BMJ Best Practice

Common cutaneous drug reactions

Straight to the point of care

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Table of Contents

Summary

Defined as a drug reaction that affects the structure or function of the skin, its appendages, or mucous membranes.

Common adverse skin reactions to systemic drugs include: maculopapular skin reactions; urticaria and angio-oedema; and the spectrum of skin lesions including fixed drug eruptions, erythema multiforme, DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome), Stevens-Johnson syndrome, and toxic epidermal necrolysis. Together these account for the majority of all drug-induced skin manifestations.

Any drug can cause a predictable or unpredictable reaction; those commonly implicated include beta-lactam antibiotics, muscle relaxants used in anaesthesia, sulfonamides and structurally related drugs, contrast media, and gelatins.

Withdrawal of the suspected drug is essential. A history of previous reactions to drugs should always be taken before prescribing.

Skin tests (prick tests, intradermal tests, patch tests) can occasionally be useful in diagnosing allergic reactions retrospectively, especially contact dermatitis.

After anaphylactic reactions, serum tryptase activity can help in diagnosis.

Definition

Cutaneous drug reactions are common.[1] They are adverse drug reactions (ADRs) producing a wide range of skin manifestations. An ADR may be defined as an undesirable clinical manifestation resulting from administration of a particular drug. Another definition is that of an appreciably harmful or unpleasant reaction resulting from an intervention related to using a medicinal product.[2] An ADR may be either immunological (i.e., drug allergy) or non-immunological (i.e., drug intolerance). Drug allergies are estimated to account for <10% of all adverse drug reactions, with drug intolerance accounting for the other 90%.[3] [4]

Adverse reactions usually predict hazard from receiving the drug in the future and warrant prevention, specific treatment, alteration of the dose regimen, or withdrawal of the product. They range from common irritant eruptions to rare, life-threatening drug-induced diseases.

A serious adverse reaction is any untoward medical occurrence that at any dose: results in death; is life threatening; requires or prolongs hospital admission; requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; is a congenital anomaly; or is any medical event that would be regarded as serious if it had not responded to immediate treatment.

The most common skin drug eruptions typically present as pruritus, maculopapular eruptions, urticaria, angio-oedema, phototoxic and photoallergic reactions, fixed drug reactions, vesiculobullous reactions, and exfoliative lesions. These manifestations clinically resemble an allergic response and are considered drug hypersensitivity reactions.[5]

Drug reactions can be solely limited to the skin, or they may be part of a systemic reaction.

Epidemiology

In one US study of 15,438 consecutive medical inpatients, 347 patients had 358 skin reactions, an overall reaction rate of 2.2%.[24] Each had taken a mean of 8 different drugs. Rashes were attributed to 51 drugs, and 75% of the allergic skin reactions were attributed to antibiotics, blood products, and inhaled mucolytics. Amoxicillin (51 reactions per 1000 patients exposed), trimethoprim/sulfamethoxazole (co-trimoxazole; 34 reactions per 1000 patients exposed), ampicillin (33 reactions per 1000 patients exposed), and cephalosporins (13 reactions per 1000 patients exposed) had the highest rates. In a Finnish study, about 30% of reported adverse reactions to systemic drugs involved the skin.[25] Of these, about 46% were maculopapular rashes, 23% urticaria, 10% fixed eruptions, and 5% erythema multiforme. In Mexico, 35 (prevalence of 0.7%) adverse cutaneous drug reactions (ACDR) were seen among 4785 discharged patients.[26] Drugs that were most frequently associated with ACDR were amoxicillin/clavulanate, amphotericin B, and metamizole. The most commonly seen dermatoses were morbilliform rash (51.2%), urticaria (12.2%), and erythema multiforme (4.9%). Six of the 35 cases identified were in patients who had been admitted to hospital due to a severe drug reaction (1.3/1000 patients). One died from complications directly related to the ACDR, representing a 16.6% mortality among those admitted for an ACDR and 0.02% among the global mortality.

In children, cutaneous drug reactions are the most prevalent ADRs in those hospitalised, with an estimated rate of 2% to 3%. In a study of 326 children with cutaneous ADR, L-asparaginase (16%), amoxicillin (8.3%), trimethoprim/sulfamethoxazole (7.2%), carbamazepine (4.9%), and lamotrigine (3.7%) accounted for 40% of all suspected medications.[27]

The rates of reactions to specific drugs are difficult to assess because many are reported only anecdotally.[28] Allergic reactions to beta-lactam antibiotics occur in about 3% of exposed people. Of those who develop a class I allergic reaction to a penicillin, a high proportion cross-react to a cephalosporin; those who have class III reactions have a low risk of cross-reaction.

The risks of contact dermatitis with topical medications are not well described, because most cases are reported anecdotally. The risk of contact dermatitis with topical corticosteroids may be as high as 6%.[29]

Aetiology

Any drug can cause any adverse effect on the skin. Adverse skin reactions are not associated pathognomonically with particular drugs, and no reactions are specific for drug-induced lesions. In most cases, no specific features distinguish patients who are at increased risk of adverse skin reactions. However, some well-described susceptibility factors, including the association between Epstein-Barr virus and cytomegalovirus infection and sensitivity to ampicillin/amoxicillin, infection with HIV, and specific human leukocyte antigen polymorphisms, are well recognised.[30]

Pathophysiology

In most patterns of drug reactions, the pathogenesis is unknown. Classic immune mechanisms do not appear responsible for most adverse drug reactions. However, the rapid reappearance of many reactions on re-exposure strongly suggests immunological memory.

The histological changes in certain lichenoid eruptions and fixed drug eruptions are not pathognomonic, but are sufficiently characteristic to be of importance in differential diagnosis. In lichenoid eruptions, the

presence of focal parakeratosis, focal interruption of the granular layer, and cytoid bodies in the cornified and granular layers suggest a drug cause.[31] In the late phase of fixed eruptions, there is increased melanin in the epidermis and within melanophages in the dermis.

It is impossible to identify an offending drug on the basis of histopathology or clinical appearances alone. The drug-induced forms of skin lesions are often indistinguishable from non-drug-induced forms. However, a peripheral blood eosinophilia and tissue infiltration of eosinophilic polymorphonuclear leukocytes may suggest a drug-induced lesion.

Classification

Rawlins and Thompson pharmacological classification

The traditional classification of adverse drug reactions (ADRs) divides these into 2 major subtypes: type A reactions, which are dose-dependent and predictable, and type B, which are neither.[6] The majority of ADRs are predictable (type A) reactions. Unpredictable (type B) reactions include drug hypersensitivity reactions (DHRs). Predictable ADRs are usually dose-related and a function of the known pharmacological actions of the drug. Unpredictable reactions are dose-independent and not related to the pharmacological action of the drug. They may have a basis in pharmacogenetic variation, or in drug or metabolite detoxification or clearance.[7] However, this classification is likely to become obsolete as it is increasingly recognised that genetic factors such as human leukocyte antigen (HLA) alleles may predict hypersensitivity reactions, such as that seen with abacavir in those who are HLA-B*5701 carriers.[8]

Traditional classification of adverse drug reactions (still applies to most scenarios):[9]

Unpredictable

- Non-immunological
    - Idiosyncrasy
    - Intolerance
- Immunological
    - IgE-dependent drug reactions
    - Immune complex-dependent drug reactions
    - Cytotoxic drug-induced reactions
    - Cell-mediated reactions.

Predictable

- Non-immunological
    - Accumulation
    - Delayed toxicity
    - Drug interactions
    - Chromosomal damage
    - Exacerbation of disease
    - Facultative effects
    - Metabolic alterations
    - Activation of effector pathways

- Overdose
- Side effects
- Teratogenicity.

Gell and Coombs classification of immunological reactions[10]

Delineates 4 types of immunological reaction:

- Type I: acute IgE-mediated reactions that cause mast cell degranulation (e.g., urticaria, angio-oedema, anaphylactic reactions)
- Type II: cytotoxic reactions, due to antigen-antibody interactions that result in local production of anaphylotoxin (C5a), recruitment of polymorphonuclear leukocytes, and tissue injury due to the release of hydrolytic neutrophil enzymes (e.g., vasculitis, thrombocytopenic purpura)
- Type III: delayed immune complex reactions, in which antigen-antibody complexes are formed in the circulation and deposited in the tissues (e.g., maculopapular rashes, interstitial nephritis)
- Type IV: cell-mediated or delayed hypersensitivity reactions, in which T-lymphocytes are sensitised by a hapten-protein antigenic complex and inflammation results (e.g., contact dermatitis).

Allergy nomenclature

Drug reactions are classified as immunological (allergic or hypersensitivity) or non-immunological (nonallergic). When immunological mechanisms have been demonstrated, either antibody or cell-mediated, the reactions should be referred to as drug allergy.[11]

Allergic reactions are further classified as IgE mediated and non-IgE mediated.

Types of adverse skin reaction to systemic drugs

- Allergic skin reactions to systemic drugs include maculopapular skin rashes, urticaria, and angio-oedema. The spectrum of skin lesions includes fixed drug eruptions, erythema multiforme, DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome), Stevens-Johnson syndrome, and toxic epidermal necrolysis. Together these account for most drug-induced skin manifestations.
- Non-allergic reactions include acneiform eruptions; alopecia; bullous eruptions - pemphigus and pemphigoid; photosensitivity and phototoxicity reactions; purpura due to various causes; pustular eruptions (e.g., acute generalised exanthematous pustulosis); Sweet's syndrome (acute febrile neutrophilic dermatosis); and various forms of vasculitis. Contact dermatitis is common after the use of topical drugs and cosmetics.

Case history

Case history #1

A 73-year-old woman was given intravenous vancomycin to treat *Staphylococcus aureus* osteomyelitis; 20 days into treatment she developed a generalised maculopapular exanthem with intense pruritus, malaise, and fever.[12] Blood biochemistry showed transaminitis. Vancomycin was withdrawn and prednisolone was prescribed. Her condition improved and resolved over 12 days.

Other presentations

There are a wide variety of clinical presentations due to adverse drug reactions (non-allergic reactions), including, for example: brown discoloration of the nails, particularly affecting the thumbs, caused by a 15-day course of doxycycline;[13] and a blue-grey discoloration of the face and other exposed areas, caused by amiodarone taken for 3 years. In the latter case study, protected areas, such as the forehead by a broad-brimmed hat and the skin under a wrist watch, were not affected.[14]

A high incidence of rashes in patients with cancers has been reported in those taking tyrosine kinase inhibitors including erlotinib, nilotinib, and vandetanib, and an increased risk of hand-foot skin reaction (palmar-plantar erythrodysaesthesia) has been reported in patients taking vascular endothelial growth factor receptor inhibitors including sorafenib, sunitinib, pazopanib, and axitinib.[15] [16] [17] [18] [19] The risk of rash is also high in HER2-positive metastatic breast cancer patients taking the HER2/neu receptor antagonist pertuzumab, and for ipilimumab, which is used for melanoma.[20] [21] Psoriasis, either de novo or worsened, can occur paradoxically with beta-blockers and TNF-alpha inhibitors.[22] Acne-like rashes have been reported in patients receiving epidermal growth factor receptor antagonists, such as cetuximab.[23]

Approach

In most cases, there is no definitive method for making a diagnosis of a drug-related adverse reaction. In some cases, the probability that a drug has caused a clinical outcome can be assessed by considering certain features of the drug in relation to the adverse reaction. These include dose, time, and susceptibility factors. Most combine 5 criteria: challenge, dechallenge, rechallenge, previous description in the medical literature, and consideration of other possible causes. If feasible, these help to clarify the relation of the reaction to a specific drug. If in doubt, further testing will help to clarify the presence of a drug-induced reaction as well as the cause.

Age is not a helpful feature because drug-induced skin lesions can occur at any age.

The first step in evaluating a potential drug reaction is to diagnose the cutaneous eruption by clinical pattern. In determining whether the patient's current eruption could be related to a specific medication, the association increases when the use and frequency of this pattern of reaction with the drug has been determined.

Features of reaction types

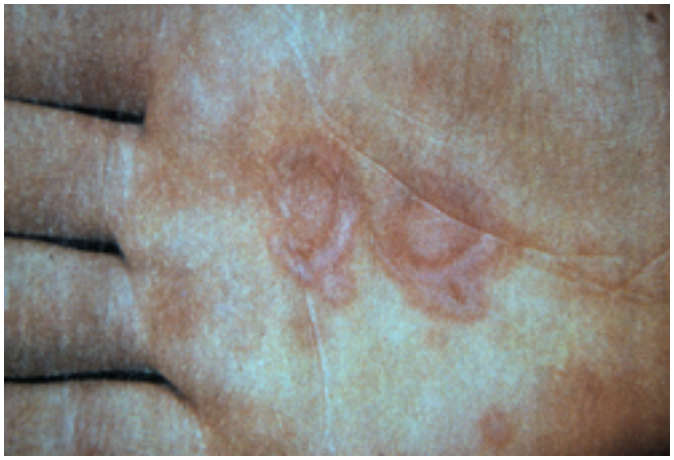
Anaphylactic reactions, whether immunoglobulin E (IgE)-mediated or non-IgE-mediated, present with a range of signs and symptoms, depending on the intensity of the reaction. These include rhinitis and conjunctivitis; urticaria and pruritus; angio-oedema and laryngeal oedema; asthma and pulmonary oedema; nausea, vomiting, and abdominal pain; faintness, lightheadedness, and a sense of impending doom; and tachycardia and hypotension (anaphylactic shock).

Erythema multiforme presents with a wide range of polymorphous, and often painful, erythematous. Maculopapular lesions are widely spread, so-called target lesions are typical, and less than 10% of the body is affected. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), regarded by some as severe forms of erythema multiforme, involve respectively up to 10% and over 30% of the body surface area. In SJS, vesicles and large blisters can occur in the mucous membranes of the eyes and mouth. In TEN there is widespread desquamation. However, some regard erythema multiforme as a separate condition and distinguish minor and major erythema multiforme from SJS/TEN.

In DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome) there is a maculopapular rash, fever over 38°C (100°F), abnormal liver function tests or evidence of other organ involvement, lymphadenopathy in at least 2 sites, and blood count abnormalities (lymphocytopenia or lymphocytosis, eosinophilia, or thrombocytopenia).[35]

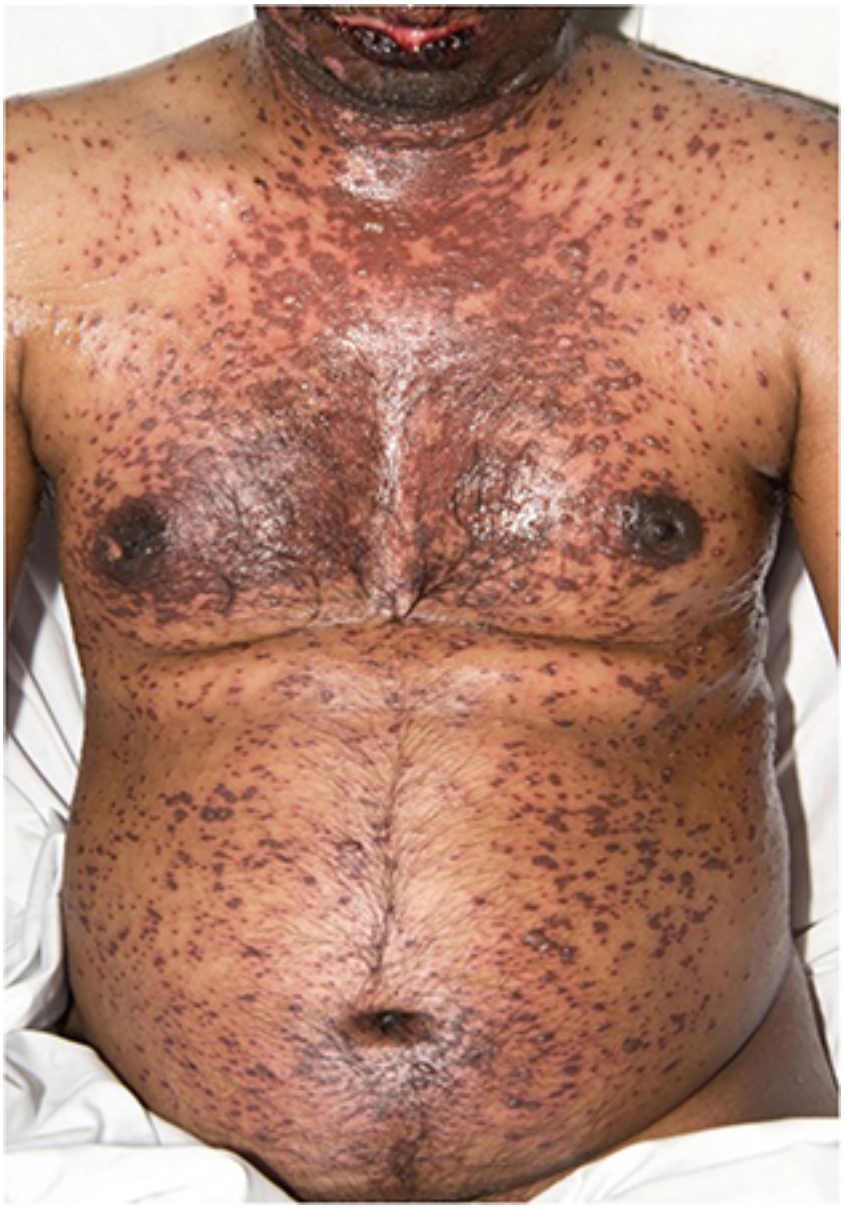
Acute generalised exanthematous pustulosis is characterised by fever and widespread small sterile pustules within large areas of oedematous erythema.[36]

