Allergy Medicine 2020

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Conflict of Interest Disclosures

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None

Objectives

- Identify the major causes of acute and chronic urticaria and angioedema
- Review emerging concepts in allergic illness
- Understand conventional and new options for the treatment of allergic disease

Definitions

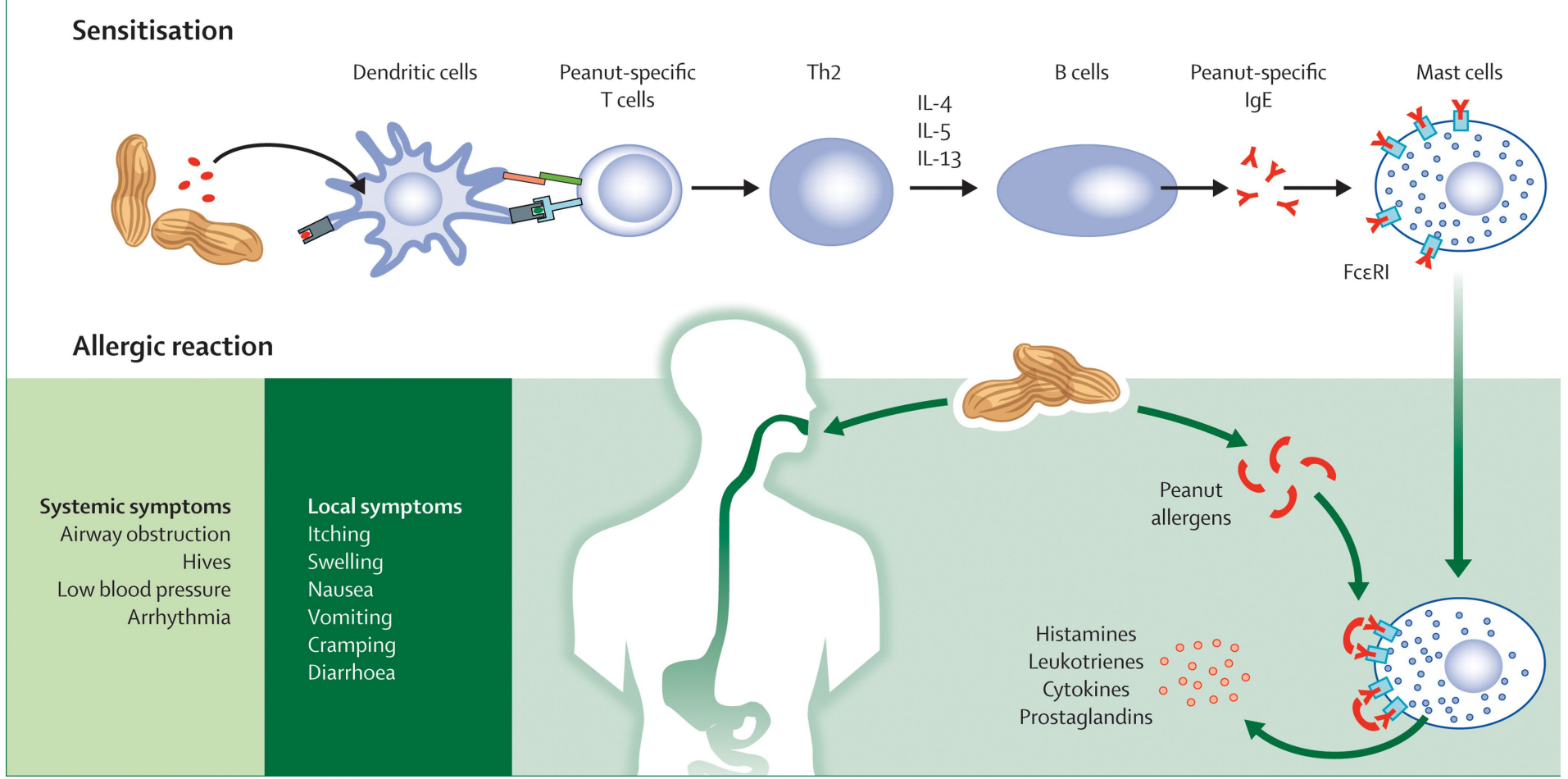
- Urticaria
  - erythematous, well circumscribed wheals
  - dilated blood vessels & edema in *superficial* dermis

