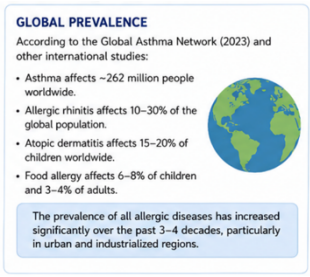
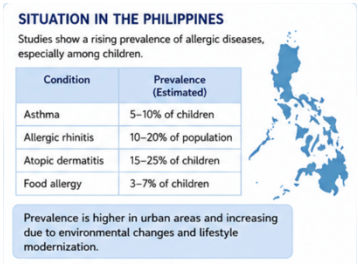
ALLERGY AND IMMUNOLOGY
Kristel Marie C. Cadiz-Sagabaen, RND, MD, DPPS, MMHoA

Learning Objectives:
- Burden of Disease
- Principles of Allergic Disorders
- Common Allergic Triggers
- Mechanism of Allergic March
- Clinical Presentations of Allergy
- Common Allergic Disorders of Adverse Reactions
- History, PE and Diagnosis of patients with Allergies
- Management of patient with Allergies
- Basic principles of treatment
- Common Allergic Emergencies

Allergy: Clinical expression of IgE-mediated allergic diseases that have familial predisposition and that manifest as hyperresponsiveness in target organs such as the lung, skin GI tract and nose.

Prevalence





Allergens:
- almost always proteins, but not all proteins are allergens.
- Biochemical properties:
  - *Innate Immune response stimulation*
  - *Allergen stability in tissue, digestive system, skin, or mucosa*
  - *dose and time of stay in lymphatic organs* during the interaction
- Molecular weight:
  - *Most are 10 – 70 kDa*
  - *<10 kDa: Do not bridge adjacent IgE molecules on mast cells or basophils*
  - *>70 kDa: Do not pass through mucosal surfaces to reach APCs*
  - Proteases
- Low-molecular weight moieties
- Carbohydrate structure

T-helper type 2 (Th2)
- Atopic individuals exhibit rapid expansion to Th2 cells secreting cytokines (IL-4,IL-5 and IL-13) favoring IgE synthesis and Eosinophilia
  - IL-4, IL-13: Key role in immunoglobulin isotype switching to IgE
  - IL-5, IL-9: important in differentiation and development of eosinophils
  - IL-3, IL-4, IL-9: Contribute to mast cell activation
  - IL-9: Responsible for mucus production
  - IL-25, IL-33, TSLP: Secreted by epithelial cells on allergen/virus exposure, contribute to TH2 response and eosinophilia
  - TH2 cytokines: effector molecules in asthma and allergic diseases; acute reactions show Th2 infiltration
  - TH1: involved in eradicating intracellular organisms.
    - contributes to chronicity and the effector phase in allergic disease.
    - Secrete *interferon-γ (IFN-γ), tumor necrosis factor (TNF)-α, and Fas ligand*

Antigen-Presenting Cells

- Dendritic cells (DCs)
- Langerhans cells
- Monocytes
- Macrophages
  - *have the ability to present allergens to T cells and thereby modulate allergic inflammation by controlling the type of T-cell development.*
- heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC)
- found primarily in lymphoid organs and the skin

Dendritic Cells and Langerhans cells

- *responsible for the primary immune response*
- *the sensitization phase of allergy*

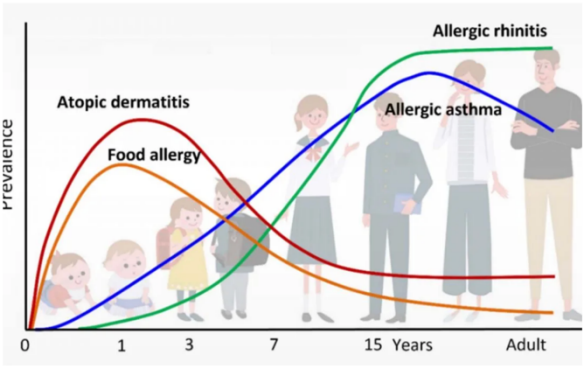
Monocyte and Macrophages

- *Activate memory T-cell responses on reexposure to allergen*
- *Elicitation phase of allergY*

