

Dermatologic drug reactions

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Adverse reactions to medications are estimated to occur in 0.1% to 1% of patients using systemic medications. Certain medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and anticonvulsants, have drug eruption rates approaching 1% to 5% [1]. Approximately 30 drug-related cutaneous reaction patterns are described (Box 1) [2]. In addition, the same medication may evoke a different reaction pattern in different individuals. This fact makes identification of the offending agent difficult for primary care physicians, allergists, and dermatologists. An estimated 2% of medication-related skin eruptions meet the World Health Organization definition of a serious reaction [3]. Of these reactions, several constitute truly life-threatening emergencies and need rapid accurate diagnosis and intervention.

This review describes common, serious, and distinctive drug reaction patterns in skin. The pathogenesis of drug allergy is discussed with respect to immunologic mechanisms; nonimmunologic drug reactions may also occur. Basic classification of skin lesions is reviewed; however, this discussion centers on identification of the most common or serious cutaneous reaction patterns.

Pathogenesis

Many drug eruptions are the result of a hypersensitivity reaction with an underlying immunologic mechanism. Drugs, or their metabolites, act as haptens through covalently binding to peptides and modifying them to become immunogenic, inducing a specific cell-mediated or humoral immune response. Pharmacologic interaction of drugs with immune receptors may also occur. Chemically inert drugs activate certain T cells that bear T-cell receptors that interact with the drug [4]. Drug reactions secondary to nonimmunologic mechanisms result from a

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Box 1. Drug-mediated cutaneous reaction patterns

Acanthosis nigricans
 Acneform lesions
 Acute generalized exanthematous pustulosis
 Alopecia
 Angioedema
 Aphthous stomatitis
 Black hairy tongue
 Bullous eruptions
 Erythema multiforme and Stevens-Johnson syndrome
 Erythema nodosum
 Exanthems
 Exfoliative dermatitis
 Fixed drug eruption
 Gingival hyperplasia
 Lichenoid (lichen planus – like) eruptions
 Lupus erythematosus
 Onycholysis
 Pemphigus vulgaris
 Photosensitivity
 Pigmentation
 Pityriasis rosea – like eruptions
 Pruritus
 Psoriasis
 Purpura
 Raynaud's phenomenon
 Toxic epidermal necrolysis
 Urticaria
 Vasculitis
 Xerostomia

variety of factors, including cumulative toxicity, overdose, drug-drug interactions, and metabolic alterations.

Immunologically mediated drug reactions can be characterized based on the Gell and Coombs classification of hypersensitivity. Type I, IgE-mediated reactions occur when mast cell and basophil mediators are released following the bridging of antigen between two IgE antibody molecules on sensitized mast cells and basophils. Mast cell mediators such as histamine and leukotrienes are released locally in the skin, blood vessels, gastrointestinal tract, and respiratory tract. Type I reactions in skin typically manifest as urticaria and angioedema. After the administration of an oral medication, there can be a delay of 1 to 2 hours before such symptoms occur. With parenteral administration of medication, the

reaction can occur almost immediately. Anaphylaxis may result from any route of administration and may develop rapidly. The reaction may appear to diminish after several hours only to exacerbate again for days because of the late phase response that characterizes IgE-mediated reactions [5]. Reactions also may be prolonged with medications that have a long half-life or that are administered as a long-acting formulation or intramuscular depot.

In type II or cytotoxic reactions, antigen-specific IgG or IgM antibodies interact with drug antigens on cell membranes. In the presence of complement, the antibody-coated cell is either removed or destroyed by the reticuloendothelial system. Antibiotic-induced hemolytic anemia and thrombocytopenia are type II reactions. Variations of this reaction type may be autoimmune bullous disease, such as drug-induced pemphigus or linear IgA bullous disease, although it is not known why autoantibodies form to keratinocyte antigens in these diseases and whether drug antigens are involved.

Type III reactions occur when circulating soluble complexes of drug antigens and specific IgG or IgM antibodies deposit in tissue. Tissue damage occurs when the complement system is activated. Serum sickness and the Arthus reaction are examples of type III reactions. This hypersensitivity reaction occurs when antibody-antigen complexes deposit in small vessels of the skin, joints, and other tissues. Serum sickness–like reactions usually occur 7 to 21 days after drug administration. Antibiotics cause the majority of drug-related type III reactions.

Type IV reactions, also known as delayed-type hypersensitivity reactions, are mediated by activated T lymphocytes that recognize antigens. Contact dermatitis is an example. Drug-related delayed-type hypersensitivity reactions include exanthematous, fixed, lichenoid, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN). Recent work has proposed that type IV reactions be divided into four subtypes based on the T-lymphocyte subset and cytokine expression profile involved [4].

Diagnosis of drug eruptions

A logical approach to diagnosing a drug eruption begins with an accurate description of the primary skin lesion, including the distribution, configuration, and any secondary skin changes (Table 1). Information needs to be collected regarding all of the medications taken by the patient, both prescription and nonprescription. This list should include any nutritional and herbal supplements. Often, the patient's pharmacist and primary care physician are helpful in constructing a medication profile, both present and past.

The chronology of drug administration is important. A drug timeline can be helpful in assessing the timing of medications relative to the cutaneous eruption. Most immunologically mediated drug reactions occur within 8 to 21 days of initiating a new medication. Knowledge of the half-lives of the respective medications is also important. Drug eruptions should resolve with removal of the offending agent; however, for medications with long half-lives, this can be

