

Anaphylaxis and Urticaria



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KEYWORDS

• Anaphylaxis • Urticaria • Treatment • Prevention

KEY POINTS

- Anaphylaxis is a serious, life-threatening allergic reaction that affects approximately 2% of the population.
- Urticaria is a rash of transient, erythematous, pruritic wheals that affects up to 25% of the population.
- All cases of anaphylaxis warrant thorough clinical evaluation by the allergist-immunologist, although most cases of urticaria are self-limited and do not require specialist referral.

INTRODUCTION

Anaphylaxis is an acute, severe systemic allergic reaction that can ultimately lead to death if not recognized early and treated properly. Resulting from the rapid release of mast cell-derived and basophil-derived mediators, an anaphylactic reaction can begin quickly and be difficult to control. Fortunately, if recognized early, anaphylaxis can be easily treatable.

Although often a component of anaphylaxis, urticaria is a common allergic complaint that can occur as an isolated incident or as a recurring problem. Urticaria is a rash that consists of transient, erythematous, pruritic, and usually blanching wheals. They can be found on any part of the body and can be triggered by a multitude of eliciting factors. Often, urticaria is quite bothersome and can last from minutes to months.

This article summarizes our current knowledge on the epidemiology, pathogenesis, associated triggers, diagnosis, and treatment of both anaphylaxis and urticaria. Preventative strategies are also discussed.

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ANAPHYLAXIS
Epidemiology

Anaphylaxis is an acute, life-threatening systemic allergic reaction that affects up to 2% of the population.^{1,2} The majority of cases of anaphylaxis are in children, where the prevalence of food allergy has been estimated as high as 8%.²⁻⁴ The exact proportion of cases resulting in fatality is unknown, but is rare overall.⁵

Recently a nationwide, cross-sectional, random digital dial telephone survey of 1000 adults was completed. In this population, nearly 8% of participants reported a prior anaphylactic reaction, but, when symptoms were evaluated, the lifetime prevalence of anaphylaxis was 1.6%.⁶

Previously, anaphylaxis was characterized as an allergic reaction that involved 2 or more organ systems or hypotension.⁷ However, in the last 10 years, formal clinical diagnostic criteria for anaphylaxis have been developed by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network (now known as Food Allergy Research and Education; **Box 1**).⁸ Despite these criteria,

Box 1
Diagnostic criteria for anaphylaxis

Anaphylaxis is diagnosed when 1 of the following criteria is met:

1. Development of acute illness within minutes to hours after exposure causing skin and/or mucosal tissue involvement (eg, rash, generalized urticaria, pruritus, flushing, angioedema, laryngeal edema).

And at least 1 of the following are present:
 - Evidence of respiratory compromise (eg, dyspnea, cough, difficulty breathing, wheezing, stridor);
 - Hypotension (defined in point 3) or evidence of end organ dysfunction (eg, syncope, hypotonia, urinary incontinence).
2. Development of 2 or more of the following within minutes to hours after exposure to a likely allergen for that patient:
 - Skin or mucosal tissue involvement, including rash, generalized urticaria, pruritus, flushing, angioedema, laryngeal edema;
 - Respiratory compromise, including dyspnea, cough, difficulty breathing, wheezing, stridor, and hypoxia;
 - Hypotension or symptoms concerning for hypotension, including syncope, hypotonia, and urinary incontinence; and
 - Gastrointestinal symptoms, including nausea, vomiting, diarrhea, and crampy abdominal pain.
3. Development of hypotension within minutes to hours after exposure to a known allergen for that patient:
 - Infants and children age less than 1 year: SBP less than 70; children ages 1 to 10 years: SBP < (70 mm Hg + [2 × age in years]); children ages 11 to 17 years: SBP less than 90 mm Hg; or for all children: A greater than 30% decrease from that person's baseline.
 - Adults: SBP less than 90 mm Hg or greater than 30% decrease from that person's baseline.