Common Allergic Triggers

- House Dust Mites
- Pollen Grains
- Molds
- Food
- Drugs
- Animal Dander

Allergic March



Diagnosis of Allergic Disease

- Allergy History
  - *Age*
  - *Describe the symptoms*
  - *Timing and duration of symptoms*
  - *Review the setting and Exposure to common allergens*
  - *Responses to previous therapies*
  - *Family History*
    - 1 parent = 50%
    - Both parents = 66%

Characteristic behaviors:

- Allergic salute
- Nasal crease
- Grinding of the eyes
- Allergic Cluck

Physical Examination

- General Survey
- Vital Signs:
  - *Respiratory Rate*
  - *Pulse Oximetry*
- Anthropometrics:
  - *Height*
  - *BP*
- Skin
  - *Xerosis*
  - *Keratosis pilaris*
  - *Hyperlinearity in palms and soles*
- Head
- Face
- General Survey
- Vital Signs:
  - *Respiratory Rate*
  - *Pulse Oximetry*
- Anthropometrics:
  - *Height*
  - *BP*
- Skin
  - *Xerosis*
  - *Keratosis pilaris*
  - *Hyperlinearity in palms and soles*
- Eyes
  - *Allergic shiners*
    → blue gray to purple discolorations beneath the child's lower eyelids
  - *Dennie-Morgan folds (Dennie lines)*
    → prominent infraorbital skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin
  - *Lacrimation*
  - *Conjunctival injection*
  - *Edema*
  - *Keratoconus:* protrusion of the cornea
- Ears
  - *Check the external ear for eczema*
- Nose and paranasal sinuses
  - *Nasal obstruction*
  - *Nasal crease*
  - *Turbinate hypertrophy*
  - *Thin and clear nasal secretions*
- Lips
  - *Cheilitis*
- Chest and Lungs
  - *Audible wheezes*
  - *retractions*

ALLERGIC RHINITIS

- common chronic disease affecting 20–30% of children
- Inflammatory disorder of the nasal mucosa marked
  - *nasal congestion*
  - *Rhinorrhea*
  - *Itching*
  - *Sneezing*
  - *conjunctival inflammation.*
- Associated with a 3-fold increase in risk for asthma at an older age

ETIOLOGY and PATHOGENESIS

- 2 factors for expression of AR:
  - Sensitivity to allergen
  - Presence of allergen in the environment

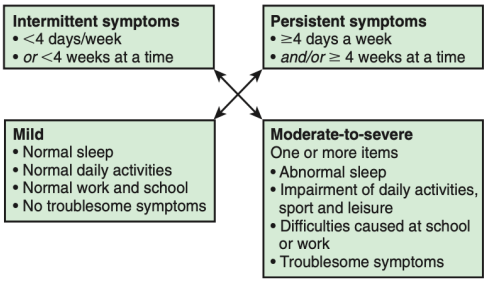
Early Phase:

- *degranulation of mast cells, release of preformed and newly generated inflammatory mediators*

Late Phase:

- *4-8hrs after allergen exposure, inflammatory cells infiltrate the nasal mucosa*

ARIA Classification of Allergic Rhinitis



CLINICAL MANIFESTATIONS:

- *Allergic salute*
- Nasal crease
- Nasal congestion
- Itching, sneezing
- Clear rhinorrhea
- Conjunctival irritation
- *Allergic gape – open mouth breathing*
- *Allergic shiners*

DIFFERENTIAL DIAGNOSIS:

- Nonallergic rhinitides – without elevated IgE antibodies
- Vasomotor rhinitis
- Rhinitis medicamentosa
- Structural problems – nasal polyps, septal deviation

LABORATORY FINDINGS

- Skin test
  - *Prep:* Withhold montelukast for 1 day, most sedating antihistamine for 3-4 days &nonsedating antihistamines for 5-7days
- Epicutaneous skin tests (Patch Test)
- Serum immunoassays for sIge

