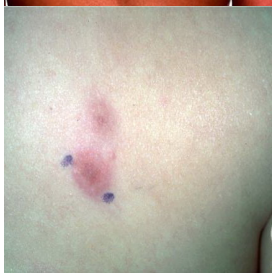







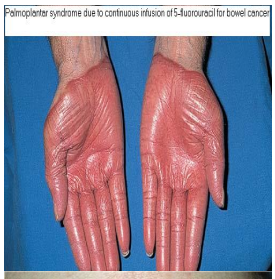


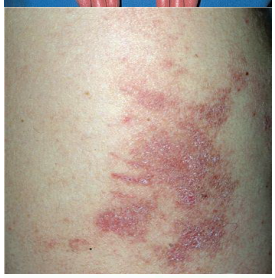







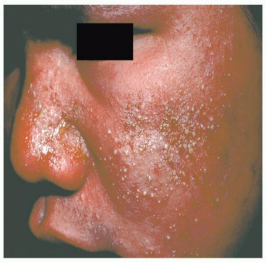


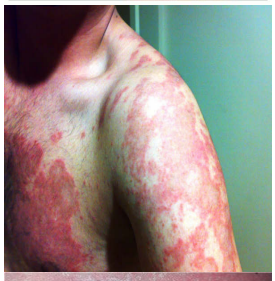







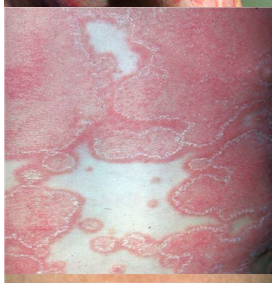







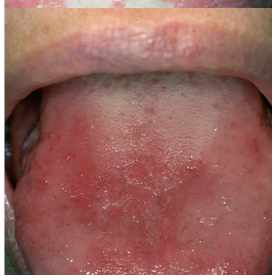

Palmoplanter syndrome due to continuous infusion of 5-fluorouracil for bowel cancer

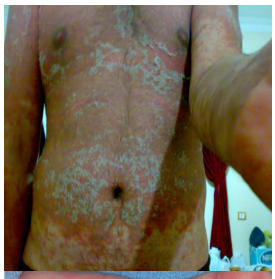
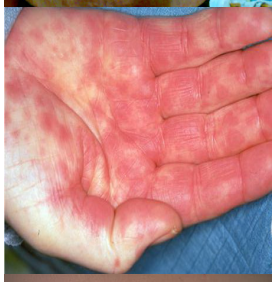
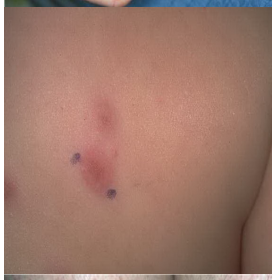
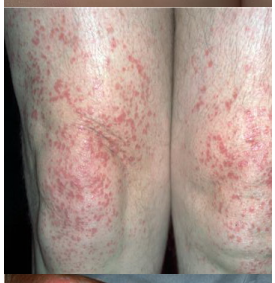
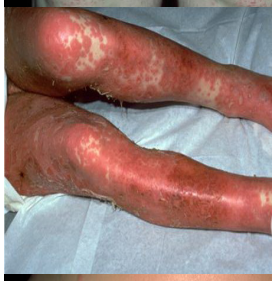
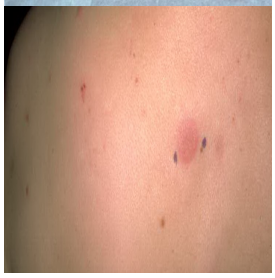


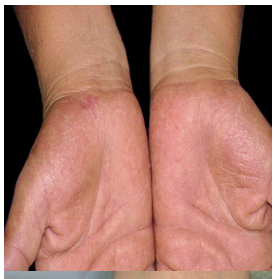


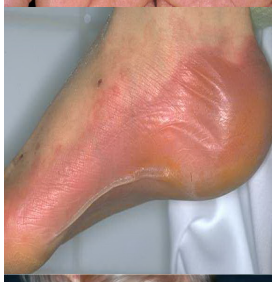


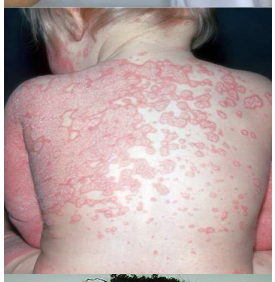


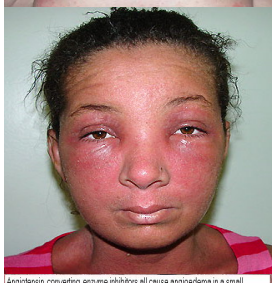


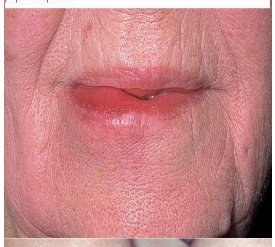


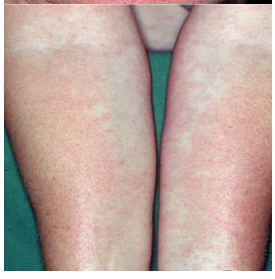


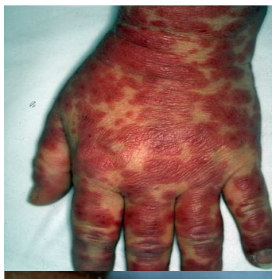
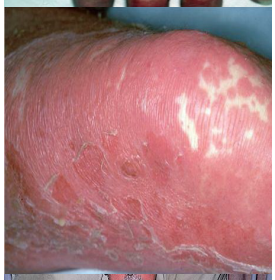
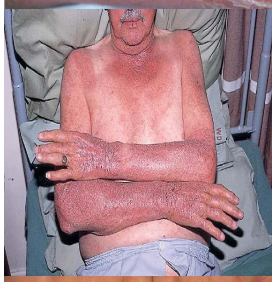
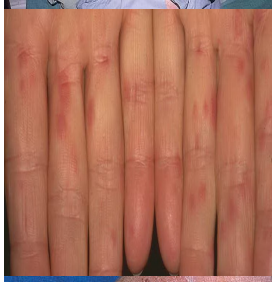
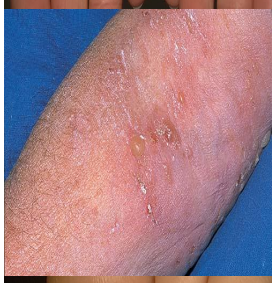
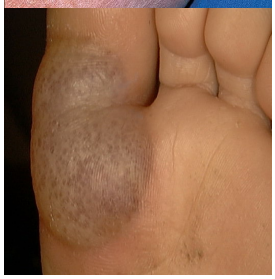


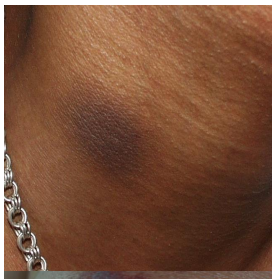
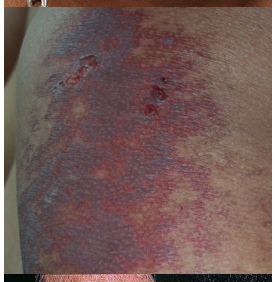
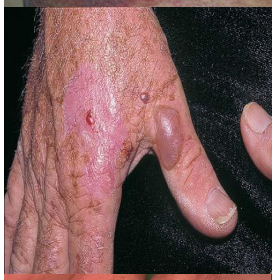
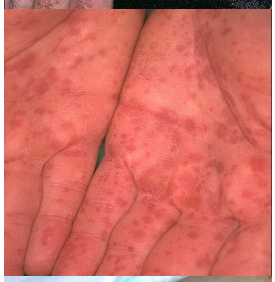
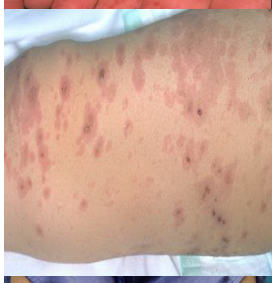
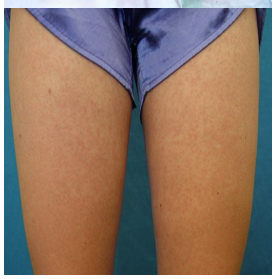