Abbreviation: SBP, systolic blood pressure.
Adapted from Sampson HA, Muñoz-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. *Ann Emerg Med* 2006;47(4):374; with permission.

several retrospective chart analyses of emergency department visits have confirmed the underdiagnosis of anaphylaxis, with reports of 25% to 57% of anaphylaxis cases not properly diagnosed as anaphylaxis.^{7,9,10} The true prevalence of anaphylaxis is likely underreported owing to underdiagnosis.¹¹ Several studies have reported increasing prevalence over the last few decades.^{12–15}

Pathophysiology

Murine studies have revealed both immunoglobulin (Ig)E-dependent and IgE-independent mechanisms of anaphylaxis.^{16–18} IgE-mediated reactions result after allergen sensitization has occurred. During sensitization, allergen-specific IgE antibodies bind with high affinity to FcεRI receptors on both tissue mast cells and circulating basophils. Upon exposure to the sensitized allergen, IgE cross-linking promotes the immediate release of several mediators and cytokines, including histamine, tryptase, chymase, platelet-activating factor, prostaglandin D₂, cysteinyl leukotrienes, interleukin-6, and tumor necrosis factor-α.^{19,20} Rapid degranulation of these substances into the systemic circulation contributes to the multiorgan dysfunction seen in anaphylaxis and ultimately can result in death.²¹

In an IgE-independent mechanism initiated by allergen exposure, IgG can bind to form IgG-antigen immune complexes.¹⁶ These immune complexes cross-link with FcγRIII receptors found on macrophages and induce the release of additional platelet-activating factor, but not histamine or tryptase.^{22,23}

By inducing smooth muscle constriction and augmenting vascular permeability, histamine is responsible for the flushing, pruritus, rhinorrhea, tachycardia, and bronchospasm seen in anaphylaxis. The release of tryptase from mast cells allows for the amplification of the allergic response by stimulating further mast cell degranulation. Additionally, tryptase activates downstream pathways, including the complement cascade, coagulation pathway, and the kallikrein-kinin system. These pathways contribute to the hypotension and angioedema seen in many cases of anaphylaxis. Like histamine, platelet-activating factor enhances vascular permeability and contributes to the clinical manifestations, notably the hypotension, seen in anaphylaxis.^{19,21,22,24} Recently, platelet-activating factor levels were found to correlate directly and significantly with severity scores of anaphylaxis, and this clinical correlation was not observed with tryptase and histamine levels.²⁵

Triggers

Immunoglobulin E-mediated triggers

The most commonly identified cause of anaphylaxis is food allergy, contributing up to 50% of all cases of anaphylaxis (**Box 2**).²⁶ Affecting up to 8% of American children, food allergy is the major cause of anaphylaxis in children.^{1,3,27} Although any food can cause anaphylaxis, the most commonly implicated foods are peanuts, tree nuts, and shellfish, with peanuts being the most common cause in children and shellfish the most common cause in adults.^{28,29} Although the prevalence of tree nut allergy is lower than peanut allergy, a higher rate of fatal anaphylaxis has been reported with tree nut allergy.³⁰ Milk, soy, eggs, wheat, fish, food additives, and spices have also been associated with severe reactions.³¹

Delayed anaphylaxis occurring 4 to 6 hours after ingestion of mammalian meat, particularly beef, has recently been described. These patients were found to have sensitization to the carbohydrate galactose-α-1,3-galactose, which is found in select mammalian meats.³² Sensitization to galactose-α-1,3-galactose has been described after bites of *Ixodes* ticks.³³

Box 2**Common triggers of anaphylaxis and urticaria**

Allergic triggers: Reaction owing to immunoglobulin E-mediated response to allergen

Foods, such as peanut, shellfish, tree nuts, milk, soy, wheat, egg, and fish

Drugs, such as β -lactam antibiotics and nonsteroidal anti-inflammatory drugs

Insect venom, such as from honey bee, wasps, yellow jackets, hornets, and fire ants

Biologics, such as allergen immunotherapy, vaccine additives, monoclonal antibodies

Latex

Food additives, such as carmine, gelatin, and spices

Nonimmunologic triggers: Reaction owing to direct activation of mast cells and basophils

Physical factors, such as exercise, cold, and heat

Medications, such as opioids

Radiocontrast media

Other systemic triggers

Systemic mastocytosis or a clonal mast cell disorder

Idiopathic anaphylaxis

Data from Refs.^{2,8,21}

Drug allergy is also a common cause of anaphylaxis, particularly in adults.^{1,2,6} Of the countless drugs that have been implicated in anaphylaxis, most reactions are secondary to antibiotic exposure. Anaphylaxis owing to β -lactam antibiotics have been reported for over 50 years.^{21,34} The incidence of penicillin-associated anaphylaxis has been reported as high as 1 to 5 per 10,000 patient courses of treatment.³⁵ Nonsteroidal anti-inflammatory drugs are identified frequently as common triggers of anaphylaxis, with ibuprofen and naproxen being implicated most often.^{1,36} Webb and Lieberman²⁷ identified aspirin-associated anaphylaxis in 35% of drug allergy anaphylaxis. Although any medication can cause anaphylaxis, frequent reports have been described after treatment with insulin, heparin, erythromycin, and cancer chemotherapeutics.^{27,37}

