Drug hypersensitivity: Classification and clinical features

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INTRODUCTION

Drug hypersensitivity reactions (DHR) include allergic, exaggerated pharmacologic, and pseudoallergic reactions to medications that result from an enhanced immunologic or inflammatory response.

The classification and clinical features of drug hypersensitivity will be reviewed here, beginning with a categorization of the different types of adverse drug reactions. A detailed discussion of the pathogenesis of drug hypersensitivity and an approach to the diagnosis and management of these conditions are found separately. (See "Drug allergy: Pathogenesis" and "An approach to the patient with drug allergy".)

CATEGORIES OF ADVERSE DRUG REACTIONS

An adverse drug reaction is a general term referring to any untoward reaction to a medication. Adverse drug reactions may be broadly divided into two types, type A and type B (table 1).

Type A reactions — Type A reactions make up 85 to 90 percent of all adverse drug reactions. These can affect any individual, given sufficient dose and exposure, and are predictable from the known pharmacologic properties of a drug. Examples of type A reactions include diarrhea in response to antibiotics, gastritis in association with long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), or aminoglycoside nephrotoxicity.

Type B reactions — Type B reactions represent hypersensitivity reactions. They make up 10 to 15 percent of adverse drug reactions, occur in a susceptible subgroup of patients, and have signs and symptoms that are different from the pharmacologic actions of the drug. The great majority of hypersensitivity reactions are mediated by immunologic and/or inflammatory mechanism. In addition, there are reactions, referred to as idiosyncratic drug reactions and exaggerated sensitivity reactions, which present with symptoms that do not involve the immune system or inflammatory cells.

- **Drug hypersensitivity reactions (DHR)** are the result of immune or inflammatory cell stimulations by the medication. They account for about 6 to 10 percent of all adverse drug reactions, but up to 10 percent of fatal reactions [1]. Hypersensitivity reactions are the focus of this review.

- **Idiosyncratic drug reactions and exaggerated sensitivity** – Idiosyncratic drug reactions are qualitatively distinct from the known pharmacologic toxicities of the drug. These reactions can arise from genetic differences in the patient, such as primaquine causing nonimmune hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency or azathioprine toxicity developing in patients with thiopurine methyltransferase (TPMT) deficiency [2-4]. Other patients experience an **exaggerated sensitivity** at low and sometimes subtherapeutic doses. An example would be the individual who develops tinnitus in response to a single dose of aspirin. This putatively reflects altered drug metabolism or increased end-organ sensitivity. (See "Drug-induced hemolytic anemia".)

Definition of drug hypersensitivity reactions — DHRs may be defined as reactions resulting from unintended and unwanted stimulation of immune or inflammatory cells by a medication.

CLASSIFICATION OF DRUG HYPERSENSITIVITY

Drug hypersensitivity can be subdivided based on time of appearance of symptoms, mode of action of the drug on immune/inflammatory cells, or on immunologic mechanism. In practice, a drug hypersensitivity reaction (DHR) is often defined by a combined approach, considering time of appearance, possible mode of action (mechanism of immune stimulation), and resulting pathophysiology [5].

It is important to differentiate between DHRs elicited by small molecules used as medications and DHRs induced by large proteins used as medications (eg, monoclonal antibodies), because the modes of action and resulting adverse reactions differ substantially [6].

Based on timing of symptom onset — The World Allergy Organization (WAO) has recommended dividing immunologic drug reactions into immediate reactions (ie, onset within one hour of exposure) and delayed reactions (onset after one hour), based on the timing of the appearance of symptoms [7].

Immediate — The WAO distinction between immediate and delayed drug reactions is intended to distinguish IgE-mediated, type I reactions from other types. Type I reactions classically begin within one hour of the first administered dose. However, some IgE-mediated reactions appear after one hour, particularly if the drug was administered orally and with food, which slows absorption. Nevertheless, this period of one hour identifies the majority of IgE-mediated reactions, which carry the risk of anaphylaxis if the patient is reexposed.

Delayed — Reactions appearing after one hour are classified as delayed, although most delayed reactions begin after six hours and typically after days of treatment. As an example, delayed reactions to amoxicillin classically start on day 7 to 10 of treatment, and may even begin one to three days after cessation of treatment. These reactions may be caused by several different mechanisms, but they are not IgE mediated. Types II, III, and IV immunologic reactions are all considered delayed reactions.

Some delayed reactions begin after weeks of continuous treatment. One such disorder is "drug rash with eosinophilia and systemic symptoms" (DRESS), which is a systemic drug reaction that begins 1 to 12 weeks into continuous treatment [8]. This reaction, which is also called "drug-induced hypersensitivity syndrome" (DiHS), is characterized by fever, rash, and multiorgan involvement, and may or may not be associated with eosinophilia and lymphocytosis. The liver (hepatitis) and heart (hypersensitivity myocarditis) may be affected. These reactions can persist for weeks to months, even after the medication is stopped. (See 'Type IV reactions' below and "Myocarditis: Causes and pathogenesis", section on 'Hypersensitivity myocarditis'.)

Based on mode of action — Drugs, which are small molecular compounds, often with a size <1000 Daltons, can interact with the immune and inflammatory system in different ways:

Drug allergy/immune reactions — Most drugs are chemicals that are too small to elicit immune responses. However, some drugs have or gain the ability to bind covalently to proteins, which can transform a self-protein to a new antigen (hapten protein or hapten-peptide complex). Such hapten-protein complexes act like classical antigens and thus elicit immune reactions to the hapten-modified protein/peptide, which can be mediated by IgE, IgG, or by lymphocytes. These reactions can result in the many different clinical pictures of drug allergy (eg, contact dermatitis to 1-chloro-2,4-dinitrobenzene (DNCB), IgE-mediated anaphylaxis to

penicillin). The different types of immunologic drug reactions are described below. (See 'Based on immunologic mechanism' below.)

Pharmacologic interaction with immune receptors (p-i reactions) — A substantial part of immune-mediated DHR is due to an "off-target" activity of a drug on immune receptor proteins, such as HLA proteins and T cell receptors (TCR). These interactions are called "pharmacologic interaction with immune receptors," or p-i reactions. P-i mediated immune stimulations do not result from the drug acting as a new antigen. Rather, the drug forms a strong, noncovalent bond directly with the immune receptor on antigen presenting cells (HLA) or on T cells (TCR), leading to stimulation of the T cell [9]. The stimulation may be either direct, if it binds to TCR, or indirect, if the drug binds to the HLA-protein and thereby elicits a T cell reaction directed to the drug-modified HLA-protein-peptide complex. Thus, in all p-i reactions, the clinical symptoms are due to activation of T cells and the effects of that activation on the involved cells. The clinical picture can be maculopapular eruption, SJS/TEN, DRESS, hepatitis, etc. As p-i reactions are typical pharmacologic drug-receptor interactions, they are dose-dependent to some degree.

If the drug binds preferentially to a certain HLA-protein (eg, abacavir to HLA-B*57:01), then the reactions disproportionately or exclusively affect individuals with these alleles [10]. This explains the HLA-linkage of some DHRs and means that certain p-i mediated forms of DHR are predictable. Well-investigated examples of p-i reactions occur with abacavir, carbamazepine, allopurinol, dapsone, and flucloxacillin hypersensitivity reactions. HLA testing of patients is recommended before administering abacavir and carbamazepine in populations in which there is a significant prevalence of the genotype. Specific screening recommendations are discussed in more detail separately. (See 'Drug-induced hypersensitivity syndrome' below and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Carbamazepine'.)

Pseudoallergy — Another heterogeneous form of adverse drug reaction is drug intolerance or pseudoallergy [11,12]. Pseudoallergic reactions resemble immunologic drug reactions but lack evidence of specific immune system involvement (drug-specific IgE, IgG, or specifically activated T cells) (table 2). The pathomechanism of these reactions is only partly understood [13]. The signs and symptoms of most pseudoallergic reactions are similar to IgE-mediated (immediate) allergic reactions. Both appear rapidly (within minutes), and both can involve urticaria, angioedema, or anaphylaxis due to mast cell degranulation. In pseudoallergy due to NSAIDs, there is both mast cell activation and eosinophilic inflammation. Pseudoallergic reactions to NSAIDs are reviewed in more detail separately. (See "NSAIDs (including aspirin): Allergic and pseudoallergic reactions".)