Fixed drug eruptions are variable in presentation. Most commonly there is a pruritic, round or oval, sharply demarcated, red or purple, slightly raised plaque of variable size. There is usually only a single lesion, but multiple lesions can occur. A generalised reaction is rare and can include vesicles and blisters. The lips, hands, and genitalia are typically affected, and occasionally the oral mucosa.[37]



Palmar target lesions in erythema multiforme

From the personal collection of Nanette Silverberg, MD, FAAD, FAAP



Blistering targetoid lesions on the trunk, carbamazepine induced Stevens-Johnson syndrome

Khoo AB, Ali FR, Yiu ZZ, et al. Carbamazepine induced Stevens-Johnson syndrome. BMJ Case Rep. 2016;2016. pii: bcr2016214926. Used with permission

Oral and mucosal ulcerations, carbamazepine induced Stevens-Johnson syndrome

Khoo AB, Ali FR, Yiu ZZ, et al. Carbamazepine induced Stevens-Johnson syndrome. BMJ Case Rep. 2016;2016. pii: bcr2016214926. Used with permission

Lesion identification

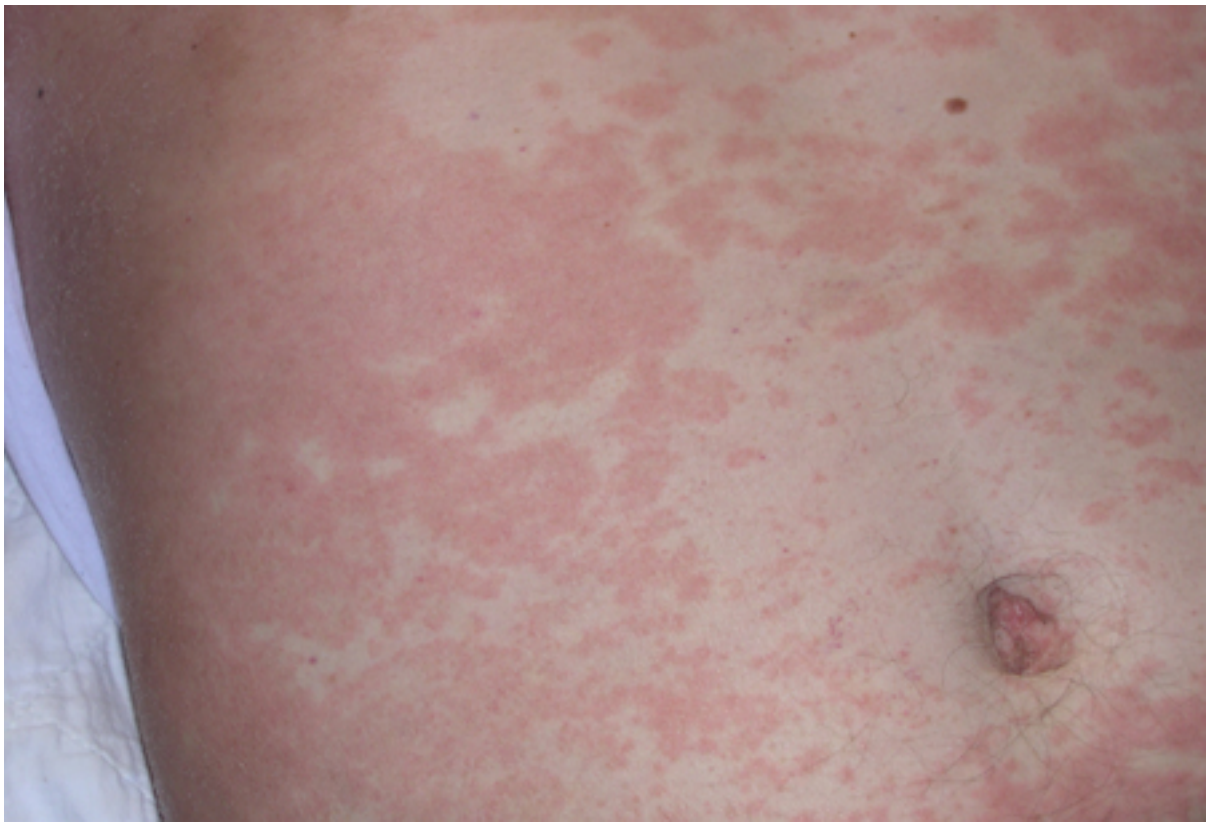
Adverse drug reactions can cause any type of skin lesion. Common adverse skin reactions to systemic drugs include maculopapular skin reactions, urticaria and angio-oedema, the spectrum of skin lesions encompassing erythema multiforme (EM), SJS, and TEN; and fixed drug eruptions. EM can be described as annular erythematous rings with an outer erythematous zone and central blistering sandwiching a zone of normal skin tone. SJS is generally regarded as on a spectrum of disease with TEN (most severe). SJS is characterised by severe macular (atypical target) lesions that coalesce, resulting in epidermal blistering, necrosis, and sloughing; <10% of total body surface area is affected, and SJS can present with only mucosal involvement (e.g., in the conjunctivae and mucous membranes of the mouth). TEN is also characterised by severe macular (atypical target) lesions that coalesce, resulting in epidermal blistering, necrosis, and sloughing, but >30% of total body surface area is affected.

Less common reactions include acneiform eruptions, alopecia, bullous eruptions (pemphigus and pemphigoid), photosensitivity and phototoxicity reactions, purpura due to various causes, pustular eruptions (e.g., acute generalised exanthematous pustulosis), Sweet's syndrome (acute febrile neutrophilic dermatosis), and various forms of vasculitis. Contact dermatitis arises after the use of topical drugs and cosmetics.

DRESS, which is rare, is a systemic disease that can occur after exposure to many drugs, including anticonvulsants and sulfonamides. It usually occurs 1 to 8 weeks after exposure and consists of fever, a skin eruption, and multi-organ involvement. It may be one of a spectrum of allergic disorders that include

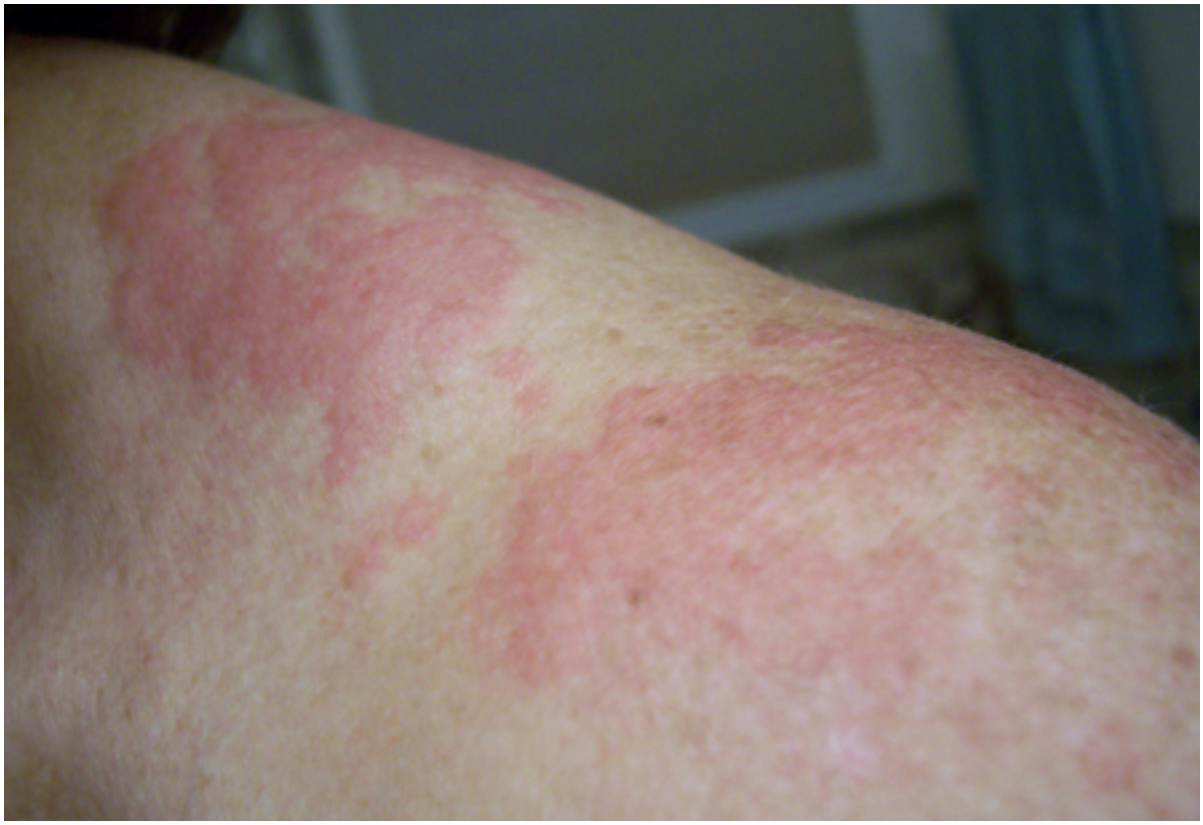
such conditions as drug-induced hypersensitivity syndrome, sulfonamide syndrome, and anticonvulsant hypersensitivity syndrome. It has been associated with infection with human herpesvirus-6.[38]

Pruritus and pain, although symptoms of an adverse drug reaction, are indistinguishable from those occurring in non-drug-induced lesions.



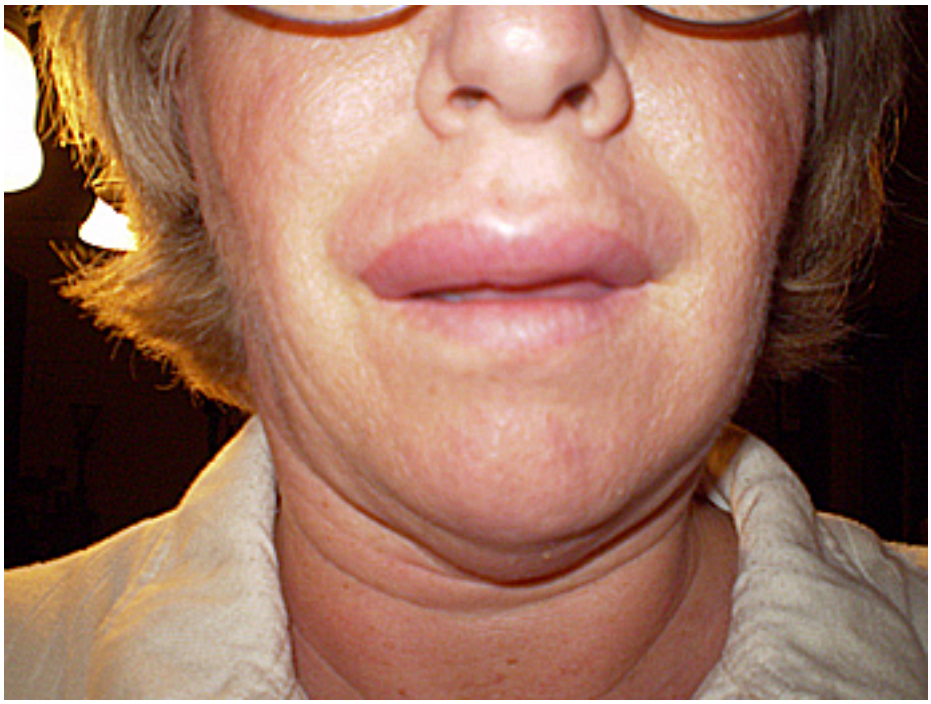
Drug exanthem due to phenytoin

Photography courtesy of Brian L. Swick



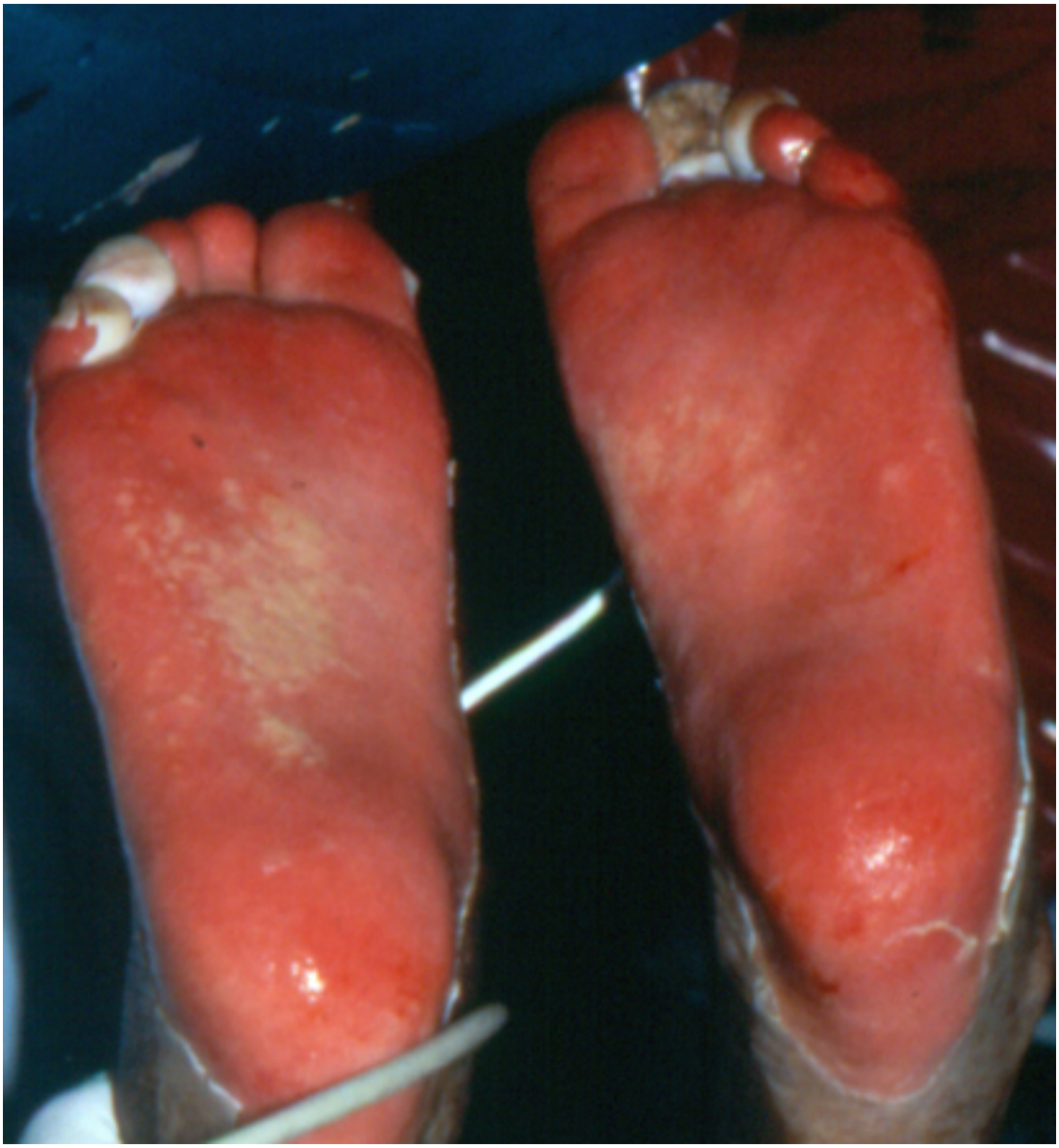
Typical lesions seen in acute or chronic urticaria