Table 1
Types of skin lesions that may be observed in drug reactions

Lesion name	Description
Primary lesions	
Circumscribed, flat, nonpalpable change in skin color	
Macule	Lesion, 1 cm
Patch	Lesion, 1 cm
Palpable, elevated solid masses	
Papule	Mass, 0.5 cm
Plaque	Mass, 0.5 cm
Nodule	Mass, 0.5–2 cm; firmer than a papule and with depth
Tumor	Mass >2 cm
Wheal	Irregular, superficial area of localized skin edema
Circumscribed, superficial skin elevations of free fluid in a cavity within the skin	
Vesicle	Filled with serous fluid, 0.5 cm
Bulla	Filled with serous fluid, 0.5 cm
Pustule	Filled with purulent material
Secondary lesion	
Loss of skin surface	
Erosion	Loss of superficial epidermis
Ulcer	Loss of epidermis and dermis
Fissure	Deep linear crack, extends into the dermis
Material on the skin surface	
Crust	Dried residue of serum, pus, or blood
Scale	Thin flake of exfoliated dermis
Miscellaneous lesions	
Lichenification	Thickened epidermis with prominent skin lines
Atrophy	Thinning of the skin, loss of skin lines, shiny
Excoriation	Scratch of the epidermis
Scar	Fibrous tissue replaces tissue in the dermis
Keloid	Hypertrophied scar extending beyond the injury
Shape and arrangement of lesions	
Linear	Arrangement of lesions in a line, often externally induced
Annular/arciform	Ring-shaped or half-circle, with a clear center
Iris or “bull’s eye”	Annular lesion with central macule or papule
Reticular	Netlike, lacy pattern
Grouped lesions	
Herpetiform	Clusters of vesicles
Zosteriform	Dermatomal grouping of lesions
Distribution of lesions	
Solitary (isolated), localized, regional, scattered, diffuse, generalized	

several weeks. Not infrequently, the offending agent is discounted as being causative because the eruption did not seem to resolve in a timely manner.

Withdrawal of the suspected medication should occur as soon as possible. This withdrawal is of utmost importance in life-threatening drug reactions, such as anaphylaxis, Stevens-Johnson syndrome, and TEN [6]. De-challenge (taking away the putative offending agent) and re-challenge (re-exposure to the putative offending agent) are important diagnostic maneuvers. Removal of all nonessential medications will help pare down the medication list. Medications should then

be added back one-by-one, as slowly as possible, and the clinical response assessed. The risk-benefit potential should be determined before discontinuing any necessary medications. Non-cross-reacting medications should be substituted when possible. A positive re-challenge is the strongest diagnostic clue, but de-challenge and re-challenge of medications should not be performed with a medication believed to be responsible for a serious drug reaction. Diagnostic or confirmatory tests to establish the responsible drug are not readily available and are of little help in the clinical setting, except with penicillin antibiotics causing an IgE-mediated reaction. Moreover, if the eruption is not serious, the duration of treatment is finite, and there is no suitable alternative, the offending medication can be continued cautiously with symptomatic treatment.

It is also useful to know which medications rarely cause drug eruptions (Box 2) [7]. Immunocompromised patients paradoxically have a higher incidence of adverse drug reactions. The reasons for this are unclear but may be related to multiple drug therapy, chronic drug exposure, and altered immunity and metabo-

Box 2. Drugs rarely causing cutaneous eruptions (rates estimated to be 3 cases per 1000)

Acetaminophen
Antacids: aluminum hydroxide, magnesium hydroxide
Antihistamines: diphenhydramine (may cause contact dermatitis if applied topically)
Atropine
Benzodiazepines
Chloral hydrate
Cromolyn
Digitalis
Ferrous sulfate
Insulin
Laxatives: bisacodyl, dioctyl, mineral oil, fiber
Local anesthetics
Muscle relaxants
Nitrates: isosorbide dinitrate
Nystatin
Oral contraceptives
Prednisone
Promethazine
Propanolol
Spironolactone
Theophylline
Thyroid hormones
Vitamin B complex and ascorbic acid

lism. A well-documented example of this risk is the increased incidence of trimethoprim-sulfamethoxazole hypersensitivity in patients with AIDS [8].

Common cutaneous drug eruptions

Exanthematous drug eruptions

Exanthems, skin lesions similar in appearance to those caused by viruses,¹ are the most common type of cutaneous drug eruption. The term *maculopapular* is a frequently used description for this cutaneous reaction pattern; however, it tends to be applied indiscriminately to many other eruptions and should be avoided. A large number of drugs can give rise to an exanthematous eruption. Of these drugs, the penicillin family is the most commonly implicated [1]. Viral infections may increase the incidence of morbilliform (measles-like) drug reactions. The frequency of aminopenicillin-induced exanthematous eruptions in patients with infectious mononucleosis is nearly 100%. It has been suggested that reactive drug metabolites alter the regulation of the cytotoxic immune response to virally infected cells [9].

The cutaneous eruption characteristically begins 7 to 14 days after the start of a new medication. When the medication is a re-challenge, it may occur much sooner. The pruritic lesions begin as erythematous macules that can evolve into papules and coalesce into plaques (Fig. 1). Urticaria-like lesions are also seen. Usually, the eruption begins on the upper trunk or head and neck. It spreads outward to the limbs in a bilateral and symmetric pattern. The involved areas often develop regions of confluence and can be accompanied by pruritus and fever. The eruption typically resolves in 1 to 2 weeks without sequelae.

The differential diagnosis is primarily a viral exanthem. It can be difficult to distinguish between these two entities if no eosinophils are identified on skin biopsy, which typically are found in drug reactions. Clinicopathologic correlation is always important, because similar histopathologic findings, lymphocytic perivascular inflammation with eosinophils, can be found in a number of distinct clinical entities [10]. In the adult population with exanthema, a drug eruption is favored over a viral cause. The opposite usually holds true in the pediatric population [11]. The association of an exanthematous eruption with a high fever may also herald a drug hypersensitivity syndrome, particularly in the presence of marked eosinophilia [12]. Elimination of the offending agent is the most important step in treatment. Symptomatic treatment with oral antihistamines and

¹ Six exanthems (or exanthematous diseases) have been described that have similar rashes. They have classically been referred to as numbers in the order in which they were originally reported: first (measles), second (scarlet fever), third (rubella), fourth (Dukes' disease), fifth (erythema infectiosum), and sixth (exanthema subitum). The term *exanthematous* is used to describe skin lesions that appear similar to these viral eruptions. (Available at:



Fig. 1. Exanthematous drug eruption caused by amoxicillin. Numerous generalized pruritic erythematous macules and papules.

topical glucocorticoids is usually sufficient. In more severe cases, systemic glucocorticoids may help provide relief more quickly.