Treatment

- Sealing the patient's mattress, pillow, and covers in allergen-proof encasings
- Bed linen and blankets should be washed every week in hot water >54.4°C [130°F])
- Removal of the pet
- Air conditioning
- HEPA filters
- Antihistamines (second-generation)
- +/- pseudoephedrine
- Intranasal decongestants
- Intranasal corticosteroids – *most effective therapy*
- Immunotherapy
  - *Sublingual immunotherapy (SLIT)*
  - *Allergy immunotherapy (AIT)*
- Nasal Saline irrigations

Table 168.2 Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
SECOND-GENERATION ANTIHISTAMINES			
Desloratadine			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo-5 yr: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr: 2.5 mg once daily Adults and adolescents ≥12 yr: 5 mg once daily
Levocetirizine dihydrochloride			
Xyzal Oral Solution	0.5 mg/mL	Solution	6 mo-5 yr: max 1.25 mg once daily in the PM 6-11 yr: max 2.5 mg once daily in the PM
LEUKOTRIENE ANTAGONIST			
Montelukast			
Singulair	10 mg	Tablets	6 mo-5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

*Contains phenylalanine.
Dosing recommendations taken in part from Engorn B, Flerlage J, for the Johns Hopkins Hospital: *The Harriet Lane Handbook*, ed 20, Philadelphia, 2015, Elsevier/Saunders.

Table 168.3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton OTC (over the counter)	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (max 6 mg/day) 6-11 yr: 2 mg every 4-6 hr (max 12 mg/day)
Chlor-Trimeton Syrup OTC	2 mg/5 mL	Syrup	>12 yr: 4 mg every 4-6 hr (max 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup OTC	1 mg/mL	Syrup	6-12 mo: 2.5 mg once daily 12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Children's Zyrtec Chewable OTC	5 mg, 10 mg	Chewable tablets	2-5 yr: 2.5 mg/day; may be increased to max of 5 mg/day given either as a single dose or divided into 2 doses
Zyrtec tablets OTC	5 mg, 10 mg	Tablets	

Table 168.3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)—cont'd

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
Zyrtec Liquid Gels OTC	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into 2 doses
Levocetirizine	5 mg	Tablet	2-5 yr: 1.25 mg once daily in the evening
Xyzal	0.5 mg/mL	Oral solution	6-11 yr: 2.5 mg orally once daily in the evening ≥12 yr: 5 mg orally once daily in the evening
Desloratadine Clarinex	0.5 mg/mL	Oral solution	6-11 mo: 2 mL once daily 12 mo-5 yr: 2.5 mL once daily 6-11 yr: 5 mL once daily
Desloratadine Clarinex	5 mg	Tablet	12-adult: 5 mg once daily
Fexofenadine HCl OTC	30 mg, 60 mg, 180 mg	Tablet	6-11 yr: 30 mg twice daily 12-adult: 60 mg twice daily; 180 mg once daily
Children's Claritin OTC	5 mg/5 mL	Syrup	2-5 yr: 5 mg once daily 6-adult: 10 mg once daily
Children's Allegra OTC ODT*	30 mg	Orally disintegrating tablets	6-11 yr: 30 mg twice daily
Children's Allegra Oral Suspension OTC	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra OTC	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg once daily
Loratadine			
Alavert OTC ODT*	10 mg 10 mg 10 mg 5 mg 1 mg/mL	Orally disintegrating tablets Tablets Liquid-filled caps Chewable tablets Syrup	2-5 yr: 5 mg once daily >6 yr: 10 mg once daily or 5 mg twice daily

ATOPIC DERMATITIS (ECZEMA)

- most common chronic relapsing skin disease seen in infancy and childhood
- 10–30% of children
- Infants with Atopic Dermatitis predisposed to Allergic March

Etiology

- Defective skin barrier
- Reduced skin innate immune responses
- Chronic skin inflammation

Pathology

- Acute Atopic Dermatitis
- Chronic, lichenified Atopic Dermatitis

Pathogenesis

- Atopic eczema (IgE mediated)
- Nonatopic eczema
- Increased expression of IL4 & IL13
- Genetic mutations in Filaggrin gene