Biologic agents have also been associated frequently with anaphylaxis. Commonly implicated biologic agents include allergen immunotherapy, vaccinations, adjuvants, immune-modulating agents, and monoclonal antibodies.^{8,38,39}

Anaphylaxis has been reported with latex exposure, especially among health care workers, patients with frequent procedures or genitourinary abnormalities, and workers with frequent occupational exposure to latex.^{40,41} In patients without a known latex exposure, latex allergy has also been associated with atopy and family history of latex allergy.⁴²

Anaphylaxis owing to Hymenoptera venom allergy can occur in up to 3% of insect stings in adults and 1% in children. In particular, honey bee, wasps, yellow jackets, white-faced hornets, yellow hornets, and fire ants have been associated with anaphylaxis, and first-time sting reactions can be fatal.^{8,43,44} Bites from the deer fly and *Triatoma* have been reported in rare cases of anaphylaxis.²⁷

Non-Immunoglobulin E-mediated triggers

Although diagnostic testing and clinical history aid substantially in our ability to identify a cause of anaphylaxis, up to 60% of anaphylaxis cases have no discernible basis.^{27,45}

Idiopathic anaphylaxis is a diagnosis of exclusion that results when there are no identifiable triggers and other systemic disorders, such as mastocytosis, have been ruled out. Most cases of idiopathic anaphylaxis occur in adult women.^{27,46} Idiopathic anaphylaxis is more prevalent among atopic individuals, with nearly 50% having associated atopy in 1 large cohort of patients with idiopathic anaphylaxis.⁴⁶

Anaphylaxis has been reported to occur through non-IgE-mediated mechanisms. In particular, immediate mast cell and basophil degranulation can be triggered after exposure to radiocontrast media, opioid medications, and vancomycin.^{47–50} Antigen–antibody immune complexes can also form after the administration of blood products and intravenous immunoglobulins. The immune complexes activate the complement system, which allows for the circulation of C3a, C4a, and C5a. These anaphylatoxins can trigger systemic mast cell and basophil degranulation leading to anaphylaxis.⁵¹

Physical stimuli, such as exercise, have also been reported to induce anaphylaxis. Exercise-induced anaphylaxis is most commonly reported in young adults, but can occur at any age.^{52–54} Most cases of exercise-induced anaphylaxis present with symptoms during exercise or shortly afterward (<15 minutes). The pathophysiology of exercise-induced anaphylaxis remains unclear, but proposed mechanisms include release of endorphins and neuropeptides, such as gastrin, during exercise that trigger mast cell degranulation.^{52,55,56}

Food-dependent, exercise-induced anaphylaxis has also been widely reported, usually with exposure to a specific food within minutes to hours before exercise and anaphylaxis with or immediately after activity. Foods that have been commonly implicated include wheat, soy, and nuts, although it can occur with others foods.^{52,54,57–59} Taking aspirin or other nonsteroidal anti-inflammatory drugs before exercise has also been associated with anaphylaxis.^{60,61}

Opioid medications, such as morphine, codeine, and meperidine, have been reported to elicit clinical anaphylaxis. Opioids can directly stimulate mast cell degranulation, releasing histamine and tryptase into circulation and contributing to the symptoms of anaphylaxis.^{62,63}

Mastocytosis is a rare, heterogeneous group of disorders characterized by clonal proliferation of mast cells in 1 or more organ systems. Systemic disease, in which there is significant bone marrow involvement, often presents with anaphylaxis.^{64,65} This is owing to the propensity of the abundant and disruptive mast cells to degranulate. As a result, patients often have elevated baseline tryptase levels (>20 ng/mL).⁶⁶ Systemic mastocytosis is associated with c-KIT point mutations.⁶⁷ Other common symptoms of systemic mastocytosis include flushing, pruritus, syncope, urticaria, abdominal pain, tachycardia, and hypotension.

Diagnosis

The diagnosis of anaphylaxis relies heavily on the clinician obtaining a thorough history and physical examination, while paying particular attention to any possible or known allergen exposures. Because anaphylaxis is a systemic allergic reaction, the signs and symptoms can affect multiple organ systems (**Box 3**). The skin and mucosal tissues are most commonly involved, with urticaria and/or angioedema reported in nearly 90% of anaphylactic reactions.²⁷

In 2005, the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network developed clinical diagnostic criteria to define anaphylaxis (see **Box 1**). In 2012, Campbell and colleagues⁶⁸ evaluated the validity of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis and results yielded a sensitivity of 96.7% and a specificity of 82.4%.