Fixed drug eruptions

Fixed drug eruptions represent an interesting cutaneous reaction pattern. They are the second most common drug eruption after exanthematous eruptions in children and adults. Exposure to a drug results in the appearance of solitary or sometimes multiple well-demarcated lesions on the skin. When multiple lesions are present, the reaction is referred to as a generalized fixed drug eruption [13]. The color varies and includes red, red-brown, gray, blue, and violaceous. The lesions can also develop blisters in the center and can be difficult to distinguish from erythema multiforme [14] (Fig. 2A). Lesions typically develop within 1 to 2 weeks of starting a new medication. When the patient is re-challenged with the offending drug, the eruption recurs at the exact location previously involved. The recurrence often occurs within 30 minutes to 8 hours. Following an exacerbation, some patients demonstrate a refractory period (weeks to several months), during which the offending drug does not activate the lesion. Lesions can occur anywhere on the body but tend to favor the face, lips, hands, feet, and genitalia (Fig. 2B) [15]. Hyperpigmentation of the skin can persist for weeks to months after resolution of the eruption.

The most common drugs causing fixed drug eruptions are sulfonamides, tetracyclines, NSAIDs, barbiturates, and carbamazepine [16]. Because phenolphthalein has been removed from most laxatives, it is much less often the culprit than in years past. Interestingly, certain medications seem to favor certain body sites. Involvement of the glans penis is frequently caused by tetracycline [17] (Fig. 2B). The reason for this is unknown.

Most fixed drug eruptions are asymptomatic. Removal of the offending agent is the primary therapeutic intervention. When there is a single lesion, the dif-

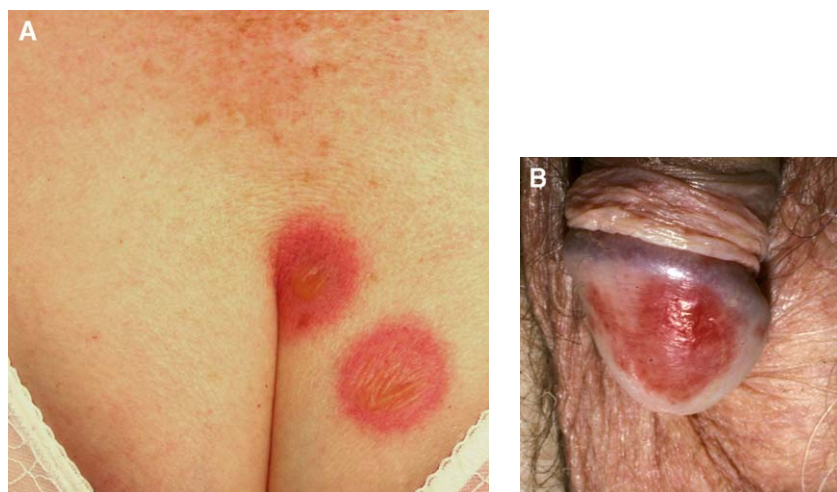


Fig. 2. Fixed drug eruption. (A) Bullous fixed drug eruptions from naproxen. Several well-demarcated bullae are pictured, each on an erythematous base. (Photograph courtesy of Nancy J. Samolitis, MD.) (B) Fixed drug eruption on the glans penis from tetracycline. (Photograph courtesy of Leonard J. Swinyer, MD.)

ferential diagnosis includes an insect bite. Diagnostic difficulty arises when there is an atypical presentation of a fixed drug eruption. A generalized fixed drug eruption with blistering has been reported and mistaken for Stevens-Johnson syndrome [18]. Re-challenge is a usual diagnostic maneuver and helps identify the offending agent when positive. The mechanism for fixed drug eruptions is unknown. Familial cases have been reported, and genetic susceptibility may have a role [19]. An association with HLA-B22 has been reported [20].

Urticaria, angioedema, and anaphylaxis

Acute urticaria is an eruption of edematous papules and plaques that are pruritic and transient. Central pallor is frequently seen. The lesions are generally polymorphic and multiple. They can occur anywhere on the body, including the palms, soles, and mucous membranes. Because of the diversity of clinical presentations and the involvement of acral surfaces, urticaria can be misdiagnosed as erythema multiforme. The duration of lesions is usually several hours, but less than 24 hours, and individual lesions resolve without sequelae. Lesions that remain fixed for greater than 24 hours or that show residual petechiae should raise the suspicion of urticarial vasculitis.

Urticaria results from a local increase in the permeability of capillaries and small venules that leads to dermal edema. The release of histamine from skin mast cells mediates this response in part. Other mediators that are likely important include prostaglandins, leukotrienes, neutrophil and eosinophil chemotactic

factors, platelet-activating factor, interleukin-1, and kinins [21]. Circulating total IgE levels may or may not be elevated; IgE-specific antibodies may be present in the absence of increased IgE levels [22].

Urticaria is characterized as acute when it lasts 6 weeks or less and chronic when it persists beyond this. It is often difficult to identify the inciting agent or factor that precipitates an episode of acute urticaria. The exception to this is a drug-related eruption. Several drugs can induce acute urticaria. Lesions appear within minutes to several days of exposure, depending on prior sensitization. The major drugs responsible for immunologically based urticaria are the penicillins, cephalosporins, and, less frequently, sulfonamides and tetracyclines [23]. Furthermore, urticaria may result from an interaction between an infectious agent and a medication. The classic example of this is Epstein-Barr virus (and infectious mononucleosis) with amoxicillin therapy, which frequently leads to an eruption that appears urticarial or exanthematous.

Anaphylactoid reactions mimic IgE-induced type I reactions but are caused by nonimmunologic release of histamine from mast cells. Aspirin and other NSAIDs may induce or exacerbate existing urticaria by this mechanism. Other drugs known to induce urticaria by nonimmunologic mast cell degranulation include morphine, codeine, quinine, curare, and radiographic contrast media [24].

Urticaria may progress to angioedema and anaphylaxis. Angioedema represents transient edema of the subcutaneous or submucosal tissues. It can be accompanied by life-threatening anaphylaxis. The most severe cases start within minutes of drug administration. Swelling typically involves the lips, eyelids, oropharynx, and tongue. Involvement of the larynx and epiglottis can lead to stridor. When the edema involves the gastrointestinal mucosa, it can result in abdominal pain, diarrhea, nausea, and vomiting.

The most common drugs contributing to angioedema are angiotensin-converting enzyme (ACE) inhibitors, penicillin, NSAIDs, radiographic contrast media, and monoclonal antibodies [25]. The incidence of angioedema in patients starting ACE inhibitors is 1 to 2 cases per 1000 new users [26]. Persons with a history of idiopathic angioedema and African-Americans have an increased risk for ACE inhibitor-induced angioedema. Angiotensin II receptor blockers do not cross-react with ACE inhibitors but can also lead to angioedema [27].

