Acute Symptoms of Drug Hypersensitivity (Urticaria, Angioedema, Anaphylaxis, Anaphylactic Shock)

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Drug hypersensitivity reactions (HSRs) are the adverse effects of drugs which, when taken at doses generally tolerated by normal subjects, clinically resemble allergy.[1] Although they occur in a small percentage of patients (about one-third of all adverse drug reactions, which affect 10% to 20% of the hospitalized patients and more than 7% of the general population), these reactions are often unpredictable and can be life threatening.[2,3] Only when a definite immunologic mechanism (either drug-specific antibody or T-cell) is demonstrated should these reactions be classified as drug allergy. For general communication, when a drug allergic reaction is suspected, "drug HSR" is the preferred term, because true drug allergy and nonallergic drug HSR[4] may be difficult to differentiate from the clinical presentation alone, especially in situations of acute severe HSR, such as anaphylaxis. However, for a long-term plan of treatment and prevention, referral to an allergist-immunologist for confirmation of diagnosis is needed to offer specific preventive measurements.

The European Network for Drug Allergy (ENDA), working under the aegis of the European Academy of Allergy and Clinical Immunology (EAACI), has simplified the clinical classification of drug HSRs into 2 types, according to the delay of onset of the reaction after the last administration of the drug[5,6]: (1) *immediate reaction,* occurring less than 1 hour after the last drug intake, usually in the form of urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, and anaphylaxis or anaphylactic shock;

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and (2) *nonimmediate reaction*, with variable cutaneous symptoms occurring after more than 1 hour and up to several days after the last drug intake, such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, or drug reaction with eosinophilia and systemic symptoms (DRESS). The first category is mostly mediated through specific IgE, whereas the latter is specifically T-cell–mediated.

Acute urticarial and angioedema reactions are common clinical problems frequently encountered by internists and general practitioners. Although most are benign and self limiting, a mucocutaneous swelling of the upper respiratory tract could be life threatening by itself or a feature of anaphylaxis.[7–9] By contrast, urticaria and angioedema alone are not specific to drug allergic reaction, and can be caused by various pathogenic mechanisms.[10] In this article, the authors review acute symptoms of drug HSRs, especially urticaria, angioedema, anaphylaxis, and anaphylactic shock, and how to approach these problems in general.

URTICARIA AND ANGIOEDEMA

Acute urticaria and angioedema are common clinical problems with an estimated lifetime incidence of 15% to 25% in the general population.[10,11] Acute urticaria is more common in children, young adults, and people with atopic diseases, whereas the chronic form is more prevalent in middle-aged women, with peak incidence during the third and fourth decades.[10,12] Isolated angioedema is still a poorly understood clinical issue and a difficult subject to approach for both internists and specialists.[13]

Clinical Features of Urticaria and Angioedema

Urticaria (or "hives") gives rise to blancheable, raised (edematous), smooth, pink to red papules, although classically it produces pale wheals surrounded by an erythematous flare and is characteristically intensely pruritic. These lesions are usually discrete, round or oval in shape, can vary in size from 1 mm to many centimeters, and may occur anywhere on the body (**Fig. 1**). In the vast majority of cases the wheals are transient, lasting for only a few hours in any one place, but with new wheals appearing in other places. Most urticarial eruptions therefore "move" around the body—a useful pointer from clinical history that the eruption is urticarial.[10,11,14,15]

Angioedema, also called Quincke edema, is characterized by an acute, transient, nonpitting, red to skin-colored, well-demarcated, edematous swelling that involves deeper layers of skin (deep dermis, or subcutaneous and submucosal layers); it occurs in an asymmetric distribution, and has no predilection for dependent areas. Angioedema usually affects the face (particularly the lips, tongue, perioral, and periorbital areas) (**Fig. 2**), extremities, genitalia, scalp, as well as the upper respiratory airways and the intestinal epithelial lining. Pruritus is characteristically absent or minimal, but can be accompanied by a sense of burning, pressure or tightness, or by a dull ache in the affected area. Moreover, whereas most urticarial lesions regress within 24 hours, angioedema may last for several days.[10,13]

Differentiation Between Urticaria and Angioedema

Identifying and distinguishing angioedema from urticaria is important. First, along with anaphylaxis, angioedema is the only truly potentially life-threatening aspect of acute immediate hypersensitivity reactions, if the airway is affected. Patients should maintain ready access to epinephrine, because laryngeal edema is a cause of death if
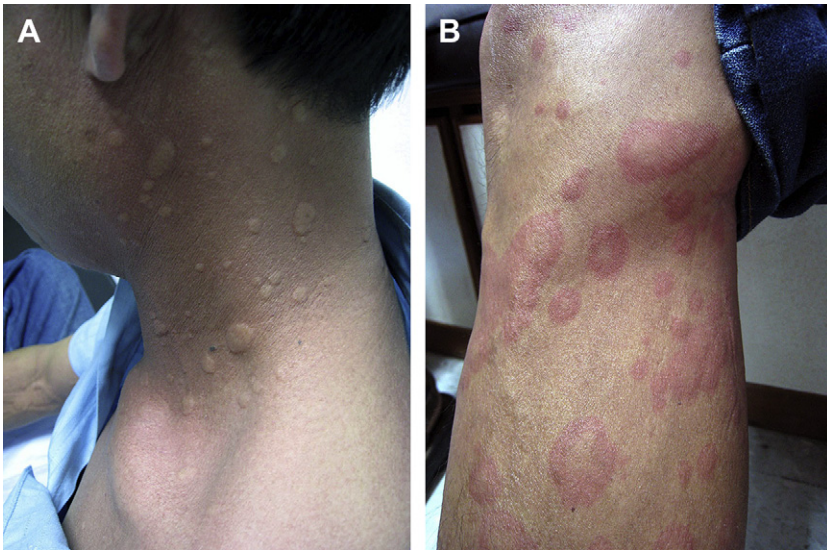
Fig. 1. Urticarial lesions with typical raised, edematous, pink, smooth papules and classically surrounded by erythematous flare (*A*), and gyrate pattern of urticaria (*B*).