From the personal collection of Stephen Dreskin, MD, PhD



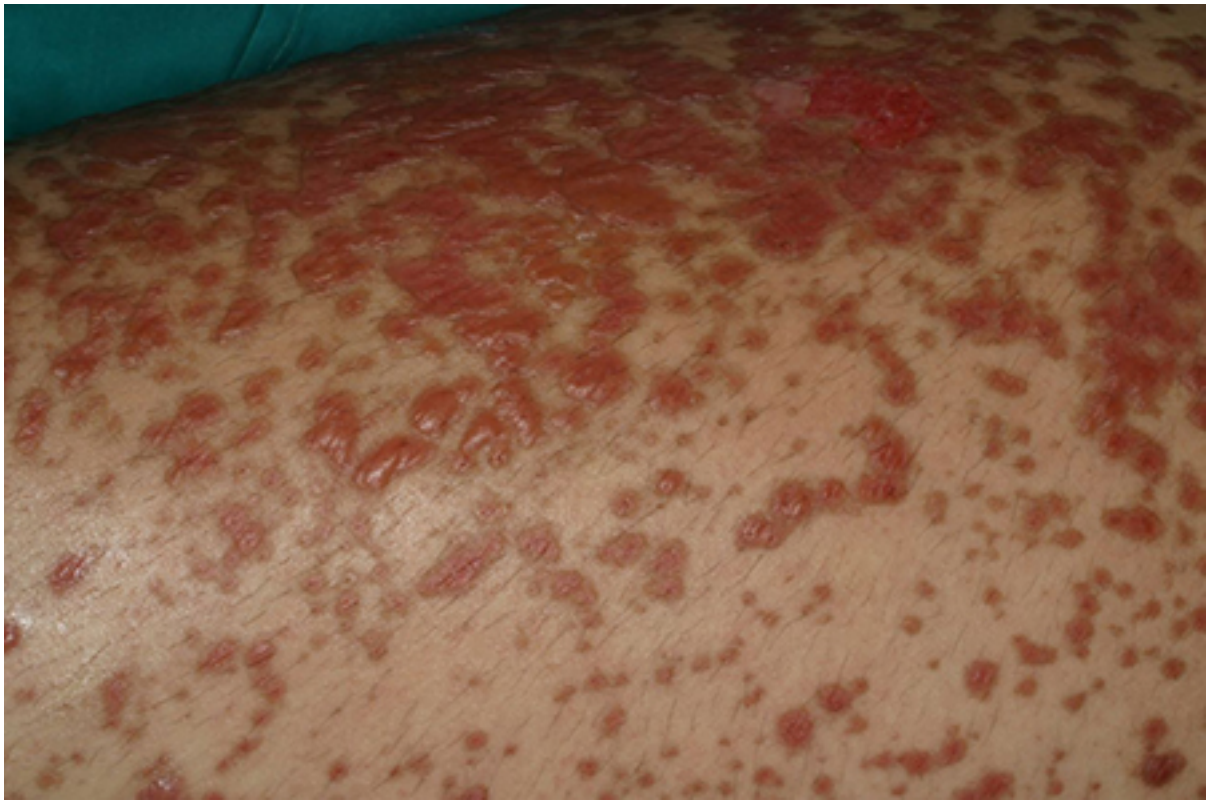
Angio-oedema of the lips in a patient who also has urticaria

From the personal collection of Stephen Dreskin, MD, PhD



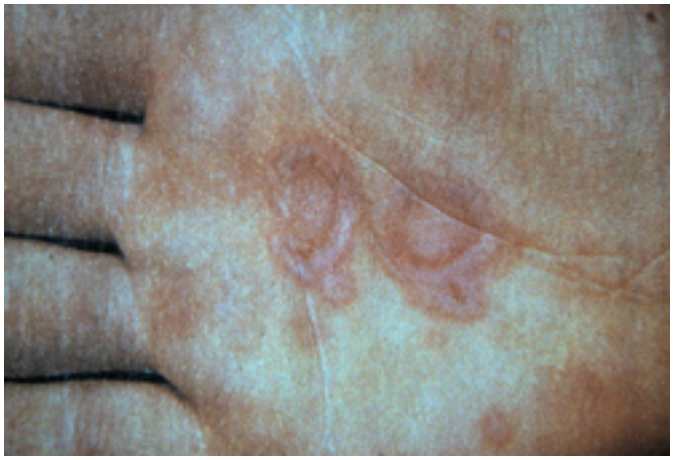
Stevens-Johnson syndrome: epidermal loss on soles of feet

From the personal collection of Areta Kowal-Vern, MD



Initial phase of toxic epidermal necrolysis with diffuse erythema and vesicles that will evolve to full epidermal necrosis

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission



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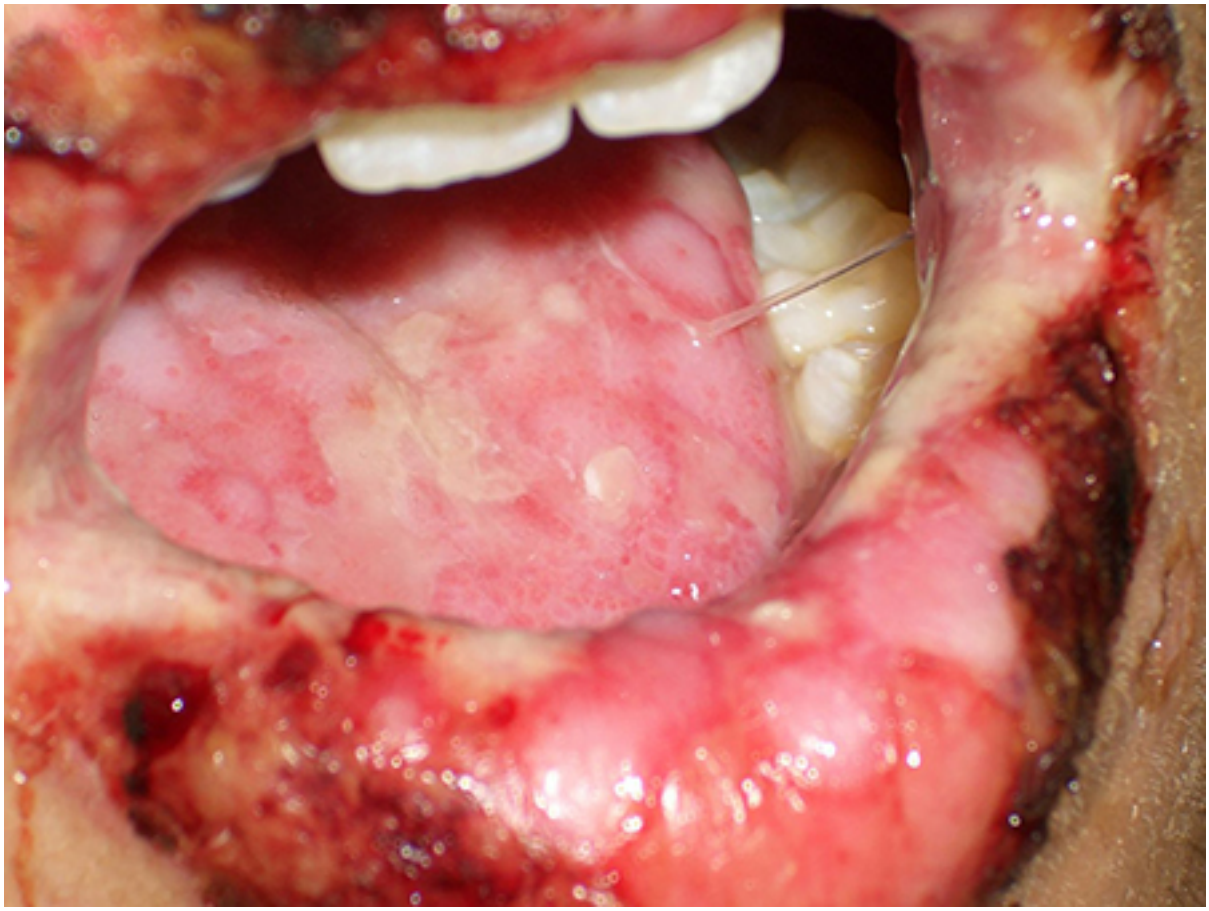
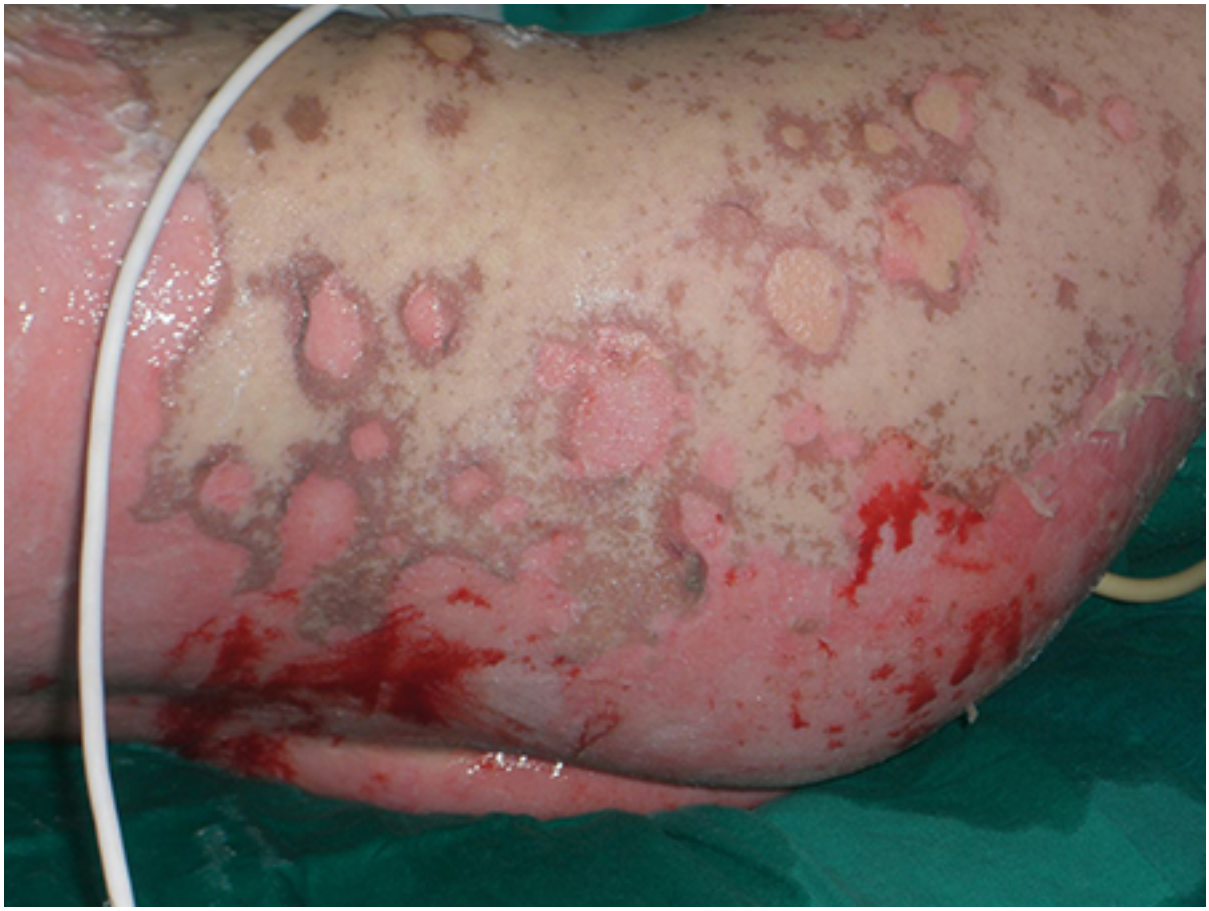


A 17-year-old male patient diagnosed with Stevens-Johnson syndrome due to azitromicine. Erosions and crusts on the lips with diffuse ulcers on the tongue

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission



A 5-year-old female patient with toxic epidermal necrolysis with three suspected drugs (penicillin, ibuprofen, and paracetamol)

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission

Time course

For initiation (priming), drug-hypersensitivity reactions require 5 to 7 days of exposure. Frequently, hypersensitivity reactions arise later than this (e.g., DRESS commonly arises after 3 to 4 weeks of therapy). After sensitisation, on subsequent exposure, hypersensitivity reactions within minutes for IgE-mediated allergic reactions and within hours for T-cell-mediated hypersensitivity reactions. Therefore, exposure time is central in establishing causality. Non-immune hypersensitivity reactions arise with a very variable time course and a few reactions occur very late, for example, lichenoid eruptions, which can take months or years to develop.[39]

History

In all cases, a full drug history, including dietary supplements and alternative medications, should be taken. Exposure to a drug within the previous few minutes or hours (acute allergic reactions) or up to 2 weeks before should suggest the possibility of a drug-induced lesion. Any drug can cause an allergic reaction; beta-lactam antibiotics, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants used in anaesthesia, sulfonamides and related drugs, contrast media, and gelatins (plasma substitutes) are commonly implicated. A previous similar reaction strengthens the likelihood of an association with a specific drug.

Hypersusceptibility reactions are dose-related at doses below the usual therapeutic range but not at doses within the therapeutic range. Collateral reactions occur at doses within the therapeutic range and the severity of the reaction varies with dose, while toxic reactions occur at doses above the therapeutic range. Lowering the dose (i.e., partial dechallenge) may result in disappearance of the adverse reaction. The absence of a dose-related reaction in the therapeutic range of doses suggests either a hypersusceptibility reaction or a cause other than a drug.[40]

Susceptibility factors

If the patient has a known susceptibility factor for an association between the suspected drug and the adverse event, a causative association is more likely.

Patients with the following history may have a higher rate of reactions to certain medications:

- Cytomegalovirus or Epstein-Barr virus infections increase the risk of ampicillin and amoxicillin rash.
- HIV infection increases the risk of hypersensitivity reactions to sulfonamides and structurally related compounds.
- Specific human leukocyte antigen polymorphisms increase the risk of abacavir-, carbamazepine-, and allopurinol-induced reactions.
- Adverse drug reactions to the Chinese medicine Shuanghuanglian injection are more likely in individuals with previous reactions to penicillins or sulfonamides.[41]

Dechallenge and rechallenge

Disappearance of the lesion after withdrawal of a suspected drug (dechallenge) increases the probability of a causative association; failure to resolve after withdrawal is against the diagnosis. However, non-drug-induced skin lesions can resolve coincidentally after withdrawal of a drug, and drug-induced lesions can persist despite drug withdrawal.

Recurrence of the lesion after rechallenge, if feasible, strongly suggests a drug-induced lesion. In cases of fixed drug eruption, the lesion will reappear at the same site and in the same form.

However, systemic rechallenge is not advised after allergic reactions. Drug challenges are generally contraindicated after severe cutaneous adverse reactions (DRESS, SJS/TEN, acute generalised exanthematous pustulosis) and other more severe non-IgE-mediated reactions (e.g., drug-induced liver injury or cytopenias).[42] Guidelines recommend shared decision making if the benefit of the drug outweighs the risk of performing a challenge in patients with a higher probability of true allergy or a history of more severe reactions.[42] In some cases, rechallenge can be placebo controlled, for example, photoallergic contact dermatitis might be reproduced by applying the suspected drug to skin on one side of the body and a placebo on the other and exposing both areas to light. Guidelines recommend considering placebo-controlled drug challenges for patients with subjective symptoms or multiple reported drug allergies.[42]

Rechallenge recommendations are available for specific drugs and drug classes (e.g., antibiotics, non-steroidal anti-inflammatory drugs, chemotherapy drugs, immune checkpoint inhibitors, biologicals).[42] [43][44]

Confirmation of drug-induced adverse reaction

In a few cases, histological features of the lesion may suggest a drug-related cause. Infiltration of eosinophilic polymorphonuclear leukocytes may suggest a drug-induced lesion.

The following tests are indicated to confirm specific conditions.

- Serum tryptase concentration is raised during the first few hours after an anaphylactic reaction.[45] [46]
- C4 measures should be taken during an attack in angio-oedema alone (no urticaria). If C4 is low, C1-esterase levels should be measured. Occasionally, C1-esterase function needs to be measured if the enzyme is not low but inactive.
- Full blood count is usually normal in drug-induced lupus, in contrast to abnormal findings in systemic lupus erythematosus. In drug-induced lupus, anti-histone antibodies are found.

Skin tests (prick tests, intradermal tests, patch tests) can occasionally be useful in diagnosing allergic reactions retrospectively, especially contact dermatitis. Skin tests may also be useful adjuncts for establishing causality and cross-reactivity for delayed hypersensitivity reactions.[42] However, skin tests are limited by low sensitivity and thus results should be interpreted with caution, particularly in the setting of severe reactions given the imperfect negative predictive value. Due to the risk of relapse, skin tests for DRESS should be delayed for at least 6 months after the acute reaction and/or 1 month after discontinuation of corticosteroids.[42]

In vitro tests such as drug-specific IgE, basophil activation test, lymphocyte proliferation assay, and enzyme-linked immunospot assay (ELISPOT test) can be helpful, particularly in the case of negative skin tests or severe life-threatening reactions (e.g., anaphylactic reactions to beta-lactam antibiotics).[47] [48] However, these tests are largely research tools at present and should be interpreted only in conjunction with patient history and clinical findings; specialist advice should be sought.

Other identifiable causes

Identification of another cause may allow a drug-induced cause to be ruled out.

The Naranjo scoring system

Some diagnostic features of common cutaneous drug reactions have been summarised in the Naranjo scoring system.[49]

The following scores give the likelihoods of an adverse reaction:

- ≥9 = definite
- 5 to 8 = probable
- 1 to 4 = possible
- 0 = doubtful.

	Yes	No	Don't know
1. Previous conclusive reports of an association between drug and effect	+1	0	0
2. The adverse event occurred after the drug was given	+2	–1	0
3. It improved after withdrawal or administration of a specific antagonist	+1	0	0
4. It recurred when the drug was given again	+2	–1	0
5. There are alternative possible causes	–1	+2	0
6. It occurred when a placebo was given	–1	+1	0
7. The drug was detected in the blood in a toxic concentration	+1	0	0
8. The reaction was more/less severe at a higher/lower dose	+1	0	0
9. The patient had a similar reaction to the same or a similar drug before	+1	0	0
10. Supporting objective evidence that the drug was to blame	+1	0	0

The Naranjo scoring system

Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-245

The Bradford Hill guidelines

Austin Bradford Hill outlined some of the diagnostic features of common cutaneous drug reactions as guidelines for suggesting cause and effect.[50] These guidelines have been adapted and renamed as follows:[51]

Direct evidence

1. Size of effect not attributable to plausible confounding
2. Appropriate temporal and/or spatial proximity (cause precedes effect and effect occurs after a plausible interval; cause occurs at the same site as the intervention)
3. Dose responsiveness and reversibility.