Anaphylaxis represents a life-threatening emergency. It presents with urticaria or angioedema with hemodynamic instability (hypotension, tachycardia, shock). The symptoms develop rapidly and peak within 5 to 30 minutes [28]. The earliest symptoms include itching of the palms and soles with tingling of the soft palate. Respiratory symptoms also develop and manifest as wheezing secondary to bronchospasm. The earliest intervention is discontinuation of the causative agent. This step is followed by rapid treatment with subcutaneous or intramuscular (preferred in patients with hypotension) epinephrine, intravenous antihistamines, and oral or intravenous glucocorticoids. Hospital admission for observation and airway management may be required. It is imperative that the patient understands the severity of potential re-exposure to the offending agent. Patients should have an epinephrine injection kit readily available for inadvertent re-exposure in the

future. Systemic glucocorticoids are not likely to be helpful in managing the acute stages of anaphylaxis but may help prevent the late phase response.

For uncomplicated urticaria without symptoms of upper airway involvement, oral H₁ antihistamines are the first line of therapy [29]. Second-generation, nonsedating oral antihistamines represent the most common therapeutic choice. Adjunctive therapy with H₂ antagonists is frequently employed. Sedating (first-generation) antihistamines, such as hydroxyzine, are useful for evening or bedtime use. Doxepin, a sedating tricyclic antidepressant, also has potent H₁ and H₂ antagonism and can be used in place of hydroxyzine. Oral glucocorticoids are not typically required for acute uncomplicated urticaria and are best reserved for the more severe presentations.

Neutrophilic drug-mediated eruptions

Acute generalized exanthematous pustulosis (AGEP) is a rare adverse drug reaction characterized by fever and generalized erythema followed by the sudden appearance of widespread pustules [30]. It typically has a rapid onset after ingestion of a medication, but its course is self-limited.

The onset of AGEP is abrupt, with high fever (39°C) accompanying or preceding the rash, which usually begins in the skin creases, sometimes on the face, and spreads within 24 hours. It manifests first as an edematous burning or pruritic confluent erythema of skin, which is quickly covered by numerous small pustules less than 5 mm in diameter (Fig. 3). Other features may include edema of the face, purpura on the legs, vesicles or blisters, some erythema multiforme–like atypical targets, and mucous membrane erosions of the mouth and tongue. In some patients, the confluence of pustules may lead to superficial detachment of



Fig. 3. Acute generalized exanthematous pustulosis from amoxicillin. Widespread pustules with associated erythema are shown.

the skin, mimicking TEN. AGEP has been misidentified as TEN on several occasions [31]. The pustules last for 5 to 10 days, followed by a superficial desquamation that lasts for a few days. Neutrophil counts are elevated above $7.0 \times 10^9/L$, and mild-to-moderate eosinophilia is present in about one third of cases. The pustules are sterile. There is usually no visceral involvement, and spontaneous healing occurs in 10 to 15 days. The prognosis is good despite the dramatic clinical presentation, which is sometimes mistaken for an infection. The mortality rate is less than 1% to 2%, and death occurs mainly in elderly persons with previous chronic diseases [32].

Because of the clinical and histologic similarity of the pustules, differentiating AGEP from acute pustular psoriasis can be difficult [33]. The acute presentation of AGEP and an association with drug ingestion aid in its identification. AGEP occurs in patients with psoriasis more frequently than expected by chance alone, suggesting that AGEP is a drug reaction pattern associated with psoriasis [34,35].

Although some cases of AGEP have been attributed to a viral eruption, at least 90% of AGEP cases are drug induced. In contrast with most drug eruptions, the interval between introduction of the drug and the reaction is very short, often 2 to 3 days when antibacterial agents are responsible [35]. With other medications, a more usual timing of 1 to 3 weeks is observed. The shorter interval may be a recall phenomenon reflecting previous sensitization to topical antibiotics. The drugs most frequently implicated are antibacterial agents. More than 50% of the responsible drugs are aminopenicillins and macrolids. Other antibiotics that can cause AGEP include cephalosporins, imipenem, fluoroquinolones, isoniazid, vancomycin, minocycline, and doxycycline.

Patch tests of the offending drug are more frequently positive than with other types of drug-related eruptions. The tests are often strongly positive, sometimes with pustules. This observation suggests that contact exposure to a medication, or a cross-reacting medication, sensitizes the patient and has a role in the pathogenesis of AGEP [36]. No specific therapy is required except for patients with high fever or significant pruritus. These patients can benefit from an antipyretic medication, topical glucocorticoids, or oral antihistamines.

Leukocytoclastic vasculitis

Cutaneous vasculitis is the most commonly encountered vasculitic manifestation in clinical practice. Palpable purpura is the most frequent presentation of small-vessel vasculitis. Lesions are usually round and 1 to 3 mm in diameter. They may coalesce to form plaques, and they may ulcerate. Palpable purpura is most frequently observed on the legs (Fig. 4), but any cutaneous surface can be involved. Cutaneous vasculitis is characterized histologically by the presence of small-vessel inflammation within the dermis, often with leukocytoclasia (cellular disruption of white blood cells with nuclear fragmentation, “nuclear dust”) on examination of a skin biopsy specimen. Immunofluorescence studies of a skin biopsy specimen are also helpful in the diagnosis of cutaneous vasculitis, in which vascular immunoglobulin and complement deposition are characteristically found.



Fig. 4. Leukocytoclastic vasculitis involving the lower extremity, demonstrating classic palpable purpura.

In more than 70% of cases, cutaneous vasculitis occurs in the setting of an underlying process, such as a medication exposure, infection, malignancy, or connective tissue disease, or as a manifestation of a primary systemic vasculitis. Antibiotics are the most common drugs that can cause cutaneous vasculitis, particularly beta-lactams. NSAIDs and diuretics also frequently cause vasculitis. Almost all drugs are potential causes. A diagnosis of idiopathic cutaneous vasculitis should be made only after other causes have been ruled out. Progression to a systemic vasculitis occurs infrequently.