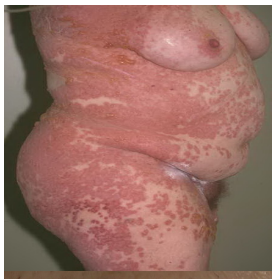
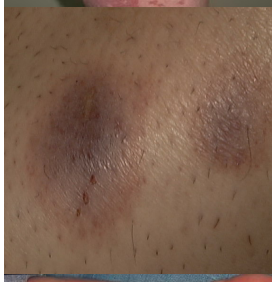
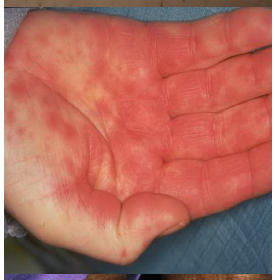
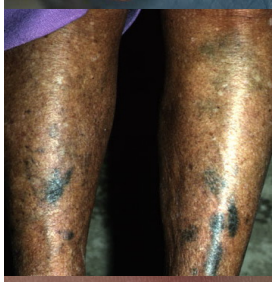
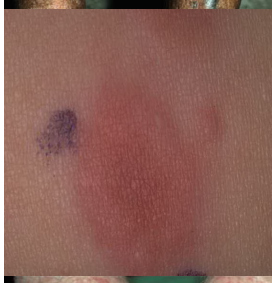
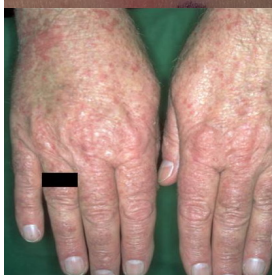
Angiotensin-converting-enzyme inhibitors all cause angioedema in a small proportion of patients

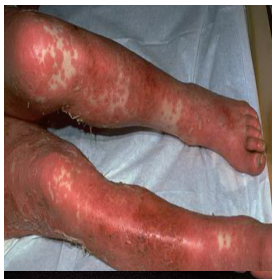


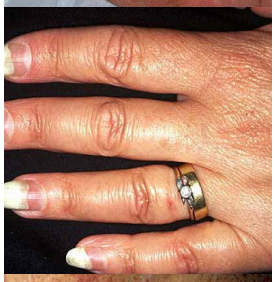


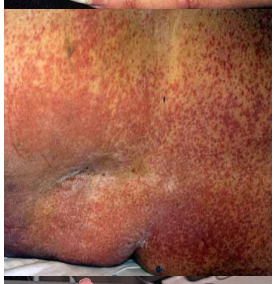







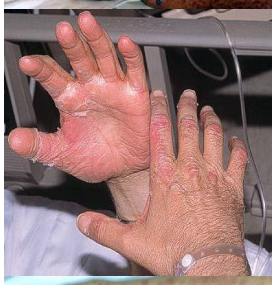







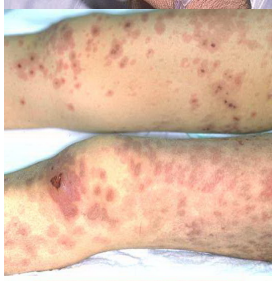







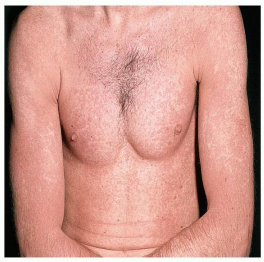


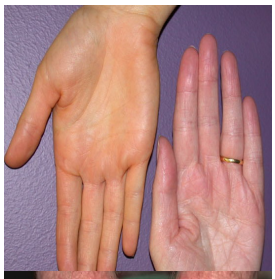
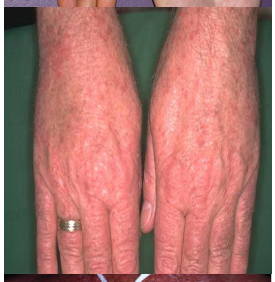
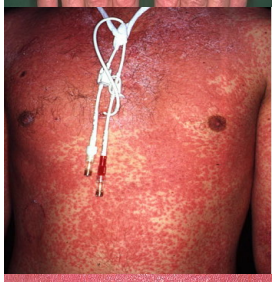
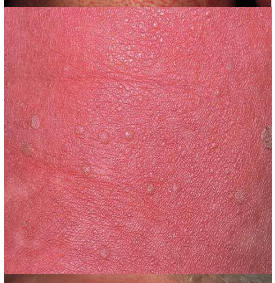
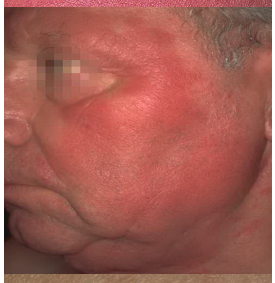
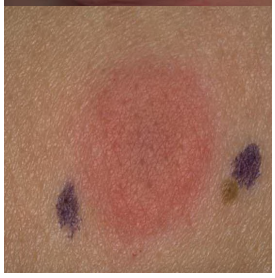


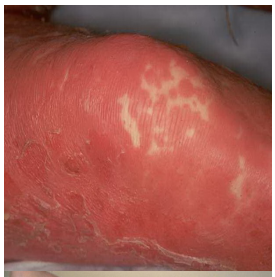


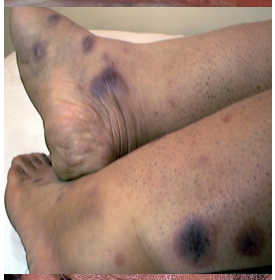


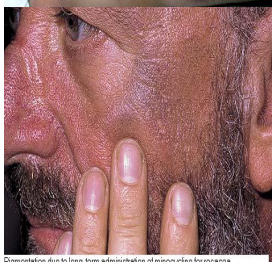




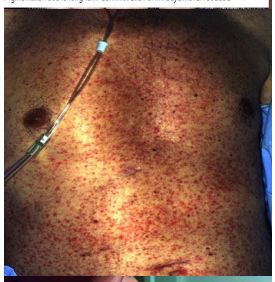







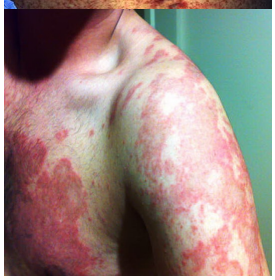


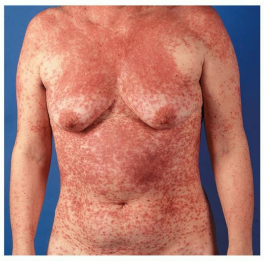


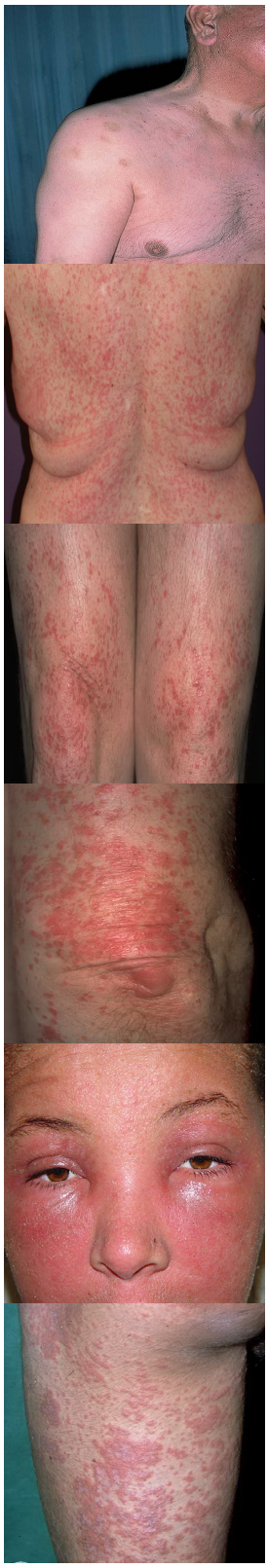


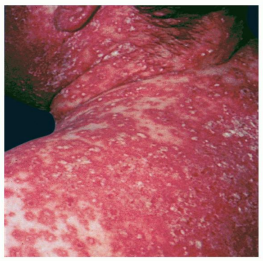
Pigmentation due to long-term administration of minocycline for rosacea