Mechanistic evidence

- Evidence for a mechanism of action (biological, chemical, mechanical)
- Coherence (with current scientific knowledge).

Parallel evidence

- Replicability (i.e., rechallenge)
- Similarity (to previous reactions).

This system can be used to help clinicians decide whether causality is likely in an individual case; the more criteria that are fulfilled, the more likely the association.

DIAGNOSIS

History and exam

Key diagnostic factors

presence of risk factors (common)

- Anyone can develop an adverse cutaneous reaction to a drug. Key risk factors to certain drugs or reactions include history of hereditary angio-oedema (allergic type I reactions), cytomegalovirus and

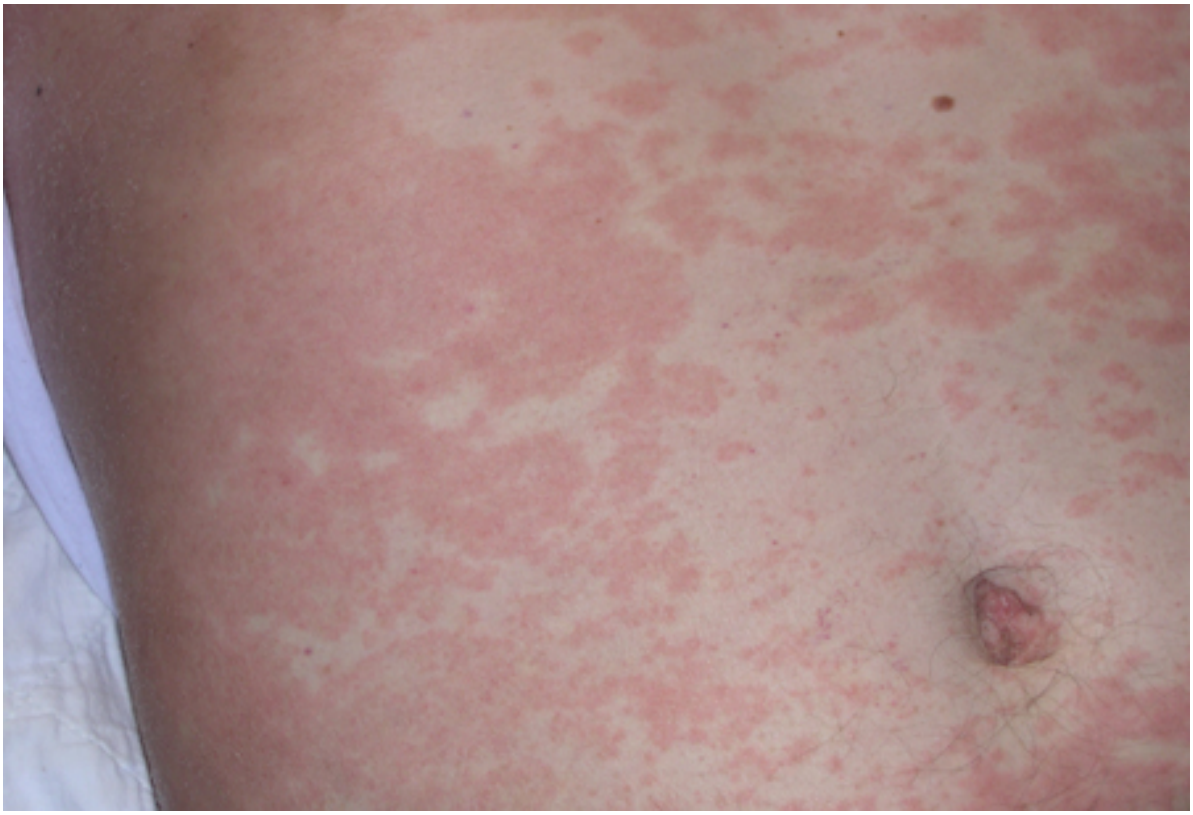
Epstein-Barr virus infections or lymphoid malignancy (ampicillin and amoxicillin rash), HIV infection (hypersensitivity to sulfonamides and related compounds), HLA-B*5701 polymorphism (abacavir-induced skin hypersensitivity reactions), HLA-B*1502 polymorphism (carbamazepine-induced skin hypersensitivity reactions), and HLA-B*5801 polymorphism (allopurinol-induced skin reactions).

history of drug exposure (common)

- Exposure to a drug within the previous few minutes or hours (acute allergic reactions) or up to 2 weeks before suggests the possibility of a drug-induced lesion.
- Any drug can cause an allergic reaction; commonly implicated are beta-lactam antibiotics, non-selective non-steroidal anti-inflammatory drugs, muscle relaxants used in anaesthesia, sulfonamides and structurally related drugs, contrast media, and gelatins.

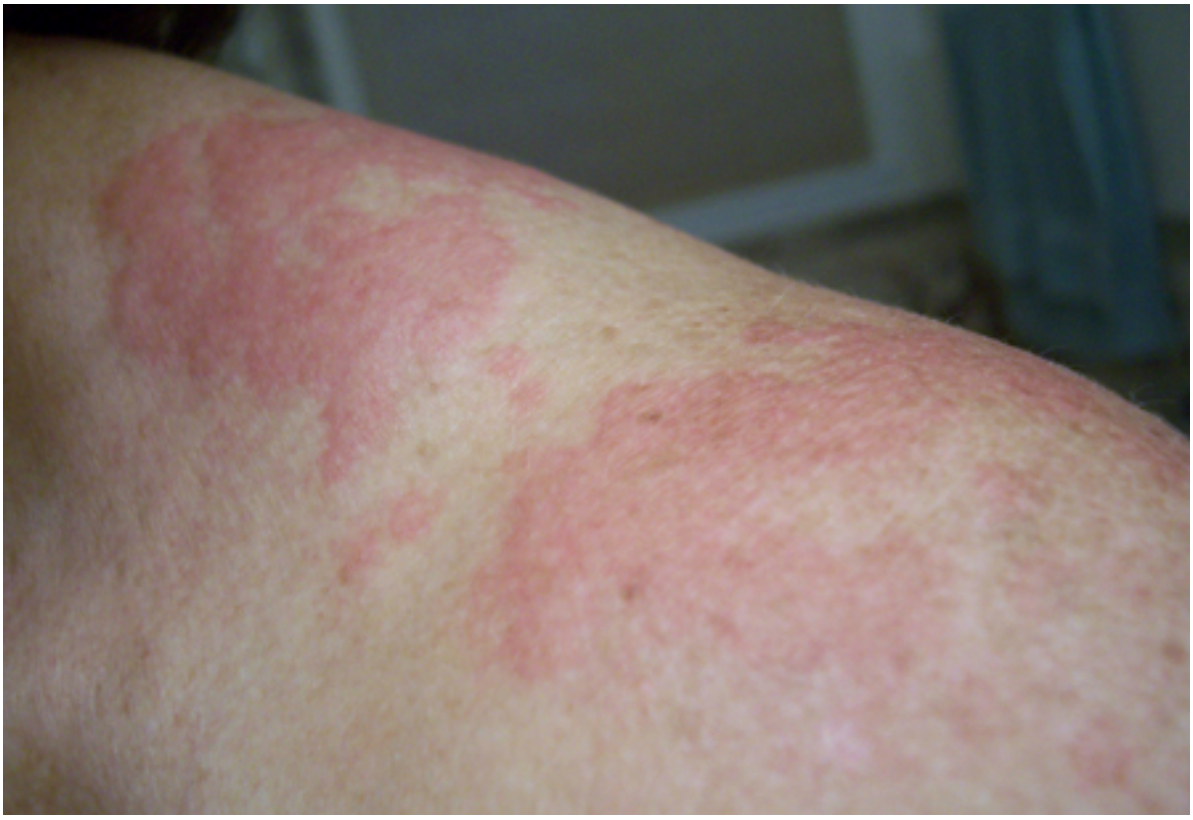
skin lesions (common)

- Adverse drug reactions can cause any type of skin lesion. Common adverse skin reactions to systemic drugs include maculopapular skin reactions; urticaria and angio-oedema; the spectrum of skin lesions encompassing erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis; and fixed drug eruptions. Together these account for the majority of all drug-induced eruptions. More severe reactions, such as toxic epidermal necrolysis and drug hypersensitivity syndrome, can initially present as morbilliform eruptions.
- Macroscopic appearances of drug-induced skin lesions are indistinguishable from those of non-drug-induced lesions.



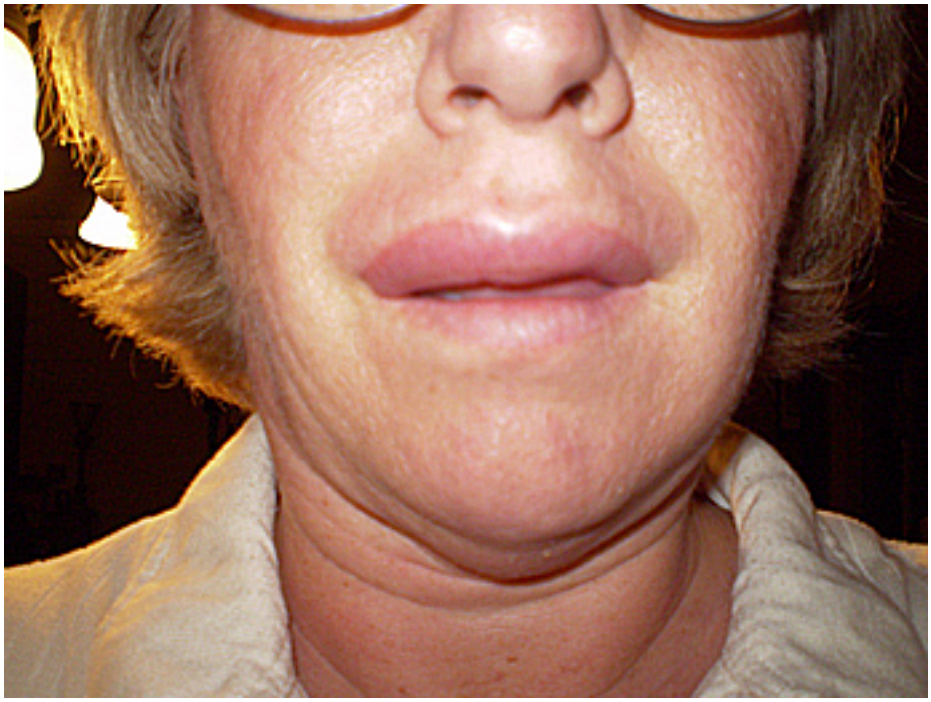
Drug exanthem due to phenytoin

Photography courtesy of Brian L. Swick



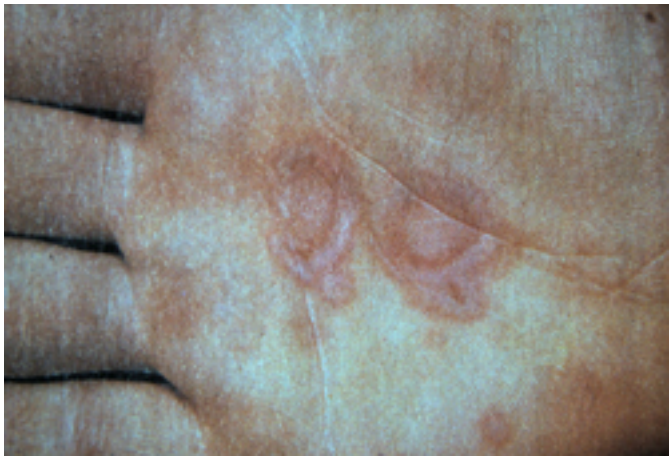
Typical lesions seen in acute or chronic urticaria

From the personal collection of Stephen Dreskin, MD, PhD



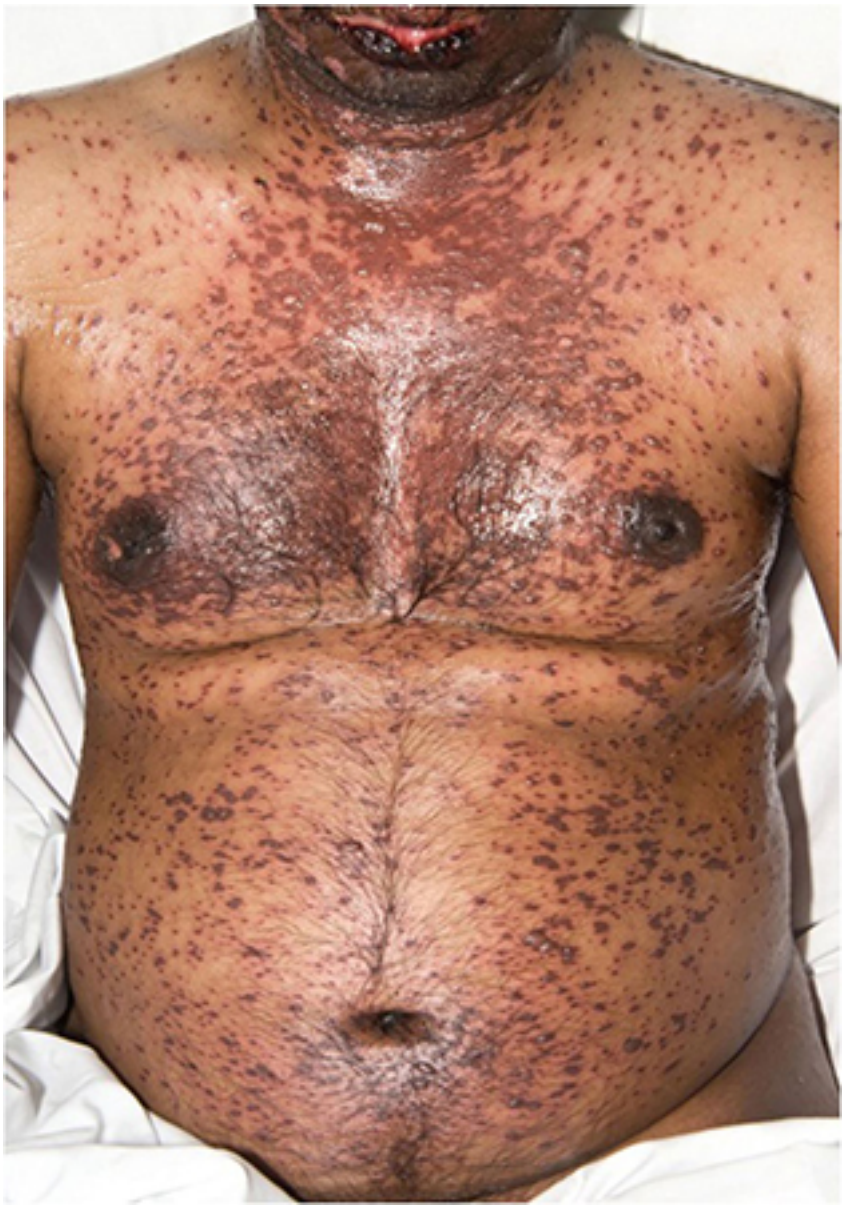
Angio-oedema of the lips in a patient who also has urticaria

From the personal collection of Stephen Dreskin, MD, PhD



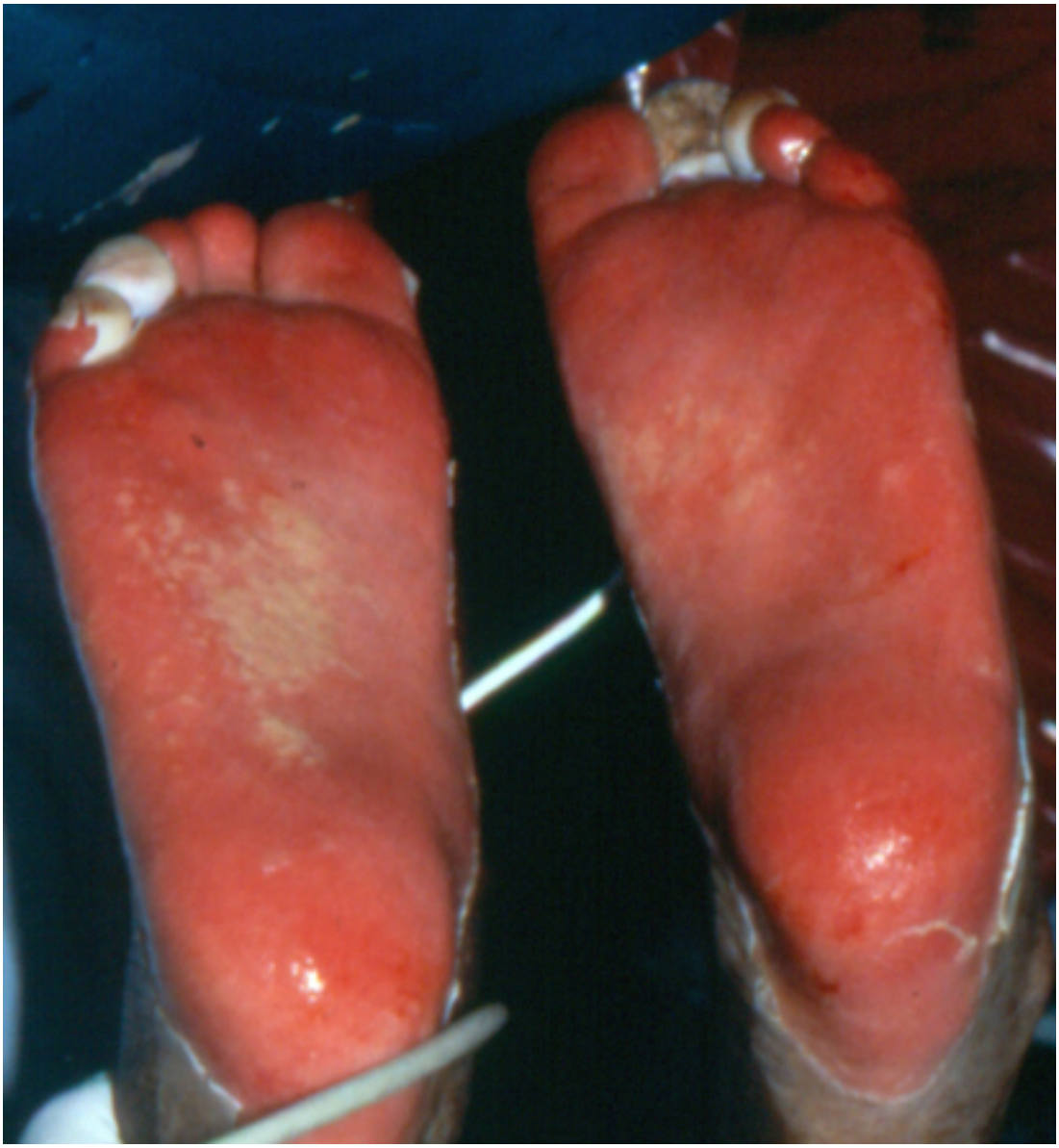
Palmar target lesions in erythema multiforme