- Angioedema
  - well-demarcated, often painful, swelling of skin
  - dilated blood vessels & edema in *deep* dermis
  - distinguish from hydrostatic edema
    - nondependent, asymmetric & transient

Definitions

- Anaphylaxis
  - a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.
  - involves multiple systems which may including cutaneous, respiratory, gastrointestinal and cardiovascular systems

(JACI 2006;117:391-397)

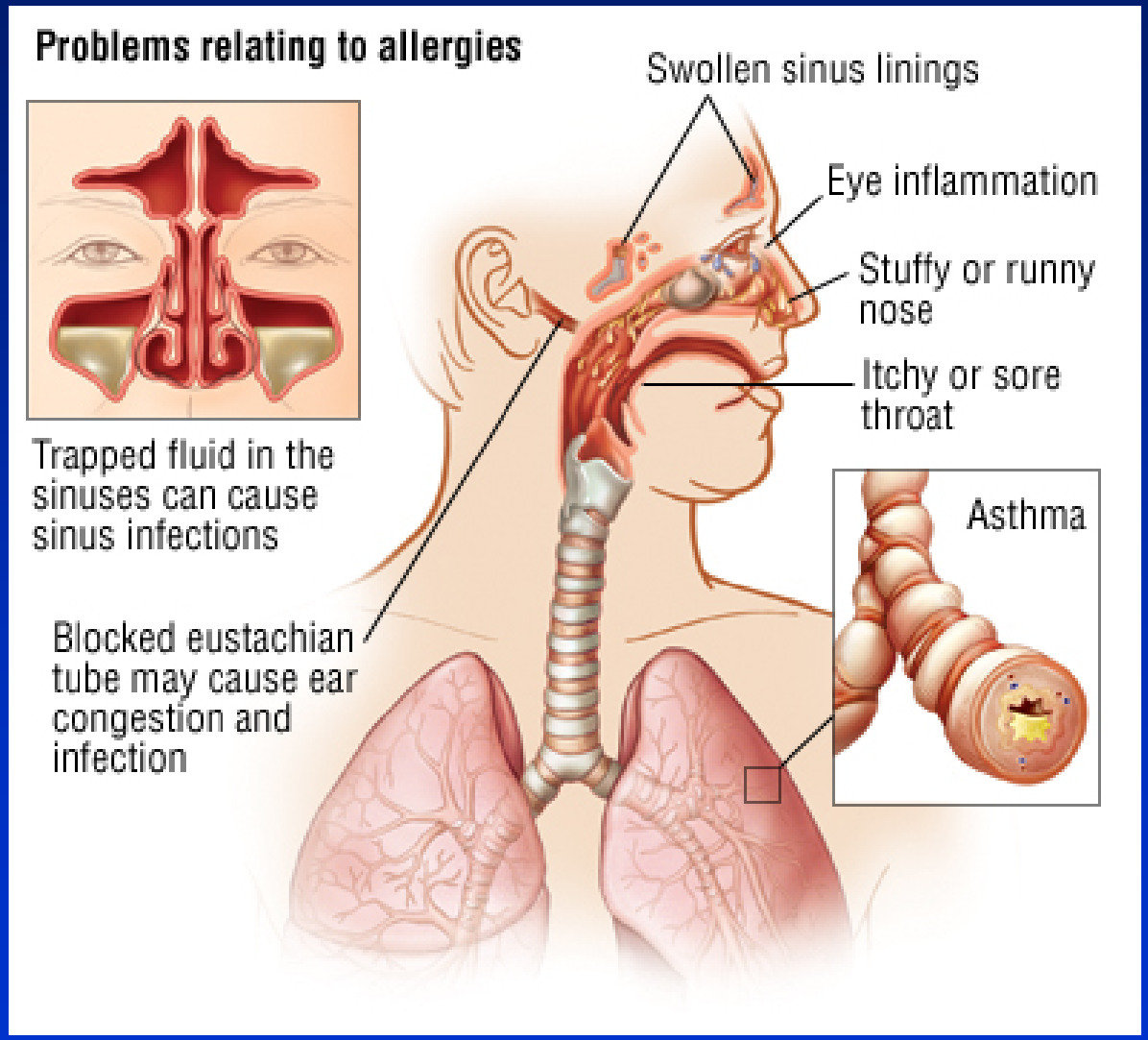


Key Mediators

IL-4 – switch factor to make IgE
IL-5 – eosinophil colony stimulating factor
IL-13 – IgE synthesis, goblet cell hyperplasia (mucous production)