Based on immunologic mechanism — Historically, immunologic reactions, whether caused by drugs, infections, or autoimmune processes, have been divided into four categories (I to IV) according to the Gell and Coombs system (table 3):

- Type I – Immediate in onset and mediated by IgE and mast cells and/or basophils.
- Type II – Delayed in onset and caused by antibody (usually IgG) mediated cell destruction.
- Type III – Delayed in onset and caused by IgG:drug immune complex deposition and complement activation.
- Type IV – Delayed in onset and T cell mediated. Of note, this classification was established before a detailed analysis of T cell subsets and functions was technically possible. As new immunologic tools were developed, type IV reactions were further subdivided into types IVa, IVb, IVc, and IVd (figure 1) [14]. (See 'Subcategories of type IV' below.)

Medications cause types I and IV reactions far more commonly than types II and III, which usually follow prolonged, higher dose therapy. Most medications cause just one type, although certain drugs, such as penicillin, can induce all four types.

TYPES OF IMMUNOLOGIC DRUG REACTIONS

Type I reactions — Type I reactions require the presence of drug-specific IgE. A small minority of patients form drug-specific IgE upon exposure to a medication, while most do not even with prolonged treatment.

Once formed, drug-specific IgE occupies surface receptors on mast cells and basophils throughout the body. If the drug is encountered again, it (or its metabolite) may bind to these IgE molecules, causing crosslinking of the receptors and activation of the cells, resulting in symptoms. IgE-mediated reactions are dose dependent, although this may not be clinically apparent because even very low doses they can cause severe systemic symptoms.

Clinical features — The signs and symptoms of type I reactions are directly attributable to the vasoactive mediators released by mast cells and basophils. The most common signs and symptoms are urticarial rash (picture 1 and picture 2); pruritus; flushing; angioedema of the face, extremities, or laryngeal tissues (leading to throat tightness with stridor, or rarely asphyxiation); wheezing; gastrointestinal symptoms; and/or hypotension.

Anaphylaxis is the most severe presentation of an IgE-mediated drug reaction. Mast cell tryptase and histamine can be elevated in the circulation in the first several hours after

anaphylaxis, and the detection of these mediators implicates mast cells and basophils in the reaction, supporting the diagnosis of anaphylaxis. (See "Anaphylaxis: Emergency treatment" and "Laboratory tests to support the clinical diagnosis of anaphylaxis".)

The presence of urticaria is useful in identifying IgE-mediated reactions, because the classical wheal and flare are hallmark signs of mast cell degranulation. However, other skin findings in drug reactions can mimic urticaria and it can be difficult to discern if a rash was truly urticarial based on history alone. Many delayed reactions involve a pruritic exanthem or rash that causes diffuse swelling of the skin, and affected patients will report raised, itchy areas of skin. However, these delayed-onset edematous exanthems are NOT urticarial rashes. In addition, they are generally not dangerous, provided the skin does not blister or slough and there are no signs of organ inflammation. Reactions involving rash and organ inflammation are discussed below. Conversely, urticarial rashes may be altered in appearance or suppressed by ongoing antihistamine therapies, such that in such patients the absence of urticaria should not be taken as evidence against anaphylaxis. (See 'Type IV reactions' below.)

Neither fever nor elevations in serum C-reactive protein are seen with IgE-mediated reactions. The absence of these features can help distinguish IgE-mediated reactions from some other adverse drug reactions.

Timing — The timing of onset of type I reactions is rapid, but varies with the clinical setting and presentation. IgE-mediated reactions occur rapidly after the last administered dose, which underlies the designation of immediate by the World Allergy Organization (WAO). The time to onset is influenced by the route of administration; intravenously administered medications may cause symptoms in seconds to minutes, while the same drug administered orally may cause symptoms in 3 to 30 minutes if taken on an empty stomach, and in 10 to 60 minutes if taken with food.

- IgE-mediated anaphylactic reactions should NOT begin several days into a course of therapy, if the patient's exposure to the drug has been continuous. However, if several doses are skipped, symptoms can appear when the drug is resumed.
- Urticaria appearing within minutes to hours after drug intake can also be seen in "pseudoallergic" reactions. (See 'Pseudoallergic reactions' below.)
- Isolated urticarial skin eruptions can occur late during continuous therapy:
    - The delayed appearance of urticarial rashes with known allergenic drugs like beta-lactam antibiotics may reflect time required for significant IgE responses, (similar to late-occurring serum sickness reactions).

- Urticaria appearing one to two weeks after therapy, and accompanied by arthralgias and fever suggests serum sickness. (See 'Pseudoallergic reactions' below and 'Serum sickness' below.)

- Urticarial eruptions, often appearing days after start of therapy, sometimes also have maculopapular features. These urticarial rashes typically occur with drugs that rarely cause acute allergy (eg, macrolide antibiotics), and are unlikely to be IgE mediated. T cells may also be involved, although the pathogenesis is not known.

Commonly-implicated drugs — The drugs most commonly implicated in type I reactions include the following:

- Beta-lactam drugs (penicillins and cephalosporins). (See "Penicillin allergy: Immediate reactions".)

- Neuromuscular blocking agents. (See "Perioperative anaphylaxis: Clinical manifestations, etiology, and management".)

- Quinolones – Quinolone antibiotics have been implicated as a common cause of hypersensitivity reactions in Europe, but less commonly in the United States, so there may be important geographical variations that will become more apparent over time [15]. Only some of these reactions are IgE mediated [16,17]. (See "Hypersensitivity reactions to fluoroquinolones".)

- Platinum-containing chemotherapeutic agents, such as carboplatin and oxaliplatin. (See "Infusion reactions to systemic chemotherapy".)

- Foreign proteins, including chimeric antibodies, such as cetuximab and rituximab. The frequency with which these agents cause anaphylaxis can also vary by geographical location (eg, cetuximab-induced anaphylaxis was initially reported mostly in the southern United States). (See "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy".)

Previous exposure to the suspect drug — IgE-mediated reactions generally require previous exposure to the drug in question. However, the absence of a known prior exposure does not exclude an IgE-mediated reaction, because sensitization may have occurred from exposure to a cross-reactive compound, even though the patient showed no signs of allergy to the sensitizing product.

The following examples illustrate this phenomenon:

- A significant percentage of patients experiencing anaphylaxis upon first exposure to neuromuscular blocking agents are believed to have been previously sensitized through the use of various cosmetics, personal products, and nonprescription cough remedies (eg, pholcodine in Norway) that contain tertiary and quaternary ammonium groups [18-20]. The ammonium groups shared by all of these agents are highly immunoreactive and can induce cross-reactive IgE antibodies. (See "Perioperative anaphylaxis: Clinical manifestations, etiology, and management".)

- Some patients develop anaphylaxis to cetuximab and appear to have been previously sensitized to oligosaccharides present on the drug [21]. The same oligosaccharides are found on several nonprimate mammalian proteins, such as beef, pork, and lamb. The source of the original sensitization is still uncertain, although bites of certain tick species have been implicated. (See "Allergy to meats", section on 'Alpha-gal' and "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy", section on 'Cetuximab'.)

Type II reactions — Type II reactions are uncommon and involve antibody-mediated cell destruction. Type II reactions may arise when drugs bind to surfaces of certain cell types and act as antigens. Subsequent binding of antibodies to the cell surface results in the cells being targeted for clearance by macrophages. Type II reactions may involve complement activation, but this is variable.

Clinical manifestations require the presence of high titers of preformed drug-specific IgG (or rarely IgM) antibodies, which are only made by a small percentage of individuals and usually in the setting of high-dose, long-term, or recurrent drug exposure. The factors predisposing individuals to form these antibodies are not fully understood.

Clinical features and timing — Type II drug reactions usually present as hemolytic anemia, thrombocytopenia, or neutropenia, since these are the cell types that are most often affected.

The clinical presentation can vary widely in severity; patients may be asymptomatic or present with fulminant illness. Symptoms usually appear at least five to eight days after exposure, but may begin after much longer periods of treatment. Symptoms can start within hours if the causative drug is stopped and then restarted.

Specific presentations — Specific manifestations depend on the cell type involved:

- **Drug-induced hemolytic anemia** – Hemolytic anemia may present with dyspnea, varying degrees of fatigue, pallor, jaundice, dark urine, splenomegaly, or signs and symptoms of the hyperdynamic state, such as bounding pulses, palpitations, and "roaring in the ears."

The drugs most commonly implicated in hemolytic anemia are cephalosporins, penicillins, nonsteroidal anti-inflammatory drugs (NSAIDs), and quinine-quinidine. The evaluation and diagnosis of drug-induced hemolytic anemia are discussed in greater detail separately. (See "Diagnosis of hemolytic anemia in adults".)

- **Drug-induced thrombocytopenia** – Thrombocytopenia typically presents with petechial bleeding in the skin and buccal mucosa and isolated thrombocytopenia, often severe (ie, <20,000/microL) in a patient taking one or several medications. There may be splenomegaly and hepatomegaly due to platelet sequestration in these organs.