From the personal collection of Nanette Silverberg, MD, FAAD, FAAP



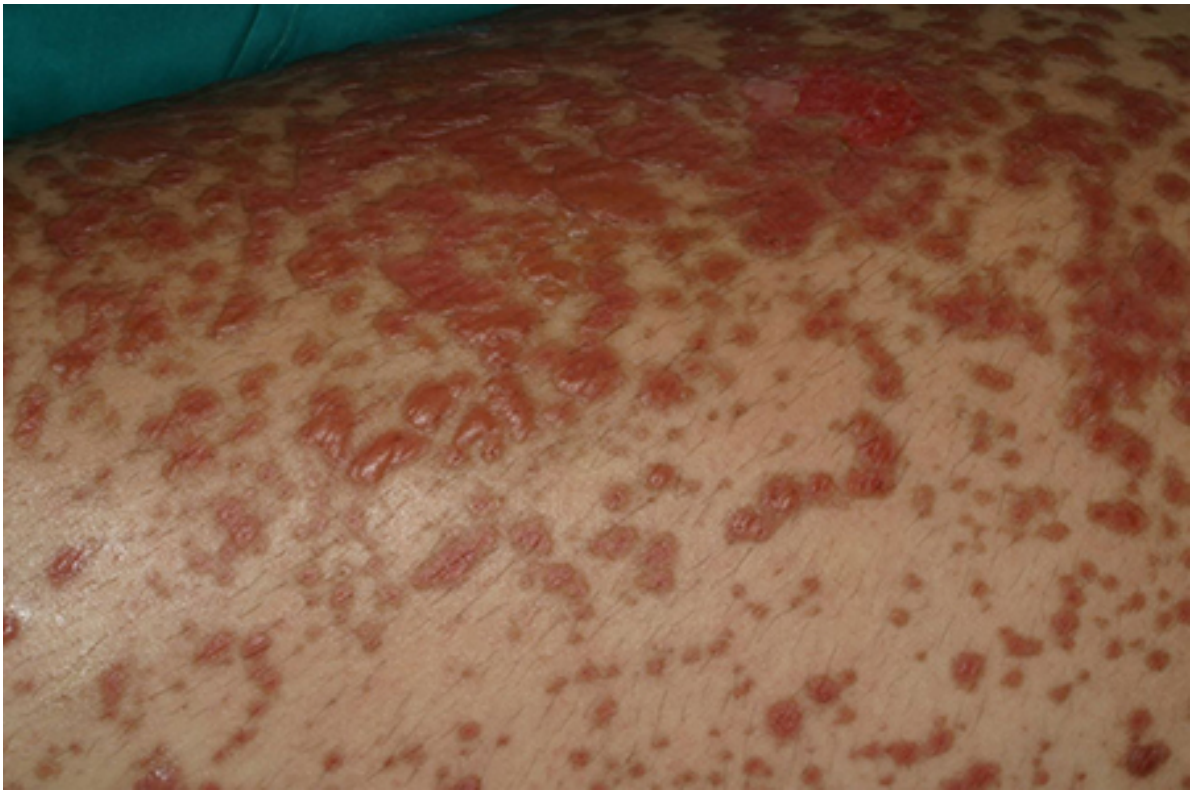
Blistering targetoid lesions on the trunk, carbamazepine induced Stevens-Johnson syndrome

Khoo AB, Ali FR, Yiu ZZ, et al. Carbamazepine induced Stevens-Johnson syndrome. BMJ Case Rep. 2016;2016. pii: bcr2016214926. Used with permission



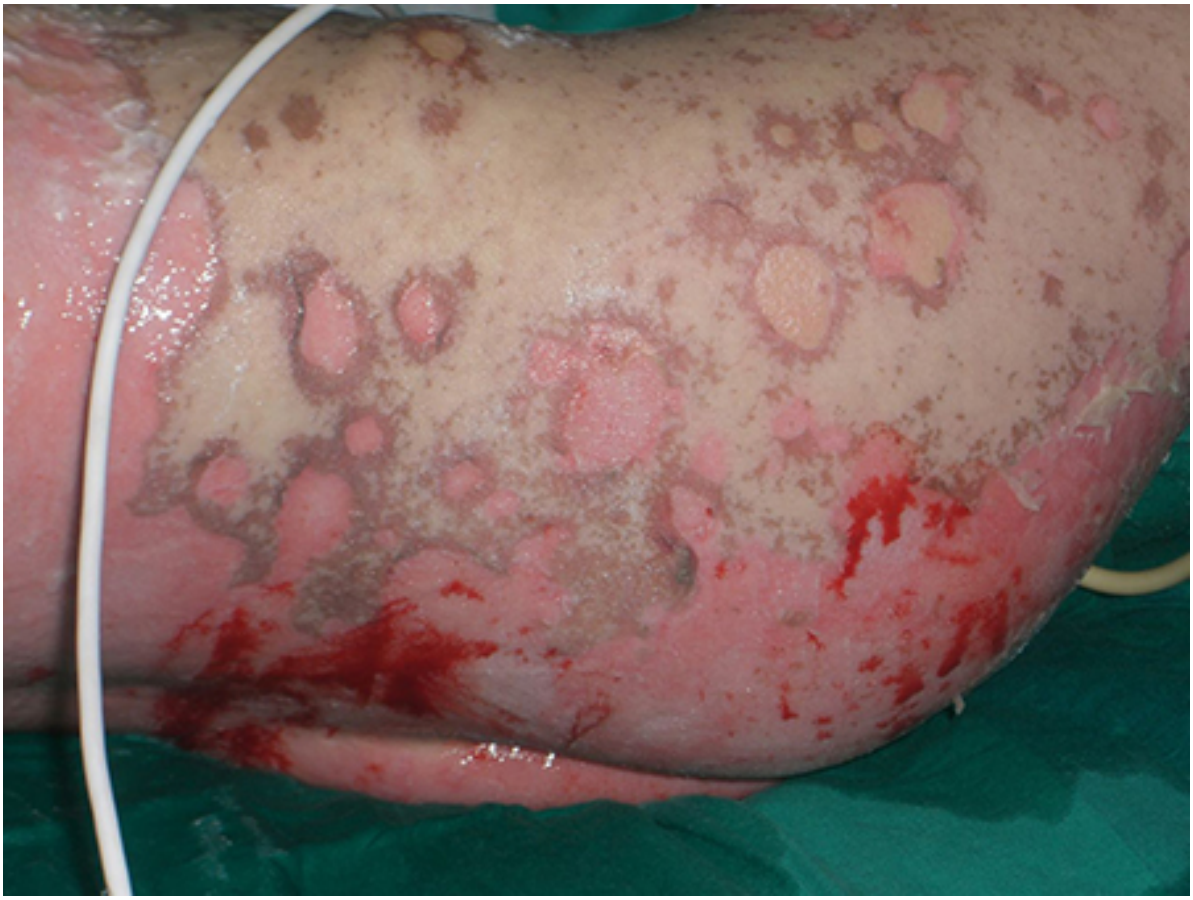
Stevens-Johnson syndrome: epidermal loss on soles of feet

From the personal collection of Areta Kowal-Vern, MD



Initial phase of toxic epidermal necrolysis with diffuse erythema and vesicles that will evolve to full epidermal necrosis

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission



A 5-year-old female patient with toxic epidermal necrolysis with three suspected drugs (penicillin, ibuprofen, and paracetamol)

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission

variable skin reactions within 5 to 15 minutes of drug exposure (common)

- Usually occur within 5 to 15 minutes (e.g., acute IgE-mediated reactions), but can occur up to several hours after exposure.[7] [40]

variable skin reactions within a few hours of drug exposure (common)

- Occur within a few hours of each exposure (e.g., fixed drug eruptions).[7] [40]

variable skin reactions within 2 weeks of drug exposure (common)

- Most drug-induced skin reactions occur within 2 weeks of initial exposure.[7] [40]

variable skin reactions within months to years of drug exposure (uncommon)

- A few reactions occur very late (e.g., lichenoid eruptions, which can take months or years to develop).[7] [40]

previous exposure and reaction to drug (uncommon)

- Similar previous reaction strengthens likelihood of an association.

Other diagnostic factors

pruritus (common)

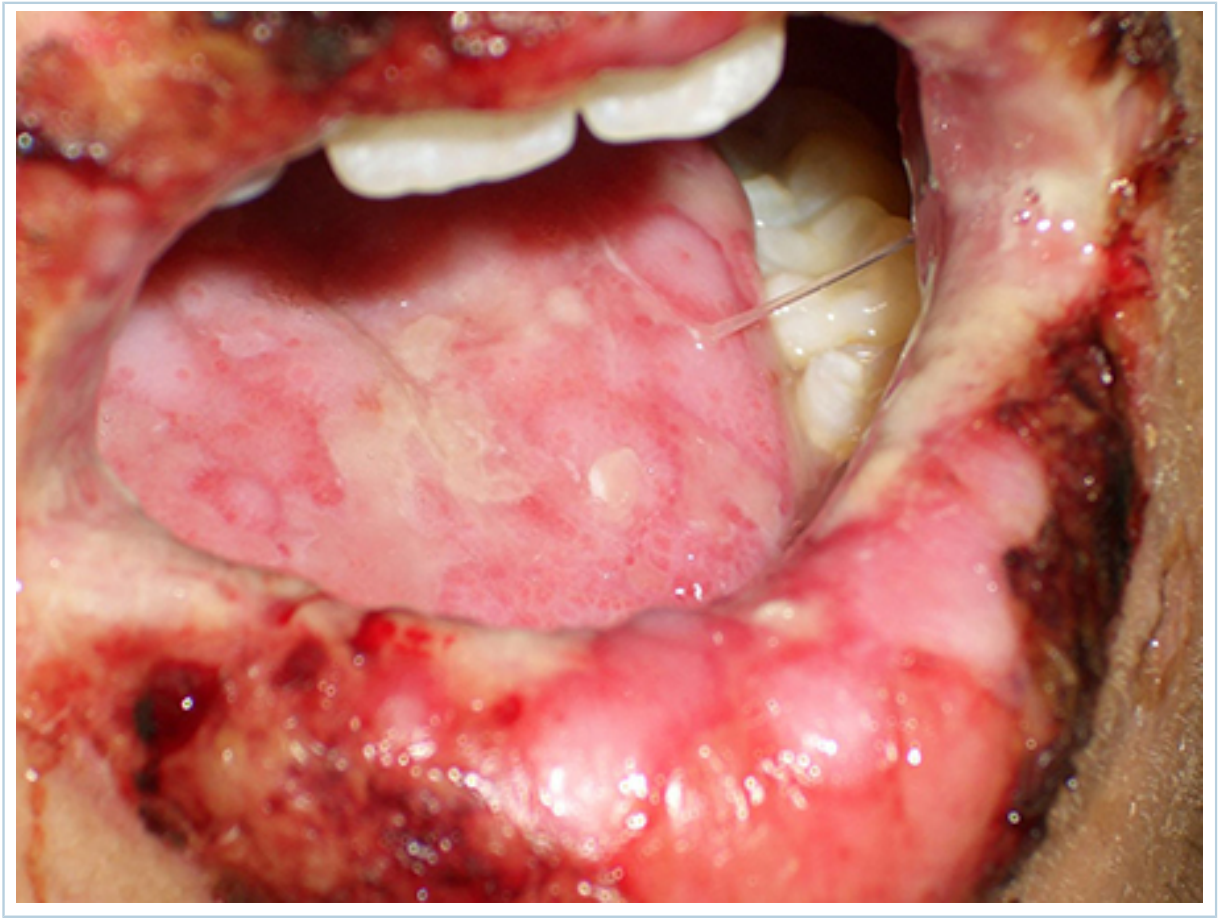
- Can be a symptom of an adverse drug reaction, indistinguishable from its occurrence in non-drug-induced lesions.

associated non-cutaneous features (common)

- Cutaneous drug reactions may be associated with a wide spectrum of symptoms depending on the type of reaction. These reactions include: anaphylactic reactions, erythema multiforme (including SJS [Stevens-Johnson syndrome] and TEN [toxic epidermal necrolysis]), DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome), acute generalised exanthematous pustulosis, and fixed drug eruptions. Atopic symptoms such as rhinitis, conjunctivitis, and respiratory wheeze may be seen. Non-specific symptoms such as nausea, vomiting, abdominal pain, and dizziness may also be seen. DRESS is associated with fever and lymphadenopathy in at least 2 sites. Blisters and mucosal involvement may be seen in fixed drug reactions and SJS/TEN.

Oral and mucosal ulcerations, carbamazepine induced Stevens-Johnson syndrome

Khoo AB, Ali FR, Yiu ZZ, et al. Carbamazepine induced Stevens-Johnson syndrome. BMJ Case Rep. 2016;2016. pii: bcr2016214926. Used with permission



A 17-year-old male patient diagnosed with Stevens-Johnson syndrome due to azitromicine. Erosions and crusts on the lips with diffuse ulcers on the tongue

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission

pain (uncommon)

- Can be a symptom of an adverse drug reaction, indistinguishable from its occurrence in non-drug-induced lesions.

Risk factors

Strong

virus infections

- Increased risk of the ampicillin and amoxicillin rash in patients with certain virus infections (cytomegalovirus and Epstein-Barr virus).

HIV infection

- Increased risk of hypersensitivity reactions (drug reaction with eosinophilia and systemic symptoms [DRESS]; also called drug hypersensitivity syndrome), for example to sulfonamides and related compounds.