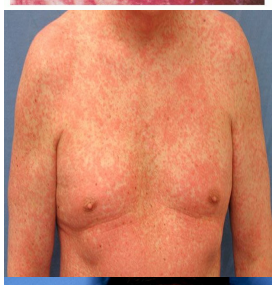


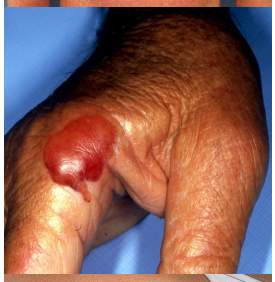


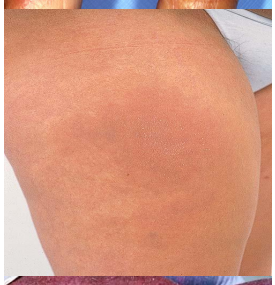


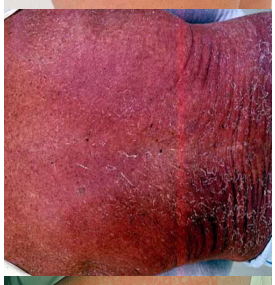


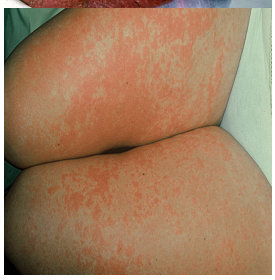




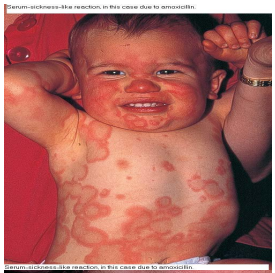




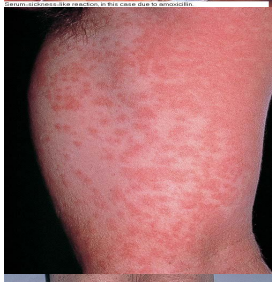


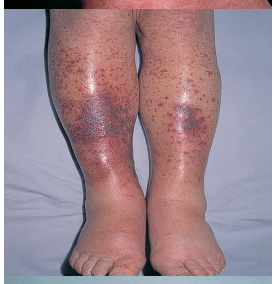


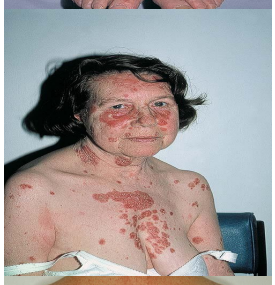
Serum-sickness-like reaction, in this case due to amoxicillin.

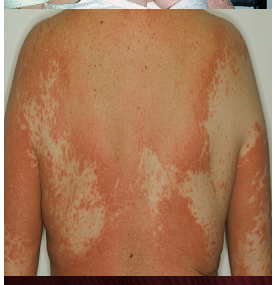


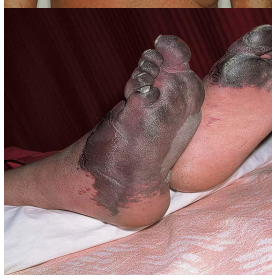
Serum-sickness-like reaction, in this case due to amoxicillin.

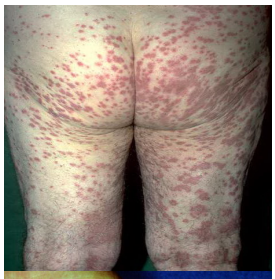
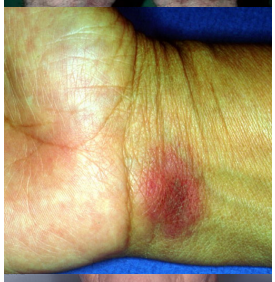
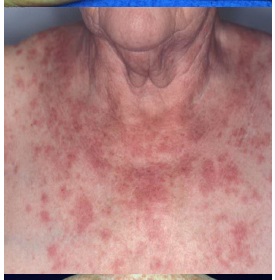
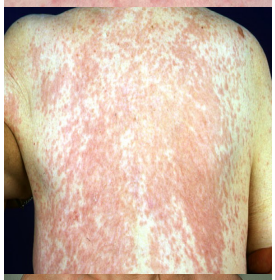
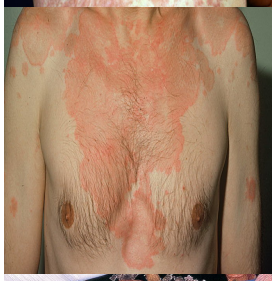
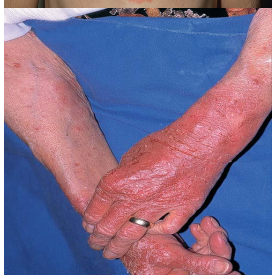


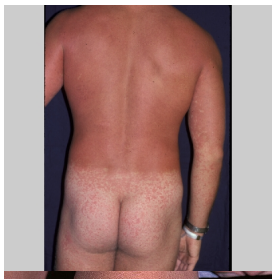


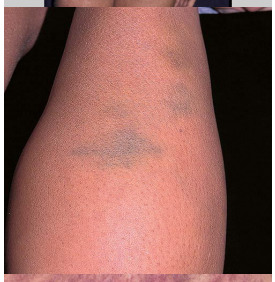


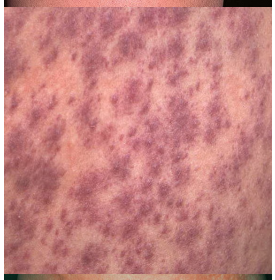


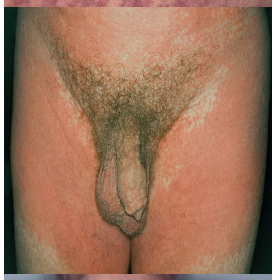


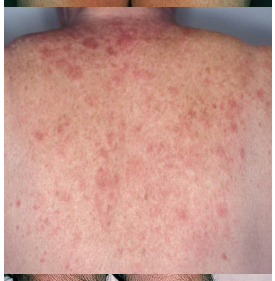







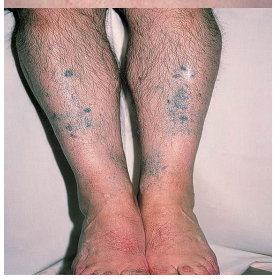


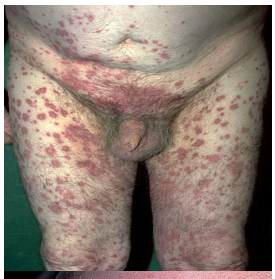
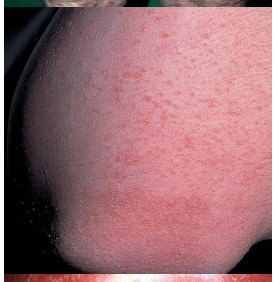
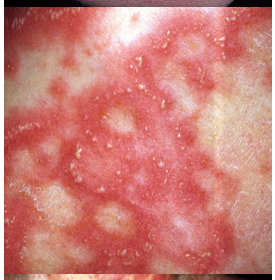
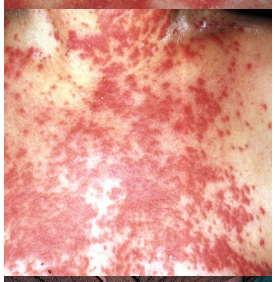
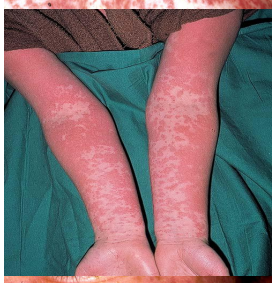
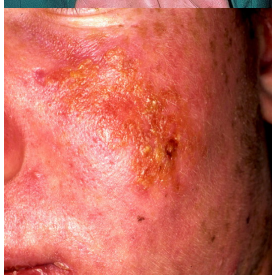