IgE – Ab involved in Type 1 mediated hypersensitivity

Inhalant Allergic Disease



Pathophysiology

- IgE dependent (mast cell – histamine)
  - drug, food, insect stings, latex, inhaled allergens
- Kinin - mediated
  - hereditary angioedema (HAE), ACE inhibitors
- Direct mast cell releasing agents
  - radiocontrast media, vancomycin, opiates
- Altered arachidonic acid metabolism
  - ASA, NSAIDS
- Idiopathic (autoimmune)

Temporal Features

- Acute vs chronic urticaria
  - *Acute*: < 6 weeks duration
    - peak incidence: childhood & early adulthood
    - cause found 15-20% of cases
  - *Chronic*: > 6 weeks duration
    - peak in 30's – 40's
    - female >> male
    - cause elusive (< 5% of cases)

Acute Urticaria:
Etiologic Classification

- Drug allergy *
- Food allergy *
- Insect sting allergy *
- Latex allergy *
- Inhalant allergens (e.g cat dander)
- Contact allergens (e.g nettle)
- Transfusion reaction *
- Viral infections
- Idiopathic *

* may also be associated with anaphlyaxis

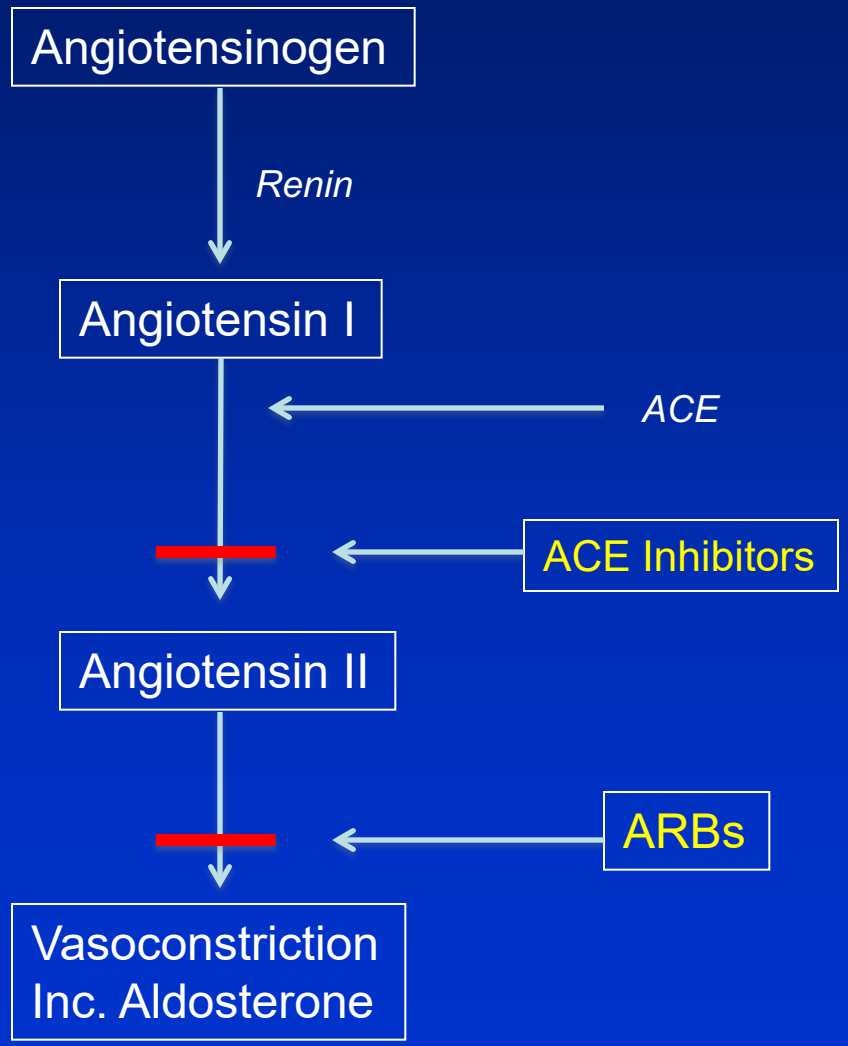
Drug Allergy

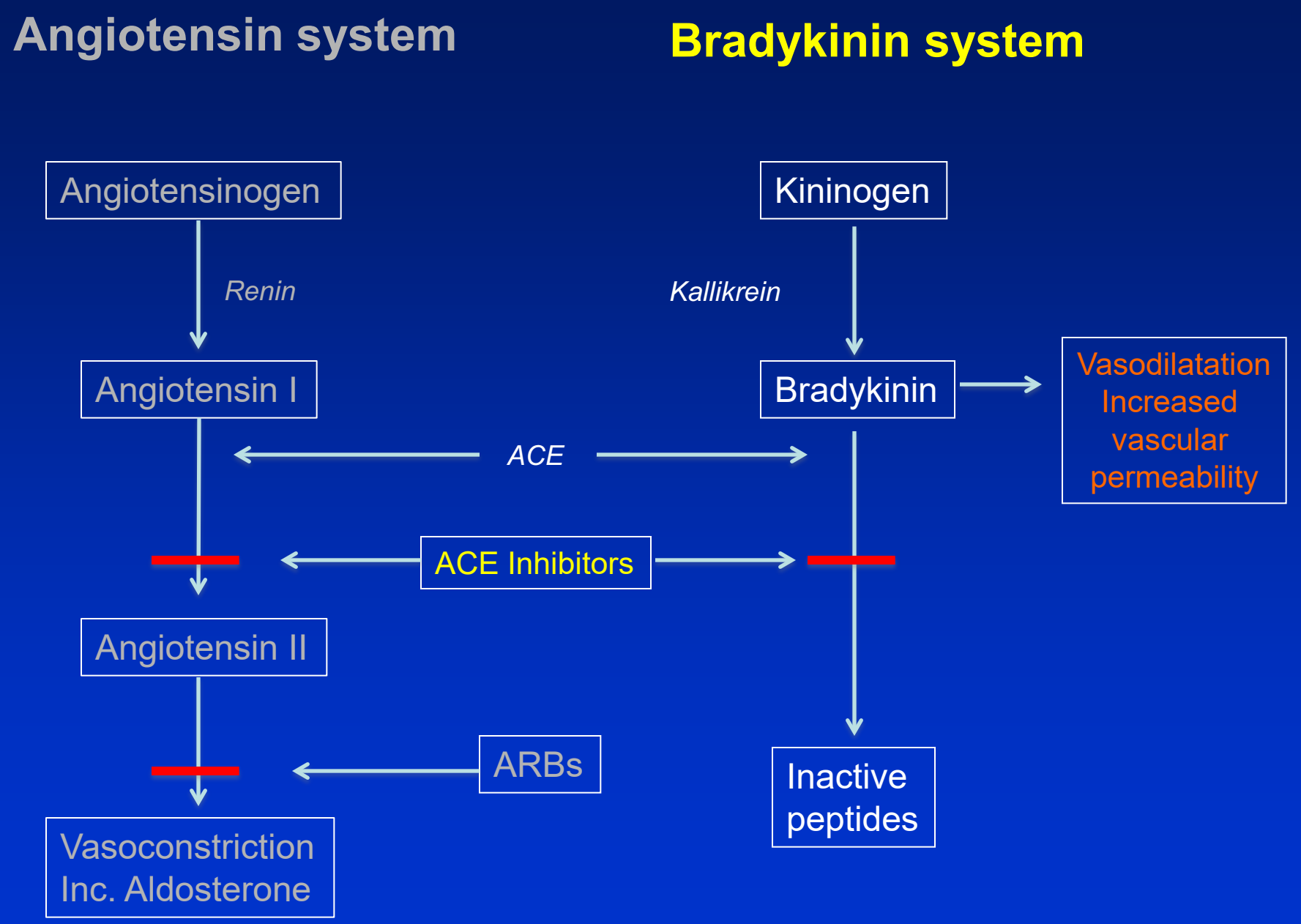
- Urticaria/angioedema may occur with any drug
- Seen most commonly with:
  - Antibiotics (beta lactams, sulfa), NSAIDs, proteins or serums
- Acute, self-limited urticaria
- Resolves with discontinuation of the offending agent