  Drugs implicated in thrombocytopenia include heparin, abciximab, quinine and quinidine, sulfonamides, vancomycin, gold compounds, beta-lactam antibiotics, carbamazepine, NSAIDs, and others. This evaluation and diagnosis of this disorder are reviewed elsewhere. (See "Drug-induced immune thrombocytopenia".)

- **Drug-induced neutropenia or agranulocytosis** – Severe neutropenia or agranulocytosis due to type II drug reactions presents days to weeks after beginning the medication, often with acute and clinically apparent symptoms of infection, such as fever, stomatitis, pharyngitis, pneumonia, or sepsis. Rechallenge or inadvertent subsequent administration is associated with a prompt recurrence, even with low doses.

  Culprit drugs include propylthiouracil (PTU), the antimalarial drug amodiaquine and one of its major metabolites, mono-desethyl amodiaquine, and flecainide. The evaluation and diagnosis of this disorder are presented separately. (See "Drug-induced neutropenia and agranulocytosis".)

Type III reactions — Type III reactions are mediated by antigen-antibody complexes and usually present as serum sickness, vasculitis, or drug fever. These reactions are uncommon and usually seen in the context of high-dose, prolonged drug administration, similar to type II reactions.

In a type III reaction, the drug (including biologicals) is believed to act as a soluble antigen. In this capacity, the drug binds drug-specific IgG, forming small immune complexes that can activate complement and precipitate in various tissues, including blood vessels, joints, and renal glomeruli. These immune complexes bind to Fc-IgG receptors of inflammatory cells and/or activate complement, and an inflammatory response ensues. Re-exposure to similar or higher doses of the same drug can cause a more rapid and severe recurrence.

Timing — Signs and symptoms take one or more weeks to develop after drug exposure, since significant quantities of antibody are needed to generate symptoms related to antigen-

antibody complexes.

Clinical presentation — Type III reactions can take several forms:

Serum sickness — Classic serum sickness involves fever, urticarial or purpuric rash, arthralgias, and/or acute glomerulonephritis. Alternatively, just one or two of these features may be apparent. Other findings include lymphadenopathy, low serum complement levels, and an elevated erythrocyte sedimentation rate. Serum sickness is a complication of several antitoxins, including those for rabies, botulism, and venoms. (See "Serum sickness and serum sickness-like reactions".)

Vasculitis — Drug-induced hypersensitivity vasculitis typically presents as palpable purpura and/or petechiae, fever, urticaria, arthralgias, lymphadenopathy, elevated erythrocyte sedimentation rate, and low complement levels. Purpuric lesions often affect the lower extremities. Uncommonly, other organs are involved, such as the gastrointestinal tract or kidneys. The most common culprits are penicillins, cephalosporins, sulfonamides (including most loop and thiazide-type diuretics), phenytoin, and allopurinol. (See "Overview of cutaneous small vessel vasculitis".)

Arthus reaction — An Arthus reaction is a localized type III hypersensitivity reaction in which antibody-antigen complexes that fix complement are deposited in the walls of small blood vessels, causing acute inflammation, infiltration of neutrophils, and localized skin necrosis. Arthus reactions were initially described in hyperimmunized laboratory animals. Whether significant local reactions to booster doses of modern vaccines are true Arthus reactions has not been demonstrated conclusively. Typically, such reactions present as painful local swelling and erythema beginning within a few hours and usually peaking by 24 hours at sites of booster injections of a vaccine. This type of reaction has been reported with tetanus, diphtheria, and hepatitis B vaccines [22-24].

Type IV reactions — Type IV reactions are not mediated by antibodies, in contrast to the other three types above. Type IV drug reactions involve the activation and expansion of T cells, which requires time (normally many hours or days after antigen exposure), hence the name delayed-type hypersensitivity (DTH). In some cases, other cell types (eg, macrophages, eosinophils, or neutrophils) are also involved. Type IV reactions can take many different forms, which vary in significance from inconvenient to life threatening.

Timing of type IV reactions — Type IV reactions are typically delayed in onset by at least 48 to 72 hours and sometimes by days to weeks following exposure to the culprit drug. On rechallenge, symptoms may appear within 24 hours. The time to symptom onset for reactions depends in part on the number of T cells activated by the drug. These responses are polyclonal,

and symptoms appear rapidly if the drug stimulates a large number of different T cell clones. In contrast, a drug that activates just a few clones may not cause clinical symptoms until these T cells have proliferated for several weeks.

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DiHS), the most dangerous of the delayed drug hypersensitivity reactions, often appear after weeks of uncomplicated treatment, at which point patients suddenly develop signs and symptoms of a fulminant immune reaction. This presentation results from uncontrolled expansion of oligoclonal T cells that have been massively stimulated by the drug, reminiscent of superantigen-like stimulation [25]. (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis", section on 'Clinical course'.)

Subcategories of type IV — T cells can orchestrate different forms of inflammation depending on the cytokines produced and the other types of cells that become involved, leading to the subcategories of types IVa to IVd (figure 1) [14]. These subcategories are discussed in detail separately. (See "Drug allergy: Pathogenesis".)

Clinical presentations — Reactions involving T cells have prominent skin findings, because the skin is a repository for an enormous number of T cells [26]. Many cutaneous T cells are primed memory-effector cells, which react rapidly if immunogenic agents penetrate the skin barrier or diffuse into the skin from the circulation [27].

Recognized patterns of cutaneous involvement include the following:

Contact dermatitis — Contact dermatitis is a reaction to topically applied drugs, which is characterized by erythema and edema with vesicles or bullae that often rupture, leaving a crust [28]. Subacute and chronic contact dermatitis are characterized by lichenification, erythema, and scaling (picture 3). (See "Contact dermatitis in children" and "Common allergens in allergic contact dermatitis".)

Maculopapular (including morbilliform) eruptions — Maculopapular eruptions are one of the most common forms of delayed drug reactions and may arise from type IV immunologic reactions, as well as from other mechanisms (picture 4). They are often called "rashes," a term which includes exanthems with varying degrees of cell infiltrations and thus papular component ("maculopapular"). (See "Exanthematous (maculopapular) drug eruption".)

SDRIFE — "Symmetrical drug-related intertriginous and flexural exanthem" (SDRIFE), formerly called baboon syndrome, is a distinctive drug eruption that typically develops within a few hours to days of drug exposure and presents with demarcated, V-shaped erythema in the

gluteal/perianal or inguinal/perigenital areas, often with involvement of at least one other flexural area, such as the axillae, elbows, or knees (picture 5). (See "Exanthematous (maculopapular) drug eruption", section on 'Intertriginous and flexural reaction pattern'.)

Some forms of SDRIFE may be related to neurophilic inflammations, such as acute generalized exanthematous pustulosis (AGEP). (See 'Acute generalized exanthematous pustulosis' below.)

Acute generalized exanthematous pustulosis — AGEP is a rare type of reaction characterized by superficial pustules, usually appearing within 24 hours after the administration of the culprit drug (picture 6 and picture 7). Antimicrobial drugs (amoxicillin), antimalarials, and calcium channel blockers are the most frequently reported triggers of AGEP. This disorder is discussed in more detail separately. (See "Acute generalized exanthematous pustulosis (AGEP)".)

Drug fever — Fever can be the sole symptom or the most prominent symptom of drug hypersensitivity, accompanied in a minority of cases by nonurticarial rash or other organ involvement. Medications implicated in causing drug fever include azathioprine, sulfasalazine, minocycline, trimethoprim-sulfamethoxazole, sirolimus, and tacrolimus. Patients with active HIV infection or cystic fibrosis appear to be at particular risk, with higher rates of drug fever to antiretroviral drugs and piperacillin-tazobactam, respectively [29]. (See "Drug fever", section on 'Hypersensitivity'.)

Stevens-Johnson syndrome and toxic epidermal necrolysis — Severe blistering dermatitides, such as SJS and TEN, are potentially life-threatening reactions characterized by fever and mucocutaneous lesions leading to necrosis and sloughing of the epidermis (picture 8 and picture 9 and picture 10). (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis" and "Stevens-Johnson syndrome and toxic epidermal necrolysis: Management, prognosis, and long-term sequelae".)

Drug-induced hypersensitivity syndrome — DiHS, also called DRESS, is a severe drug hypersensitivity reaction involving rash, fever (38 to 40°C) and multiorgan failure. The liver, kidneys, heart, and/or lungs are most often affected in DiHS/DRESS. It is discussed briefly here and reviewed in more detail elsewhere. (See "Drug reaction with eosinophilia and systemic symptoms (DRESS)".)

Debate is ongoing about the most accurate name for this syndrome, as only about 70 percent of cases show peripheral eosinophilia (eg, those caused by abacavir or lamotrigine typically do not). The presence of atypical lymphocytes (activated CD8+) is a more consistent finding, which may persist for months after drug withdrawal.