Box 3 Common signs and symptoms of anaphylaxis
<i>Skin or mucosal tissue</i>
Rash
Generalized urticaria
Flushing
Pruritus
Angioedema
Piloerection
Oral pruritus or tingling
Conjunctival erythema
Laryngeal edema
<i>Respiratory</i>
Dyspnea
Cough
Difficulty breathing
Wheezing
Stridor
Chest tightness
Rhinorrhea
Nasal congestion
Sneezing
Nasal pruritus
Dysphonia
Hoarseness
<i>Cardiovascular</i>
Syncope
Feeling faint or dizzy
Confusion
Altered mental state
Chest pain
Heart palpitations
Tachycardia
Bradycardia
Urinary incontinence
Cardiac arrest
<i>Gastrointestinal</i>
Nausea
Vomiting
Diarrhea

Crampy abdominal pain

Difficulty swallowing

Neurologic

Anxiety

Feeling of impending doom

Seizures

Headache

Irritability

Confusion

Data from Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(3 Suppl 2):S483–523; and Lieberman P. Middleton's allergy: principles and practice. Seventh edition. In: Adkinson NF, et al, editors. Anaphylaxis, Chapter 59. vol. 2. Philadelphia: Elsevier Inc; 2010. p. 1027–50.

Although anaphylaxis is a clinical diagnosis, laboratory testing may aid in confirming the severe systemic reaction. Because tryptase is among the early mediators released by mast cells during an acute allergic reaction, serum tryptase levels are often elevated (>11.5 ng/mL) in anaphylaxis. Serum tryptase levels peak 1 to 2 hours after symptom onset and normalize after 5 to 6 hours. It is crucial to obtain the serum tryptase level during its narrow window in circulation, usually within 3 hours of symptom onset.^{69,70} Mast cells in the gastrointestinal and respiratory tracts may contain less tryptase per cell, contributing to inconsistently elevated tryptase levels in food-induced anaphylaxis.⁵ Because of this variation, it is important to understand that an elevated tryptase level with a concerning clinical history is highly suggestive of anaphylaxis, although a normal tryptase level does not rule out anaphylaxis. Histamine is the first mediator released by mast cells; however, it normalizes within 45 minutes so is often of little diagnostic value.⁷¹

All patients who experience anaphylaxis should be referred for allergy-immunology evaluation. Depending on the clinical history, assessment of IgE-mediated sensitization to allergens of interest may be warranted. In vivo and in vitro tests to evaluate for IgE-mediated allergy are available for most foods, latex, and a few medications. Skin prick testing with extracts from suspected foods have a high negative predictive value and high sensitivity in predicting clinical allergy.^{72–74} IgE antibody directed at specific allergens can also be measured in the blood. Patients with a clinical history concerning for allergy and evidence of IgE-directed sensitization, either by skin prick test or allergen-specific IgE antibody, are viewed to have clinical allergy. False-positive results can occur; therefore, the clinical history is most important.

Although anaphylaxis most commonly presents as an acute systemic reaction, secondary and delayed reactions have also been reported. Occurring up to 72 hours after an exposure to an allergen, biphasic reactions can occur in up to 25% of fatal or near-fatal anaphylactic reactions.⁷⁵

Treatment and Prevention

The most crucial step in treating anaphylaxis is quickly recognizing the signs and symptoms so that therapy can be started immediately. Delayed treatment is

associated with death.^{5,30,74,76,77} As with any medical emergency, the clinician should first ensure that the patient's airway is protected and preserved. If there is evidence of respiratory compromise, the patient may need intubation and/or oxygen. Vital signs should be quickly assessed, and if there is evidence of circulatory compromise the patient should be placed in the recumbent position with legs elevated.

Intramuscular epinephrine is the first-line therapy for anaphylaxis.^{78,79} Epinephrine should be injected into the front-lateral thigh, because studies have shown this location produces a rapid rise in plasma and tissue epinephrine levels.^{80,81} The recommended adult dose is 0.3 mg of 1:1000 solution (1 mg/mL). Children should receive 0.01 mg/kg of 1:1000 solution with a maximum single dose of 0.3 mg. For ease of administration during anaphylaxis, there are several epinephrine autoinjectors available commercially. These autoinjectors come in standard adult doses (0.3 mg) and pediatric doses (0.15 mg) for children less than 25 kg. Additional doses of epinephrine may be given every 5 to 15 minutes if clinical symptoms do not improve. It is crucial for all patients and their families to be educated on proper technique of autoinjector administration. Because of the risk for a biphasic reaction, every patient who receives epinephrine should seek medical care for continuous monitoring of vital signs and clinical symptoms.