Table 170.1 Clinical Features of Atopic Dermatitis

MAJOR FEATURES
Pruritus
Facial and extensor eczema in infants and children
Flexural eczema in adolescents
Chronic or relapsing dermatitis
Personal or family history of atopic disease
ASSOCIATED FEATURES
Xerosis
Cutaneous infections (*Staphylococcus aureus*, group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
Nonspecific dermatitis of the hands or feet
Ichthyosis, palmar hyperlinearity, keratosis pilaris
Nipple eczema
White dermatographism and delayed blanch response
Anterior subcapsular cataracts, keratoconus
Elevated serum IgE levels
Positive results of immediate-type allergy skin tests
Early age at onset
Dennie lines (Dennie-Morgan infraorbital folds)
Facial erythema or pallor
Course influenced by environmental and/or emotional factors

Differential Diagnosis
- Seborrheic Dermatitis
- Nummular Dermatitis
- Irritant Contact Dermatitis
- Allergic Contact Dermatitis
- Lichen Simplex Chronicus
- Asteatotic Eczema
- Dermatophyte infection
- Scabies, Impetigo, HIV
- Icthyosis vulgaris
- Acrodermatitis enterohepatica (zinc)
- Biotin deficiency, Pellagra (niacin)
- Kwashiorkor, PKU
- Cutaneous T-cell lymphoma
- Langerhans cell histiocytosis

Treatment
- **Moisturizers** – *first line of therapy*
- **Topical corticosteroids** – *cornerstone of therapy*
- Topical Calcineurin Inhibitors (>2yo)
- Topical PDE-4 Inhibitor (Crisaborole)
- Antihistamine
- Systemic Corticosteroids
- Cyclosporine
- Dupilumab
- Antimetabolites (*MMF, MTX, Azathioprine)*
- Phototherapy

AVOIDING TRIGGERS
- Irritants
  - *Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity*
- Food Allergy
  - *May induce eczematous dermatitis, urticarial reactions, wheezing, or nasal congestion*
- Aeroallergens
- Infections

COMPLICATIONS
- Exfoliative Dermatitis
  - *generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever*
- Allergic Keratoconjunctivitis
  - *Bilateral*
  - *disabling symptoms that include itching, burning, tearing, and copious mucoid discharge*

- Vernal Conjunctivitis
- *associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva*

■ Keratoconus
- *conical deformity of the cornea as a result from chronic rubbing of the eyes*

PROGNOSIS
- Severe and persistent in young children
- Spontaneous resolution after age 5 (40-60%)
  Adults: Hand dermatitis

Poor prognostic factors:
- Widespread AD during childhood
- FLG null mutations
- Concomitant AR and asthma
- Family history of AD in parents and siblings
- Early age at onset of AD
- Only child
- Very high serum IgE levels

PREVENTION
- Breastfeeding
- Probiotics and Prebiotics
- Identify and eliminate triggering factors
- Emollient therapy

INSECT ALLERGIES

- Allergic reactions caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and asthma.

Clinical Manifestations
- Simple local reactions involve limited swelling and pain and generally last <24 hr
- Large local reactions develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days
- Generalized cutaneous reactions typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting.
- Systemic reactions are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm and hypotension.
- Stings from a large number of insects at once may result in toxic reactions of fever, malaise, emesis, and nausea because of the chemical properties of the venom in large doses.
- Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as delayed/late reactions to stinging insects.
- Insect bites are usually urticarial but may be papular or vesicular.
  - Papular urticaria affecting the lower extremities in children is usually caused by multiple bites.
  - IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Diagnosis
- The diagnosis of allergy from stinging and biting insects :history of exposure, typical symptoms, and physical findings.
  - The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by skin-prick testing or in vitro testing.
    - The primary reasons to pursue testing are to confirm reactivity when venom immunotherapy (VIT) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction.
- Elevated basal tryptase level is associated with more severe reactions to venom stings.
  - Basal tryptase should be measured if there is a history of severe reaction to a sting, hypotensive reaction, lack of urticaria in a systemic sting reaction, or negative venom IgE in a patient who has a history of systemic reaction to a sting.
- Skin-prick or in vitro immunoassay tests for specific IgE to the insect are used to confirm inhalant insect allergy.