unrecognized and/or inadequately treated.[16–18] Second, patients with urticaria and angioedema tend to have more severe disease, more prolonged disease, and symptoms that are less responsive to therapy as compared with patients with urticaria alone.[7,11,19] Finally, although about half of the patients with urticaria also have angioedema, as there is often a continuum spectrum of manifestations ranging from superficial wheals in the upper dermis merging with angioedema of the subcutaneous and submucosal tissues,[8] 40% of the patients have urticaria alone and 10% have isolated angioedema.[7] Thus for angioedema with urticaria the approach scheme is the same as for urticaria, whereas isolated angioedema is a separate entity requiring a different clinical approach.[13]

Fig. 2. Angioedema presenting as bilateral eyelid swelling, from nonsteroidal anti-inflammatory drug–induced angioedema.

Differential Diagnosis of Urticaria

Although urticaria is generally not difficult to diagnose, classifying patients with drug-induced urticaria is crucial for developing a meaningful differential diagnosis, identifying specific triggers, and choosing allergy tests. The following conditions should be ruled out:

1. Dermatographism represents the most common physical urticaria, affecting 2% to 5% of the population. In contrast to the normal urticarial lesions, which are usually round or oval in shape, dermatographism consists of linear pruritic wheals appearing on areas of skin within 2 to 5 minutes of stroking and resolves after 30 minutes or up to 3 hours. Only a small portion of affected patients are symptomatic and require treatment with antihistamines. Systemic symptoms are absent. Common triggers include scratching the skin and contact with clothing, towels, or sheets. Dermatographism may follow an acute viral infection or drug reaction, and the duration is variable.[10]

2. Urticarial vasculitis should be suspected when the lesions are painful (more than pruritic), last more than 24 hours, leave permanent pigmentary change, are non-blancheable, form vesicles, or are accompanied by purpura. Questions regarding systemic (vasculitis) symptoms including fever, arthralgia or arthritis, renal disease with proteinuria or hematuria, gastrointestinal manifestations of nausea and abdominal pain, and pulmonary disease with cough, dyspnea, or hemoptysis should be addressed. Frequently the provoking antigen cannot be found, but diagnostic tests classically reveal elevated acute-phase proteins, including an erythrocyte sedimentation rate and low complement serum levels (CH50 or C1q, C2, or C4). Skin biopsies help confirmation of diagnosis by revealing the classic features of leukocytoclastic vasculitis; this can be associated with systemic lupus erythematosus, rheumatic fever, juvenile rheumatoid arthritis (Still disease), or other connective tissue diseases. It is a rule of thumb to perform skin biopsies of urticarial lesions if they persist at the same site for more than 24 hours.[10,11]

3. Contact urticaria, in which contact of the skin with an allergen causes immediate hives at the site of contact, can be either allergic, such as allergy to natural rubber latex, or nonallergic, due to, for example, certain chemicals in foods and cosmetics. The disease can be complicated by angioedema and even severe anaphylaxis, especially in IgE-mediated allergic contact urticaria.[12,15]

4. Erythema multiforme is an acute disorder characterized by persistent targetlike lesions, which are symmetric, round, red or purple, with characteristically dark cyanotic centers that are typically less pruritic than urticaria. Also, these lesions are usually found on the extremities, including the palms and soles, dorsa of the hands and the feet, forearms, and lower legs. These lesions are self limiting with a recovery phase of approximately 3 weeks.[10] In the absence of severity criteria such as the widespread distribution of skin lesion or cutaneous detachment, the reaction is usually associated with herpes simplex or mycoplasma infection, and mostly affects children and young adults.[20] It is not uncommon for these virus-triggered reactions to recur.

5. Primary mast cell disorders, although rare, account for a few cases of urticaria; physicians should recognize these disorders. Solitary mastocytomas are more common in children, with the classic lesion of hyperpigmented macule or papule, which when mechanically irritated by rubbing the skin develop a wheal and flare (Darier's sign). More than half of childhood mastocytomas resolve during puberty. In contrast, urticaria pigmentosa is rarely confused with urticarial

lesions, given the distinctive pigmented cutaneous lesions for which it is named. Even less common is systemic mastocytosis, a highly symptomatic but rarely malignant clonal disorder of the mast cell and its CD34+ precursors. This condition is almost always accompanied by other symptoms, including prominent gastrointestinal symptoms, neuropsychiatric symptoms, and recurrent anaphylaxis, as a result of increased total numbers of mast cells deposited in various organs, especially skin, bone marrow, gastrointestinal tract, liver, spleen, or lymph nodes, and elevations of the constitutively expressed α-form of tryptase in the serum. A bone marrow biopsy is needed for the diagnosis.[11,21]

Differential Diagnosis of Angioedema

Angioedemas are frequently erroneously labeled when there are clinical manifestations of swollen skin or mucosa around the facial area. Many conditions may mimic angioedema.[13]