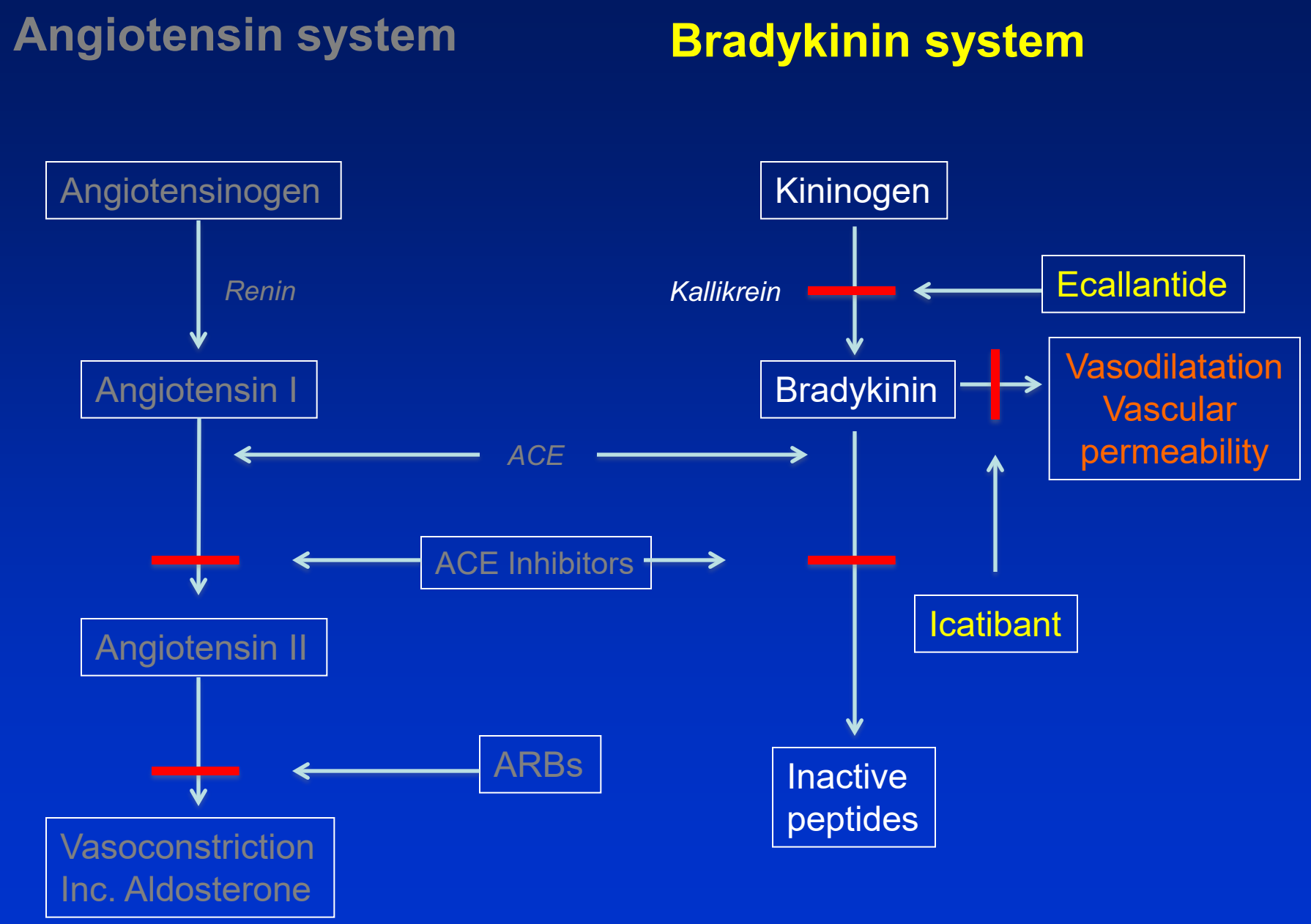
ACE Inhibitor Induced Angioedema

- Incidence of angioedema: 0.1 – 0.7%
- Idiosyncratic reaction
- Predilection for the head & neck
- Onset:
  - most often in first week of treatment
  -may be delayed for months – years
- Mechanism:
  -disruption of the bradykinin degradation pathway
  -non-histaminergic