HLA-B*5701 polymorphism

- Confers an increased risk of abacavir-induced skin hypersensitivity reactions. This polymorphism has a near 100% negative predictive value, and screening reduces the risk from about 10% to nearly 0%.[32]

HLA-B*1502 polymorphism

- Han Chinese people with this polymorphism are at increased risk of carbamazepine-induced skin hypersensitivity reactions.[33]

HLA-B*5801 polymorphism

- Han Chinese people with this polymorphism are at increased risk of allopurinol-induced skin reactions.[33]

Weak

female sex

- Women are slightly more likely than men to report adverse drug reactions.[34]

Investigations

Other tests to consider

Test	Result
blood (whole blood, plasma, serum) drug concentration • Can be useful when the usual target blood (whole blood, plasma, or serum) concentration range of the suspected drug is known.	**concentration above the usual target range increases suspicion of drug-induced cause**
serum tryptase concentration (anaphylaxis) • The 2023 American Academy of Allergy, Asthma & Immunology practice parameter on anaphylaxis recommends taking one sample as soon as possible (ideally within 2 hours of symptom onset) and a second sample at a later time to establish the baseline value.[46] UK guidance recommends ideally taking 3 samples: one as soon as possible after starting emergency treatment, a second 1-2 hours (but no later than 4 hours) after symptom onset, and a third at least 24 hours later to establish the baseline value.[45] • An acute tryptase level that is elevated above the (laboratory-defined) upper limit of normal is supportive of a diagnosis of anaphylaxis, as is an acute level that shows significant elevation from the patient's baseline tryptase level (even where the acute level is still within the normal range, i.e., an acute tryptase level in the normal range does not rule out anaphylaxis).[46] • Elevation of tryptase levels may also exist in non-anaphylactic conditions, such as systemic mastocytosis.	**raised during the first few hours after an anaphylactic reaction, both IgE and non-IgE mediated, due to mast cell degranulation**
complement pathway assay • C4 measures should be taken during an attack in angio-oedema alone (no urticaria). If C4 is low, C1-esterase levels should be measured. Occasionally, C1-esterase function needs to be measured if the enzyme is not low but inactive. • C1 esterase levels can be low in hereditary angio-oedema and autoimmune disorders. C4 can be normal in bradykinin-mediated angio-oedema.	**low levels of C4 are a strong indication of complement pathway problems such as acquired or inherited deficiency of C1-esterase inhibitor**
histology of lesion biopsy • A sample of the lesion and the surrounding normal skin is taken. • Some drug-induced skin rashes have a characteristic histology, whereas others are indistinguishable from non-drug-induced forms.	**infiltration of eosinophilic polymorphonuclear leukocytes may suggest drug-induced lesion**
FBC and differential • Anaemia, leukopenia, thrombocytopenia, and rarely pancytopenia can be caused by adverse drug effects, but eosinophilia can be a useful sign of drug allergy.	**FBC usually normal in drug-induced lupus; peripheral blood eosinophilia may suggest a drug allergy reaction**
anti-histone antibodies to single-stranded DNA (lupus-like syndrome) • Systemic lupus erythematosus is associated with antibodies to double-stranded DNA; drug-induced lupus is associated with anti-histone antibodies.	**drug-induced lupus is associated with antibodies to histones**

Test	Result
skin tests (prick tests, intradermal tests, patch tests) • Specialist advice should be sought. Skin tests can help to identify a causative drug after an allergic reaction; mainly useful in contact dermatitis. • Skin tests may also be useful adjuncts for establishing causality and cross-reactivity for delayed hypersensitivity reactions.[42] However, skin tests are limited by low sensitivity and thus results should be interpreted with caution, particularly in the setting of severe reactions given the imperfect negative predictive value. Due to the risk of relapse, skin tests for DRESS should be delayed for at least 6 months after the acute reaction and/or 1 month after discontinuation of corticosteroids.[42]	**identification of causative drug after an allergic reaction**

Emerging tests

Test	Result
drug-specific IgE • Can be helpful, particularly in the case of negative skin tests or severe life-threatening reactions (e.g., anaphylactic reactions to beta-lactam antibiotics). Specialist advice should be sought.[52]	**positive drug-specific IgE results are strongly supportive of anaphylaxis on re-exposure to the drugs; however, false negative results are a common problem with this assay. Test results should only be interpreted in conjunction with patient history and clinical findings**
basophil activation test • Can be helpful, particularly in the case of negative skin tests or severe life-threatening reactions (e.g., anaphylactic reactions to beta-lactam antibiotics). Specialist advice should be sought. Remains largely a research tool at present.	**drug-induced basophil activation; test results should only be interpreted in conjunction with patient history and clinical findings**
lymphocyte proliferation assay (LPA/LTT) • Can be helpful, particularly in the case of negative skin tests or severe life-threatening reactions (e.g., anaphylactic reactions to beta-lactam antibiotics). Specialist advice should be sought. Remains largely a research tool at present.	**drug-induced in vitro proliferation of T cells with a stimulation index greater than 2 is widely regarded as a useful cut-off threshold for determining positive test results. The test results should only be interpreted in conjunction with patient history and clinical findings**
enzyme-linked immunospot assay (ELISPOT test) • Can be helpful, particularly in the case of negative skin tests or severe life-threatening reactions (e.g., anaphylactic reactions to beta-lactam antibiotics). Specialist advice should be sought. Remains largely a research tool at present.	**drug-induced cytokine detection above background cytokine release is the minimum threshold for positive test results; test results should only be interpreted in conjunction with patient history and clinical findings**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Systemic lupus erythematosus	• Systemic lupus erythematosus (SLE) usually occurs in young women; drug-induced lupus can occur in anyone. • SLE commonly involves the kidneys, drug-induced lupus rarely.	• FBC: anaemia, leukopenia, thrombocytopenia; rarely pancytopenia. (Drugs and infections should be excluded as a cause.) • Serum complement: often low. • SLE is associated with antibodies to double-stranded DNA; drug-induced lupus is associated with antibodies to single-stranded DNA.
Auto-immune blistering disorders	• Pemphigus vulgaris and linear IgA disease may both cause mucosal and cutaneous blistering and can be very difficult to distinguish clinically from Stevens-Johnson Syndrome (SJS)/ toxic epidermal necrolysis (TEN).	• Skin histology and direct immunofluorescence studies are critical.
Staphylococcal scalded skin syndrome	• Staphylococcal scalded skin syndrome (SSSS) typically arises in children, whereas toxic epidermal necrolysis (TEN) is more common in adults. Both cause blistering/ peeling of the skin. However, the level of split is much higher in the epidermis than with TEN. SSSS is not associated with prominent mucosal involvement and often has a perioral focus.	• Skin histology shows full-thickness necrosis in TEN.
Infection	• Infections can cause a variety of exanthems, often with fever, which can be difficult to distinguish from hypersensitivity reactions.	• Microbiological culture (bacteria), PCR (viruses). • Infections will often worsen on withdrawal of antimicrobial treatment and may improve with introduction of treatment.
Psoriasis	• Typically presents as erythematous, circumscribed, scaly papules and plaques on elbows, knees, extensor surfaces of limbs, and the scalp.	• Skin biopsy shows that psoriasiform lesions caused by practolol are accompanied by fibrosis, which is not normally a feature of psoriasis.

Condition	Differentiating signs / symptoms	Differentiating tests
Lichen planus	• Cutaneous lichen planus typically presents with intensely pruritic lesions on flexor wrists, ankles, trunk, and extremities.	• Biopsy of lesional skin for histopathology shows lymphohistiocytic infiltrate and necrotic keratinocytes with hyperorthokeratosis and hypergranulosis in non-drug-induced lichen planus. • In lichen planus, parakeratosis, spongiosis, and patchy inflammatory changes suggest a drug-induced cause.
Other non-drug-related rashes	• Differential diagnosis of any drug-related rash is the non-drug-related form of the condition that it looks like; in a few cases, such as SLE, psoriasis, and lichen planus, features help to distinguish drug-related from non-drug-related rashes.	• Peripheral blood eosinophilia and an eosinophilic cellular infiltrate in any lesion suggest a drug-related effect. • Exanthematous reactions are often due to infections; a specific diagnosis may be possible if the causative organism can be identified.

Screening

In a few cases, screening for pharmacogenetic variants can predict an increased risk. Patients with these variants can avoid the drug. This has been particularly well demonstrated for the association between the HLA-B*5701 polymorphism and the risk of abacavir-induced hypersensitivity reactions. Han Chinese people with the HLA-B*1502 polymorphism are at increased risk of carbamazepine-induced skin hypersensitivity reactions; those with the HLA-B*5801 polymorphism are at increased risk of allopurinol-induced skin hypersensitivity reactions.[33]

Approach

All adverse drug reactions need to be meticulously recorded and the patient fully informed. Withdrawal of the suspected drug is essential, after which in many cases the lesions will resolve spontaneously within 1 to 2 weeks. Fixed drug eruptions resolve on withdrawal but can leave residual scarring or pigmentation.[53] Otherwise, treatment should be the same as for non-drug-induced skin lesions.

Serious adverse cutaneous reactions

Adverse cutaneous reactions can be considered to be serious if they affect the structure or function of the skin, its appendages, or mucous membranes. The main potentially serious drug-induced cutaneous allergic reactions are Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), exfoliative dermatitis, hypersensitivity DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome), serum sickness and vasculitis, and anaphylaxis.

Acute anaphylactic reactions

Attending healthcare professionals should call for help as this is a medical emergency.[45]
See Anaphylaxis (Management approach) .

Key considerations

Acute anaphylactic reactions are treated by having the patient lie down if they are hypotensive, sitting them up if they are having trouble breathing, or lying them in the recovery position if they are unconscious.[45] The offending drug should be withdrawn, and intramuscular adrenaline (epinephrine) given as soon as possible. A further follow-up dose of intramuscular adrenaline can be given after 5 to 15 minutes if necessary (guidelines vary on the precise timing of repeat dose[s] so check your local protocol). If required, intravenous adrenaline should be given under the guidance of a physician experienced in the use and titration of vasopressors.[45][54] Take an ABCDE approach and give high-flow supplemental oxygen and intravenous fluids (e.g., normal saline) if indicated.[45] [55][56] If there is marked stridor, nebulised adrenaline should be administered. If the patient has persistent bronchospasm despite adrenaline, an inhaled beta-2 agonist (e.g., salbutamol) is indicated.[45][55] [56]

Biphasic reactions can occur.[45] Antihistamines and/or corticosteroids are not reliable in preventing biphasic anaphylaxis but may be considered as secondary treatment.[45][54]

For possible future anaphylactic reactions, the patient should be equipped with 2 adrenaline auto-injector pens and taught how to use them correctly.[54] A warning bracelet is advisable. Information about drug allergy status (drug name; signs, symptoms, and severity of reaction; and date when the reaction occurred) should be updated and included in hospital discharge letters and medical records.

Stevens-Johnson syndrome and toxic epidermal necrolysis

Patients with Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) should be assessed in the same way as a patient with cutaneous burns, using a structured approach to evaluate airway, breathing, and circulation. See Cutaneous burns (Diagnosis approach) .

Treatment requires a multidisciplinary team so that patients receive optimal daily wound care, nutrition, critical care, pain management, and supportive care.[57] Transfer to a burn centre, a specialised wound care centre, or a dermatology intensive care unit is recommended.[57] [58]

Exact treatment will depend on the extent of skin involvement. See Stevens-Johnson syndrome and toxic epidermal necrolysis (Management approach) .

Hypersensitivity reactions

Systemic corticosteroids may be required in acute hypersensitivity reactions (e.g., DRESS).

Non-serious reactions unresponsive to withdrawal of drug

Topical corticosteroids are often used when drug-induced lesions do not resolve spontaneously; oral corticosteroids are used in severe cases.

In mild cases, topical hydrocortisone can be used. For more severe disease, alternatives include betamethasone, clobetasol, fluocinolone, and triamcinolone.

In severe reactions unresponsive to withdrawal of the drug, oral prednisolone can be used.

Management of drug-induced urticaria

Treatment of drug-induced urticaria is withdrawal of the suspected drug, and an antihistamine if needed. A non-sedating antihistamine is preferred for daytime use. If nocturnal symptoms are a problem, a sedating antihistamine can be used at night.

Desensitisation

Patients who have had an allergic reaction to a drug can prevent future reactions by strictly avoiding the drug. It is rarely necessary to attempt desensitisation, and it should not be attempted unless the benefit of continuing to use the drug outweighs the potential harm of desensitisation and when there is no alternative therapy.

Recommendations for alternative therapy and desensitisation are available for specific drugs and drug classes (e.g., antibiotics, non-steroidal anti-inflammatory drugs [NSAIDs], chemotherapy, immune checkpoint inhibitors, biological agents).[43][44] [45]

Specialist referral

Referral to a specialist drug allergy service should be considered for: suspected anaphylaxis; severe/life-threatening episodes (e.g., DRESS, Stevens-Johnson syndrome, toxic epidermal necrolysis); severe reactions to NSAIDs with ongoing need for NSAID therapy; suspected beta-lactam allergy (if alternative antibiotics are not available); and problems related to general and local anaesthesia.[52]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)

serious cutaneous adverse reactions

	1st	withdrawal of suspected drug
acute anaphylactic reactions	plus	adrenaline (epinephrine) + supportive care
Stevens-Johnson syndrome or toxic epidermal necrolysis	plus	topical dressings + supportive management
DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome)	plus	corticosteroid

non-serious cutaneous adverse reactions

	1st	withdrawal of suspected drug
unresponsive to withdrawal of drug	plus	corticosteroid
drug-induced urticaria	plus	antihistamine

Ongoing (summary)

following acute episode

	1st	avoidance of offending drug where possible
history of anaphylactic reaction	plus	self-administered adrenaline (epinephrine) + action plan
continued drug use outweighs potential harm + no alternative therapy	plus	drug desensitisation

MANAGEMENT

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

serious cutaneous adverse reactions

serious cutaneous adverse reactions — **1st** — **withdrawal of suspected drug**

» Withdrawal of the suspected drug is essential.

acute anaphylactic reactions — **plus** — **adrenaline (epinephrine) + supportive care**

Treatment recommended for ALL patients in selected patient group

Primary options

» adrenaline (epinephrine): consult specialist for guidance on dose

» Call for help and treat as an emergency.[45] See Anaphylaxis (Treatment algorithm) .

» Key considerations are as follows.

» Acute anaphylactic reactions are treated by having the patient lie down if they are hypotensive, sitting them up if they are having trouble breathing, or lying them in the recovering position if they are unconscious.[45] The offending drug should be withdrawn, and intramuscular adrenaline given as soon as possible. A further follow-up dose of intramuscular adrenaline can be given after 5 to 15 minutes if necessary (guidelines vary on the precise timing of repeat dose[s] so check your local protocol). If required, intravenous adrenaline should be given under the guidance of a physician experienced in the use and titration of vasopressors.[45][54]

» Take an ABCDE approach and give high-flow supplemental oxygen and intravenous fluids (e.g., normal saline) if indicated.[45] [55][56] If there is marked stridor, nebulised adrenaline should be administered. If the patient has persistent bronchospasm despite adrenaline, an inhaled beta-2 agonist (e.g., salbutamol) is indicated.[45] [55][56]

» Biphasic reactions can occur.[45] Antihistamines and/or corticosteroids are not reliable in preventing biphasic anaphylaxis but may be considered as secondary treatment.[45] [54]

Acute

Stevens-Johnson syndrome or toxic epidermal necrolysis — **plus** — **topical dressings + supportive management**

Treatment recommended for ALL patients in selected patient group

» Withdrawal of the suspected drug is essential. Patients with Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) should be assessed in the same way as a patient with cutaneous burns, using a structured approach to evaluate airway, breathing, and circulation. See Cutaneous burns (Diagnosis approach) .

» Treatment requires a multidisciplinary team so that patients receive optimal daily wound care, nutrition, critical care, pain management, and supportive care.[57] Transfer to a burn centre, a specialised wound care centre, or a dermatology intensive care unit is recommended for patients with SJS/TEN.[57] [58]

» Exact treatment will depend on the extent of skin involvement. See Stevens-Johnson syndrome and toxic epidermal necrolysis (Management approach) .

DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome) — **plus** — **corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» betamethasone valerate topical: (0.1%) children and adults: apply sparingly to the affected area(s) once daily for 7-14 days

OR

» prednisolone: children and adults: 0.5 to 1 mg/kg/day orally, taper gradually according to response

» Systemic treatment may be required in severe cases such as severe liver dysfunction. A topical corticosteroid (e.g., betamethasone) may be used in mild cases.

» Care should be taken not to withdraw corticosteroid too early as this might result in re-occurrence.

non-serious cutaneous adverse reactions

non-serious cutaneous adverse reactions — **1st** — **withdrawal of suspected drug**

MANAGEMENT

Acute

» Withdrawal of the suspected drug is essential. In many cases, the lesions will resolve spontaneously thereafter, within 1 to 2 weeks.

unresponsive to withdrawal of drug **plus** **corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» hydrocortisone topical: (0.5 to 1%) apply sparingly to the affected area(s) twice daily

OR

» betamethasone valerate topical: (0.1%) apply sparingly to the affected area(s) once or twice daily

OR

» clobetasol topical: (0.05%) apply sparingly to the affected area(s) twice daily

OR

» fluocinolone topical: (0.025%) apply sparingly to the affected area(s) twice daily

OR

» triamcinolone topical: (0.1%) apply sparingly to the affected area(s) twice daily

Secondary options

» prednisolone: children: 1-2 mg/kg/day orally, taper gradually over 3 weeks according to response; adults: 30-60 mg orally once daily, taper gradually over 3 weeks according to response

» Topical corticosteroids are often used when skin eruptions are symptomatic (especially for itch). In mild cases, hydrocortisone can be used. For more severe problems, alternatives include betamethasone, clobetasol, fluocinolone, and triamcinolone.

» In severe reactions unresponsive to withdrawal of the drug, oral prednisolone can be used.

» Severity refers to the intensity of the reaction. A severe (intense) headache need not be serious, and a mild arrhythmia (e.g., a ventricular extra beat) can have a serious outcome (a fatal cardiac arrhythmia).

Acute

» A serious cutaneous adverse reaction affects the structure or function of the skin, its appendages, or mucous membranes.

drug-induced urticaria **plus** **antihistamine**

Treatment recommended for ALL patients in selected patient group

Primary options

» cetirizine: 10 mg orally once daily

OR

» loratadine: 10 mg orally once daily

OR

» fexofenadine: 180 mg orally once daily

OR

» mizolastine: 10 mg orally once daily

OR

» hydroxyzine: 25 mg orally once daily at night

» Treatment of drug-induced urticaria is withdrawal of the suspected drug and possibly a brief dose of antihistamine.

» A non-sedating antihistamine (e.g., cetirizine, loratadine, fexofenadine, or mizolastine) is preferred for daytime use; if nocturnal symptoms are a problem, a sedating antihistamine (hydroxyzine) can be used at night.

Ongoing

following acute episode

following acute episode — **1st** — **avoidance of offending drug where possible**

» Avoidance of the offending drug is essential where possible.

- **history of anaphylactic reaction** — **plus** — **self-administered adrenaline (epinephrine) + action plan**

Treatment recommended for ALL patients in selected patient group

Primary options

» adrenaline (epinephrine): children <30 kg: 0.15 mg intramuscularly as a single dose, may repeat in 10-20 minutes; children >30 kg and adults: 0.3 mg intramuscularly as a single dose, may repeat in 10-20 minutes

» All adverse drug reactions need to be meticulously recorded and the patient fully informed. For possible future anaphylactic reactions, the patient should be equipped with 2 adrenaline auto-injectors.[54]

» After receiving adrenaline, the patient should present to the accident and emergency department for monitoring and further treatment as required until stable.