Although not the preferred route of administration, epinephrine can slowly be given intravenously (usually over 5 minutes) at a dose of 0.1 mg of 1:10,000 solution (0.1 mg/mL). Usually, intravenous epinephrine is reserved for patients who do not respond to repeated intramuscular injections.⁸²

As adjuncts to epinephrine, but not in place of it, nebulized short-acting bronchodilators and antihistamines are used to reduce symptoms associated with anaphylaxis. In particular, H1 and H2 antagonists are commonly used to halt the progression of hives, flushing, and pruritus. Additionally, using a combination of both has shown superior effect in anaphylaxis than using an H1 antagonist alone.⁸³

The use of corticosteroids in the acute management of IgE-mediated anaphylaxis is unclear. Although the Cochrane Database Systemic Review on corticosteroid use in anaphylaxis was unable to identify benefits in the acute management in anaphylaxis, Tole and Lieberman⁷⁵ demonstrated potential efficacy in reducing the frequency of biphasic anaphylactic reactions.⁸⁴

Although rare, death from anaphylaxis results from cardiovascular collapse or respiratory failure. The most common triggers in anaphylaxis-related death have been insect stings, food allergy, drug allergy, and radiocontrast media.^{30,85} Several studies have shown that a delay in epinephrine administration is a risk factor for anaphylaxis-related death and biphasic anaphylactic reactions.^{5,30,75,77}

The crucial step in preventing anaphylaxis is identifying the trigger. Once identified, avoidance of this trigger is essential. This may mean avoiding particular foods, medications, outdoor areas where insects may habitate, or reducing exercise. Venom immunotherapy has proven successful in preventing stinging insect anaphylaxis in up to 98% of patients who previously had anaphylaxis from a sting.⁴⁴ For patients who have had anaphylaxis to a medication but require future doses, an induction of tolerance procedure may be performed under an allergist's care to safely administer the medication. Formerly known as drug desensitization, induction of tolerance is temporary and achieved by administering small but gradually increasing doses of the medication.³⁷ Patients who have been diagnosed with anaphylaxis should carry a medical alert identifying the allergy and an epinephrine autoinjector at all times.

URTICARIA

Epidemiology

Urticaria is an allergic rash that affects up to 25% of the population at some point in their lifetime.^{86–89} The rash usually consists of transient, erythematous, pruritic, and circumscribed wheals, or hives (**Fig. 1**). There are 2 main categories of urticaria depending on the time course of the rash: Acute and chronic. Although each urticarial lesion may last minutes to hours, acute urticaria is an episode of hives that lasts less than 6 weeks. Chronic urticaria is hives that persist or recur, usually multiple days in a week, for longer than 6 weeks' duration.^{86,90} Acute urticaria occurs more frequently in children than adults. Similar to anaphylaxis, acute urticaria is more prevalent in adult females than males.^{87,91–95}

Affecting up to 1% of the population, chronic urticaria is more common in adults than children. Chronic urticaria often begins in the third to fifth decade of life and is most prevalent among women.^{87,96–98} Although both acute and chronic urticaria usually resolve on their own, chronic urticaria may persist for years. Autoantibody-associated urticaria is responsible for 30% to 50% of all cases of chronic urticaria and is now considered a subset of chronic idiopathic urticaria.⁹⁰ As in anaphylaxis, physical activity can trigger urticaria. Physical urticaria represents 20% to 30% of all cases of chronic urticaria.⁹⁹ Another subtype of chronic urticaria is cholinergic urticaria, which accounts for 5% of all cases.^{100,101}

Pathophysiology

As seen in anaphylaxis, urticaria results from the activation and degranulation of mast cells, which are abundant in the skin. Mast cell degranulation incites the rapid release



Fig. 1. Classic urticaria with scattered erythematous, pruritic, and usually blanching wheals.

of mediators and cytokines, including histamine, substance P, platelet-activating factor, tumor necrosis factor- α , interleukin-1, prostaglandin D₂, and leukotrienes C₄ and D₄. Each of these contributes to the vasodilation, increased vascular permeability, and acute inflammation that leads to urticaria.^{102,103}

Although urticaria can occur as a result of direct mast cell activation and degranulation, most urticaria results from immune-mediated hypersensitivity reactions.¹⁰² The most common immunologic pathway in acute urticaria is IgE mediated, similar to that seen in anaphylaxis.