Angiotensin system




Angiotensin system
Bradykinin system
Angiotensinogen
Renin
Angiotensin I
Angiotensin II
ACE
ACE Inhibitors
ARBs
Vasoconstriction
Inc. Aldosterone
Kininogen
Kallikrein
Bradykinin
Vasodilatation
Increased
vascular
permeability
Inactive
peptides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peptides

Drug Allergy: ACE Inhibitors

- Treatment Recommendations
  - Manage the airway
  - Antihistamines, steroids, epinephrine: ? helpful
  - Case reports: fresh frozen plasma (JACI 109(2); 370; Ann. Allergy 92(5) 573)
  - Icatibant - bradykinin receptor antagonist (NEJM 2015:372; 418-25)
  - Ecallantide – kallikrein inhibitor (Ann Emerg Med 2014, Aug 30)
  - Do not substitute other drugs from this class
  - ACE receptor antagonist class: not an absolute contraindication
  - Caution: ACE inhibitors in pts with hx of angioedema

Drug Allergy: Penicillin

- Antibiotics are the most important causes of immediate hypersensitivity reactions, particularly beta lactams.
- ~ 10% of patients report a history of penicillin allergy, however, ~ 90% of these individuals are able to tolerate penicillin
- Use of broad-spectrum antibiotics in patients designated as being “penicillin allergic” is asso- ciated with higher costs, increased antibiotic resistance, and may compromise optimal medical care.

Ann Allergy 105(2); p273 2010.

Drug Allergy: Penicillin

- Penicillin alergy wanes over time with 80% of patients becoming tolerant after a decade.
- Penicillin skin testing is a reliable method for evaluating IgE-mediated penicillin allergy.
- Decision support and test dosing has become the standard of care

JAMA 2019 Jan 15:321(2): 188-199

Penicillin / Cephalosporin Hypersensitivity Pathway

Type II-IV HSR^

Serum Sickness

Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS / TEN)

Acute Interstitial Nephritis (AIN)

Drug Rash Eosinophilia with Systemic Symptoms (DRESS)

Hemolytic Anemia

Drug Fever

↓

Avoid using penicillin, cephalosporin, or carbapenem;* use alternative agents by microbial coverage‡

If penicillin or cephalosporin is clinically indicated, please involve the Infectious Disease or Allergy / Immunology services.

Type I (IgE-mediated) HSR^

Anaphylaxis
Hypotension
Angioedema
Laryngeal edema
Wheezing
Hives / Urticaria

OR

unknown reaction WITHOUT mucosal involvement, skin desquamation, or organ involvement

↓

Okay to use:
3rd / 4th / 5th generation cephalosporin or carbapenem* by **Test Dose Procedure**

OR

aztreonam*

OR

alternative agent by microbial coverage‡

OR

If penicillin or 1st / 2nd generation cephalosporin is preferred, penicillin skin testing is indicated. Please call / contact Allergy / Immunology service.

Mild Reaction

Minor rash (not hives)

Maculopapular rash
(mild Type IV HSR^)

Medical record lists allergy, but patient denies history of allergy

↓

Okay to use:
3rd / 4th / 5th generation cephalosporin as full dose

OR

penicillin or 1st / 2nd generation cephalosporin by **Test Dose Procedure**

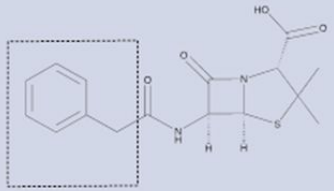
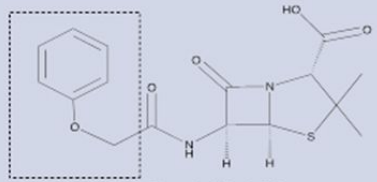
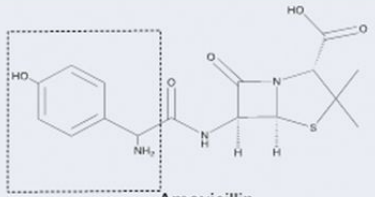
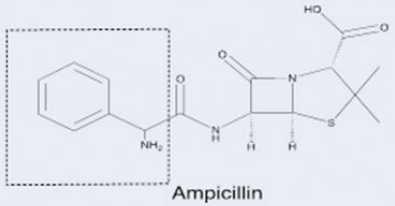
OR