Drugs that have been implicated in causing DRESS/DiHS include several antiepileptics (including carbamazepine, phenytoin, lamotrigine, and phenobarbital), minocycline, allopurinol, dapsone, abacavir, and nevirapine.

HLA associations — Some DiHS/DRESS reactions occur more frequently in patients with certain human leukocyte antigen (HLA) types, since the drugs have been shown to bind to the certain HLA-allele itself predominantly (eg allopurinol/oxypurinol to the HLA-B*58:01) or exclusively (abacavir and HLA-B*57:01) [30], a phenomenon that is also seen in SJS and TEN. Specific examples include:

- DiHS/DRESS and SJS/TEN to allopurinol is associated with HLA-B*58:01 [31]. This B*58:01 association is less stringent in Caucasians (approximately 60 percent), in whom other alleles are also involved in SJS/TEN due to allopurinol [32].
- DiHS/DRESS, and in some cases SJS/TEN, to carbamazepine disproportionately affects several groups.
  - Han Chinese patients with HLA-B15:02 [33], as well as Thai, Malaysian, and Indian patients with this same allele [34-36].
  - Japanese and European patients with HLA-A*31:01 [37,38].
- DiHS/DRESS to abacavir occur exclusively in patients with HLA-B*57:01; milder reactions to this drug are not associated with a certain HLA-allele.
- Dapsone hypersensitivity syndrome disproportionately affects Chinese patients with HLA-B*13:01 [39].

Once a patient has been identified as having a high-risk HLA profile, family members of that patient should also be advised to avoid the relevant drug, as familial occurrence of such hypersensitivity reactions has been noted. Recommendations have been made for screening patients for specific alleles prior to administration of carbamazepine, oxcarbazepine, abacavir, and allopurinol [40]. (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis", section on 'HLA types' and "Abacavir hypersensitivity reaction", section on 'Screening prior to abacavir exposure' and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Carbamazepine' and "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Oxcarbazepine'.)

Single organ involvement — Occasionally with T cell mediated hypersensitivity, organ involvement occurs in the absence of skin findings, or skin findings are minor and overlooked.

Presentations include isolated, drug-induced hepatitis, isolated interstitial nephritis, and isolated pneumonitis. As examples, flucloxacillin, as well as the combination drug amoxicillin-clavulanate potassium, may elicit cholestatic hepatitis, while allopurinol can cause nephritis [41], and abacavir and nitrofurantoin can cause pneumonitis. Identification of this presentation as drug allergy can be challenging. These disorders are discussed elsewhere. (See "Drugs and the liver: Metabolism and mechanisms of injury", section on 'Immune-mediated' and "Drug-induced liver injury" and "Clinical manifestations and diagnosis of acute interstitial nephritis", section on 'Drugs' and "Nitrofurantoin-induced pulmonary injury".)

Association with viral infections — There is a higher risk of several type IV drug allergic reactions (ranging from simple exanthema to SJS/TEN) during generalized viral infections and exacerbations of autoimmune diseases, disorders in which T cell reactivity is enhanced by widespread immune activation of T cells, high cytokine levels, and an increased expression of major histocompatibility complex (MHC) and costimulatory molecules.

Viral infections that predispose patients to reactions to certain drugs include the following:

- Epstein Barr virus (with amoxicillin). (See "Clinical manifestations and treatment of Epstein-Barr virus infection".)
- Cytomegalovirus (with antibiotics) [42]. (See "Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults", section on 'CMV mononucleosis'.)
- Human herpes virus 6 (with anticonvulsants and other agents). (See "Human herpesvirus 6 infection in children: Clinical manifestations, diagnosis, and treatment".)
- HIV infection (with trimethoprim-sulfamethoxazole and other agents). (See "Fever and rash in patients with HIV", section on 'Drug reactions'.)
- In young children, treatment with amoxicillin (and to a lesser extent with other antibiotics) often elicits exanthematous reactions. Most of these children tolerate the same drug if given again later on [43]. It is likely that systemic viral infections are facilitating these reactions as well, although this has not been conclusively demonstrated. Rhinoviruses, which cause only local infections of the nasopharynx and respiratory tract, are unlikely to have this effect because they do not stimulate the immune system to the same degree. (See "Penicillin allergy: Delayed hypersensitivity reactions", section on 'Relationship with viral infections'.)

Impact of dose and duration of treatment — Dose seems to play an important role in developing delayed hypersensitivity reactions. Most delayed drug hypersensitivity reactions occur to drugs which are given in daily doses of 100 to 1000 mg. Allopurinol and lamotrigine are two examples [44-46]. In contrast, drugs that are dosed lower than 10 mg daily are rarely involved in delayed hypersensitivity reactions.

In allopurinol hypersensitivity, there are clinical and in vitro data to suggest that starting dose may also be relevant for developing hypersensitivity [44,45]. Thus, for drugs such as allopurinol or lamotrigine, lower initial doses may lower the incidence of hypersensitivity. (See "Pharmacologic urate-lowering therapy and treatment of tophi in patients with gout", section on 'Allopurinol'.)

Length of treatment also appears to be a factor, as more than 10 days of gemifloxacin caused maculopapular exanthema in nearly one-third of females in one study, while this was rare with three days of treatment [17]. (See "Hypersensitivity reactions to fluoroquinolones", section on 'Delayed maculopapular exanthema'.)

Other types of immunologic reactions — Two additional types of immunologic drug reactions that cannot be readily classified within the Gell and Coombs system are drug-induced autoimmunity and fixed drug eruption.

Drug-induced autoimmunity — Drugs can induce autoimmune diseases [47]. Despite intensive scrutiny, the pathogenesis of these reactions has not been elucidated, although the finding that drug binding to HLA molecules can induce changes of the presented peptides has opened new pathways of research [30,48]. However, a definitive link between these findings and drug-induced autoimmune diseases has not yet been established.

- The best known example is a lupus-like disease, which can develop after exposure to procainamide, phenytoin, isoniazid, sulfasalazine, amiodarone, minocycline, and penicillamine [47,49-51]. (See "Drug-induced lupus".)
- Penicillamine can also cause a pemphigus-like disorder. (See "Pathogenesis, clinical manifestations, and diagnosis of pemphigus", section on 'Drug exposure'.)
- IgA bullous dermatosis has been associated with vancomycin (picture 11) and various other drugs, including ceftriaxone, ciprofloxacin, and metronidazole. (See "Linear IgA bullous dermatosis".)

Fixed drug eruption — Fixed drug eruption is a relatively common reaction, which is characterized by erythematous and edematous plaques with a grayish center or frank bullae.

Lesions recur at exactly the same sites (typically lips and tongue, genitalia, face, and acral areas) with drug re-exposure (picture 12 and picture 13). These site(s) develop postinflammatory pigmentation. Fixed drug eruption can occur in response to sulfonamides, anticoagulants, and many other drugs [52]. The mechanism is unknown, although T cells residing in the skin produce interferon gamma [53,54]. (See "Fixed drug eruption".)

PSEUDOALLERGIC REACTIONS

Pseudoallergic drug reactions are adverse drug reactions with signs and symptoms that mimic immunologic drug allergies, but in which immunologic mechanisms have not been demonstrated (table 2). They are a subset of type B drug hypersensitivity reaction (DHR) and are also called "nonimmune hypersensitivity reactions" [7]. (See 'Categories of adverse drug reactions' above.)

Pseudoallergic reactions are difficult to distinguish clinically because they are similar or identical in presentation to true allergic reactions. Some pseudoallergic reactions arise from direct (rather than immunologic) activation of immune and inflammatory cells, so the final steps in pathogenesis and the resultant clinical features are indistinguishable from those of allergic reactions. The complete mechanisms underlying most of them are not known and may differ from one another (table 2).

A single receptor, known as MRGPRX2 (Mas-Related G-Protein Coupled Receptor Member X2) in humans and Mrgprb2 (Mas-Related G-Protein Coupled Receptor Member B2) in mice, was found to be crucial for IgE-independent, direct mast cell stimulation [13]. Fluoroquinolone antibiotics and neuromuscular blocking agents (NMBA) are known to bind to this receptor and to cause systemic, nonallergic (pseudoallergic, anaphylactoid) reactions via this mechanism. Some of the drugs listed below (common culprit drugs) may act via this mechanism. Why only some patients develop pseudoallergic symptoms is presently unclear.

Importantly, the diagnosis, prognosis, and prevention of pseudoallergy may be different from true allergic reactions. In particular, pseudoallergic reactions are not diagnosed with skin or in vitro allergy testing and do not worsen with repeated exposure. (See 'Common culprit drugs' below.)