1. Edema refers to the swelling of tissue due to excess fluid in an interstitial space. Edema and angioedema show a predilection for areas where the skin is lax rather than taut (especially the eyelids and genitalia), but only edema occurs predominantly in dependent areas such as the buttocks and lower extremities.
2. Facial cellulitis, caused by an infectious process of adjacent organs, is often painful, lasts for several days, is associated with fever and followed by peeling.
3. Superior vena cava syndrome is caused by a progressive obstruction or narrowing of the superior vena cava vein frequently by tumor invasion or mass effect, resulting in the gradual swelling of eyelids, lips, and venous engorgement at the face, neck, and upper part of the thorax.
4. Swelling of the oropharynx should be differentiated from tonsillitis, peritonsillar abscess, and pharyngeal foreign body.
5. Acute (facial) eczema is caused by the direct contact of certain sensitizers with the skin, leading to a pruritic papulovesicular dermatitis characterized early by erythema and edema.
6. Facial swelling as an early manifestation of DRESS (**Fig. 3**) is accompanied by lymphadenopathy, hypereosinophilia, lymphocytosis, and hepatitis.
7. Dermatomyositis presents with heliotrope (violaceous edema of the eyelids), which is persistent and associated with systemic symptoms and characteristic musculocutaneous symptoms such as muscular weakness from myositis and cutaneous eruptions (**Fig. 4**).

ANAPHYLAXIS AND ANAPHYLACTIC SHOCK

Anaphylaxis is the most serious systemic immediate hypersensitivity reaction, often but not always IgE-dependent, is rapid in onset, and can cause death.[22] Although the true prevalence of anaphylaxis is unknown, it is not as rare as generally believed; rather, it seems to be underrecognized and undertreated. In children, adolescents, and young adults, foods are the most common trigger. In middle-aged and older adults, drugs and stinging insect venoms are important causes, as is idiopathic anaphylaxis.[23] An estimated incidence of anaphylaxis is 50 to 2000 episodes per 100,000 person-years with a possible lifetime prevalence of 0.05% to 2%.[24] Although death from anaphylaxis is considered rare (< about 1%), some drugs have been associated with these fatalities, such as β-lactams, radiocontrast media (RCM), and muscle relaxants.[25]

Fig. 3. Face swelling in early manifestation of DRESS syndrome.

Clinical Presentation and Diagnosis of Anaphylaxis and Anaphylactic Shock

In the diagnosis of anaphylaxis, the clinical history and physical examination are the most important instruments. Although recently a multidisciplinary group of experts in the United States has suggested clinical criteria for diagnosing anaphylaxis by the division into 3 categories[22] according to the previous history of allergic reaction and known exposure, in order to include atypical presentation, here the authors

Fig. 4. Heliotrope sign in dermatomyositis, showing swelling and violaceous discoloration of eyelids.

have simplified the procedure by presenting only the first category, in which the diagnosis is based on a combination of clinical signs and symptoms of at least 2 organ involvements (**Table 1**). Skin (urticaria and/or angioedema) is involved in almost 90% of the episodes. Conjunctivitis is part of an acute mucosal allergic reaction to drugs (**Fig. 5**).[16,26] Other organ involvements include the lower respiratory system (dyspnea, wheezing, hypoxemia) in more than half of the patients, the upper respiratory airway system (laryngeal or tongue swelling) in up to 20%, gastrointestinal manifestations (nausea, vomiting, diarrhea, abdominal pain), and cardiovascular manifestations (dizziness, syncope, hypotension, or collapse) in about one-third of the patients.[16,25–27] The presence of hypotension and shock are not always necessary in the diagnosis of anaphylaxis.[22] However, when there is a drop in blood pressure of more than 30% from the patient's baseline or the systolic blood pressure is lower than the standard value, the term "anaphylactic shock" is used; this can be an isolated manifestation in rare patients who experience an acute hypotensive episode after exposure to a known allergen or in a specific situation such as perioperative anaphylaxis.[22] In these situations where diagnosis of anaphylaxis poses difficulties, laboratory tests such as plasma histamine or total tryptase may be helpful. However, these tests do have certain limitations: (1) suboptimal specificity and sensitivity; (2) plasma histamine not available worldwide and requiring special handling (eg, centrifuging and freezing the plasma promptly); (3) limited timing for taking the blood sample (30–60 minutes after the onset of the episode). Although plasma or serum total tryptase levels are more practical (ie, increased from 15 minutes to 3 hours after symptom onset and requiring no special handling), they are seldom increased except in anaphylactic shock triggered by an injected agent, such as an injectable antibiotic or anesthetic agent.[23]

Symptom onset varies widely but generally occurs within seconds or minutes after exposure. The intravenous route of drug administration is usually associated with

Table 1
Clinical diagnosis of anaphylaxis

Anaphylaxis is highly likely when there is an acute onset of clinical symptoms involving *at least 2* organ systems together with skin and mucosal tissue involvement	
Skin and mucosal tissue	Urticaria, angioedema, generalized pruritus or flushing, rhinitis, conjunctivitis
Respiratory system	Lower airway: dyspnea, wheezing, bronchospasm, reduced peak expiratory flow, hypoxemia Upper airway: stridor or upper airway obstruction from laryngeal edema or tongue swelling, together with hypersialorrhea, dysphonia, or dysphagia
Gastrointestinal symptoms	Crampy abdominal pain, nausea, vomiting, diarrhea
Cardiovascular system	Dizziness, syncope, hypotension (collapse)
Anaphylactic shock is defined as anaphylaxis accompanied by reduced blood pressure. On rare occasions, patients can present with isolated acute hypotensive episodes	
Infants and children	Low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure
Adults	Systolic blood pressure <90 mm Hg or >30% decrease from patient's baseline