The evaluation of patients with vasculitis involves a work-up for the presence of systemic disease. Testing of all adult patients includes a complete blood count with differential, erythrocyte sedimentation rate, urinalysis, and blood chemistry panel [37]. If bowel symptoms are present, a stool guaiac for fecal blood should be obtained along with other bowel studies that are indicated. If an obvious underlying disease etiology is lacking, serologic studies should include assays for antinuclear antibodies, antiproteinase 3, antimyeloperoxidase (previously referred to as antineutrophil cytoplasmic antibodies or ANCA), and rheumatoid factor. Serologic testing for a possible streptococcal infection should be considered. Tests should also be performed for serum protein electrophoresis, cryoglobulins, and hepatitis C antibody in patients without otherwise identified diseases [38,39]. Complement levels, including total hemolytic complement (CH100 or CH50), C3 levels, and C4 levels, may be ordered for patients suspected of having lupus erythematosus or patients who have urticarial vasculitis [40]. Hepatitis B has been associated with vasculitis in the past; however, it seems that the association may have occurred as a result of co-infection with hepatitis C [41]. Measurement of hepatitis B surface antigen may not be required in all cases.

Once a diagnosis of cutaneous small-vessel vasculitis is established and the patient is fully evaluated, specific or nonspecific management options may be used. If an underlying disease or exposure is identified, management of this process forms the initial basis for treating the cutaneous vasculitis. Elevation of the legs or compression stockings may be of use, because the disease often affects dependent areas. Removal of a drug thought to be causing the vasculitis may result in relatively rapid clearing in to 2 to 3 weeks [37]. When these measures are not sufficient, systemic glucocorticoids, colchicine, or dapsone may be administered for patients with disease of skin with or without joint manifestations [42,43]. Sometimes a combination of immunosuppressive agents is needed to control disease manifestations. This regimen is usually necessary when the vasculitis is associated with a systemic or chronic idiopathic process rather than a drug exposure.

Drug-mediated photosensitive cutaneous eruptions

Certain cutaneous drug eruptions occur only on sun-exposed skin and are called photosensitive drug reactions. Depending on the type of photosensitizing drug, a phototoxic or a photoallergic rash will occur. A phototoxic drug reaction involves absorption of ultraviolet radiation and the release of energy causing damage to epidermal cells. Medications frequently associated with a phototoxic reaction include hydrochlorothiazide, furosemide, diltiazem, sulfonamides, psoralens, fluoroquinolones, and tetracyclines [44]. A photoallergic drug reaction occurs when ultraviolet energy causes the drug to bind as a hapten to native protein on epidermal cells, creating a complete antigen that sensitizes nearby lymphocytes. Medications frequently associated with a photoallergic reaction include dapsone, quinidine, hydrochlorothiazide, and chlorpromazine [44]. After cessation of the drug, re-exposure to sunlight may cause a recurrence of skin lesions with photoallergic, but not phototoxic, cutaneous eruptions.

Patients who report photosensitivity should be questioned about the medications they are taking and the products they are applying to the skin. Sunscreens, fragrances, and, occasionally, antibacterial soaps may cause photoallergic reactions when applied to the skin. Establishing whether the photosensitivity can be elicited with exposure to sunlight through window glass may provide useful information about the wavelengths of light that cause the response; ultraviolet (UV)-B light does not penetrate window glass, whereas UV-A light and visible light do.

Phototoxic and photoallergic reactions occur in sun-exposed areas of skin, including the face, “V” area of the neck, dorsa of the hands, and forearms. The hair-bearing scalp, postauricular, periorbital areas, and submental portion of the chin are usually spared. A widespread eruption suggests exposure to a systemic photosensitizing agent, whereas a localized eruption indicates a reaction to a locally applied topical photosensitizer.

Photopatch testing is an important tool in the diagnosis of photoallergic contact dermatitis. Suspected photoallergens are applied to the back in two sets.

One set is removed after 24 hours and irradiated. Both sets of patch tests are evaluated for a positive reaction after 48 hours. Erythema, edema, or vesiculation at an irradiated site indicates a positive reaction. A positive reaction at both sites is interpreted as an allergic contact dermatitis. A positive reaction at the un-irradiated site with a stronger one at the irradiated site should be interpreted as allergic dermatitis and photoallergic contact dermatitis [45].

Phototesting with UV-A and UV-B is helpful in diagnosing photosensitivity disorders. This test is performed by treating small areas of skin on the back or inner aspect of the forearms with gradually increasing doses of light. The minimum dose of light required to produce uniform erythema over the entire irradiated site after 24 hours is called the minimum erythema dose (MED). If no photoallergens were applied to the skin and no phototoxic agents are still present after systemic administration, the MED for UV-A and UV-B light should be normal in drug-induced photosensitivity disorders.

Photoallergic reactions typically develop in sensitized individuals 1 to 2 days after exposure. The reaction usually manifests as a pruritic eczematous eruption. Erythema and vesiculation are present in the acute phase. Chronic exposure results in erythema, lichenification, and scaling. Hyperpigmentation does not occur in photoallergic reactions. Photoallergic reactions develop in a minority of individuals exposed to the drug and ultraviolet light, and the incidence is less than that of phototoxic skin reactions [44]. The amount of drug required to elicit photoallergic reactions is considerably smaller than that required for phototoxic reactions. Photoallergic reactions are delayed-type hypersensitivity, and their onset is often delayed by as long as 24 to 72 hours after exposure to the drug and light. By contrast, phototoxic responses often occur within minutes or hours of light exposure.

Acute phototoxicity often begins as an exaggerated sunburn reaction with erythema and edema within minutes to hours of light exposure. Vesicles and bullae may develop with severe reactions. The lesions can be pruritic and often heal with residual hyperpigmentation, which resolves in weeks to months. Chronic phototoxicity also may appear as an exaggerated sunburn reaction. Often, lichenification occurs because of repeated rubbing and scratching of the photosensitive area (Figs. 5A and B). Distinguishing phototoxic reactions from photoallergic reactions based strictly on the physical appearance of the lesions may be difficult. Discriminating between photosensitivity diseases and heat-related exacerbation of skin diseases may also be difficult. The clinician should assess symptoms of other diseases that are known to cause photosensitivity and determine whether a family history of photosensitivity exists. Connective tissue disease, such as lupus erythematosus, can present with photosensitivity and can have a genetic predisposition. In most patients, the physical examination suggests a photosensitivity reaction based on the distribution of skin lesions. The physician should inquire about intolerance to the sun. The laboratory work-up should include an assessment of urine porphyrin levels. These levels are elevated in porphyria and are normal in drug-induced photosensitivity. Antinuclear antibody and Ro (SS-A) antibody levels should be evaluated for lupus erythematosus, particularly subacute cutane-



Fig. 5. Chronic phototoxic drug reaction. (A) Lichenified papules and plaques with excoriations. Prominent sparing of the anterior neck and nasolabial folds and involvement of the V of the neck are features of sun-related eruptions. (B) Phototoxic drug eruption, lateral view. There is notable sparing of the postauricular skin and anterior neck, "chin shadow."

ous lupus erythematosus, which is an exquisitely photosensitive type. Phototesting as described previously should also be performed.