Reactions that resemble anaphylaxis — Idiosyncratic reactions that mimic IgE-mediated, type I allergic reactions are among the most important for clinicians to understand. Like IgE-mediated reactions, nonimmunologic activation of mast cells and basophils results in the release of vasoactive mediators. These pseudoallergic reactions range in severity from mild to

fatal. Accordingly, acute nonimmunologic anaphylaxis should be treated in the same manner as immunologic anaphylaxis.

Nonimmunologic reactions resembling anaphylaxis are often referred to as "anaphylactoid." Unfortunately, the term anaphylactoid has been widely misinterpreted to mean a reaction that was similar to anaphylaxis but less severe, and has led to the undertreatment of patients with nonimmunologic anaphylaxis. Therefore, the term anaphylactoid is now discouraged, and the concept of nonimmunologic anaphylaxis is preferred. Clinicians should understand that all forms of anaphylaxis are potentially life threatening. (See "Anaphylaxis: Emergency treatment".)

It is unclear how certain drugs elicit these reactions. Some affected patients have underlying dermographism and seem to have an "instability" of their mast cells, which degranulate already upon pressure or by exposure to various small molecules.

Common culprit drugs — Drugs that can cause nonimmunologic anaphylaxis are listed below, and the clinical syndromes associated with each are reviewed separately:

- Radiocontrast agents (see "Diagnosis and treatment of an acute reaction to a radiologic contrast agent")
- Opiates (see "Perioperative anaphylaxis: Clinical manifestations, etiology, and management", section on 'Opioids')
- Nonsteroidal anti-inflammatory drugs (NSAIDs) (see "NSAIDs (including aspirin): Allergic and pseudoallergic reactions")
- Vancomycin (see "Vancomycin hypersensitivity")
- Local anesthetic agents (see "Allergic reactions to local anesthetics")
- Chemotherapeutic agents (see "Infusion reactions to systemic chemotherapy")
- Monoclonal antibodies and other biologic therapies used in cancer therapy (see "Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy")

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer

short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient education" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Drug allergy (The Basics)")

SUMMARY

- **Categories of adverse drug reactions** – Adverse drug reactions may be broadly divided into types A and B (table 1). Type A represent the majority of reactions, can affect any individual, and are predictable from the known pharmacologic properties of a drug. Type B reactions are less common, occur in susceptible patients, and usually cannot be predicted from the known pharmacologic properties of a drug. (See 'Categories of adverse drug reactions' above.)

- **Immunologic/allergic reactions** – Immunologic drug reactions, or allergic drug reactions, are a subset of type B reactions. Immunologic drug reactions are traditionally divided into four categories according to the Gell and Coombs system (table 3). Types I and IV are far more common in clinical practice than types II and III (see 'Classification of drug hypersensitivity' above):

  - **Type I** – Immediate in onset and mediated by IgE and mast cells/basophils.

  - **Type II** – Delayed in onset and caused by antibody (usually IgG) mediated cell destruction.

  - **Type III** – Delayed in onset and caused by IgG:drug immune complex deposition and complement activation.

  - **Type IV** – Delayed in onset and T cell mediated. Type IV reactions are further subdivided into types IVa, IVb, IVc, and IVd, depending on the other cell types involved (figure 1).

- **Distinguishing among subtypes** – Clinically, the different types of reactions have characteristic signs and symptoms, and the timing of onset of symptoms may also be

helpful in distinguishing one type from another. However, there is significant clinical overlap among them. (See 'Type I reactions' above and 'Type II reactions' above and 'Type III reactions' above and 'Type IV reactions' above.)

- **Other immunologic reactions** – Drug-induced autoimmunity and fixed drug eruption are other types of immunologic drug reactions that are not easily classified within the Gell and Coombs classification. (See 'Other types of immunologic reactions' above.)

- **Pseudoallergic reactions** – Pseudoallergic drug reactions are a subset of type B (hypersensitivity) drug reactions with signs and symptoms that mimic immunologic drug allergies but are not immunologic. Pseudoallergic reactions are especially difficult to distinguish clinically because they can be similar or identical in presentation to true allergic reactions. However, the diagnosis, prognosis, and prevention of pseudoallergic reactions are different. (See 'Pseudoallergic reactions' above.)

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Topic 2086 Version 23.0

GRAPHICS

Classification of adverse drug reactions

Drug reaction	Examples
Type A: Reactions occurring in most normal patients, given sufficient dose and duration of therapy: Common and predictable	
Overdose	Hepatic failure (acetaminophen) Metabolic acidosis (aspirin)
Side effects	Nausea, headache (with methylxanthines) Oral thrush or vaginal candidiasis (with glucocorticoids) Nephrotoxicity (with aminoglycosides)
Secondary or indirect effects	Diarrhea due to alteration in GI bacteria after antibiotics Phototoxicity (with doxycycline or thiazide diuretics)
Drug interactions	Macrolide antibiotics increasing theophylline, digoxin, or statin blood levels
Type B: Drug hypersensitivity reactions restricted to a small subset of the general population: Rare and mostly unpredictable	
Intolerance*	Tinnitus after a single aspirin tablet
Idiosyncrasy[¶] (pharmacogenetics)	G6PD deficiency: Hemolytic anemia after antioxidant drugs (eg, dapsone)[Δ] TPMT deficiency: Toxicity during azathioprine therapy[Δ] Pseudoallergic reaction (with NSAIDs)
Immunologic drug reactions (allergy)	Anaphylaxis from beta-lactam antibiotics Photoallergy with quinidine Immune-mediated thrombocytopenia (with heparin) Serum sickness (with antivenom preparations) Vasculitis (with phenytoin) Stevens-Johnson syndrome (with trimethoprim-sulfamethoxazole) Drug-induced hypersensitivity syndrome (with allopurinol in HLA-B*58:01 individuals)[Δ]

GI: gastrointestinal; G6PD: glucose-6-phosphate dehydrogenase; TPMT: thiopurine methyltransferase; NSAIDs: nonsteroidal anti-inflammatory drugs.

* Side effects at subtherapeutic doses.

¶ Drug effect not attributable to known pharmacologic properties of drug and not immune-mediated.

Δ This is an example of a type B reaction that is predictable.

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Graphic 51797 Version 11.0

Common examples of pseudoallergic drug reactions

Drug	Clinical reaction(s)	Presumed mechanism
Aspirin and other NSAIDs	Exacerbations of rhinitis, asthma (in patients with aspirin-exacerbated respiratory disease) Urticaria/angioedema (NOTE: Urticaria may also result from a type I, IgE-mediated allergic reaction)	Inhibited prostaglandin production and enhanced leukotriene production
Opiates	Pruritus, urticaria	Direct stimulation of mast cells and/or basophils causing release of mediators
Vancomycin	Flushing during infusion	Direct stimulation of mast cells through MRGPRX2, causing release of mediators
Radiocontrast media	Anaphylaxis, shock (NOTE: Some may be type I, IgE-mediated allergic reactions)	Unknown mechanism
Ciprofloxacin	Urticaria (most reactions)	Direct stimulation of mast cells through MRGPRX2, causing release of mediators
Local anesthetics	Syncope	Vasovagal reflex
Protamine	Hypotension, pulmonary hypertension	Unknown mechanism
Choline	Pruritus, urticaria	Unknown mechanism
Isoniazid	Hepatitis	Unknown mechanism

NSAIDs: nonsteroidal anti-inflammatory drugs: IgE: immunoglobulin E; MRGPRX2: Mas related protein coupled receptor member X2.

Graphic 79967 Version 8.0

Gell and Coombs classification of immunologic drug reactions

Type	Description	Mechanism	Clinical features
I Immediate reaction (within one hour)	IgE-mediated, immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances, such as histamine, prostaglandins, and leukotrienes.	Anaphylaxis Angioedema Bronchospasm Urticaria (hives) Hypotension
II	Antibody-dependent cytotoxicity	An antigen or hapten that is intimately associated with a cell binds to antibody, leading to cell or tissue injury.	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage is caused by formation or deposition of antigen-antibody complexes in vessels or tissue. Deposition of immune complexes causes complement activation and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors.	Serum sickness Arthus reaction
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (ie, types IVa to IVd).	Contact dermatitis Some morbilliform reactions Severe exfoliative dermatoses (eg, SJS/TEN) AGEP DRESS/DiHS Interstitial nephritis Drug-induced hepatitis Other presentations

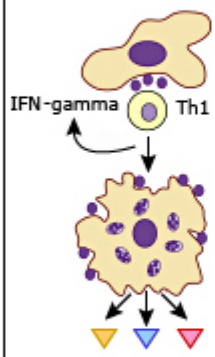
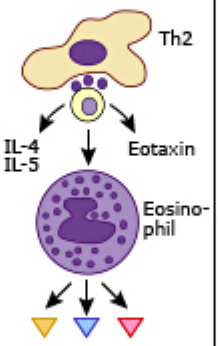
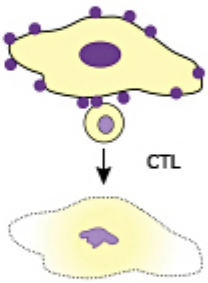
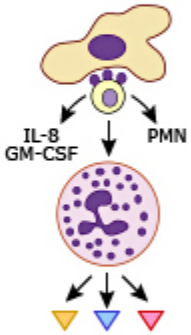
IgE: immunoglobulin E; Fc IgG: Fc portion of immunoglobulin G; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis;

DRESS/DiHS: drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome.