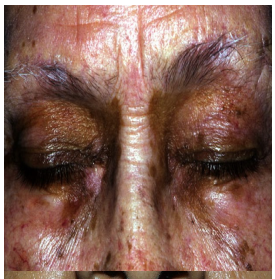


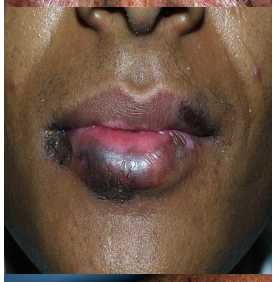


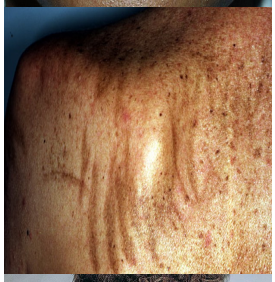


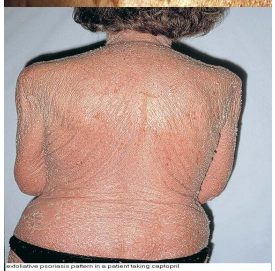


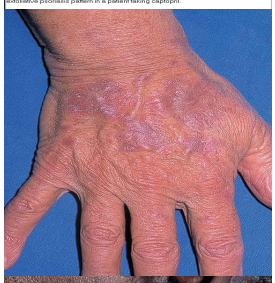


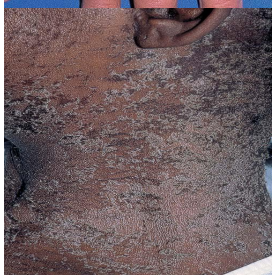


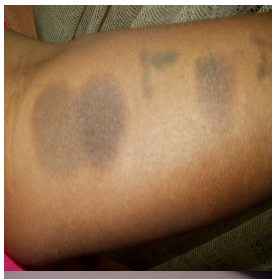
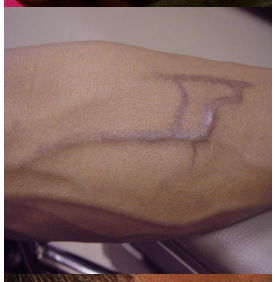
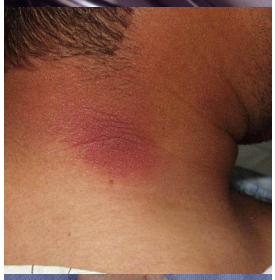
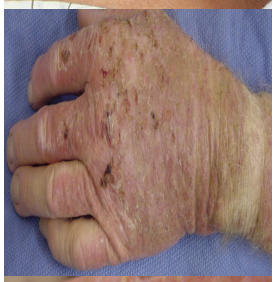
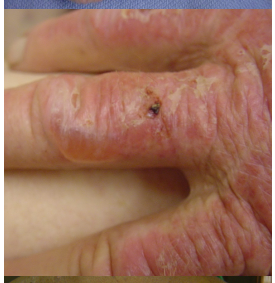
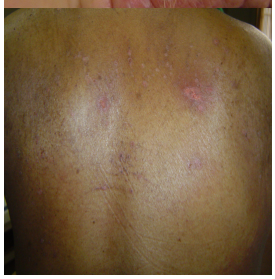


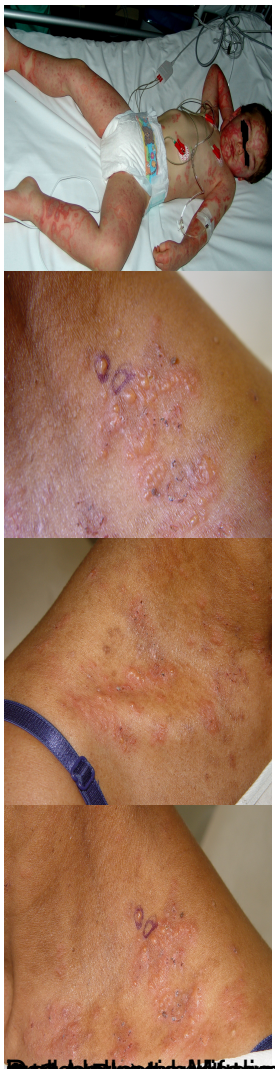


exfoliative psoriasis pattern in a patient taking captopril







## Pathophysiology

Drug eruptions may be divided into immunologically and nonimmunologically mediated reactions.

### Immunologically mediated reactions

Coombs and Gell proposed 4 types of immunologically mediated reactions, as follows:

- Type I is immunoglobulin E (IgE)–dependent reactions, which result in urticaria, angioedema, and anaphylaxis

Type II is cytotoxic reactions, which result in hemolysis and purpura

- Type III is immune complex reactions, which result in vasculitis, serum sickness, and urticaria.
- Type IV is delayed-type reactions with cell-mediated hypersensitivity, which result in contact dermatitis, exanthematous reactions, and photoallergic reactions.

Insulin and other proteins are associated with type I reactions. Penicillin, cephalosporins, sulfonamides, and rifampin are known to cause type II reactions. Quinine, salicylates, chlorpromazine, and sulfonamides can cause type III reactions. Type IV reactions, the most common mechanism of drug eruptions, are often encountered in cases of contact hypersensitivity to topical medications, such as neomycin. Sulfonamides are most frequently associated with toxic epidermal necrolysis (TEN).

Although most drug eruptions are type IV hypersensitivity reactions, only a minority are IgE-dependent. That is, antibodies can be demonstrated in less than 5% of cutaneous drug reactions. Type IV cell-mediated reactions are not dose dependent, they usually begin 7-20 days after the medication is started, they may involve blood or tissue eosinophilia, and they may recur if drugs chemically related to the causative agent are administered.

**Nonimmunologically mediated reactions**

Nonimmunologically mediated reactions may be classified according to the following features: accumulation, adverse effects, direct release of mast cell mediators, idiosyncratic reactions, intolerance, Jarisch-Herxheimer phenomenon, overdosage, or phototoxic dermatitis. (Symptoms of Jarisch-Herxheimer reactions disappear with continued therapy. Drug therapy should be continued until the infection is fully eradicated.)

An example of accumulation is argyria (blue-gray discoloration of skin and nails) observed with use of silver nitrate nasal sprays.

Adverse effects are normal but unwanted effects of a drug. For example, antimetabolite chemotherapeutic agents, such as cyclophosphamide, are associated with hair loss.

The direct release of mast cell mediators is a dose-dependent phenomenon that does not involve antibodies. For example, aspirin and other NSAIDs cause a shift in leukotriene production, which triggers the release of histamine and other mast-cell mediators. Radiographic contrast material, alcohol, cytokines, opiates, cimetidine, quinine, hydralazine, atropine, vancomycin, and tubocurarine also may cause release of mast-cell mediators.

Idiosyncratic reactions are unpredictable and not explained by the pharmacologic properties of the drug. An example is the individual with infectious mononucleosis who develops a rash when given ampicillin.

Imbalance of endogenous flora may occur when antimicrobial agents preferentially suppress the growth of one species of microbe, allowing other species to grow vigorously. For example, candidiasis frequently occurs with antibiotic therapy.