IgG antibodies to both IgE and/or the FcER1 α -subunit have been described to be pathogenic in patients with chronic urticaria. Through this autoimmune mechanism, histamine release theoretically can be triggered. Because these autoantibodies have also been reported in healthy subjects, there is controversy over the clinical pathogenicity.^{102–104} In patients with autoantibody-associated urticaria, there is significant prevalence of other autoimmune conditions, including autoimmune thyroid disorders, celiac disease, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes.^{90,105}

Both immune complex-mediated and cytotoxic hypersensitivity are thought to be involved with urticaria owing to infectious processes.^{106–108} Additionally, cytotoxic reactions have been reported after blood product transfusions.¹⁰²

Most physical urticarias result from the direct mast cell degranulation initiated by the specific physical stimulus, such as with heat, water, or vibration.⁹⁹ The pathogenesis of cholinergic urticaria is not well understood. Because cholinergic urticaria has been associated with hypohidrosis, the urticaria could result from leakage of the sweat into the dermis. Other theories include a muscarinic-mediated mechanism and a neurogenic reflex.^{87,109–111}

Although the pathogenesis of nonsteroidal anti-inflammatory drug-induced urticaria is not well understood, the suggested mechanism stems from the inhibition of cyclooxygenase-1, which shunts the metabolism of arachidonic acid toward the 5-lipoxygenase pathway. This ultimately leads to increased production and release of cysteinyl leukotrienes, thus contributing to urticaria formation.¹¹² Molecular genetic mechanisms are also being sought in patients with nonsteroidal anti-inflammatory drug-induced urticaria. Although several target genes related to histamine and leukotriene metabolism have been suggested to be involved, research on the pathogenesis is ongoing.¹¹³

Triggers

Acute urticaria

Similar to anaphylaxis, 30% to 50% of acute urticaria cases are idiopathic (see **Box 2**).^{114–116} Despite this, an allergy and immunology evaluation may be warranted in some cases because identifying the trigger may prevent future reactions. IgE-mediated hypersensitivity reactions to foods, medications, latex, and insect stings can trigger urticaria and anaphylaxis (see **Box 2**). Nonsteroidal anti-inflammatory drugs are particularly prone to inducing urticaria.¹¹² Additionally, patients who are sensitized to environmental aeroallergens, such as grass or pet dander, can develop acute urticaria after contact with the allergen.⁸⁷ A similar postinflammatory reaction can occur after bites from mosquitos, fleas, and bedbugs, and is known as papular urticaria.¹¹⁷

In children, infections are a major cause of acute urticaria. Although the pathogenesis of infection-related urticaria is unclear, the development of urticaria during an acute infectious process has been well described. Among the infectious agents, upper respiratory tract viruses, *Mycoplasma pneumoniae*, and parasitic infections have been

commonly reported in children.^{88,118,119} In adults, infectious hepatitis and mononucleosis have been implicated in acute urticaria.^{120,121}

Chronic urticaria

Thirty percent to 60% of patients with chronic urticaria have positive autoantibodies directed at IgE, the FcER1 α -subunit, or positive autologous serum skin tests.^{87,90,105} Chronic urticaria has also been associated with infection. Microbes that have been commonly associated with chronic urticaria include *Helicobacter pylori*, Group A *Streptococci*, hepatitis B and C, Epstein–Barr virus, and parasitic infection.^{90,119,122–125}

The physical urticarias and their known triggers have been well described. Dermatographism results from friction applied to the skin, such as by stroking with a smooth, blunt object. Cold and heat urticaria presents minutes after contact or exposure to cold or hot objects, liquids, or air. Aquagenic urticaria results from direct skin contact with water, and can result from exposure to any water source and regardless of the water temperature. Cholinergic urticaria is precipitated by an increase in core body temperature and most often associated with exercise. Clinically, cholinergic urticaria is distinct from typical urticaria because they are smaller (usually 1–3 mm in diameter), punctate, and usually found in primarily on the chest and back. Delayed pressure urticaria results from sustained pressure. Vibratory urticaria is elicited after direct exposure to vibration. Solar urticaria is triggered by direct skin exposure to sunlight. Removal of these physical stimuli usually results in quick resolution of the urticaria.^{99,126}

Chronic urticaria has also been associated with a variety of systemic disorders, including malignancy (eg, B-cell lymphoma, Hodgkin lymphoma), connective tissue disorders, Schnitzler syndrome, mastocytosis, hypereosinophilic syndrome, and Muckle–Wells syndrome.¹⁰⁵ Those patients with chronic urticaria and no identifiable trigger are ultimately diagnosed with chronic idiopathic urticaria.