- **continued drug use outweighs potential harm + no alternative therapy** — **plus** — **drug desensitisation**

Treatment recommended for ALL patients in selected patient group

» Patients who have had an allergic reaction to a drug can prevent future reactions by strictly avoiding the drug. Attempting desensitisation is rarely necessary; it should not be attempted unless the benefit of continuing to use the drug outweighs the potential harm of desensitisation and when there is no other alternative therapy.

» Recommendations for alternative therapy and desensitisation are available for specific drugs and drug classes (e.g., antibiotics, non-steroidal anti-inflammatory drugs, chemotherapy, immune checkpoint inhibitors, biological agents).[42] [43] [44]

Emerging

Icatibant

Bradykinin (B2) receptor antagonists, such as icatibant, inhibit the action of bradykinin at its receptors. Icatibant has been used to treat attacks of hereditary angio-oedema,[59] and bradykinin receptor antagonists may in future be useful in the treatment of acute anaphylactic reactions.

Primary prevention

Prevention of drug-induced skin lesions is by avoiding the drug. Taking a history of drug allergy is important before any prescribing.

Secondary prevention

All adverse drug reactions need to be meticulously recorded and the patient fully informed.[60] Patients who have had an acute severe anaphylactic reaction should be given an adrenaline (epinephrine) pen for emergency use and taught how to use it properly. Ensure that information about drug allergy status (e.g., date of reaction, drug name [chemical and generic], route of administration, time interval between first dose and event, reaction type, and nature and severity of symptoms) is updated and included in hospital discharge letters and medical records. Links to photographs, results of any testing already performed, and management recommendations (e.g., safe alternatives or consideration for desensitisation) should also be included in health records where possible.[60] Patients should also be advised to wear a medical bracelet. Mobile apps are also available to help patients keep track of their allergies, which may help facilitate future communication with healthcare professionals.[60]

Patient discussions

Avoiding a drug that has caused an allergic reaction is essential.

Patients should be educated about which measures to take in case of a future anaphylactic reaction: for example, immediately administer adrenaline (epinephrine) and take an antihistamine, call emergency services, or go to the nearest accident and emergency department (for further observation even if feeling better after adrenaline). Patients are at risk of a further biphasic reaction that can occur 4 to 6 hours after the initial reaction. Patients should also be advised to wear a medical bracelet.

Mobile apps are also available to help patients keep track of their allergies, which may help facilitate future communication with healthcare professionals.[60]

Complications

Complications	Timeframe	Likelihood
pigmentation disorders	**long term**	**low**
Hyperpigmentation or hypopigmentation can occur as uncommon post-inflammatory complications of a non-pigmented rash. Hyperpigmentation can occur as a direct adverse effect of a drug (e.g., tetracyclines, amiodarone, hydroxychloroquine).		
scarring	**long term**	**low**
Post-inflammatory scarring occasionally occurs.		

Prognosis

Most drug-induced skin lesions resolve after withdrawal of the causative drug. In severe reactions, death can occur. Stevens-Johnson syndrome is fatal in about 5% of cases and toxic epidermal necrolysis in about 30%. Mortality in DRESS (drug reaction with eosinophilia and systemic symptoms; also called drug hypersensitivity syndrome) cases are reported to be 10%.[52] The case-fatality rate in acute anaphylaxis is <1.0%, but the risk is increased in people with asthma.

Diagnostic guidelines

United Kingdom

Drug allergy: diagnosis and management (https://www.nice.org.uk/guidance/cg183)

Published by: National Institute for Health and Care Excellence **Last published:** 2014

North America

Anaphylaxis: a 2023 practice parameter update (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters)

Published by: American Academy of Allergy, Asthma & Immunology **Last published:** 2024

Drug allergy: a 2022 practice parameter (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters)

Published by: American Academy of Allergy, Asthma & Immunology **Last published:** 2022

Treatment guidelines

United Kingdom

Emergency treatment of anaphylactic reactions (https://www.resus.org.uk/anaphylaxis)

Published by: Resuscitation Council (UK) **Last published:** 2021

Management of Stevens-Johnson syndrome/toxic epidermal necrolysis in children and young people (https://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines)

Published by: British Association of Dermatologists **Last published:** 2019

Management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults (http://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines)

Published by: British Association of Dermatologists **Last published:** 2016

International

Anaphylaxis guidance (https://www.worldallergy.org/disease-focus/anaphylaxis)

Published by: World Allergy Organization **Last published:** 2020

North America

Anaphylaxis: a 2023 practice parameter update (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters)

Published by: American Academy of Allergy, Asthma & Immunology **Last published:** 2024

Drug allergy: a 2022 practice parameter (https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters)

Published by: American Academy of Allergy, Asthma & Immunology **Last published:** 2022

Guidelines for CPR and ECC (https://cpr.heart.org/en/resuscitation-science/cpr-and-ecc-guidelines)

Published by: American Heart Association **Last published:** 2020

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S2213-2198(22)00825-X/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36151034?tool=bestpractice.bmj.com)

Images

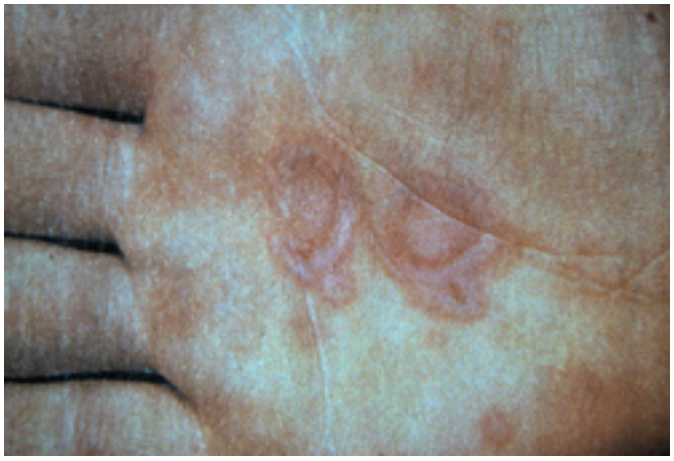

Figure 1: Palmar target lesions in erythema multiforme

From the personal collection of Nanette Silverberg, MD, FAAD, FAAP

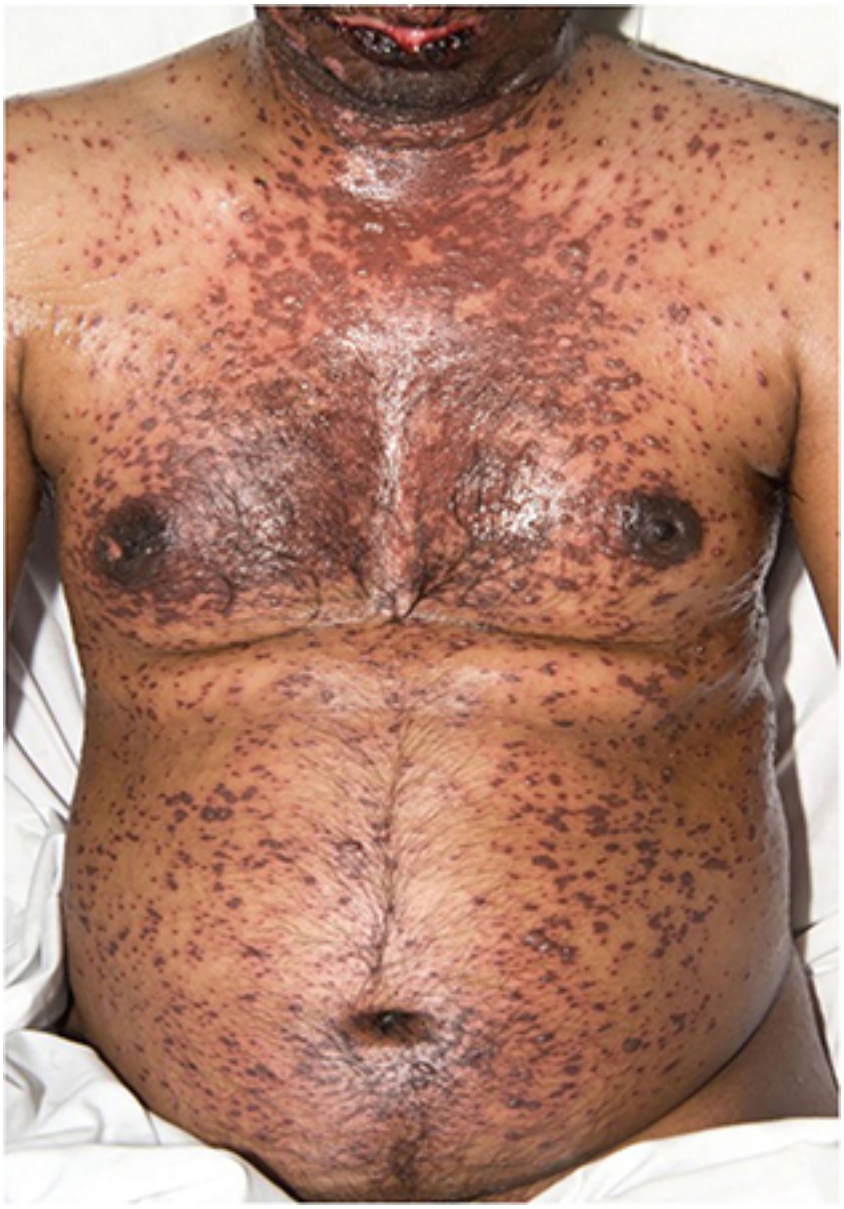

Figure 2: Blistering targetoid lesions on the trunk, carbamazepine induced Stevens-Johnson syndrome

Khoo AB, Ali FR, Yiu ZZ, et al. Carbamazepine induced Stevens-Johnson syndrome. BMJ Case Rep. 2016;2016. pii: bcr2016214926. Used with permission

Figure 3: Oral and mucosal ulcerations, carbamazepine induced Stevens-Johnson syndrome

Khoo AB, Ali FR, Yiu ZZ, et al. Carbamazepine induced Stevens-Johnson syndrome. BMJ Case Rep. 2016;2016. pii: bcr2016214926. Used with permission