Data from Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391–7; and Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis. A review of 266 cases. Arch Intern Med 1995;155(16):1749–54.
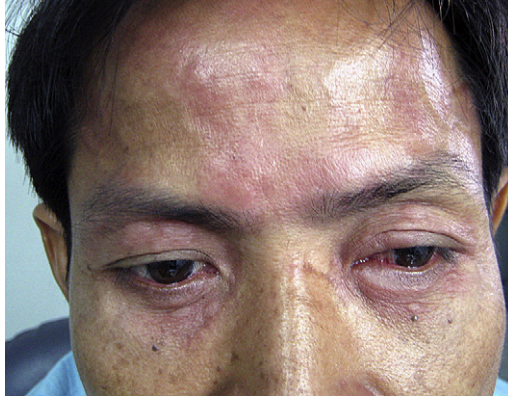
Fig. 5. Urticaria and angioedema involving eyelids, forehead, and face, associated with conjunctivitis and bronchospam, after positive oral aspirin challenge.

a rapid onset of reaction, whereas symptoms associated with the ingestion of an allergen may be more delayed (within the first 2–3 hours and exceptionally even up to several hours). It should be noted, however, that the onset of symptoms can occur immediately after ingestion, and such rapidly occurring events can be fatal. There is a direct relationship between the time of onset of the symptoms after antigen administration and their severity: the more rapid the onset, the more severe the episode.[28] In rare cases, an episode can be protracted, lasting for more than 24 hours, or can recur after initial resolution (biphasic anaphylaxis).[22]

Differential Diagnosis of Anaphylaxis

When the history of exposure to an offending agent is elicited, the diagnosis of anaphylaxis is often obvious because anaphylaxis is a dynamic continuum, usually characterized by a definable exposure to a potential trigger and by rapid onset, evolution, and resolution of symptoms within minutes to hours after treatment. Skin symptoms and signs such as itching, flushing, urticaria, and angioedema are extremely helpful in the diagnosis of allergic reaction,[23] but might be absent or unrecognized in 10% or more of all episodes, especially in severe episodes.[22,25] When gastrointestinal symptoms or respiratory symptoms predominate, or cardiopulmonary collapse makes obtaining a history impossible, anaphylaxis may be confused with other entities. Some of these differential diagnoses are listed in **Table 2**. Common diagnostic dilemmas involve acute asthma, syncope, and panic attacks.[23] These conditions, however, usually lack typical cutaneous signs and symptoms, and vasovagal reaction is associated with nausea, sweating, and bradycardic hypotension whereas anaphylaxis is almost always associated with tachycardic hypotension.

TRIGGERS OF ACUTE URTICARIA, ANGIOEDEMA, AND ANAPHYLAXIS
Mechanisms Involved

Acute urticaria/angioedema or anaphylactic reactions occurring within a few hours following the last administration of the drug may be due to allergic mechanisms (either IgE-dependent or other antibodies such as IgM or IgG) or nonallergic mechanisms (**Table 3**). An allergic mechanism involves the cross-linking of IgE and aggregation of the IgE receptors on mast cells and basophils. Nonallergic reactions include

Table 2	
Differential diagnosis for anaphylaxis and anaphylactic shock	
Presentation	**Differential Diagnosis**
Hypotension	Septic shock
	Vasovagal reaction
	Cardiogenic shock (sudden asystole may be a sign of anaphylactic shock as well)
	Hypovolemic shock
Respiratory distress with wheezing or stridor	Airway foreign body, especially in small children
	Asthma and chronic obstructive pulmonary disease exacerbation
Postprandial syndromes	High monosodium glutamate ingestion
	Sulfite ingestion
	Scrombroid fish poisoning[a]
Flush syndromes	Carcinoid syndrome
	Postmenopausal hot flushes
	Alcohol-induced flush
	Red man syndrome (vancomycin injection)
Excess endogenous production of histamine syndromes	Systemic mastocytosis[a]
	Basophil leukemia[a]
	Acute promyelocytic leukemia (tretinoin treatment)[a]
Nonorganic diseases	Panic attacks
	Vocal cord dysfunction syndrome
	Munchausen stridor
Miscellaneous	Cardiovascular (myocardial infarction)[a]
	Neurologic events (seizure, cerebrovascular event)

[a] May include hypotension.

Data from Lieberman PL. Anaphylaxis. In: Adkinson NF, Busse WW, Bochner BS, et al, editors. Middleton's allergy: principles and practice. 7th edition. Elsevier; 2009. p. 1027–50; and Tang AW. A practical guide to anaphylaxis. Am Fam Physician 2003;68(7):1325–32.

nonspecific histamine release (eg, opiates, RCM, plasma volume expander, and vancomycin), induction of leukotriene synthesis (nonsteroidal anti-inflammatory drugs [NSAIDs]), or bradykinin accumulation (angiotensin-converting enzyme [ACE] inhibitors).[5,6] Regardless of the initiating trigger and mechanism, cellular events in mast cells and basophils result in the rapid release of granule-associated preformed mediators, particularly histamine and tryptase. Moreover, the downstream production of arachidonic acid metabolites (including prostaglandins, leukotrienes, and synthesis of platelet-activating factor) and array of cytokines and chemokines lead to the development of immediate anaphylactic symptoms and a late-phase reaction.[22,23] It is of interest that some drugs can trigger acute allergic symptoms via both allergic and nonallergic mechanisms, such as NSAIDs, RCM, opiates, and some chemotherapeutic agents.[29–31]