Diagnosis

As with anaphylaxis, the diagnosis of urticaria relies greatly on the clinician conducting a thorough history and physical examination. Classically, urticaria are raised erythematous wheals that are pruritic. They are usually well-circumscribed or coalescing, and often migrate around the body. Any 1 lesion should last no more than 24 hours, and lesions that last longer or are associated with bruising may suggest urticarial vasculitis. Because urticaria are often transient, photographs of the lesions may be helpful in making the diagnosis when the rash has resolved. The history alone may suggest likely triggers. Typically, urticaria caused by an allergic reaction is distinguished by appearance of symptoms shortly (usually within 2 hours) after a new exposure and a time-limited course of symptoms (resolving within 1 day). Urticaria that lasts days is very unlikely to be caused by an allergic process. The differential diagnosis is broad, but includes erythema multiforme, allergic or irritant contact dermatitis, cellulitis, urticarial vasculitis, systemic lupus erythematosus, cryoglobulinemia, mastocytosis, and malignancy.^{105,127}

If IgE-mediated hypersensitivity reaction is suspected, skin prick testing and/or serum IgE testing directed at the allergen may be available. This is often the case with food allergy, latex allergy, and rarely medication allergy. When no test is available and/or clinical suspicion is low, an allergen challenge may be done under close medical supervision.

Although blood work is not usually necessary in an initial evaluation for urticaria, a complete blood count with differential white blood cell, blood culture, C-reactive

protein, and/or erythrocyte sedimentation rate may be helpful if infection is suspected. Microbial-specific antibodies can also be done. If suspicion is high for an inflammatory or systemic cause of the urticaria, a more thorough laboratory evaluation should be pursued.

Some patients with chronic urticaria may warrant further autoantibody studies, when clinically relevant. In particular, antithyroglobulin and antimicrosomal antibodies are often checked. Some clinicians may find testing for autoantibodies directed at IgE and the FcER1 α -subunit helpful, although this does not usually change clinical management.^{86,87} Autologous serum skin tests, autologous plasma skin tests, and basophil histamine release assays have also been performed in patients with chronic urticaria. These tests are not confirmatory and routine performance of these tests is not recommended in patients with chronic urticaria.^{90,103}

A punch skin biopsy should be performed when there is refractory urticaria or a concern for urticarial vasculitis. Skin biopsy typically reveals perivascular leukocytic infiltration with eosinophils, neutrophils, and/or basophils. With urticarial vasculitis, skin biopsies should have evidence of leukocytoclasia and deposition of fibrinogen, complement, and/or immunoglobulins.^{86,105}

Because physical and cholinergic urticaria are inducible by stimuli, there are a variety of diagnostic tests available to confirm these diagnoses. Provocative testing should be done in the office setting on an area of skin that has not been recently affected by urticaria. The most common form of physical urticaria is symptomatic dermatographism, which is confirmed by the development of wheal formation and pruritus after moderate stroking of the skin by a smooth, blunt object. The ice cube test is used to confirm cold urticaria. The clinician should place an ice cube (placed in a glass object or Ziplock bag to avoid water from touching the skin), cool pack, or cold water bath on the volar aspect of the forearm for up to 5 minutes. The arm should be evaluated for urticaria formation 10 minutes after removing the ice cube. Similarly, heat urticaria can be provoked by applying a hot stimulus to the skin (eg, glass or metal container with hot water, hot pack, or hot water bath). The heated device should be at a temperature of approximately 45°C. Aquagenic urticaria is diagnosed after the application of tap or distilled water to the skin and observation for urticarial emergence.^{87,128}

Delayed pressure urticaria is evaluated by placing metal rods of various weights on the volar aspect of the forearm for 15 minutes. If urticaria appear 6 hours later, the diagnosis is confirmed. Vibratory urticaria can be diagnosed after the arm is placed on a vortex mixer for 10 minutes. The arm should be read for urticaria 10 minutes after provocation is complete. Solar urticaria can be provoked by exposing the buttocks separately to ultraviolet A, ultraviolet B, and visible light. Solar urticaria typically appears within 10 minutes after completed exposure. Cholinergic urticaria can be confirmed by following 2 steps. First, the patient should conduct moderate exercise for 15 minutes beyond the point of sweating. Ten minutes after completion, the skin should be evaluated for urticarial rash. If this test is positive, the patient should then undergo a passive warming study at least 24 hours after the exercise test. In the passive warming study, the patient should be emerged into a full bath at approximately 42°C for 15 minutes, with goal to achieve a rise in core body temperature of greater than 1°C. When differentiating cholinergic urticaria with hypotension from exercise-induced anaphylaxis, patients with exercise-induced anaphylaxis will not react with passive heating.^{99,126,128}