Adapted from: Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988; 18:515.

Graphic 80466 Version 18.0

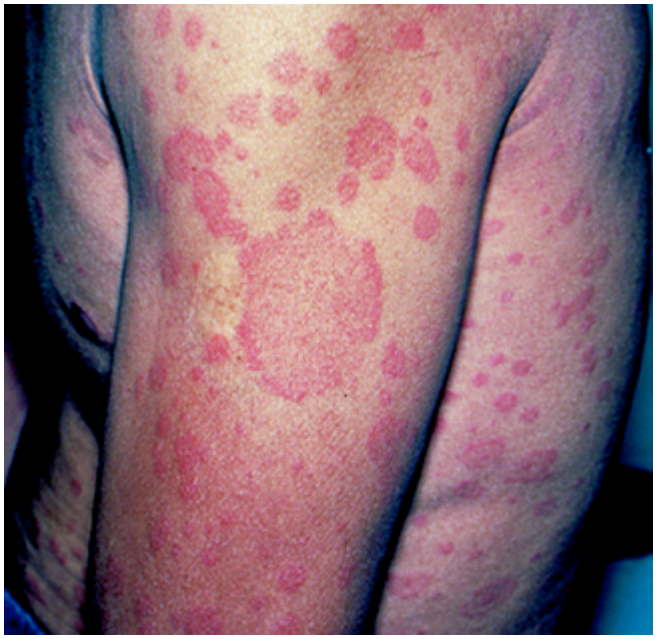
T cell-mediated hypersensitivity reactions (Gell and Coombs types IVa to IVd)

Type	Type IVa	Type IVb	Type IVc	Type IVd
Cytokines	IFN-gamma, TNF-alpha (Th1 cells)	IL-5, IL-4/IL-13 (Th2 cells)	Perforin/granzyme B (CTL)	IL-8, GM-CSF (T cells)
Antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation
Cells	Macrophage activation	Eosinophils	T cells	Neutrophils
Pathomechanism	 Chemokines, cytokines, cytotoxins	 Cytokines, inflammatory mediators		 Cytokines, inflammatory mediators
Example	Tuberculin reaction, contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema hepatitis	AGEP Behçet disease

IFN-gamma: interferon-gamma; TNF-alpha: tumor necrosis factor-alpha; Th1: T helper type 1; IL: interleukin; Th2: T helper type 2; CTL: cytotoxic lymphocyte; GM-CSF: granulocyte monocyte colony-stimulating factor; PMN: polymorphonuclear cell; AGEP: acute-generalized exanthematous pustulosis.

Graphic 75626 Version 8.0

Urticarial drug eruption



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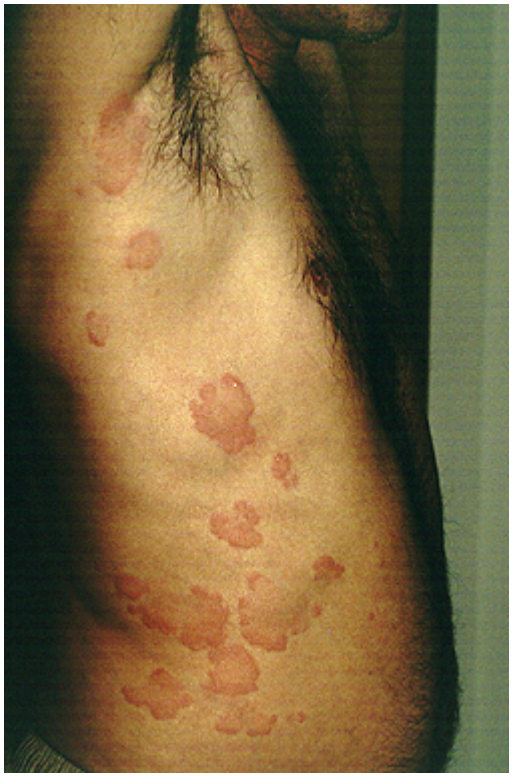
Graphic 75230 Version 3.0

Urticaria

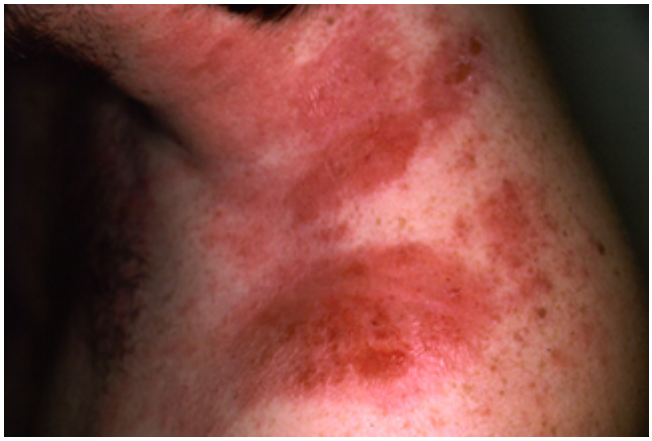


Urticaria is characterized by circumscribed, raised, erythematous, and extremely pruritic lesions. They typically appear in one area, resolve over the course of several hours, and then reappear elsewhere. Individual lesions may enlarge and develop central pallor before fading.

Courtesy of Andrew Samel, MD.

Graphic 72519 Version 1.0

Allergic contact dermatitis

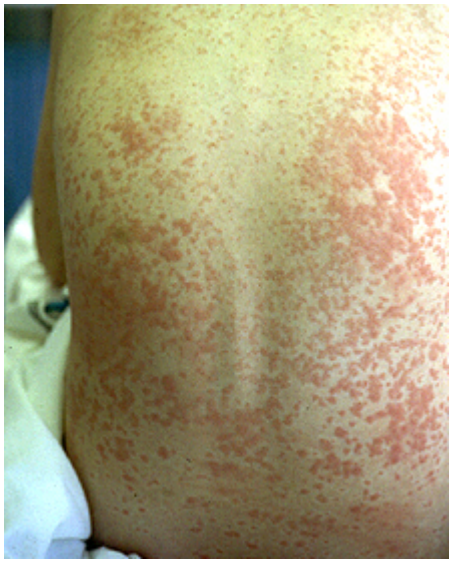


Allergic contact dermatitis is characterized by an erythematous, papular dermatitis with indistinct margins, distributed in areas of exposure.

Courtesy of James C Shaw, MD.

Graphic 71913 Version 1.0

Exanthematous (morbilliform) drug eruption

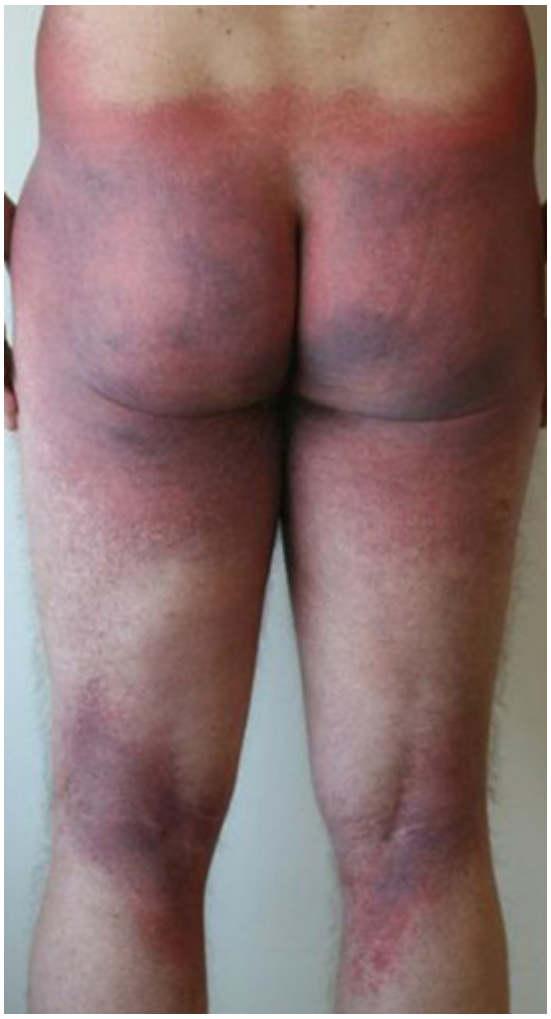


Drug-induced exanthems, such as this morbilliform eruption, often begin in dependent areas and generalize.