Urticaria should be regarded as a symptom that can be triggered by a wide range of exogenous factors or endogenous diseases with allergic, inflammatory, or infectious mechanisms, and not uniquely the allergic reaction in nature.[10] The common causes of acute urticaria/angioedema are acute infections.[32] Acute viral infection, and especially upper respiratory tract infections (URI), appear to be the most common cause of acute urticaria, which are usually present a few days before the onset of wheal formation. The prevalence of URI in acute urticaria varies between 28% and 62%.[12,32,33] Because the drugs commonly prescribed during the treatment of these infections such as antibiotics and NSAIDs can also elicit acute urticaria, they are frequently

Table 3
Common triggers of acute urticaria, angioedema, and anaphylaxis

Nonallergic Triggers	Allergic Triggers
Acute urticaria/Angioedema	Food
Viral infections	Mostly peanuts, tree nuts, shellfish,
Physical stimuli	fish, milk, and egg
Certain food like strawberries	Food-dependent exercise induced
(unknown reason)	anaphylaxis (often associated with
Chemical substances: RCM,[a] volume	sensitization to omega5-gliadin)
expanders, aspirin, NSAIDs[a]	Drug
Drug causing direct mast cell	–Common: *Antibiotics (β-lactams,*
degranulation: opiates,[a] vancomycin	*fluoroquinolone*[a]*)*
paclitaxel, docitaxel and doxorubicin,	*NSAIDs*[a]
quinolones[a]	*RCM*[a]
Acute manifestation of autoimmune	Myorelaxant
disease, connective tissue disease, or	Platinum compounds
malignancy	–Less common: opiates[a]
Isolated angioedema	Insect stings
ACE-inhibitor	Hymenoptera (bee, wasp, hornet, yellow
Aspirin, other NSAIDs[a]	jacket, sawfly), fire ant, or other biting
C1 INH deficiency (hereditary	insects (eg, flies, mosquitoes, kissing
angioedema or acquired form)	bugs)
Factor XII mutation and estrogen intake	Latex
Anaphylaxis	
Physical	
Idiopathic	

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; RCM, radiocontrast media.
  [a] Drugs capable of triggering acute HSRs either by nonallergic or allergic (IgE-specific) mechanism (see text).

accused wrongly. Unfortunately, there are no clinical predictors to differentiate between acute urticaria from infection and that from drug allergy, except the circumstantial evidence of resolution of infection and hives at the same time.[10] A significant proportion of physical stimuli (such as exposure to sun, water, or temperature extremes, pressure from, eg, wearing a heavy backpack, vibration), foods, chemical substances, and drugs (such as aspirin, NSAIDs, vancomycin, opiates, RCM, some chemotherapeutic agents, and volume expanders) can cause urticaria and angioedema by nonimmune-mediated mechanism (see **Table 3**).[9,11] Aspirin- and NSAID-induced urticaria and angioedema are common. Their prevalence in the general population has been reported to be 0.1% to 0.3%.[34] However, in selected populations, such as atopics, young adults, and 21% to 30% of patients with chronic urticaria, the risk of developing wheal and flare after the ingestion of this agent is increased.[35,36] Pathogenesis is believed to be the inhibition of cyclooxygenase (COX)-1, leading to a shunting of arachidonic acid metabolism toward the 5-lipooxygenase pathway, which results in an increased synthesis and release of cysteinyl leukotrienes.[37] The intake of aspirin and NSAIDs can also elicit adverse respiratory symptoms, such as asthmatic attacks and nasoocular symptoms (eg, conjunctivitis and rhinosinusitis) through the same pathomechanism, particularly in up to 10% of asthmatic patients and some atopic individuals.[38,39] Most sensitive persons who experience urticaria, angioedema, or respiratory symptoms may have similar reactions to chemically different conventional NSAIDs (antigenically unrelated to aspirin), so-called cross-reactivity, and must take low-dose acetaminophen or specific COX-2 inhibitors for

treatment of fever, pain, or inflammation.[40–42] Other agents capable of the direct stimulation of histamine release from mast cells include opioids (such as codeine and morphine), vancomycin (red man syndrome), RCM, and certain chemotherapeutic agents (such as paclitaxel, docetaxel, and doxorubicin).[11,31] Volume expanders, particularly gelatin and dextran, are responsible for a few cases of acute HSR during operation.[29,43] These agents, particularly via intravenous administration, can produce symptoms identical to IgE-mediated immediate type reactions, including urticaria, angioedema, bronchospasm, and anaphylaxis (formerly termed ''anaphylactoid reactions''). Other triggers are allergic, such as drug, food, insect sting, and latex (see **Table 3**). Exacerbations of chronic urticaria may be regarded as acute urticaria and allergens may be suspected. These conditions include autoimmune diseases (eg, thyroiditis and autoantibody to IgE receptor) and other systemic diseases (eg, connective tissue diseases, neoplastic conditions, and some chronic infections).[44]

Angioedema is classified as angioedema associated with mast cell degranulation from allergic reaction or nonallergic mechanism, and angioedema mediated by the accumulation of bradykinin. The first category is usually associated with urticaria and is caused by similar allergic and nonallergic triggers (see **Table 3**). The latter is usually associated with isolated angioedema and is caused by certain medications (eg, ACE inhibitors), C1 esterase inhibitors (C1 INH), or other deficiencies (hereditary or acquired angioedema, eg, lymphoma, autoimmune connective diseases).[13] *ACE inhibitor–induced angioedema* is not dose related, and is a class-specific mediated angioedema. Apart from the catalysis of the transformation of angiotensin I to angiotensin II, ACE also inactivates bradykinin. Thus, ACE inhibitors have the potential to keep bradykinin levels elevated. As bradykinin is a powerful vasoactive substance, excess levels may cause vasodilatation and increased vascular permeability. The overall incidence of ACE-induced angioedema is reported to be around 0.1% to 0.5%,[45–48] but it is the most common cause of acute angioedema cases referred to emergency hospital departments (23%–38%), in which up to 20% may be life threatening, especially when upper airway involvement occurs.[49] Furthermore, although 50% of ACE inhibitor–induced angioedema may occur during the first week of therapy, some patients may have taken the ACE inhibitor without any problem for weeks, months, or even years before the development of angioedema.[29,45] The face and oral mucosa, including the larynx and subglottal area, are most often affected, but isolated visceral angioedema, causing abdominal pain, has also been reported. Emergency treatment as well as hospitalization for observation may be necessary in severe cases. Angiotensin II receptor antagonists do not actually interfere with bradykinin metabolism; nevertheless, some reports postulate recurrent angioedema after switching to these compounds.[48,50,51]