Treatment

- cold compresses, topical medications to relieve itching, and occasionally a systemic antihistamine and oral analgesic are appropriate.
- Stingers should be removed promptly by scraping, with caution not to squeeze the venom sac because doing so could inject more venom.
- Anaphylactic reactions → Epinephrine is the drug of choice.
- Adjunctive treatment: antihistamines, corticosteroids, intravenous oxygen, and transport to the emergency
- Referral to an allergist-immunologist

Prevention: Avoidance

OCULAR ALLERGIES

- The eye is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment.
- The conjunctiva is the most immunologically active tissue of the external eye.

Clinical Manifestations

- Bilateral involvement
- Allergic Conjunctivitis: most common hypersensitivity response of the eye
    - caused by direct exposure of the mucosal surfaces of the eye to environmental allergens.
    - Ocular itching, rather than pain, with increased tearing
    - Bilateral injected conjunctivae with vascular congestion that may progress to chemosis, or conjunctival swelling, and a watery discharge
- Seasonal allergic conjunctivitis is typically associated with allergic rhinitis, most commonly triggered by pollens
- Perennial allergic conjunctivitis is triggered by allergens such as animal danders or dust mites that are present throughout the year.
- Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in a limbal or palpebral form. It may threaten eyesight if there is corneal involvement.
    - Symptoms: severe ocular itching exacerbated by exposure to irritants, light or perspiration. In addition, patients may complain of severe photophobia, foreign body sensation, and lacrimation
    - Giant papillae occur predominantly on the upper tarsal plate and are typically described as cobblestoning
    - Other signs: stringy or thick, ropey discharge, cobblestone papillae, transient yellow-white points in the limbus (Trantas dots) and conjunctiva (Horner points), corneal “shield” ulcers, and Dennie lines (Dennie-Morgan folds
- Atopic keratoconjunctivitis is a chronic inflammatory ocular disorder most often involving the lower tarsal conjunctiva.
    - May threaten eyesight if there is corneal involvement.
    - Symptoms: Severe bilateral ocular itching, burning, photophobia, and tearing with a mucoid discharge
        - The bulbar conjunctiva is injected and chemotic; cataracts may occur.
        - Trantas dots or giant papillae may also be present.
        - Eyelid eczema can extend to the periorbital skin and cheeks with erythema and thick, dry scaling.
        - Secondary staphylococcal blepharitis is common because of eyelid induration and maceration. Chronic eye rubbing associated with vernal and atopic keratoconjunctivitis can lead to keratoconus, a noninflammatory cone-shaped corneal ectasia.
        - May lead to corneal thinning and perforation.
- Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is being recognized more frequently in association with
    - Due to increased exposure to topical medications, contact lens solutions, and preservatives.

Treatment

- Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication
- Secondary treatment : oral or topical antihistamines, topical decongestants, mast cell stabilizers, and anti inflammatory agents
    - Drugs with dual antihistamine and mast cell–blocking activities
- Tertiary treatment of ocular allergy includes topical (or rarely oral) corticosteroids and should be conducted in conjunction with an ophthalmologist

** Symptoms that should prompt referral to an ophthalmologist include unilateral red eye with pain, photophobia, change in vision, refractory dry eyes, or corneal abnormality.

URTICARIA (HIVES) and ANGIOEDEMA

- Urticaria: transient, pruritic, erythematous, raised wheals that may become tense and painful.
  - lesions may coalesce and form polymorphous, serpiginous, or annular lesions
  - Individual lesions usually last 20 min to 3 hr and rarely more than 24 hr.
  - Lesions often disappear, only to reappear at another site.

- Angioedema involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, or wall of the gastrointestinal (GI) tract.