Intolerance may occur in patients with altered metabolism. For example, individuals who are slow acetylators of the enzyme *N* -acetyltransferase are more likely than others to develop drug-induced lupus in response to procainamide.

Jarisch-Herxheimer phenomenon is a reaction due to bacterial endotoxins and microbial antigens that are liberated by the destruction of microorganisms. The reaction is characterized by fever, tender lymphadenopathy, arthralgias, transient macular or urticarial eruptions, and exacerbation of preexisting cutaneous lesions. The reaction is not an indication to stop treatment because symptoms resolve with continued therapy. This reaction can be seen with penicillin therapy for syphilis, griseofulvin or ketoconazole therapy for dermatophyte infections, and diethylcarbamazine therapy for oncocerciasis.

Overdosage is an exaggerated response to an increased amount of a medication. For example, increased doses of anticoagulants may result in purpura.

Phototoxic dermatitis is an exaggerated sunburn response caused by the formation of toxic photoproducts, such as free radicals or reactive oxygen species

## History

The first step is to review the patient's complete medication list, including over-the-counter supplements. Document any history of previous adverse reactions to drugs or foods. Consider alternative etiologies, especially viral exanthems and bacterial infections. Exanthematous eruptions in children are more likely to be due to a viral infection than another infection; however, most such reactions in adults are due to medications.

Note any concurrent infections, metabolic disorders, or immunocompromise (eg, due to HIV infection, cancer, chemotherapy) because these increase the risk of drug eruptions. Immunocompromised persons have a 10-fold higher risk of developing a drug eruption than the general population. Although HIV infection causes profound anergy to other immune stimuli, the frequency of drug hypersensitivity reactions, including severe reactions (eg, TEN), is markedly increased in HIV-positive individuals. Patients with advanced HIV infection (CD4 count <200 cells/µL) have a 10- to 50-fold increased risk of developing an exanthematous eruption to sulfamethoxazole.

Note and detail the following:

- All prescription and over-the-counter drugs, including topical agents, vitamins, and herbal and homeopathic remedies
- The interval between the introduction of a drug and onset of the eruption
- Route, dose, duration, and frequency of drug administration
- Use of parenterally administered drugs, which are more likely than oral agents to cause anaphylaxis
- Use of topically applied drugs, which are more likely than other drugs to induce delayed-type hypersensitivity reactions
- Use of multiple courses of therapy and prolonged administration of a drug, which can cause allergic sensitization
- Any improvement after drug withdrawal and any reaction with readministration

## Physical

Although most drug eruptions are exanthematous, different types of drug eruptions are described.

With every drug eruption, it is important to evaluate for certain clinical features that may indicate a severe, potentially life-threatening drug reaction, such as TEN or hypersensitivity syndrome. Such features include the following:

- Mucous membrane erosions
- Blisters (Blisters herald a severe drug eruption.)
- Nikolsky sign (epidermis sloughs with lateral pressure; indicates serious eruption that may constitute a medical emergency)
- Confluent erythema
- Angioedema and tongue swelling
- Palpable purpura
- Skin necrosis

- Lymphadenopathy
- High fever, dyspnea, or hypotension

Appreciating the morphology and features of drug eruptions is important. This can help the clinician determine the causative medication and the most appropriate treatment.

- Acneiform: This is characterized by inflammatory papules or pustules that have a follicular pattern. They are localized primarily on the upper body. In contrast to acne vulgaris, comedones are absent in acneiform eruptions.
- Acral erythema (erythrodysesthesia): This is a relatively common reaction to chemotherapy and is characterized by symmetric tenderness, edema, and erythema of the palms and soles. It is thought to be a direct toxic effect on the skin. Acral erythema often resolves 2-4 weeks after chemotherapy is discontinued.
- Acute generalized exanthematous pustulosis (AGEP): Acute-onset fever and generalized scarlatiniform erythema occur with many small, sterile, nonfollicular pustules. The clinical presentation is similar to pustular psoriasis, but AGEP has more marked hyperleukocytosis with neutrophilia and eosinophilia. Most cases are caused by drugs (primarily antibiotics) often in the

first few days of administration. A few cases are caused by viral infections, mercury exposure, or UV radiation. AGEP resolves spontaneously and rapidly, with fever and pustules lasting 7-10 days then desquamation over a few days.

- Dermatomyositis like: Cutaneous findings include dermatomyositis (eg, Gottron papules), but patients tend to lack muscle involvement, associated malignancy, and antinuclear antibodies. Improvement is usually noted after the drug is withdrawn.
- DRESS (ie, drug reaction with eosinophilia and systemic symptoms) syndrome or DIHS drug-induced hypersensitivity syndrome: These are characterized by the triad of fever, skin eruption, and internal organ involvement, and they usually are associated with intake of anticonvulsant drugs.
- EM: This includes a spectrum of diseases (eg, EM minor, EM major), as described below; however, many authorities categorize SJS and TEN as EM major and differentiate them by body surface involvement
- EM minor - Overall, this is a mild disease; patients are healthy. It is characterized by target lesions distributed predominantly on the extremities (see the images below). Mucous membrane involvement may occur but is not severe. Patients with EM minor recover fully, but relapses are common. Most cases are due to infection with herpes simplex virus, and treatment and prophylaxis with acyclovir is helpful.

- SJS: This is characterized by widespread skin involvement, large and atypical targetoid lesions, significant mucous membrane involvement, constitutional symptoms, and sloughing of 10% of the skin. SJS can be caused by drugs and infections (especially those due to *Myc oplasma pneumoniae* ).

- SJS/TEN overlap: Epidermal detachment involves 10-30% of body surface area.
-
- TEN: This is a severe skin reaction that involves a prodrome of painful skin (not unlike sunburn) quickly followed by rapid, widespread, full-thickness skin sloughing. It typically affects 30% or more the total body surface area

Secondary infection and sepsis are major concerns, and pneumonia may develop from aspiration of sloughed mucosa. Most cases are due to drugs. The risk of TEN in HIV-positive patients is 1000-fold higher than in the general population.

Erythema nodosum: This is characterized by tender, red, subcutaneous nodules that typically appear on the anterior aspect of the legs. Lesions do not suppurate or become ulcerated (see

the image below). It is a reactive process often secondary to infection, but it may be due to medications, especially oral contraceptives and sulfonamides

- Erythroderma: This is widespread inflammation of the skin (see the image below), and it may result from an underlying skin condition, drug eruption, internal malignancy, or immunodeficiency syndrome. Lymphadenopathy is often noted, and hepatosplenomegaly, leukocytosis, eosinophilia, and anemia may be present.
- Fixed drug eruptions: Lesions recur in the same area when the offending drug is given (see the image below). Circular, violaceous, edematous plaques that resolve with macular hyperpigmentation is characteristic. Lesions occur 30 minutes to 8 hours after drug administration. Perioral and periorbital lesions may occur, but the hands, feet, and genitalia are the most common locations.
- Hypersensitivity syndrome: This is a potentially life-threatening complex of symptoms often caused by anticonvulsants. Patients have fever, sore throat, rash, lymphadenopathy, hepatitis, nephritis, and leukocytosis with eosinophilia. It usually begins within 1-3 weeks after a new drug is started, but it may develop 3 months or later into therapy. Aromatic anticonvulsant drugs cross-react (ie, phenytoin, phenobarbital, carbamazepine); valproic acid is a safe alternative.
- Leukocytoclastic vasculitis: This is the most common severe drug eruption seen in clinical practice (see the image below). It is characterized by blanching erythematous macules quickly followed by palpable purpura. Fever, myalgias, arthritis, and abdominal pain may be present. It typically appears 7-21 days after the onset of drug therapy, and a laboratory evaluation to exclude internal involvement is mandatory.
- Lichenoid: This reaction appears similar to lichen planus and may be severely pruritic (see the image below). The eruption may include eczematous or psoriasiform papules
- Lupus: Drug-induced systemic lupus erythematosus (SLE) produces symptoms identical to those of SLE, but skin findings are uncommon. Lesions are also identical to drug-induced subacute cutaneous lupus erythematosus (SCLE), which is characterized by annular, psoriasiform, nonscarring lesions in a photodistributed pattern.
- Morbilliform or exanthematous: This is the most common pattern of drug eruptions; it is the quintessential drug rash. Exanthem is typically symmetric, with confluent erythematous macules and papules that spare the palms and soles. It typically develops within 2 weeks after the onset of therapy.
- Pseudoporphyria[2] : While largely a drug-induced condition, it can also occur with use of tanning beds and hemodialysis. Patients have blistering and skin fragility that is clinically and pathologically (see the image below) identical to that of porphyria cutanea tarda, but hypertrichosis and sclerodermoid changes are absent and urine and serum porphyrin levels are normal. Treatment is sun protection and withdrawal of the medication.
- Serum sickness and serum sickness–like: These are type III hypersensitivity reactions mediated by the deposition of immune complexes in small vessels, activation of complement, and recruitment of granulocytes. Cutaneous signs typically begin with erythema on the sides of the fingers, hands, and toes and progress to a widespread eruption (most often morbilliform or urticarial). Viscera may be involved, and fever, arthralgia, and arthritis are common. Serum sickness–like reactions have a clinical presentation similar to that of serum sickness reactions, without the immune complex deposition. Renal involvement is rare. Serum sickness–like