Aspirin and NSAIDs can induce periorbital angioedema either in isolation or as part of an upper respiratory reaction in ''aspirin-sensitive asthma.'' Isolated periorbital angioedema is a typical manifestation of cutaneous reaction to aspirin and NSAIDs in atopic and young adults (see **Fig. 2**).[29,34,52,53] Most of these patients exhibit cross-reactivity with other NSAIDs, and should receive similar management to those presenting with urticaria and angioedema alone or with respiratory symptoms.[53]

Hereditary angioedema (HAE) is a rare, dominantly inherited disease that affects about 1 in 50,000 persons, representing approximately 1% of all cases of angioedema. HAE is mediated by bradykinin.[54] It is a result of deficiency (type 1) or dysfunction (type 2) of the plasma inhibitor of the first component of complement C1 INH. Recently a new, estrogen-dependent form, characterized by a mutation in factor XII, has been described,[55] This form of HAE affects women, and angioedematous attacks are often triggered by intake of anticonceptive hormones or pregnancy. HAE is

characterized clinically by recurrent bouts of painless, nonpruritic, nonpitting edema involving the face, larynx, gastrointestinal tract, and extremities. Attacks are triggered by emotional stress, vigorous exercise, alcohol consumption, hormonal changes, and minor trauma such as dental maneuvers, and lasts 1 to 4 days. Facial and extremity edema resolve gradually without harm, whereas untreated laryngeal edema is progressive and can result in death by asphyxiation.[10,13,54] Patients with mutations in factor XII have laryngeal edema less frequently than patients with classic C1 INH deficiency. Treatment with H1 antihistamines and corticosteroids has little effect, while CI INH reconstitution or the bradykinin receptor antagonist icatibant reduces swelling.[54]

Acquired C1 INH deficiency. C1 INH deficiency may also be acquired as a result of immune complex-mediated depletion or antibody directed against C1 INH, associated with lymphoproliferative disease, particularly B-cell lymphoma, carcinoma, or connective tissue diseases such as systemic lupus erythematosus.[10,13]

Anaphylaxis' common causes include allergic triggers such as foods, drugs, insect stings, and latex, as well as physical factors/exercise and idiopathic anaphylaxis (where no cause is identified) (see **Table 3**). Approximately one-third of anaphylactic episodes are triggered by foods such as shellfish, peanuts, eggs, milk, fish, and tree nuts. Another common cause of anaphylaxis is a sting from a fire ant or hymenoptera (bee, wasp, hornet, yellow jacket, and sawfly).[22,23] The incidence of latex allergy has stabilized after educational campaigns and the substitution of power-free latex and nonlatex gloves in hospitals. However, latex allergy still incorporates an unpredictable risk affecting the general population, in both occupational and nonoccupational settings exposed to latex (gloves, condoms, and urinary catheters).[25]

The drugs that most often cause anaphylaxis include antibiotics, NSAIDs, RCM, and muscle relaxants.

- Antibiotics: In most studies, antibacterial agents were responsible for the highest number of reports of anaphylaxis, including β-lactams (penicillins and cephalosporins) and fluoroquinolones. At one time, penicillin was probably the most common cause. Between 1 and 5 per 10,000 patient-courses with penicillin result in allergic reactions, with 1 in 50,000 to 1 in 100,000 courses having a fatal outcome.[56,57] However, it appears that during recent years the incidence of anaphylaxis to cephalosporins as well as fluoroquinolones is increasing.[43,58–63]
- Aspirin and NSAIDs: Some NSAIDs can cause anaphylaxis in the outpatient setting.[16,26,64] Propyphenazone and pyrazolone were mainly responsible for this reaction. The mechanism was thought to be allergic in nature.[43,52,53,65] However, other NSAIDs have also been reported to be associated with anaphylaxis, such as the diclofenac and oxicam groups, and celecoxib, although drug-specific IgE could not be identified.[25,29,64,66–69]
- RCM can result in severe adverse reaction at a rate of 0.2% for ionic agents and 0.04% for lower osmolarity, nonionic agents. Although they were previously thought to induce acute HSR by a nonallergic mechanism, IgE antibody–mediated mechanisms have recently been identified in some patients.[29,30,70]
- Muscle relaxants are one of the major causes of anaphylaxis during general anesthesia. IgE antibodies against quarternary ammonium ions have been identified and cross-reactivity to other muscle relaxants have been frequently observed. Patients were successfully treated with test-negative agents.[60]
- Chemotherapeutic agents, particularly platinum salts such as carboplatin, cisplatin, and oxaliplatin, are associated with acute HSR after several courses of treatment and usually with a positive skin test. Cross-reactivity to other platins

has been reported, and desensitization offers an effective means for continuation of therapy in cancer patients requiring these agents.[31]