Treatment and Prevention

Because of the transient nature of acute urticaria, treatment may not be necessary. Most episodes of acute urticaria self-resolve within 2 to 3 weeks. Prolonged episodes

have been associated with atopy.¹²⁹ If the lesions are prolonged or bothersome, an oral second-generation H1 antagonist is the first-line treatment.⁹⁰ Commonly prescribed second-generation H1 antagonists include cetirizine, levocetirizine, fexofenadine, loratidine, and desloratadine. Of these, cetirizine and levocetirizine seem to be the most clinically effective.^{87,108,130} Older H1 antagonists, such as diphenhydramine and hydroxyzine, are also still commonly used in the acute management of urticaria, but have been associated with higher levels of sedation and cognitive impairment.¹³¹ Although the addition of an H2 antagonist, leukotriene receptor antagonist, and/or oral corticosteroids may alleviate the duration and severity of symptoms, these medications are often not necessary in the management of acute urticaria.

After identification of triggers, urticaria owing to foods, medications, venom, latex, or contact with aeroallergens can be prevented with strict avoidance. When urticaria present in the setting of acute infection, the infection should be treated promptly.

The frequency, severity, and unpredictability of chronic urticaria have contributed to a decrease quality of life in affected individuals.¹³² Multiple medications are often required for the management of chronic urticaria. As with acute urticaria, second-generation H1 antagonists are first-line treatment and may require multiple doses a day for chronic suppression of symptoms. Often patients are prescribed a second-generation H1 antagonist 1 to 2 times a day with a shorter acting, first-generation H1 antagonist, such as diphenhydramine or hydroxyzine, for breakthrough symptoms. Other patients may require a second-generation H1 antagonist 4 times a day.^{87,133,134}

The combination of both H1 and H2 antagonists has had conflicting efficacy results compared with monotherapy with H1 antagonists.^{87,135–137} Of the H2 antagonists available, ranitidine, famotidine, and cimetidine are the most commonly prescribed for chronic urticaria. Combination use of H1 antagonist with a leukotriene receptor antagonist, such as montelukast and zafirlukast, has also been studied with mixed results.^{138–140} Leukotriene receptor antagonists have shown increased efficacy particularly in patients with positive autologous serum skin tests and those with aspirin intolerance.^{141,142}

For refractory urticaria, several additional agents have been used with varied results. These include corticosteroids, doxepin, sulfasalazine, dapsone, hydroxychloroquine, colchicine, mycophenolate mofetil, cyclosporine, methotrexate, and omalizumab.

Corticosteroids are often effective at resolving the urticaria; however, recurrence during taper or after completion of a course has been described commonly.¹³⁸ Systemic side effects are also reported widely with oral corticosteroids. Because doxepin has activity at both the H1 and H2 receptors, it has been used in recalcitrant urticaria.⁸⁷ Although the addition of dapsone to medication regimens has not reduced urticaria activity scores, it has shown good efficacy in inducing complete remission.^{143,144} Sulfasalazine has incidentally resolved urticaria, and hydroxychloroquine has shown significant improvement in quality of life, albeit not with a significant improvement in urticaria activity scores.^{145–148} Cyclosporine has induced remission of disease in a majority of patients, but the patients must be closely monitored for development of side effects (eg, kidney dysfunction, liver dysfunction, hypertension). In multiple, recent, randomized, multicenter trials, omalizumab has been shown to reduce significantly clinical symptoms of chronic urticaria compared with placebo.^{149–152}

Physical stimuli known to elicit urticaria should be avoided when possible. Most physical urticarias are treated with oral antihistamines, either preceding exposure to a known trigger or as maintenance therapy.⁹⁹ Omalizumab is also being explored in treatment of physical urticaria.¹²⁶

SUMMARY

Anaphylaxis and urticaria are allergic reactions that commonly present to outpatient clinics and emergency departments. Diagnosis relies heavily on obtaining a thorough clinical history and physical examination. If an allergen is suspected as the cause of the reaction, the patient should be referred to an allergist-immunologist for further evaluation. When possible, triggers should be identified to ensure avoidance and prevent future reactions. Unfortunately, a significant portion of cases are idiopathic and subsequently unpredictable. Especially in the case of anaphylaxis, patient education is essential in reducing morbidity and mortality.

Future research should focus on better elucidating the pathogenesis of chronic urticaria and idiopathic anaphylaxis so that treatment can be better targeted at their cause.

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