The mainstays of treatment are identification and avoidance of the causative agent, along with the use of sun protection and measures of symptomatic relief. Topical glucocorticoids and cool compresses may lessen the condition. The use of systemic glucocorticoids should be reserved for the most severe cases. If sunscreens are not the cause of the photosensitivity, they should be used liberally. The sun protection factor (SPF) may not be a reliable indicator of protection against drug-induced photosensitivity. The SPF refers to the degree of protection against sunlight-induced sunburn, primarily that caused by UV-B. Most drug-induced photosensitivity reactions are caused by wavelengths within the UV-A range; therefore, sunscreens that absorb UV-A should be prescribed. Sunscreens that contain Parsol 1789, titanium dioxide, and zinc oxide are effective in blocking UV-A radiation [46].

Drug-induced pseudoporphyria and porphyria

In response to medications such as NSAIDs and tetracycline, fragile blisters can develop in sun-exposed areas that are identical in appearance to porphyria cutanea tarda. Naproxen is the prototypical drug associated with this cutaneous eruption. Classic areas of involvement are the dorsum of the hands, forearms, ears, and face. These bullae are flaccid and easily rupture to form crusted erosions. In distinction to porphyria cutanea tarda, hypertrichosis and dyschromia do not

usually occur. The histology of pseudoporphyria is identical to porphyria cutanea tarda except that the serum and urine porphyrins are normal. The treatment of drug-induced pseudoporphyria is directed toward eliminating the causative agent and sun protection. Patients should be made aware that symptoms could persist for several months after discontinuation of the inciting agent.

Certain drugs, including conjugated estrogens and iron, may induce full-blown porphyria cutanea tarda. In these cases, urinary porphyrins are abnormal. Several other chemicals such as ethyl alcohol, hexachlorobenzene, and chlorinated phenols may also induce porphyria cutanea tarda; alcohol, in particular, along with the offending drug must be avoided by individuals with drug-induced disease.

Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme

Toxic epidermal necrolysis represents a dermatologic emergency. The disorder is characterized by widespread erythematous or purpuric macules and targetoid lesions. Widespread, full-thickness epidermal necrosis with involvement of more than 30% of the body surface area occurs. Commonly, the mucous membranes are also involved. Drugs are implicated in approximately 65% of cases, and the mortality rate can approach 40% [47]. Penicillins and sulfonamide antibiotics are the drugs most commonly identified as etiologic agents.

Stevens-Johnson syndrome can also present as a dermatologic emergency. It is also characterized by widespread erythematous or purpuric macules and targetoid lesions. The rate of epidermal detachment is less than 10%. Mucosal involvement is common (90%). Patients with Stevens-Johnson syndrome may progress so that a larger surface area becomes involved. “Overlap Stevens-Johnson syndrome–TEN” cases have detachment of 10% to 30% of body surface areas. Similar to TEN, medications are important inciting agents. Infections, usually with *Mycoplasma*, may induce some cases. The mortality rate for Stevens-Johnson syndrome is much lower than that for TEN and approaches 5%.

Erythema multiforme is characterized by targetoid lesions, with or without blisters, in an acral distribution. Oral lesions may occur. Most cases are secondary to prior infection with a herpes virus [48]. The condition generally has low morbidity and no mortality and is often recurrent. When erythema multiforme presents with blisters and mucosal involvement, it is often referred to as erythema multiforme major. There are conflicting opinions in the literature as to whether erythema multiforme major and Stevens-Johnson syndrome are the same disease process. In 1993, an international group proposed a consensus classification that included erythema multiforme major, Stevens-Johnson syndrome, and TEN as belonging to a spectrum of disease; however, recently, the same group has distinguished erythema multiforme major and the Stevens-Johnson syndrome/TEN spectrum as being separate entities [47].

The pathophysiologic mechanism underlying Stevens-Johnson syndrome/TEN is unknown. Patients may have genetic defects in their metabolic pathways that lead to the accumulation of toxic metabolites. For example, patients with sulfonamide-induced TEN have a slow acetylator phenotype, resulting in

increased production of sulfonamide hydroxylamine via the P-450 pathway [28,49]. These drug metabolites may have direct toxic effects or act via a hapten-mediated mechanism to break self-tolerance to endogenous proteins.

A prodrome of nausea, vomiting, diarrhea, malaise, headache, cough, coryza, sore throat, chest pain, myalgias, and arthralgia lasting up to 14 days may precede the skin eruption. TEN presents with an acute phase (8–12 days) consisting of persistent fevers, generalized epidermal sloughing, and mucous membrane involvement (Figs. 6A and B). Complications include stomatitis and mucositis, which are painful and hinder oral intake. The conjunctivae commonly are affected 1 to 3 days before the appearance of skin lesions. Buccal, nasopharyngeal, and pulmonary tract desquamation and erosion may be present. Esophageal and perineal desquamation and erosion may also be present.

Recently, investigators developed a combined prognostic index, the SCORTEN, to assess the severity of disease. Seven independent risk factors for death were identified in the SCORTEN index: age above 40 years, malignancy, tachycardia above 120 beats/min, an initial percentage of epidermal detachment above 10%, serum urea nitrogen above 10 mmol/L, serum glucose above 14 mmol/L, and bicarbonate below 20 mmol/L [50]. For each SCORTEN point, the odds ratio was 3.45. Because the risk estimates of these seven parameters were similar, a weight of 1 was assigned to each. The SCORTEN is calculated for each patient by summing the number of abnormal parameters. The probability of death is 3.2% when only one risk factor is present but reaches 90% when five or more risk factors are present at the first day of hospitalization.