reactions usually occur with antibiotic therapy, especially with cefaclor.

- Sweet syndrome (acute febrile neutrophilic dermatosis): Tender erythematous papules and plaques occur most often on the face, neck, upper trunk, and extremities. The surface of the lesions may become vesicular or pustular. Systemic findings are common and include fever (most often), arthritis, arthralgias, conjunctivitis, episcleritis, and oral ulcers. Laboratory evaluation usually reveals an elevated sedimentation rate, neutrophilia, and leukocytosis. Sweet syndrome often occurs in association with cancers, inflammatory disorders, pregnancy, and medication use.
- Urticaria: This usually occurs as small wheals that may coalesce or may have cyclical or gyrate forms. Lesions usually appear shortly after the start of drug therapy and resolve rapidly when the drug is withdrawn
- Vesiculobullous: These reactions can resemble pemphigus, bullous pemphigoid, linear immunoglobulin A (IgA) dermatosis, dermatitis herpetiformis, herpes gestationis, or cicatricial pemphigoid. Most causative drugs have a thiol group, disulfide bonds, or sulfur-containing rings that are metabolized to thiol forms. Thiol-induced pemphigus tends to resemble pemphigus foliaceus or pemphigus erythematosus; nonthiol eruptions may resemble pemphigus vulgaris or pemphigus vegetans. Mucosal findings may be most common with nonthiol drugs. Results from direct and indirect immunofluorescence may be positive in persons with drug-induced pemphigus and bullous pemphigoid. Eruptions usually resolve after the inducing drug is discontinued, but D-penicillamine–induced pemphigus may take months to resolve and corticosteroids are often needed.

Drugs associated with specific morphologic patterns are described below. The following is a list of medications that have been reported to cause specific types of cutaneous reactions. However, not every possible type of drug eruption has been listed. In addition, exclusion of a drug from the following list does not imply that it is not the cause of a patient's eruption. A high index of suspicion must always be maintained when confronted with a new onset eruption in a patient on multiple medications. Note the following:

- Acneiform - Amoxapine, corticosteroids (see the image below), halogens, haloperidol, hormones, isoniazid, lithium, phenytoin, and trazodone

- AGEP - Most commonly beta-lactam antibiotics, macrolides, and mercury; less commonly acetaminophen, allopurinol, bufexamac, buphenine, carbamazepine, carbutamide, celecoxib, chloramphenicol, clindamycin, co-trimoxazole, clobazam, cyclins (eg, tetracycline), cytarabine, diltiazem, famotidine, furosemide, ginkgo biloba, hydrochlorothiazide, hydroxychloroquine, ibuprofen, imatinib, imipenem, isoniazid, IV contrast dye, lopinavir-ritonavir, mexiletine, morphine, nadoxolol, nifedipine, nystatin, olanzapine, phenytoin, pipemidic acid, piperazine, pseudoephedrine, pyrimethamine, quinidine, ranitidine, rifampicin, salbutiamine, sertraline, simvastatin, streptomycin, terbinafine, thallium, vancomycin, calcium channel blockers, ACE inhibitors (eg, captopril, ramipril), glyburide, and gemfibrozil. [5]

- Alopecia - ACE inhibitors, allopurinol, anticoagulants, azathioprine, bromocriptine, beta-blockers, cyclophosphamide, didanosine, hormones, indinavir, NSAIDs, phenytoin, methotrexate (MTX), retinoids, and valproate
- Bullous pemphigoid - Ampicillin, D-penicillamine, captopril, chloroquine, ciprofloxacin, enalapril, furosemide, neuroleptics, penicillins, phenacetin, psoralen plus UV-A, salicylazosulfapyridine, sulfasalazine, and terbinafine
- Dermatomyositislike[6] - BCG vaccine, hydroxyurea (most common), lovastatin, omeprazole, penicillamine, simvastatin, and tegafur
- DRESS syndrome - Most commonly, aromatic anticonvulsants (phenytoin, phenobarbital [phenobarbitone], carbamazepine), sulfonamides, minocycline, and doxycycline [7]
- Erythema nodosum - Echinacea, halogens, oral contraceptives (most common), penicillin, sulfonamides, and tetracycline
- Erythroderma - Allopurinol, anticonvulsants, aspirin, barbiturates, captopril, carbamazepine, cefoxitin, chloroquine, chlorpromazine, cimetidine, diltiazem, griseofulvin, lithium, nitrofurantoin, omeprazole, phenytoin, St. John's wort, sulfonamides, and thalidomide

- Fixed drug eruptions - Acetaminophen, ampicillin, anticonvulsants, aspirin/NSAID, barbiturates, benzodiazepines, butalbital, cetirizine, ciprofloxacin, clarithromycin, dapsone, dextromethorphan, doxycycline, fluconazole, hydroxyzine, lamotrigine, loratadine, metronidazole, oral contraceptives, penicillins, phenacetin, phenolphthalein, phenytoin, piroxicam, saquinavir, sulfonamides, tetracyclines, ticlopidine, tolmetin, vancomycin, and zolmitriptan
- Hypersensitivity syndrome - Allopurinol, amitriptyline, carbamazepine, dapsone, lamotrigine, minocycline, NSAIDs, olanzapine, oxcarbazepine, phenobarbital, phenytoin, saquinavir, spironolactone, sulfonamides, zalcitabine, and zidovudine
- Lichenoid[8] - Amlodipine, antimalarials, beta-blockers, captopril, diflunisal, diltiazem, enalapril, furosemide, glimepiride, gold, leflunomide, levamisole, L-thyroxine, orlistat, penicillamine, phenothiazine, pravastatin, proton pump inhibitors, rofecoxib, salsalate, sildenafil, tetracycline, thiazides, and ursodeoxycholic acid
- Linear IgA dermatosis[9] - Atorvastatin, captopril, carbamazepine, diclofenac, glibenclamide, lithium, phenytoin, and vancomycin
- Lupus erythematosus[10] : Drug-induced SLE is most commonly associated with hydralazine, procainamide, and minocycline. Beta-blockers, chlorpromazine, cimetidine, clonidine, estrogens, isoniazid, lithium, lovastatin, methyldopa, oral contraceptives, quinidine, sulfonamides, tetracyclines, and tumor necrosis factor (TNF)–alpha inhibitors have been reported. Drug-induced SCLE is most commonly associated with hydrochlorothiazide. Calcium channel blockers, cimetidine, griseofulvin, leflunomide, terbinafine, and TNF-alpha inhibitors have been reported.
- Morbilliform (exanthematous) - ACE inhibitors, allopurinol, amoxicillin, ampicillin, anticonvulsants, barbiturates, carbamazepine, cetirizine, ginkgo biloba, hydroxyzine, isoniazid, nelfinavir, NSAIDs, phenothiazine, phenytoin, quinolones, sulfonamides, thalidomide, thiazides, trimethoprim-sulfamethoxazole, and zalcitabine
- Pemphigus[11] : Thiols include captopril, D-penicillamine, gold sodium thiomalate, mercaptopropionylglycine, pyritinol, thiamazole, and thiopronine. Nonthiols include aminophenazone, aminopyrine, azapropazone, cephalosporins, heroin, hydantoin, imiquimod, indapamide, levodopa, lysine acetylsalicylate, montelukast, oxyphenbutazone, penicillins,

phenobarbital, phenylbutazone, piroxicam, progesterone, propranolol, and rifampicin.