Courtesy of Andrew Samel, MD.

Graphic 70062 Version 5.0

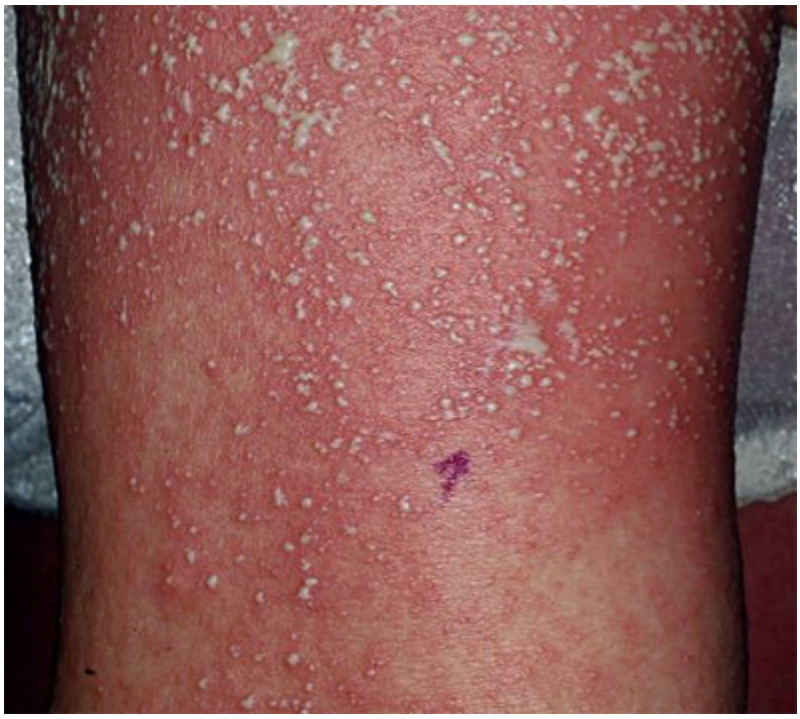
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)



Sharply demarcated erythema in the gluteal/perianal area in a patient with SDRIFE. Note the involvement of the popliteal folds.

Graphic 86506 Version 5.0

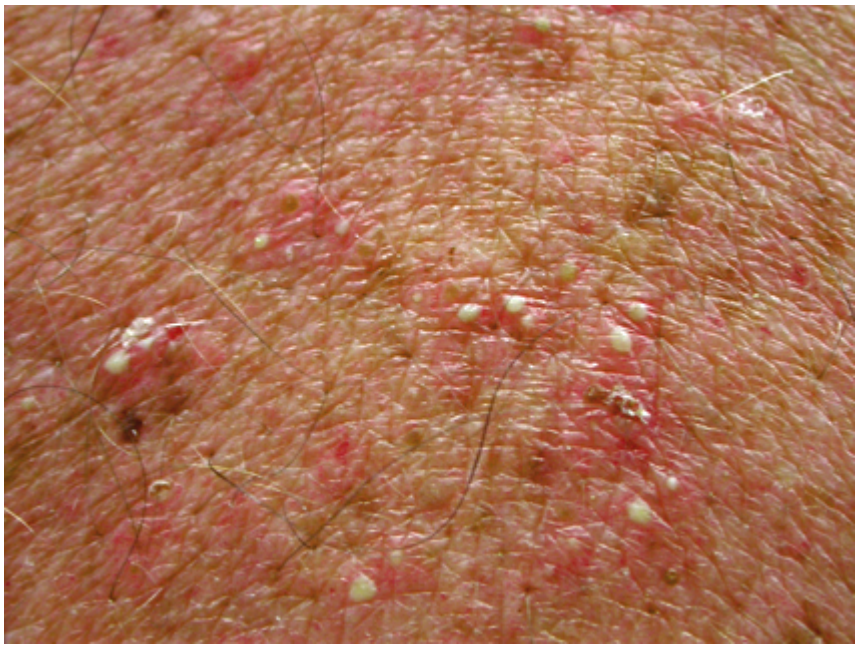
Acute generalized exanthematous pustulosis (AGEP)



Confluent nonfollicular pustules superimposed on edematous erythema in a 46-year-old woman with AGEP. A skin biopsy showed intracorneal pustules with numerous neutrophils and neutrophilic infiltration of the epidermis and upper dermis.

Graphic 56807 Version 14.0

Acute generalized exanthematous pustulosis (AGEP) detail

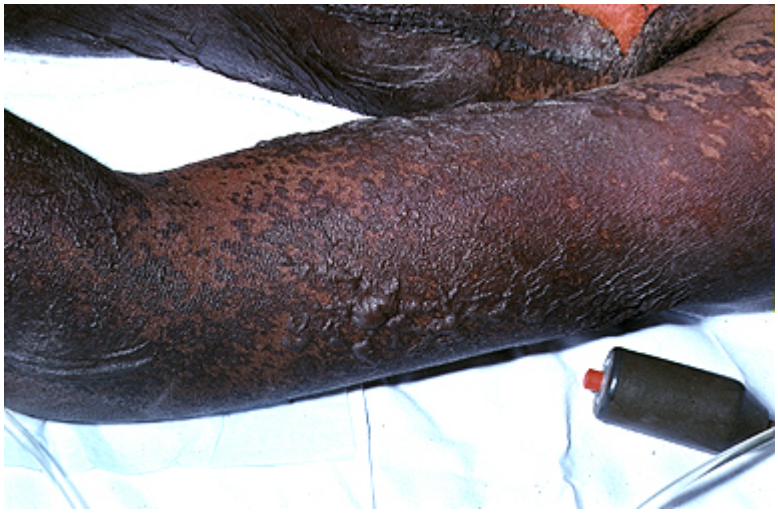


Nonfollicular, pinhead-sized pustules on a background of edematous erythema are characteristic of AGEP.

Courtesy of Werner J Pichler, MD.

Graphic 68610 Version 9.0

Toxic epidermal necrolysis (TEN)



Usually caused by drugs, TEN demonstrates widespread erythema and confluent vesiculation, leading to sloughing of the skin. Affected patients are at risk for hypernatremic dehydration and sepsis.

Courtesy of Lee T Nesbitt, Jr. The Skin and Infection: A Color Atlas and Text, Sanders CV, Nesbitt LT Jr (Eds), Williams & Wilkins, Baltimore, 1995.

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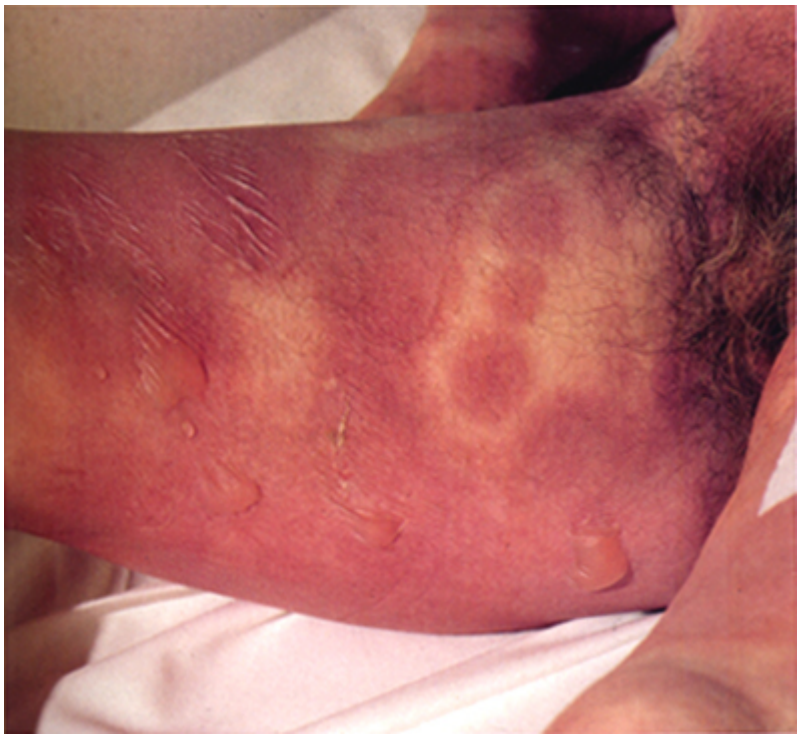
http://www.lww.com