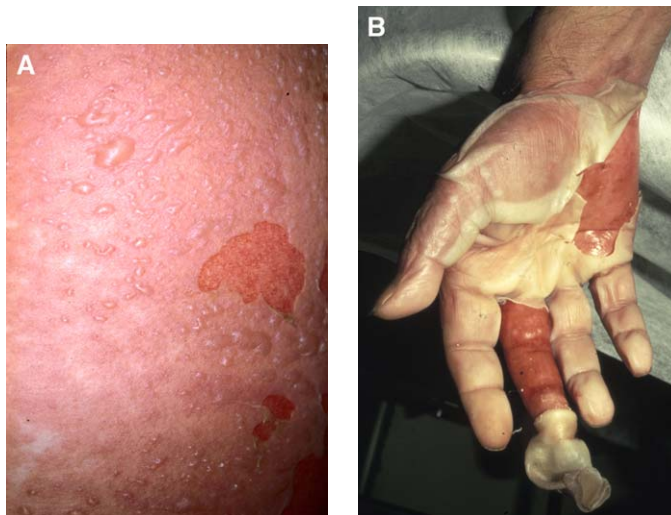


Fig. 6. Toxic epidermal necrolysis. (A) Diffuse erythema and blisters result from full-thickness necrosis of the skin. (B) Full-thickness necrosis can result in dramatic de-gloving of acral skin. (Photograph courtesy of Leonard J. Swinyer, MD.)

The extent of skin detachment is only one of seven prognostic factors and cannot by itself indicate the probability of death. It may be difficult to evaluate the body surface area involved, and the patchy nature of the eruption usually leads the medical staff to overestimate the affected area. Re-epithelialization is usually complete within 3 to 4 weeks, but pressure and mucosal areas may remain eroded and crusted for another 2 weeks or longer. Survivors of Stevens-Johnson syndrome/TEN may experience numerous long-term sequelae. Eye involvement, in particular, may cause visual impairment, including permanent vision loss.

Studies have linked the necrolysis to apoptosis of keratinocytes induced by cytotoxic T lymphocytes invading the epidermis and to the local production of cytokines. This mechanism provides a rationale for using systemic glucocorticoids, immunosuppressive drugs, and anticytokines, with the goal of halting the progression of epidermolysis [51]. The use of glucocorticoids in management of the Stevens-Johnson syndrome/TEN spectrum is one of the most controversial areas in dermatology. Administration early in the course of disease has been advocated, but multiple retrospective studies demonstrate no benefit or even higher rates of morbidity and mortality than without it [52].

Several studies support the use of pooled intravenous immunoglobulin (IVIG) in the treatment of TEN. Viard et al suggested that apoptotic cell death occurs via activation of a cell-surface death receptor [48]. In vitro, target cell death was blocked by a receptor-ligand blocking antibody and by antibodies present in pooled human IVIG. Other studies have failed to show a survival benefit with IVIG, underscoring the need for multicenter trials [53–55].

Patients with Stevens-Johnson syndrome/TEN should be treated in an intensive care unit or burn unit under the coordinated care of an intensive care unit team and consultants. The broad principles of management are fluid replacement, nutritional supplementation, sterile technique, and wound care. Studies have shown that early care by or transport to a burn center significantly reduces the mortality rate [56]. Fluid rehydration is essential, because epidermal loss results in massive fluid shifts and dehydration. Aggressive nutritional support should be initiated, because protein losses through denuded skin predispose the patient to complications and retardation of re-epithelialization. Epidermal loss predisposes patients to infection and sepsis. Silver sulfadiazine as topical treatment must be avoided, because sulfonamides are a frequent inciting drug in TEN. Debridement of all necrotic epidermis with replacement by using biologic dressings, such as collagen-based substitutes or porcine xenografts, is recommended [57]. Ophthalmologic consultation and care is essential. Frequently applied eye drops may be necessary with daily blunt disruption of synechiae. Eye drops must not contain sulfonamides, because they are frequently implicated in TEN.

Drug hypersensitivity syndrome

A wide spectrum of cutaneous drug eruptions is associated with internal organ toxicity. The triad of fever, skin eruption, and internal organ involvement is termed the *drug hypersensitivity syndrome*. This syndrome causes significant

morbidity and mortality and occurs in approximately 1 in 3000 persons who are started on associated drugs, including anticonvulsants (phenytoin, phenobarbital, carbamazepine, and lamotrigine), sulfonamide antibiotics, dapsone, trimethoprim, minocycline, metronidazole, azathioprine, and allopurinol [12]. The drug hypersensitivity syndrome usually occurs during the first prolonged course of an associated drug, typically starting 1 to 6 weeks (and occasionally 2–3 months) into therapy.

The prodrome of this syndrome can mimic a viral upper respiratory tract infection, beginning with fever, malaise, and pharyngitis, which are followed by skin lesions in 85% of patients. Cutaneous involvement ranges in severity, ranging from an exanthematous eruption, erythroderma, and Stevens-Johnson syndrome to TEN. More frequent and potentially serious internal organ manifestations are lymphadenopathy, hepatitis, nephritis, pneumonitis, and hematologic involvement. Patients often demonstrate atypical lymphocytosis and neutrophilia early in the syndrome, with eosinophilia appearing later. Agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, and aplastic anemia also can occur. Patients afflicted with drug hypersensitivity syndrome are often very sick and may take weeks to months to fully recover. Additionally, a subgroup of patients may become hypothyroid owing to autoimmune thyroiditis within 2 months after the onset of symptoms [58].

Prompt drug cessation is essential, and delay may increase morbidity and mortality. The role of disease-modifying therapies is uncertain, particularly with blistering eruptions. Careful evaluation and monitoring of patients is required, because new organ involvement can become evident even after drug cessation. Severe internal organ damage (massive hepatic necrosis, pneumonitis, carditis, and colitis) may cause death. More severe nonblistering cases are usually treated with systemic steroids that are weaned over weeks. Despite the cessation of the etiologic drug and a slow tapering course of glucocorticoid therapy, symptoms can recur and fluctuate over weeks or months before eventually lessening.