- HIVES
  - erythematous, pruritic, raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched
  - <6 wks → acute
  - >6 wks → Chronic

- Acute urticaria and angioedema
  - often caused by an allergic IgE–mediated reaction
  - self-limited → occurs when an allergen activates mast cells in the skin.
  - Common causes foods, drugs (particularly antibiotics), and stinging-insect venoms
  - If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure.
  - can also result from non–IgE-mediated stimulation of mast cells, caused by radiocontrast agents, viral agents (including hepatitis B and Epstein-Barr virus), opiates, and nonsteroidal antiinflammatory drugs (NSAIDs).
- Chronic urticaria → lesions occur on most days of the week for >6 wk and are not physical urticaria or recurrent acute urticaria with repeated exposures to a specific agent
  - Almost often accompanied by Angioedema
- Urticarial Vasculitis: Lesions that burn more than itch, last >24 hr, do not blanch, blister, heal with scarring, or that are associated with bleeding into the skin (purpura)

Table 173.1 Etiology of Acute Urticaria

Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, (direct mast cell degranulation)
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	**Bacterial** (streptococcal pharyngitis, *Mycoplasma*, sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); **Parasitic** (*Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella*); **Fungal** (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IV immune globulin administration

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: *Allergy in primary care*, Philadelphia, 2000, Saunders, p 232.

Table 173.2 Etiology of Chronic Urticaria

Idiopathic/autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria, and 60–70% are idiopathic. Of the idiopathic cases approximately 35–40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism Cholinergic urticaria Cold urticaria (see Table 173.5) Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid disease (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Leukocytoclastic vasculitis
Autoinflammatory/periodic fever syndromes	See Tables 173.3 and 173.5.
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor) Acquired angioedema Angiotensin-converting enzyme inhibitors

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: *Allergy in primary care*, Philadelphia, 2000, Saunders, p 234.

PHYSICAL URTICARIA

- Cold urticaria : development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus.
- Cholinergic urticaria: onset of small, punctate pruritic wheals surrounded by a prominent erythematous flare and associated with exercise, hot showers, and sweating
- Dermatographism (also called dermographism or urticaria factitia): ability to write on skin, may occur as an isolated disorder or may accompany chronic urticaria or other physical urticaria.
- Pressure-induced urticaria: symptoms typically occur 4-6 hr after pressure has been applied
    - Angioedema: swelling, with or without pruritus, secondary to pressure, with normal-appearing skin (no urticaria
- Solar urticaria: rare disorder in which urticaria develops withinminutes of direct sun exposure
- Aquagenic urticaria: small wheals after contact with water, regardless of its temperature

DIAGNOSIS:

- Clinical

TREATMENT:

- Acute urticaria
    - self-limited illness requiring little treatment other than antihistamine
    - avoidance of any identified trigger
    - Hydroxyzine and diphenhydramine are sedating
    - Loratadine, fexofenadine, and cetirizine: preferable because of reduced frequency of drowsiness and longer duration of action
    - Epinephrine → 1:1,000, 0.01 mL/kg (maximum 0.3 mL) intramuscularly, usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required.
    - Short course of oral corticosteroids should be given only for severe episodes of urticaria and angioedema that are unresponsive to antihistamines
- Physical Urticaria: avoidance of the stimulus
    - Antihistamines are also helpful
- Cyproheptadine in divided doses: drug of choice for cold-induced urticaria. \
- Dermatographism: local skin care and antihistamines
    - Severe symptoms, high doses may be needed.
    - Initial objective of therapy → decrease pruritus so that the stimulation for scratching is diminished.
    - Combination of antihistamines, sunscreens, and avoidance of sunlight
- Chronic urticaria only rarely responds favorably to dietary manipulation.
    - Mainstay of therapy: nonsedating or low-sedating H1 antihistamines.
    - Not showing response to standard doses, pushing the H1 blockade with higher than the usual recommended
    - 3-drug combination of H1 and H2 antihistamine with a leukotriene receptor antagonist (montelukast)
    - Monoclonal antibody omalizumab (anti-IgE) is FDA approved for the treatment of chronic urticaria in children 12 years and older

ANAPHYLAXIS

- Serious allergic reaction, rapid in onset, may cause death.
- Occurs when there is a sudden release of potent, biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (nausea, colicky abdominal pain, vomiting, diarrhea) symptoms
- Latex Allergy - most common cause occurring in the *hospital* setting
- Food Allergy – *community*
- Mostly results from activation of mast cells and basophils via cell-bound allergen-specific IgE molecules

Principal pathologic features:

- Bronchial obstruction with pulmonary hyperinflation
- Pulmonary edema
- Intraalveolar hemorrhage
- Visceral congestion
- Laryngeal edema
- Urticaria
- Angioedema

- *Ingested* allergens have delayed onset (minutes to 2hrs) compared to *injected* allergens

Initial symptoms

- Pruritus of the mouth and face
- Flushing, urticarial and angioedema
- Sensation of warmth, weakness and apprehension (sense of doom)
- Tightness in the throat, dry staccato cough, hoarseness
- Periocular pruritus
- Nasal congestion, sneezing
- Dyspnea, deep cough, wheezing
- Nausea, abdominal cramps, vomiting
- Uterine contractions (lower back pain)
- Faintness and loss of consciousness

***Cutaneous manifestations are absent in **10%** of cases & the **acute** onset of severe bronchospasm in a previously well person with asthma should suggest the diagnosis of anaphylaxis*

Table 174.4 Diagnosis of Anaphylaxis

Anaphylaxis is **highly likely** when *any 1 of the following 3 criteria* is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (e.g., *generalized* hives, pruritus or flushing, swollen lips/tongue/uvula)
   AND *at least 1 of the following*:
   a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. *Two or more of the following* that occur rapidly after exposure **to a likely allergen for that patient** (minutes to several hours):
   a. Involvement of the skin/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. **Persistent** gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP following exposure to **known allergen for that patient** (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or >30% drop in systolic BP
   b. Adults: systolic BP <90 mm Hg or >30% drop from patient's baseline

BP, Blood pressure; PEF, peak expiratory flow.
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, *J Allergy Clin Immunol* 117: 391–397, 2006.

<u>Diagnosis:</u>
Labs are nonspecific
▪ Plasma histamine
▪ Plasma tryptase

**** MEDICAL EMERGENCY!**

Treatment
Epinephrine

- Most important
- IM on the lateral thigh
- 1:1000, 0.01mg/kg max 0.5mg
- IM dose can be repeated at intervals of 5-15 min if symptoms persist or worsen
- No response to multiple doses of epinephrine, IV epinephrine using the 1 : 10,000 dilution may be needed
- IV access is not readily available, epinephrine can be administered via the endotracheal or intraosseous routes
- ▪ Biphasic Anaphylaxis – occur within *4 hours* of treatment

<u>FOOD ALLERGY and ADVERSE REACTIONS to FOOD</u>

- any untoward reaction following the ingestion of a food or food additive
  - Food intolerances -> result of a variety of mechanisms
  - Food allergies -> is predominantly caused by IgE-mediated and cell-mediated immune mechanisms
    - Cow's Milk Allergy
    - Egg Allergy
    - Peanut Allergy

CLINICAL MANIFESTATIONS:

- GI manifestations
  - Food protein–induced enterocolitis syndrome (FPIES)
  - Food protein–induced allergic proctocolitis (FPIAP)
  - Food protein–induced enteropathy (FPE)
    - Cow's milk sensitivity: most common cause of FPE
    - Celiac disease: most severe form of FPE
  - Eosinophilic esophagitis (EoE)
  - Eosinophilic gastroenteritis
  - Oral allergy syndrome (pollen-associated food allergy syndrome)
  - Acute gastrointestinal allergy
- SKIN Manifestations
  - Atopic Dermatitis
  - Acute urticaria and Angioedema
  - Perioral dermatitis
- RESPIRATORY Manifestations
  - Food-induced rhinoconjunctivitis
  - Wheezing

- Anaphylaxis → serious, multisystem allergic reaction that is rapid in onset and potentially fatal
  - Rapid onset of cutaneous, respiratory and GI symptoms
  - May demonstrate cardiovascular symptoms,including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release

DIAGNOSIS
- Thorough medical history
- Skin-prick tests and in vitro laboratory tests
- Serum food-specific IgE levels
- Trial elimination diet and oral food challenges

TREATMENT
- Self-injected Epinephrine
- Written Emergency plan
- Oral, sublingual, and epicutaneous (patch) immunotherapy
- Combining oral immunotherapy with anti-IgE treatment (omalizumab)