Graphic 66134 Version 6.0

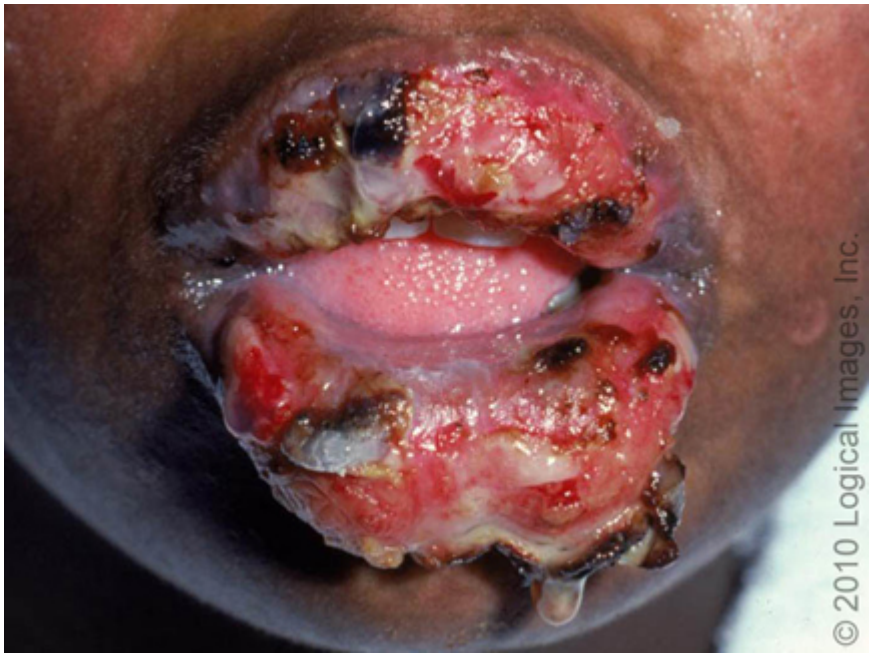
Cutaneous changes of Stevens-Johnson syndrome (SJS)



Generalized eruption of lesions that initially had a target-like appearance but then became confluent, brightly erythematous, and bullous. The patient had extensive mucous membrane involvement and tracheobronchitis.

Graphic 67632 Version 18.0

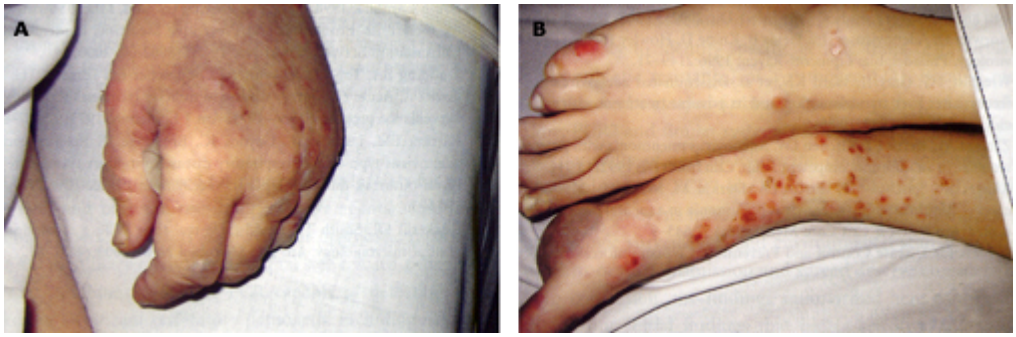
Stevens-Johnson syndrome (SJS)



Multiple erosions and crusts are present on the lips of this patient with SJS.

Graphic 68682 Version 6.0

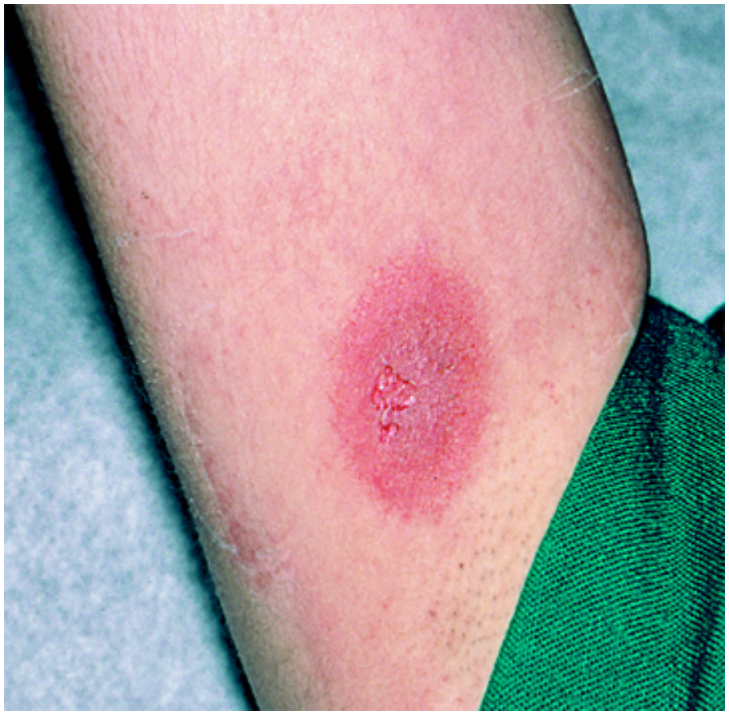
Skin lesions due to vancomycin hypersensitivity



Photographs of erythematous macules, vesicles, tense bullae, and erosions on the left hand (A) and tense bullae and erosions on the dorsal surfaces of the feet (B) in a 63-year-old man with skin eruptions after vancomycin administration.

Graphic 77601 Version 3.0

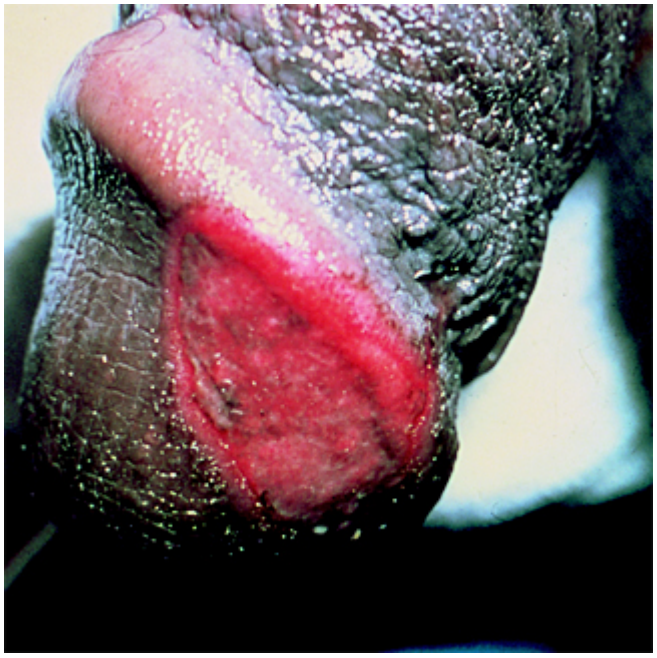
Fixed drug eruption



Fixed drug eruption. An oval lesion occurred at the identical site where it had occurred previously. In both episodes, the rash emerged after this patient ingested a sulfonamide antibiotic. Note the eroded blister in the center of the lesion.

Graphic 52192 Version 3.0

Fixed drug eruption



Fixed drug eruption. An oval erosion on the glans penis occurred in this patient who was taking minocycline. According to the patient, an identical lesion appeared when he was given minocycline previously.

Graphic 65991 Version 4.0

Contributor Disclosures

Werner J Pichler, MD Consultant/Advisory Boards: ArgeniX [Cutaneous side effect of drugs]; ILC Therapeutics [Cutaneous side effect of drugs]; Innomedica [Side effects of nanoparticles]. All of the relevant financial relationships listed have been mitigated. **N Franklin Adkinson, Jr, MD** Equity Ownership/Stock Options: AllerQuest [Penicillin allergy diagnosis]. Consultant/Advisory Boards: Aeglea [DSMB for drug products under development]; AMAG Pharma [Hypersensitivity reactions and anaphylaxis in drugs under development]; BioMarin [Hypersensitivity reactions and anaphylaxis in drugs under development]; Genzyme/Sanofi [DSMB for drug products under development]; IQVIA [DSMB for drug products under development]; Merck [Hypersensitivity reactions and anaphylaxis in drugs under development]; ViiV Healthcare [Hypersensitivity reactions and anaphylaxis in drugs under development]. All of the relevant financial relationships listed have been mitigated. **Anna M Feldweg, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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