Other drug eruptions

Drug-induced blistering disorders

Autoimmune blistering disorders, such as pemphigus, bullous pemphigoid, and linear IgA bullous dermatosis, have been associated with medications [59,60]. In approximately 80% of drug-induced pemphigus cases, a thiol group-containing medication, such as penicillamine or captopril, has been implicated [61]. Other medications in this group that have caused pemphigus include pyritinol, thiopronine, piroxicam, thiamazole, and gold sodium thiomalate. Thiols (highly reactive sulfhydryl compounds) can reduce disulfide bonds and cause acantholysis directly without antibody. Nevertheless, similar to idiopathic pemphigus, autoantibodies against cell adhesion molecules in desmosomes of keratinocytes, namely, desmogleins, have been found [60,62]. Clinically, drug-induced pemphigus

resembles pemphigus foliaceus, with superficial flaccid blisters and crusted erosions but no mucosal involvement. These lesions are prone to spontaneous remission in 35% to 50% of cases. Other medications, such as penicillin and its derivatives, piroxicam, and cephalosporins, have “masked thiols.” They contain sulfur groups that may undergo metabolic change to active thiol groups and cause a pemphigus vulgaris type of eruption (Fig. 7). In distinction to pemphigus foliaceus, mucous membrane involvement occurs in nearly half of the cases. Other medications not containing a thiol group that have induced pemphigus include enapril and dipyrone.

Drug-induced bullous pemphigoid is similar to the idiopathic disease. It presents with tense bullae distributed on the extremities, trunk, and occasionally the mucous membranes (Fig. 8). Immunofluorescence testing has revealed an IgG autoantibody directed against a 230-kD noncollagenous cytoplasmic protein (BPAg1) of the hemidesmosome [63]. Medications implicated include furosemide, ACE inhibitors (captopril, enalapril), penicillin, chloroquine, and sulfasalazine.

Linear IgA bullous dermatosis most commonly occurs with vancomycin therapy, presenting with tense blisters that mimic bullous pemphigoid. Antibodies are directed against collagen VII and BPAg1 [64, 65]. Other medications associated with linear IgA bullous dermatosis include captopril, ceftriaxone, furosemide, lithium, diclofenac sodium, penicillin, piroxicam, rifampin, trimethoprim-sulfamethoxazole, and interleukin-2 (used in cancer therapies).

Invaluable in the diagnosis of a drug-induced blistering eruption is a skin biopsy for immunofluorescence studies. False-negative studies can result when the sample is obtained from an incorrect location. Logic might dictate sampling

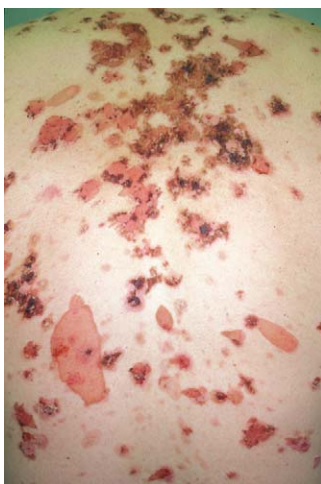


Fig. 7. Drug-induced pemphigus vulgaris from enalapril. Flaccid vesicles and bullae are distributed on the torso; many have evolved into crusted erosions.



Fig. 8. Drug-induced bullous pemphigoid from furosemide. Tense vesicles and bullae are shown on the dorsum of the foot.

the blister itself; however, frequently, the autoantibodies are degraded within the blister site by the inflammatory process. The specimen should be obtained from an inflamed site adjacent (perilesional) to the blister. Treatment for all forms of drug-induced blistering eruptions starts with discontinuation of the causative agent. Additional treatment includes topical or systemic glucocorticoids, mycophenolate mofetil, azathioprine, cyclophosphamide, and plasmapheresis.

Lichenoid drug reactions

Lichenoid drug eruptions show violaceous, polygonal, papules that mimic lichen planus. The lesions can be generalized and favor sun-exposed sites. The degree of oral involvement is variable. Idiopathic lichen planus has a predilection for the flexor aspects of the forearms and legs, whereas a lichenoid drug eruption typically has a more symmetric involvement of the trunk and extremities [66]. The drugs most commonly reported to cause lichenoid drug eruptions are ACE inhibitors, furosemide, gold, NSAIDs, proton pump inhibitors, and quinacrine.

Erythema nodosum drug reactions

Erythema nodosum is characterized by tender subcutaneous nodules, often with overlying ecchymosis. The nodules (one to several) typically occur on the anterior lower legs but may be found elsewhere on the body. Systemic symptoms, including fever and arthralgia, may or may not be present. Erythema nodosum is most likely a reactive pathogenic process; infections, especially streptococcal, are commonly implicated, but reactions to drugs may also induce erythema nodosum. Drugs implicated are sulfonamides and other antibiotics, bromides, iodides, and oral contraceptives [67].

Disease-exacerbating drug reactions

Certain drug reactions exacerbate or elicit cutaneous diseases, including acne, psoriasis, dermatitis herpetiformis, and alopecia. For the most part, the mechanisms are not known. Drugs known to exacerbate acne include hormones (glucocorticoids, oral contraceptives, androgens, and adrenocorticotrophic hormone), phenytoin, isoniazide, trazodone, lithium, and haloperidol [68]. Drugs known to exacerbate or induce psoriasis include antimalarial agents, NSAIDs, meprazine, clonidine, olanzapine, digoxin, tetracyclines, interferon, and, particularly, lithium and beta-blocking agents [69]. Topical or oral iodine may exacerbate or induce dermatitis herpetiformis. Drug-induced lupus may result from hydralazine and procainamide [70]. Several pharmacologic agents induce alopecia. Chemotherapy of various types arrests hair growth by inducing apoptosis of hair follicle cells. Other drugs causing hair thinning include anticoagulants, hormones, phenytoin, retinoids, NSAIDs, tofranil, valproate, bromocriptine, and piroxicam. Drugs that can cause increased hair growth include streptomycin, diphenylhydantoin, glucocorticoids, penicillamine, diazoxide (particularly in children), minoxidil, and cyclosporin A.

Summary

Cutaneous drug eruptions demonstrate a broad spectrum of clinical presentations. Those discussed herein represent some of the most common or serious reactions. Knowledge of these reaction patterns and their associated medications will help direct the physician in further work-up and therapy. Not all cutaneous drug reactions are serious, and, in some instances, the offending drug can be continued if medically necessary. It is imperative that individuals with life-threatening drug reactions understand the implications of potential re-exposure. Many resources are available to the physician that will aid in the diagnosis of a drug eruption. Further information can be obtained in the primary literature, specialty textbooks, and drug reference databases online.

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