- Other substances: Opioids have been reported to be a cause of anaphylaxis during general anesthesia in a small fraction of patients.[60] Rare, but important causes of anaphylaxis are also chlorhexidin (particularly in urology) and dyes such as patent blue (used in surgery to trace draining lymph nodes).[71,72]

MANAGEMENT OF ACUTE URTICARIA, ANGIOEDEMA, AND ANAPHYLAXIS
Pharmacologic Treatment

As with the treatment of any critically ill patient, the treatment of anaphylaxis begins with a rapid assessment and maintenance of the airway, breathing, and circulation. When a patient fulfills criteria for anaphylaxis, even with symptoms involving nonvital organs, the patient should receive adrenaline/epinephrine immediately intramuscularly, in an attempt to prevent more severe anaphylaxis (self-injectable epinephrine preparations normally contain 0.3 mg epinephrine for adults and 0.15 mg for children; higher doses may be required in adults or overweight persons). Delaying treatment until the development of multiorgan symptoms may be risky because the ultimate severity of anaphylaxis is difficult or impossible to predict at the time of onset of the episodes.[22,73] Subsequent management strategies are determined on the basis of the clinical course and response to adrenaline/epinephrine (**Box 1**).[22,73,74]

For urticaria and angioedema however, H1 antihistamines are the mainstay of treatment. Both first- and second-generation H1 antihistamines are effective in controlling symptoms. Second-generation H1 antihistamines are generally considered the first choice in treatment, because of the lower sedative effects.[76] The addition of a relatively brief use of systemic corticosteroids (0.5–1 mg/kg/d) may be considered in patients with severe symptoms, particularly in the presence of angioedema, to achieve better symptomatic control. These medications have serious potential side effects and may be associated with a significant flare of symptoms after tapering or withdrawal, and thus are not routinely indicated.[11,21]

Observation

After treatment of an anaphylactic reaction, an observation period should be considered for all patients, given that the reaction might recur as the effect of the adrenaline/epinephrine wears off (intramuscular injection results in increased serum levels for an hour or more) and due to the risk of a biphasic reaction (around 1%–20% of the reactions).[77] A reasonable length of time is 4 to 6 hours for most patients, with a prolonged period or hospital admission for those with severe or refractory symptoms.[22]

Evaluation and Long-Term Plan of Management of Acute Urticaria, Angioedema, and Anaphylaxis

The first step is a thorough history taking to identify the cause of urticaria, angioedema, and anaphylaxis, and to determine those at risk for future attacks. In contrast to anaphylaxis, most patients with acute urticaria and angioedema do not require extensive laboratory evaluation except to confirm a causative agent (eg, skin testing for a suspected allergen). Moreover, almost all cases of acute urticaria and angioedema in adults are self limited within 3 weeks.[78]

A complete history and physical examination are the most important tools in the diagnosis and evaluation of urticaria and angioedema. This process is frequently time consuming. Specific questions should address the following: a history of viral infection; recent insect bites or stings; suspected food; skin contact with foreign

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Box 1
Management of acute anaphylaxis

Immediate intervention

1. Assessment of airway, breathing, circulation, and consciousness

2. Administer adrenaline/epinephrine 1:1000 dilution (1 mg in 1 mL) intramuscularly, 0.2 to 0.5 mg (0.01 mg/kg in children with maximum dose of 0.3 mg) every 5 to 15 minutes, or in a situation of general anesthesia where intravenous access and cardiac monitoring are available, treatment tailored to the severity of symptoms may be used (ie, initial intravenous dose: 10–20 μg in grade II reactions, 100–200 μg in case of grade III reactions, repeated every 1–2 minutes as necessary, to control symptoms and blood pressure).

General measures

1. Place patient in recumbent position and elevate lower extremities.

2. Establish and maintain airway.

3. Administer oxygen.

4. Establish venous access and administer normal saline intravenously for fluid replacement. If severe hypotension exists, rapid infusion of volume expanders (colloid-containing solution) is necessary.

5. Seek help

Specific measures to consider after adrenaline/epinephrine injections, where appropriate

1. H1 antihistamines, such as chlorpheniramine or diphenhydramine 50 mg intravenously.

2. Nebulized β_2 agonist (eg, salbutamol) for bronchospasm resistant to epinephrine.

3. Systemic corticosteroid, such as methylprednisolone 1 to 2 mg/kg per day, are not usually helpful acutely, but might prevent prolonged reactions or relapses.

4. Vasopressor (eg, dopamine) for hypotension refractory to volume replacement and epinephrine.

5. Glucagon for patient taking β-blockers.

6. Atropine for symptomatic bradycardia.

7. Consider transportation to an emergency department or an intensive care facility.

8. For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged.

Data from[22,73,75]

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material, heat, cold, or water; and drugs. It is crucial to identify all medications (including prescription, over-the-counter, oral, topical, conventional including blood transfusion, RCM, and herbal) that are taken intermittently or regularly, and which the patient is currently using. Questioning about history of latex sensitivity or possible exposures may reveal a potential occult contact allergen.[11,21] Despite extensive evaluation, possible eliciting factors for acute urticaria and angioedema are not always identified.[78] For patients experiencing anaphylactic reaction, the evaluation and management are more complex, and are detailed in **Box 2**. The prescription of self-injectable epinephrine is mandatory until allergy testing, but is of less interest in the case of a drug allergy. A follow-up evaluation with an allergist should be made in all patients to confirm the anaphylaxis trigger and to plan for long-term individualized preventive measures (see **Box 2**).[22,23,73]

Box 2
Long-term management and preventive measures for patients with anaphylaxis

General measures to be taken before discharging a patient from an emergency department

Obtain thorough history to identify potential causes of anaphylaxis and to determine those at risk of future attacks, and organize:

1. Prescription of self-injectable adrenaline/epinephrine for patients experiencing severe anaphylactic symptoms after exposure to a known allergen in the community (such as food or insect sting).