- Photosensitivity - ACE inhibitors, amiodarone, amlodipine, celecoxib, chlorpromazine, diltiazem, furosemide, griseofulvin, lovastatin, nifedipine, phenothiazine, piroxicam, quinolones, sulfonamides, tetracycline, and thiazide
- Pseudoporphyria - Amiodarone, bumetanide, chlorthalidone, cyclosporine, dapsone, etretinate, 5-fluorouracil, flutamide, furosemide, hydrochlorothiazide/triamterene, isotretinoin, NSAIDs (including nalidixic acid and naproxen), oral contraceptive pills, and tetracycline
- Psoriasis[12,13,14] - ACE inhibitors, angiotensin receptor antagonists, antimalarials, beta-blockers, bupropion, calcium channel blockers, carbamazepine, interferon (IFN) alfa, lithium, metformin, NSAIDs, terbinafine, tetracyclines, valproate sodium, and venlafaxine

- Serum sickness[15] - Antithymocyte globulin for bone marrow failure, human rabies vaccine, penicillin, pneumococcal vaccine (in AIDS patients), and vaccines containing horse serum derivatives
- Serum sickness–like - Beta-lactam antibiotics, cefaclor (most common), minocycline, propranolol, streptokinase, sulfonamides, and NSAIDs
- SJS[16,17,18] - Allopurinol, anticonvulsants, aspirin/NSAIDS, barbiturates, carbamazepine, cimetidine, ciprofloxacin, codeine, didanosine, diltiazem, erythromycin, furosemide, griseofulvin, hydantoin, indinavir, nitrogen mustard, penicillin, phenothiazine, phenylbutazone, phenytoin, ramipril, rifampicin, saquinavir, sulfonamides, tetracyclines, and trimethoprim-sulfamethoxazole

- Sweet syndrome - All-*trans* -retinoic acid, celecoxib, granulocyte colony-stimulating factor, nitrofurantoin, oral contraceptives, tetracyclines, and trimethoprim-sulfamethoxazole

- TEN - Alfuzosin, allopurinol, anticonvulsants, aspirin/NSAIDs, sulfadoxine and pyrimethamine (Fansidar), isoniazid, lamotrigine, lansoprazole, letrozole, penicillins, phenytoin, prazosin, sulfonamides, tetracyclines, thalidomide, trimethoprim-sulfamethoxazole, and vancomycin
- Urticaria - ACE inhibitors, alendronate, aspirin/NSAIDs, blood products, cephalosporins, cetirizine, clopidogrel, dextran, didanosine, infliximab, inhaled steroids, nelfinavir, opiates, penicillin, peptide hormones, polymyxin, proton pump inhibitors, radiologic contrast material, ranitidine, tetracycline, vaccines, and zidovudine
- Vasculitis - Adalimumab, allopurinol, aspirin/NSAIDs, cimetidine, gold, hydralazine, indinavir, leflunomide, levofloxacin, minocycline, montelukast, penicillin, phenytoin, propylthiouracil, proton pump inhibitors, quinolones, ramipril, sulfonamide, tetracycline, thiazides, and thioridazine
- Vesiculobullous (other) - ACE inhibitors, aspirin/NSAIDs, barbiturates, captopril, cephalosporins, entacapone, estrogen, furosemide, griseofulvin, influenza vaccine, penicillamine, penicillins, sertraline sulfonamides, and thiazides

Psychotropic drugs associated with specific morphologic patterns are as follows[19] :

- Alopecia - Carbamazepine, fluoxetine, lamotrigine, lithium, gabapentin, and valproic acid
- EM - Barbiturates, carbamazepine, diazepam overdose, fluoxetine, gabapentin, lithium

plus trazodone concurrently, phenobarbital, risperidone, sertraline, and valproic acid

- Morbilliform (exanthematous) - Alprazolam, barbiturates, bupropion, carbamazepine, chlorpromazine, desipramine, fluoxetine, lithium, maprotiline, nefazodone, risperidone, and trazodone
- Photosensitivity - All antipsychotics, barbiturates, carbamazepine, chlorpromazine, doxepin, imipramine, thioridazine, and valproic acid
- Pigmentation - Amitriptyline, carbamazepine, chlorpromazine, clozapine, diazepam following dermabrasion, gabapentin, haloperidol, lamotrigine, perphenazine, and thioridazine

- Urticaria - Bupropion, carbamazepine, chlordiazepoxide, fluoxetine, imipramine, lamotrigine, lithium, paroxetine, and trazodone
- Vasculitis - Fluoxetine, maprotiline, paroxetine, and trazodone

Chemotherapeutic agents associated with specific morphologic patterns are as follows:

- Acneiform - Cetuximab,[20] dactinomycin, erlotinib,[20] fluoxymesterone, gefitinib, medroxyprogesterone, and vinblastine

- Acral erythema (erythrodysesthesia) - Capecitabine, cisplatin, clofarabine, cyclophosphamide, cytarabine, docetaxel, doxorubicin, fluorouracil, gemcitabine, MTX, tegafur, and vinorelbine
- Alopecia: All classes of chemotherapeutic agents are associated with alopecia. Commonly associated drugs include alkylating agents, anthracyclines, bleomycin, doxorubicin, hydroxyurea, MTX, mitomycin, mitoxantrone, vinblastine, and vincristine. Busulfan and cyclophosphamide administered in combination can cause permanent hair loss.
- EM - Busulfan, chlorambucil, cyclophosphamide, diethylstilbestrol (DES), etoposide, hydroxyurea, mechlorethamine, MTX, mitomycin C, mitotane, paclitaxel, and suramin
- Erythema nodosum - Busulfan, DES, and imatinib
- Fixed drug eruptions - Dacarbazine, hydroxyurea, paclitaxel, and procarbazine
- Hyperpigmentation - Bischloroethylnitrosourea (BCNU; carmustine), bleomycin, busulfan, brequinar, cisplatin, cyclophosphamide, dactinomycin, daunorubicin, docetaxel, doxorubicin, fluorouracil, fotemustine, hydroxyurea, ifosfamide, MTX, mithramycin, mitoxantrone, nitrogen mustard, procarbazine, tegafur, thiotepa, and vinorelbine
- Lichenoid - Hydroxyurea, imatinib, and tegafur
- Lupus - Aminoglutethimide, DES, hydroxyurea, leuprolide, and tegafur
- Morbilliform (exanthematous) - Bleomycin, carboplatin, *cis* -dichloro-*trans* -dihydroxy-*bis* -isopropylamine platinum (CHIP), chlorambucil, cytarabine, docetaxel, DES, doxorubicin, etoposide, 5-fluorouracil, hydroxyurea, MTX, mitomycin C, mitotane, mitoxantrone, paclitaxel, pentostatin, procarbazine, suramin, and thiotepa