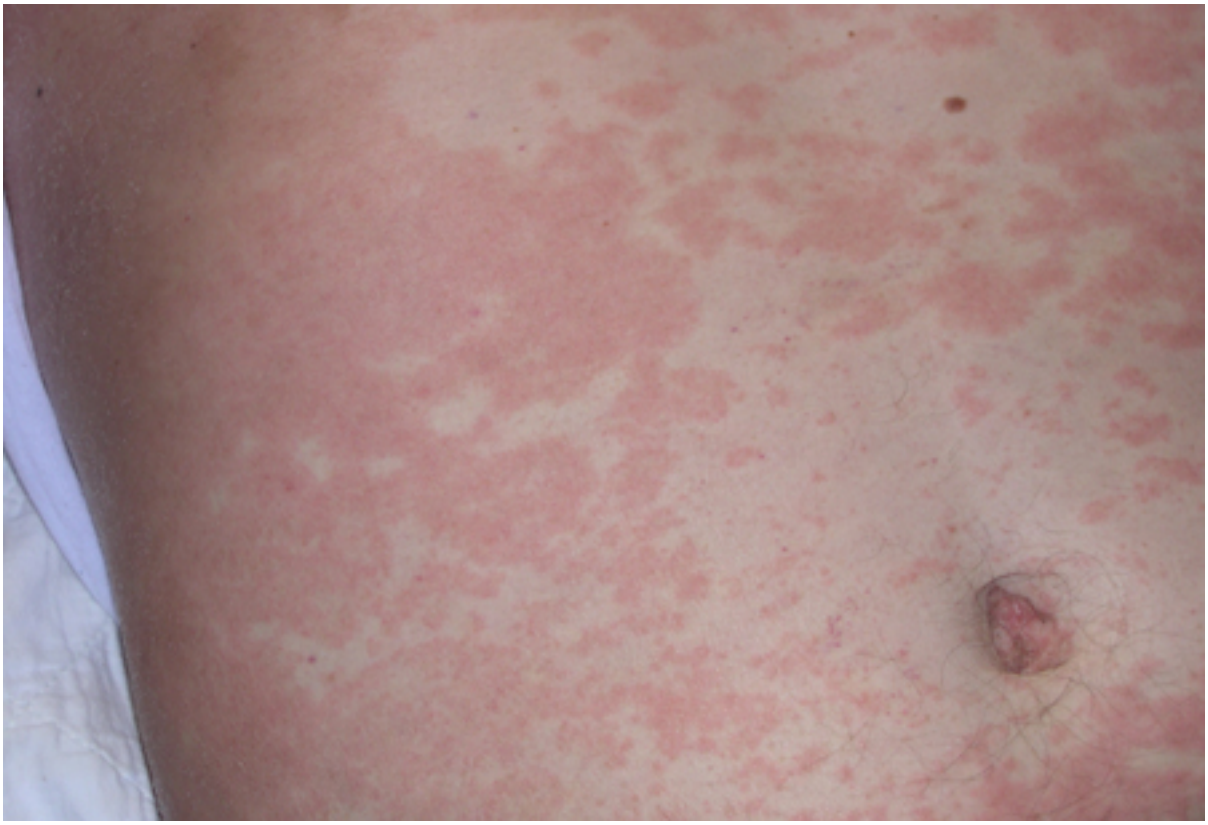

Figure 4: Drug exanthem due to phenytoin

Photography courtesy of Brian L. Swick

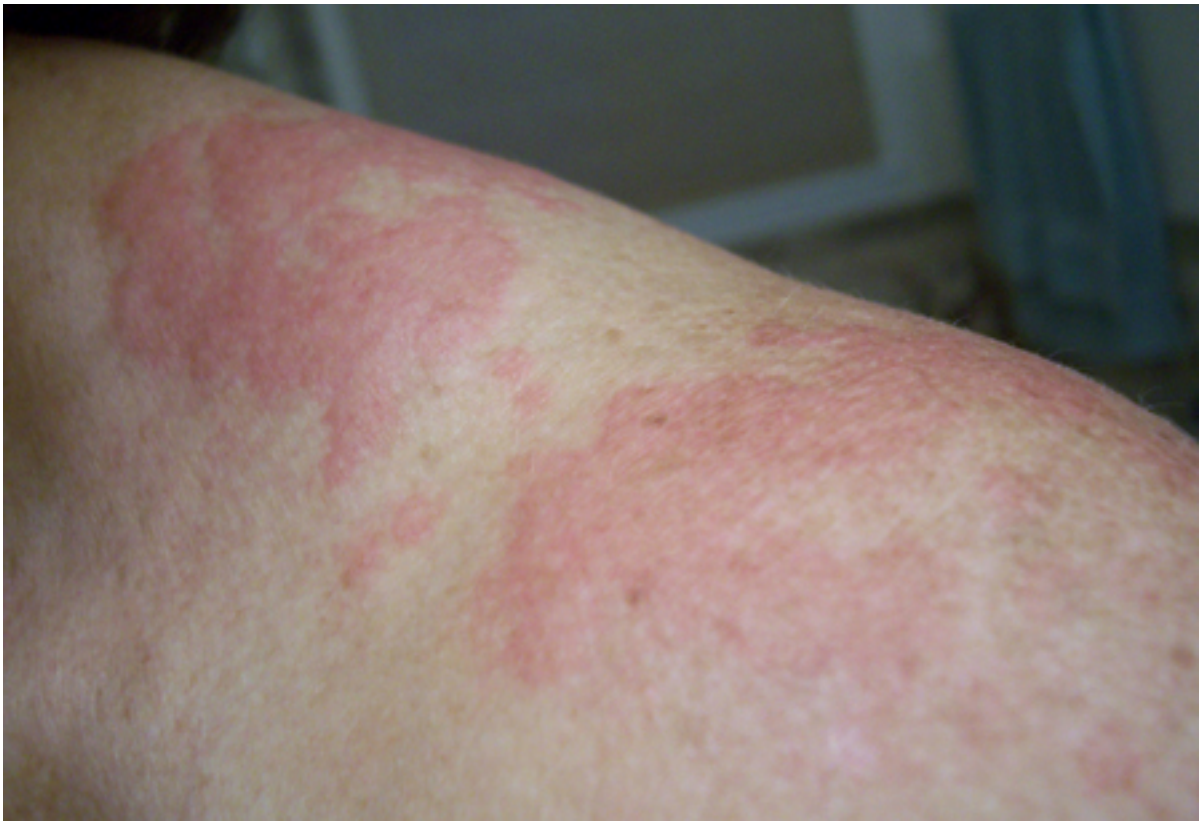

Figure 5: Typical lesions seen in acute or chronic urticaria

From the personal collection of Stephen Dreskin, MD, PhD

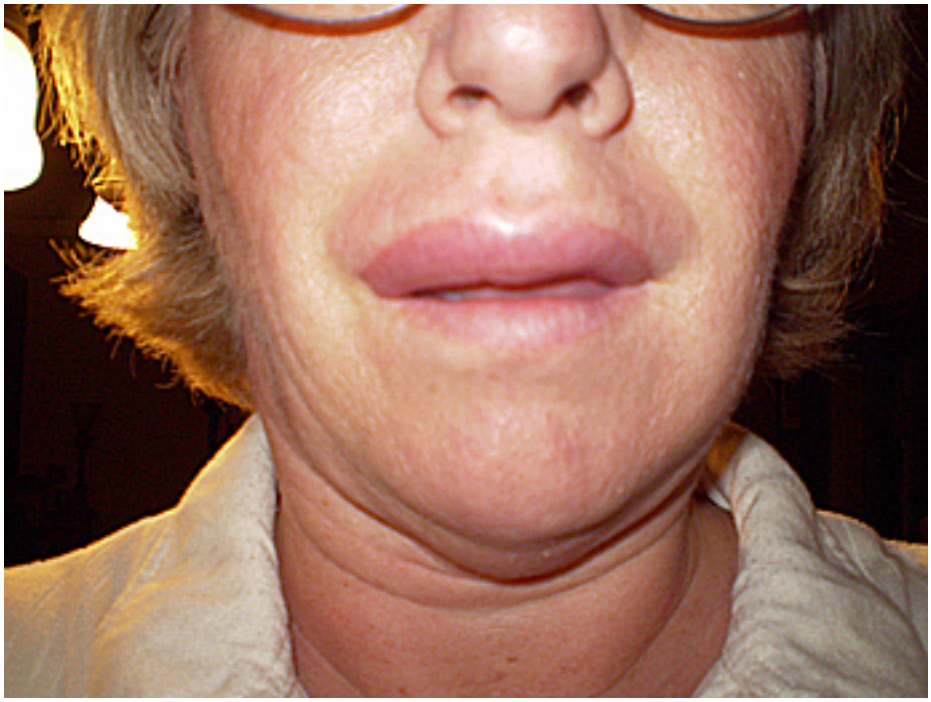

Figure 6: Angio-oedema of the lips in a patient who also has urticaria

From the personal collection of Stephen Dreskin, MD, PhD

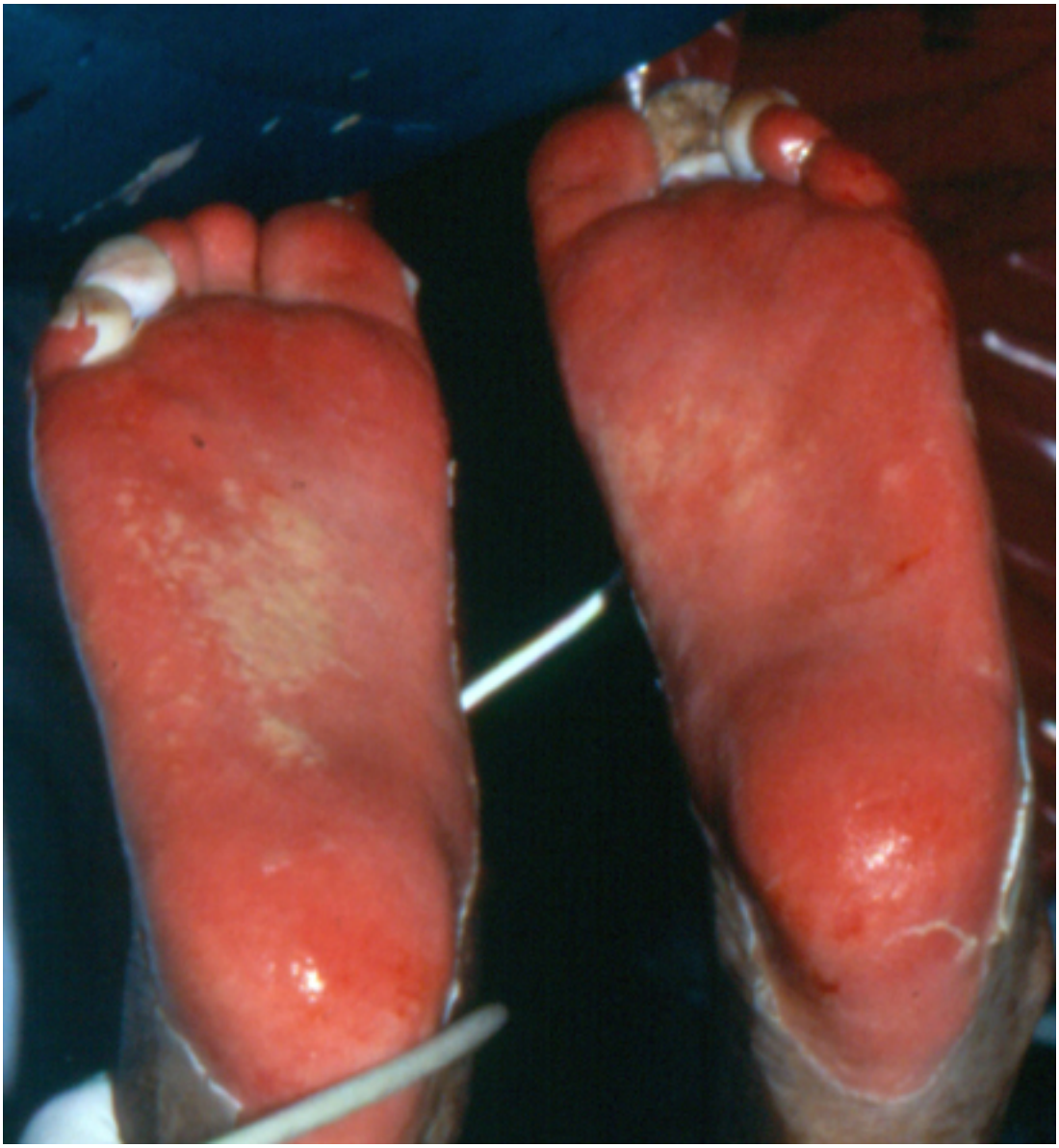

Figure 7: Stevens-Johnson syndrome: epidermal loss on soles of feet

From the personal collection of Areta Kowal-Vern, MD

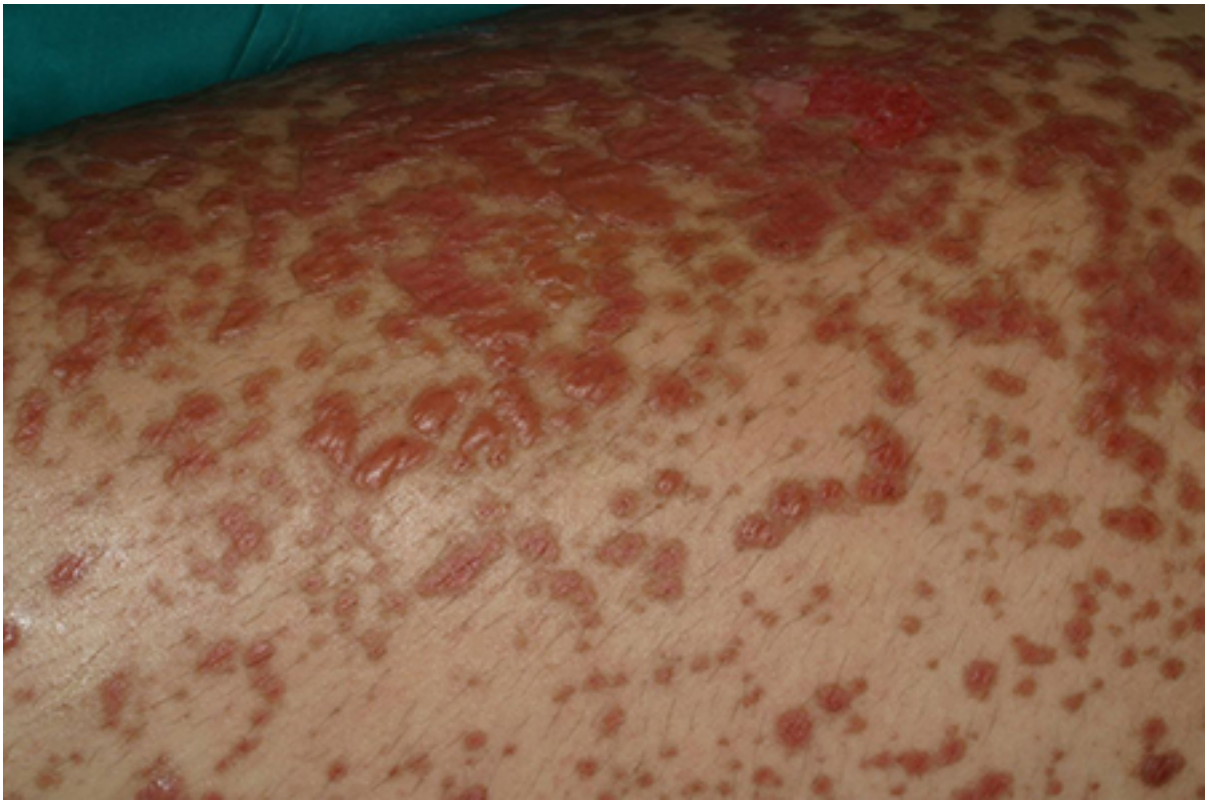

Figure 8: Initial phase of toxic epidermal necrolysis with diffuse erythema and vesicles that will evolve to full epidermal necrosis

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission

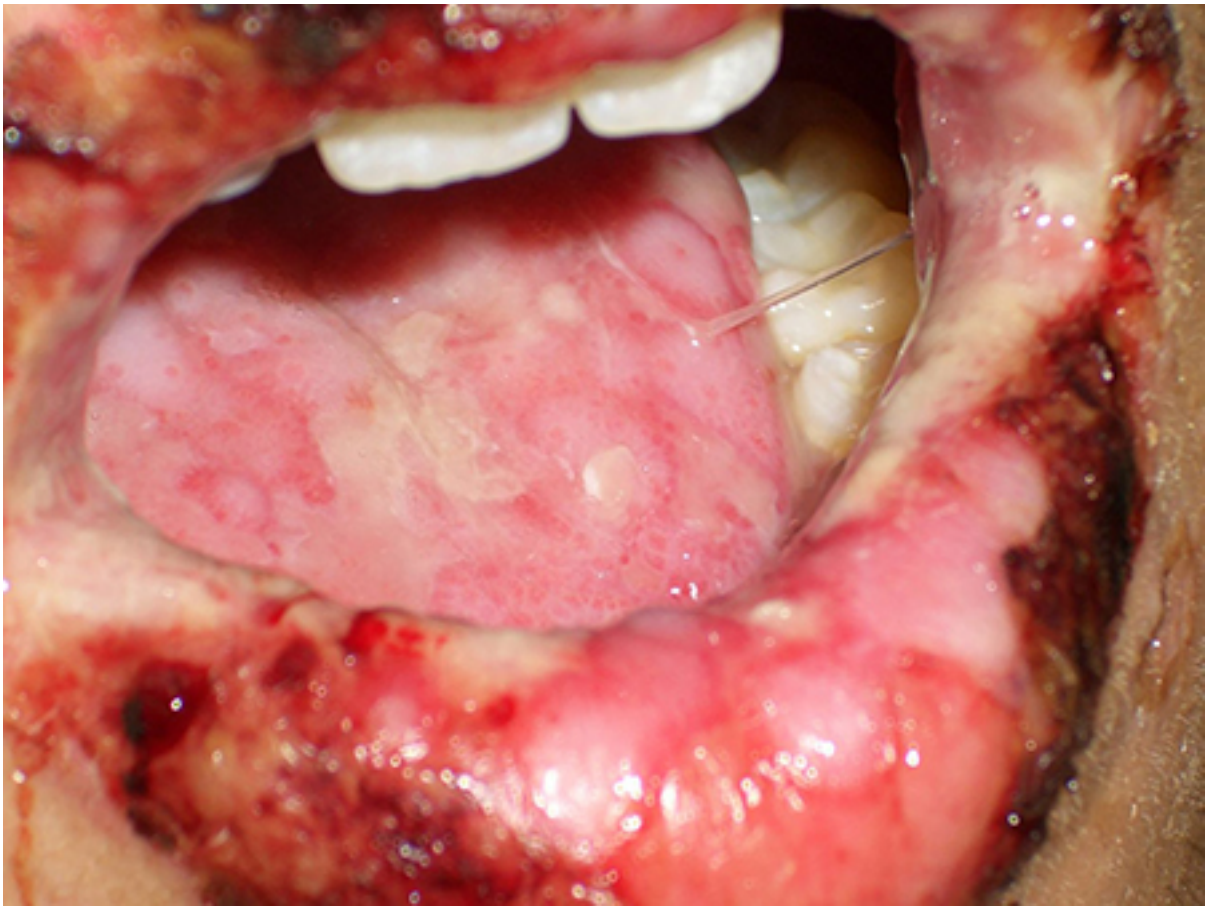

Figure 9: A 17-year-old male patient diagnosed with Stevens-Johnson syndrome due to azitromicine. Erosions and crusts on the lips with diffuse ulcers on the tongue

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission

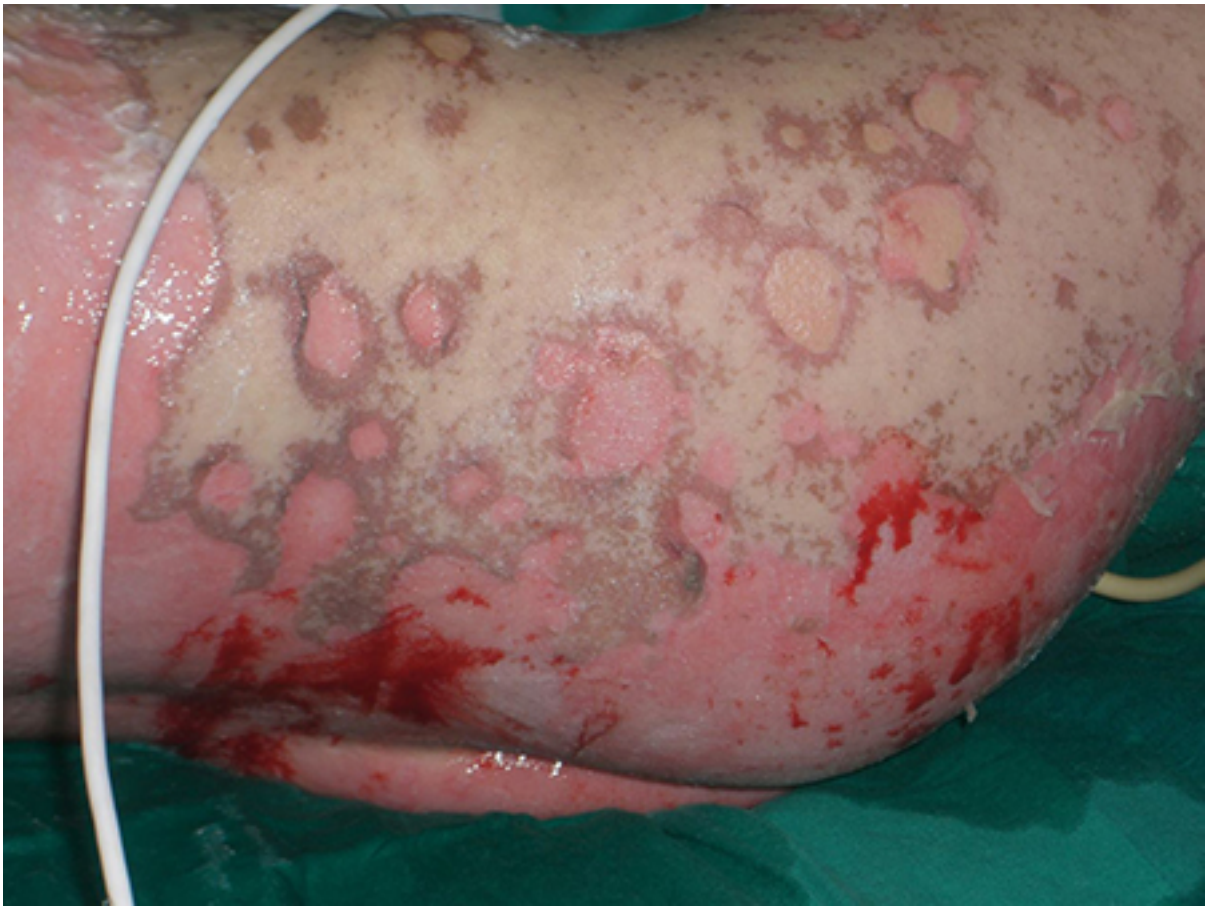

Figure 10: A 5-year-old female patient with toxic epidermal necrolysis with three suspected drugs (penicillin, ibuprofen, and paracetamol)

Ferrandiz-Pulido C, Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child. 2013;98:998-1003. Used with permission

	Yes	No	Don't know
1. Previous conclusive reports of an association between drug and effect	+1	0	0
2. The adverse event occurred after the drug was given	+2	–1	0
3. It improved after withdrawal or administration of a specific antagonist	+1	0	0
4. It recurred when the drug was given again	+2	–1	0
5. There are alternative possible causes	–1	+2	0
6. It occurred when a placebo was given	–1	+1	0
7. The drug was detected in the blood in a toxic concentration	+1	0	0
8. The reaction was more/less severe at a higher/lower dose	+1	0	0
9. The patient had a similar reaction to the same or a similar drug before	+1	0	0
10. Supporting objective evidence that the drug was to blame	+1	0	0

Figure 11: The Naranjo scoring system

Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-245

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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