2. Patient education, in particular how to avoid the allergen and its cross-reactive substances or how to recognize and treat anaphylactic episodes promptly if they occur; also how to gain access to emergency medical services and the closest emergency department.

3. Follow-up with an allergist.

Role of allergist-immunologist specialist

- Confirmation of allergic triggers

    Detailed history and physical examination

    Skin tests: prick and intradermal tests with immediate reading

    Laboratory tests: specific IgE, in vitro test for drug allergy

    Controlled administration of suspected allergen: drug provocation test, food challenge

- Individualized preventive measures and long-term management

    Desensitization (in confirmed IgE-mediated allergic reaction and no alternative measures)

    Avoidance of the causative allergen and cross-reactive substance

    Find safe alternative treatment for the patient (particularly in drug allergy)

    Premedication may be useful in nonallergic hypersensitivity reaction

Data from Refs.[6,22,23]

Diagnostic Workup for Drug Allergy

The history of drug allergy alone is in fact often not reliable because different drugs are frequently taken simultaneously, every one of which is capable of accounting for the symptoms, and it may be imprecise. Acute urticaria and angioedema are nonspecific processes and may be caused by multiple factors as described above, while anaphylaxis may be confused with other conditions as well. Depending on history only (without proving the relationship between drug intake and symptoms or clarifying the underlying pathomechanism of the reaction) leads to overdiagnosis and unnecessary elimination of useful drugs. Particularly in cases where essential and/or frequently prescribed drug classes (eg, β-lactams, paracetamol, NSAIDs, local anesthetics, and myorelaxants) are involved, a diagnosis procedure should be performed in a specialist center, which may include repeated detailed clinical history and physical examination, skin tests, laboratory tests and, ultimately, drug provocation tests.[6,79] Only a formal diagnosis of drug HSRs allows one to bring into play the measures required for prevention and treatment. Skin-prick tests and/or intradermal tests with immediate reading (after 20 minutes) are particularly important tools for demonstrating an IgE-dependent mechanism. Unfortunately, reliable skin test procedures and validated test concentrations for drug allergy are often missing. However, some agents have satisfactory high sensitivity and predictive value (eg, penicillins, cephalosporins,[80,81]

myorelaxants, iodine RCM[70]), whereas others may be specific with low sensitivity (eg, vaccines, hormones, protamine, opiates, thiopental), and the rest with unknown sensitivity and predictive value (local anesthetics, paracetamol, sulfonamides, quinolones, NSAIDs, and most other anti-infectious agents).[79] These procedures should be performed at least 4 to 6 weeks after the reaction, in a specialist environment, because the tests themselves can reproduce allergic symptoms and, rarely, an anaphylactic reaction.[6,79,82] The tests should follow standardized procedures. The laboratory tests (eg, drug-specific IgE) or in vitro tests (eg, stimulation with patient's lymphocytes or basophils with suspected drug) are few in number and rarely fully validated. However, the development of new and validated laboratory tools may, in the future, replace the need for drug provocation tests in certain high-risk patients.

Specific Management and Preventive Measures

Slow rates of infusion and premedication (antihistamines and glucocorticoids) are advised in nonallergic HSRs such as RCM, vancomycin, and certain chemotherapy drugs, but they do not prevent allergic reactions. Desensitization is a process that allows temporary tolerance to allergen, and could be considered when the offending drug is essential and no alternatives exist or are unsatisfactory.[31] Finally, a definitive diagnosis of drug allergy requires a declaration to the local Committee on Drug Safety, an "Allergy Card" specifying the culprit agent(s), the delivery of lists of drugs to avoid and of possible alternatives. Patient education regarding awareness of one's own allergies and learning how to read the package insert on all drugs is important.[22,23,73]

SUMMARY

Clinical manifestations of acute drug HSRs are variable and include urticaria, angioedema, anaphylaxis, and anaphylactic shock. Despite the simple clinical recognition and symptomatic treatment, causative agents of acute urticaria and angioedema are often difficult to define and, in most cases, may be unknown. For anaphylaxis it is unpredictable, but most useful preventive methods involve finding the culprit agent by collecting a history of previous allergic and anaphylactic episodes, testing, and replacing the offending agent with another that is not cross-reactive. At the same time, the proper recognition of anaphylaxis when it occurs, the correct administration of appropriate dose, and the suitable route of administration of adrenaline/epinephrine, including other measurements are very important. Referral to an allergist is encouraged to confirm or refuse drug allergy and to define its pathomechanism, which helps offer specific treatments and preventive measures.

In Brief

- Acute symptoms of drug hypersensitivity are variable and include urticaria, angioedema, bronchospasm, to anaphylaxis or anaphylactic shock.
- Urticaria and angioedema are nonspecific reactions, and are most commonly associated with acute viral infection, nonallergic-mediated drug reactions (such as NSAIDs, opioids, and RCM), and physical stimuli.
- Isolated angioedema should be viewed as a manifestation of adverse reactions to drugs such as ACE inhibitors and NSAIDs.
- Anaphylaxis is an acute severe systemic adverse drug reaction, associated with or without shock, and is mostly associated with allergic reactions, such as antibiotics, NSAIDs, RCM, and muscle relaxants.
- Appropriate dose and route of adrenaline/epinephrine administration is the first treatment and the treatment of choice in anaphylaxis.

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