- TEN - Asparaginase, bleomycin, chlorambucil, cladribine, cytarabine, doxorubicin, 5-fluorouracil, MTX, plicamycin, procarbazine, and suramin
- Urticaria[21] - Amsacrine, bleomycin, busulfan, carboplatin, chlorambucil, cisplatin,

cyclophosphamide, cytarabine, daunorubicin, diaziquone, didemnin, DES, docetaxel, doxorubicin, epirubicin, etoposide, 5-fluorouracil, mechlorethamine, melphalan, MTX, mitomycin C, mitotane, mitoxantrone, paclitaxel, pentostatin, procarbazine, teniposide, thiotepa, trimetrexate, vincristine, and zinostatin

- Vasculitis - Busulfan, cyclophosphamide, cytarabine, hexamethylene bisacetamide (HMBA), hydroxyurea, imatinib, levamisole, 6-mercaptopurine, MTX, mitoxantrone, rituximab, and tamoxifen

Cutaneous reactions to targeted chemotherapy are as follows:

- Epidermal growth factor receptor inhibitors (eg, gefitinib, cetuximab, erlotinib[22] - Abnormal scalp, face hair, and/or eyelash growth, anaphylactic infusion reaction (cetuximab), papules and annular plaques (see the images below), paronychia with/without pyogenic granulomas, telangiectasias, and xerosis

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## Medical Care

The ultimate goal is always to discontinue the offending medication if possible. Individuals with drug eruptions are often the most ill patients taking the most medications, many of which are essential for their survival. However, all nonessential medications should be limited. Once the offending drug has been identified, it should be promptly discontinued. Knowledge of the common eruption inducing–medications may help in identifying the offending drug.

Patients can possibly continue to be treated through morbilliform eruptions (ie, continue medication even in patients with a rash). The eruption often resolves, especially if the individual is being treated with antihistamines. Most authorities believe that exanthematous drug eruptions are not a precursor to severe reactions, such as TEN. Nevertheless, all patients with severe morbilliform eruptions should be monitored for mucous membrane lesions, blistering, and skin sloughing.

Treatment of a drug eruption depends on the specific type of reaction. Therapy for exanthematous drug eruptions is supportive in nature. First-generation antihistamines are used 24 h/d. Mild topical steroids (eg, hydrocortisone, desonide) and moisturizing lotions are also used, especially during the late desquamative phase.

Severe reactions, such as SJS, TEN, and hypersensitivity reactions, warrant hospital admission. TEN is best managed in a burn unit with special attention given to electrolyte balance and signs of secondary infection. Because adhesions can develop and result in blindness, evaluation by an ophthalmologist is mandatory. In addition, mounting evidence indicates that intravenous immunoglobulin (IVIG) may improve outcomes for TEN patients.[27,28,29]

Hypersensitivity syndrome, a systemic reaction characterized by fever, sore throat, rash, and internal organ involvement, is potentially life threatening. Timely recognition of the syndrome and immediate discontinuation of the anticonvulsant or other offending drug are crucial. Patients may require liver transplantation if the drug is not stopped in time. Treatment with systemic corticosteroids has been advocated.

## Medication

Therapy for most drug eruptions is mainly supportive in nature. Morbilliform eruptions are treated with oral antihistamines and topical steroids. IVIG is currently the most common agent used to treat TEN. Cyclosporine may also have a role in the treatment of TEN. Prednisone may be used in the treatment of hypersensitivity syndrome with heart and lung involvement, severe serum sickness–like reaction, and Sweet syndrome.

### First-generation antihistamines

These agents antagonize H1 receptors and block release of histamine. They provide symptomatic relief of pruritus and help improve eruptions.

#### Hydroxyzine HCl (Anxanil, Atarax, Atozine, Durrax, Vistaril)

Antagonizes H1 receptors in periphery. May suppress histamine activity in subcortical CNS. Available as 10-, 25-, 50-, or 100-mg tab.

**Adult**

25 mg PO q6h

**Pediatric**

10 mg/5 mL syr, 0.5-1 mg/kg/d PO qid

CNS depression may increase with alcohol or other CNS depressants (eg, meperidine, barbiturates)

Documented hypersensitivity

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**Pregnancy**

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

**Precautions**

Clinical exacerbations of porphyria (may not be safe in porphyria); ECG abnormalities (alterations in T waves) may occur; may cause drowsiness; not recommended in early pregnancy or breastfeeding

### Diphenhydramine HCl (Benadryl, Benylin, Diphen, AllerMax)

For symptomatic relief of allergic symptoms caused by release of histamine in immune reactions.

**Adult**

25-50 mg tab PO q4-6h

**Pediatric**

12.5 mg/5 mL syr, 5 mg/kg/d PO divided q4-6h

Potentiates effect of CNS depressants; because of alcohol content, do not administer syr form to patient taking medications that can cause disulfiramlike reactions

Documented hypersensitivity; MAOIs

**Pregnancy**

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

**Precautions**

May exacerbate angle-closure glaucoma, hyperthyroidism, peptic ulcer, and urinary tract obstruction

## Second-generation antihistamines, nonsedating

These agents cause less, if any, drowsiness than first-generation agents.

### Loratadine (Claritin)

Selectively inhibits peripheral histamine H1 receptors.

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**Adult**

10-20 mg PO qd

**Pediatric**

<2 years: Not established
2-6 years: 5 mg PO qd
>6 years: Administer as in adults

Ketoconazole, erythromycin, procarbazine, and alcohol may increase levels

Documented hypersensitivity

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#### Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

#### Precautions

Start at low dose in renal and liver impairment; caution in breastfeeding

## Corticosteroids

Topical agents provide symptomatic relief of pruritus. Systemic steroids are used in persons with hypersensitivity syndrome, severe serum sickness–like reactions, and Sweet syndrome.

### Desonide

For inflammatory dermatosis responsive to steroids; decreases inflammation by suppressing migration of PMN leukocytes and reversing capillary permeability.

#### Adult

Apply sparingly 2-4 times/d

#### Pediatric

Apply as in adults

None reported

Documented hypersensitivity; fungal, viral, and bacterial skin infections

#### Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

#### Precautions

Prolonged use, application over large surface areas, application of potent steroids, and occlusive dressings may increase systemic absorption and may result in Cushing syndrome, reversible HPA-axis suppression, hyperglycemia, and glycosuria

### Prednisone (Deltasone, Orasone, Sterapred)

Immunosuppressant for treatment of immune disorders; may decrease inflammation by reversing increased capillary permeability and suppressing PMN activity; available in 2.5-, 5-, 10-, 20-, or 50-mg tab.

#### Adult

1-2 mg/kg PO qd initially, taper over 4-6 wk

#### Pediatric

1-2 mg/kg PO qd or divided bid/qid; taper over 2 wk as symptoms resolve

Coadministration with estrogens may decrease clearance; when used with digoxin, digitalis

toxicity secondary to hypokalemia may increase; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics

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Absolute: Systemic fungal infection, herpes simplex keratitis, hypersensitivity (usually with corticotropin but occasionally noted with IV preparations)

Relative: hypertension, active tuberculosis, congestive heart failure, prior psychosis, positive intradermal positive protein derivative text, glaucoma, severe depression, diabetes mellitus, active peptic ulcer disease, cataracts, osteoporosis, recent bowel anastomosis, pregnancy

#### Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

#### Precautions

Abrupt discontinuation may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur

## Immunoglobulins

These agents are used to treat TEN.

### Intravenous immunoglobulin (Gammagard, Gamimune)

Blood product prepared from pooled plasma of healthy donors. Following features are possibly relevant to efficacy: neutralization of circulating myelin antibodies through anti-idiotypic antibodies; down-regulation of proinflammatory cytokines, including IFN-gamma; blockade of Fc receptors on macrophages; suppression of inducer T and B cells and augmentation of T-suppressor cells; blockade of complement cascade; promotion of remyelination; and 10% increase in CSF IgG.

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**Adult**

1 g/kg IV qd for 3 consecutive days

**Pediatric**

Administer as in adults

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