PREVENTION
- Trial of early introduction induces oral tolerance that precedes the potential sensitization to peanut via the disrupted skin barrier
- Probiotic Supplements
- Exclusive breastfeeding for the 1st 4-6 mo of life may reduce allergic disorders in the 1st few yr of life in infants at high risk for development of allergic disease.
- Hydrolyzed formulas may be beneficial if breastfeeding cannot be continued for 4-6 mo or after weaning, especially to prevent eczema in high-risk families

ADVERSE REACTIONS to DRUGS

Types of Hypersensitivity State
(Gell and Coomb's Classification)

- Type I Hypersensitivity
  (IgE-mediated reaction)
  - IgE antibodies: primary mediators
  - (+) of allergen-specific IgE on the cell surfaces of APCs gives the unique feature of Atopy
  - Exposure to Antigen → Allergen stimulates Th2 response → IgE production
  - IgE binds to FcεRI on mast cells and basophils.
  - Release of histamine, leukotrienes, prostaglandins
  - Causes:
  - *Increased vascular permeability*
  - *Bronchoconstriction*
  - *Mucus Secretion*

- Type II Hypersensitivity
  (Antibody-dependent cell cytotoxicity)
  - IgG or IgM antibodies bind to antigens on cell surfaces or extracellular matrix.
  - Tissue injury occurs through:
    1. Complement activation
    2. Opsonization and phagocytosis
    3 .Antibody-dependent cellular cytotoxicity (ADCC)
    4. Antibody-mediated alteration of cellular function

    Examples:
    - Autoimmune hemolytic anemia → destruction of RBCs
    - Goodpasture syndrome → antibodies against basement membrane
    - Graves disease → stimulation of TSH receptors
    - Myasthenia gravis → blockade of acetylcholine receptors

- Type III Hypersensitivity
  (Complement-mediated)
    - Soluble **antigen–antibody complexes** form in the circulation.
    - These complexes deposit in tissues and activate **complement**.
    - Leads to recruitment of neutrophils and **inflammation and tissue damage**

        - Systemic lupus erythematosus (SLE)
        - Serum sickness
        - Post streptococcal GN
        - Rheumatoid Arthritis

- Type IV Hypersensitivity
  (Delayed)
    - Do not involve antibodies but are mediated by **T cells**.
    - Activated by continued exposure or reexposure to the antigen
    - They damage tissue by direct toxic effects or through release of cytokines, which activate eosinophils, monocytes and macrophages, neutrophils, or natural killer cells.
        - TST
        - Contact Dermatitis
        - Drug Hypersensitivity

Type I	Type II	Type III	Type IV
• IgE-mediated reaction • Immediate/ Anaphylactic Hypersensitivity	Antibody-dependent Cell Cytotoxicity	Complement mediated	Delayed
Minutes	Minutes to Hours	Hours to Days	Days (48-72 hours)
IgE antibodies bind to mast cells and basophils, causing rapid degranulation and release of histamine	IgG or IgM antibodies bind directly to antigens and cell surfaces, leading to cell lysis via complement activation or phagocytosis	Circulating antigen-antibody complexes deposit in tissues, activating complement and recruiting inflammatory neutrophils	Sensitized T lymphocytes release cytokines that activate macrophages or directly kill target cells, without using antibodies
• Anaphylaxis • Asthma • Allergic Rhinitis	• Autoimmune Hemolytic Anemia • Blood Transfusion Reaction • Grave's Disease • Myasthenia Gravis	• Systemic Lupus Erythamatosus • Rheumatoid Arthritis	• Tuberculin Skin Test • Allergic Contact Dermatitis • Drug Hypersensitivity

- Beta-lactam Hypersensitivity
- Sulfonamides
- Steven Johnson Syndrome and Toxic Epidermal Necrolysis
- Hypersensitivity to Retroviral Drugs
- Chemotherapeutic Agents
- Vaccines
- Perioperative Agents
- Local Anesthetics
- Drug-induced hypersensitivity syndrome, or DRESS (drug rash witheosinophilia and systemic symptoms) syndrome
- Redman Syndrome
- Radiocontract Media
- Narcotics
- Aspirin and NSAIDs