carbapenem*

Penicillin Cross-reactivity

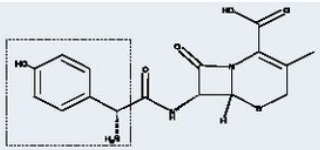
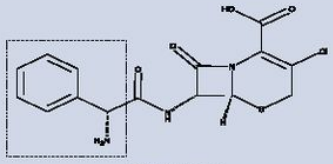
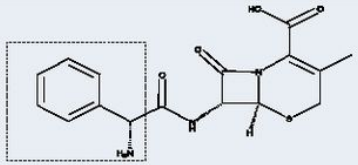
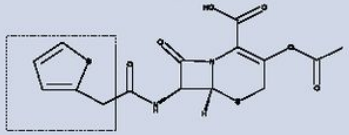
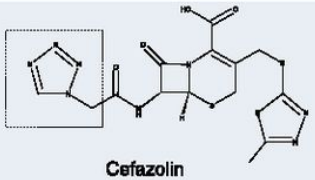
- Allergic cross-reactivity between penicillin and cephalosporins is lower than previously thought
- And cross reactivity is felt to be due to side chain similarities.
- Use of a 3rd or 4th generation cephalosporin with a dissimilar side chain in penicillin allergic patient is safe.
- There is no allergic cross-reactivity between penicillin and monobactams (e.g. aztreonam)
- The degree of cross-reactivity between penicillin and carbapenems (e.g. imipenem, meropenem) appears to be low

Penicillin-cephalosporin cross-reactivity based on side-chain similarity.

Antibiotic	R1 Structure	Shared/ Similar R1 Side Chains
Penicillin G	 Penicillin G	 Penicillin VK
Amoxicillin	 Amoxicillin	Cefadroxil Cefprozil
Ampicillin	 Ampicillin	Cefaclor Cephalexin

Allison Eaddy Norton et al. Pediatrics 2018;141:e20172497

First-generation cephalosporin cross-reactivity.

Antibiotic	R1 Structure	Shared and/or Similar R1 Side Chains
Cefadroxil	 Cefadroxil	Amoxicillin Ampicillin Cefaclor Cefprozil Cephalexin
Cefaclor	 Cefaclor	Amoxicillin Ampicillin Cefadroxil Cefprozil Cephalexin
Cephalexin	 Cephalexin	Amoxicillin Ampicillin Cefadroxil Cefaclor Cefprozil
Cephalothin	 Cephalothin	Cefoxitin
Cefazolin	 Cefazolin	None

Allison Eaddy Norton et al. Pediatrics 2018;141:e20172497

Cross-reactive beta-lactams	Penicillin	Amoxicillin	Ampicillin	Cephalexin	Cefuroxime	Cefoxitin	Ceftriaxone	Cefotaxime	Cefepime	Ceftazidime
Penicillin		X	X	X		X				
Amoxicillin	X		X	X						
Ampicillin	X	X		X						
Cephalexin	X	X	X							
Cefuroxime						X	X	X		
Cefoxitin	X				X					
Ceftriaxone					X			X	X	X
Cefotaxime					X		X			X
Cefepime							X			
Ceftazidime							X	X		

Campagna, et al. J Emerg Med 2012;42(5):612-620.

Antunez et al. J Allergy Clin Immunol 2006;117:404-10.

DePestel et al. J Am Pharm Assoc. 2008;48(4):530-40.

When skin testing is not available, there is clinical evidence to support choosing a cephalosporin with a different R1 side chain to reduce reaction risk.

Adverse Reactions to Food

- Adverse reactions to foods are common
- Need to distinguish immunologic (allergic) from non-immunologic (adverse) reactions

Adverse Reactions to Food:

Non-immunologic

Toxic / Pharmacologic

- Bacterial food poisoning
- Heavy metal poisoning
- Scromboid fish poisoning
- Caffeine
- Alcohol

Do not depend on host factors
Elicited in all with sufficient dose

Non-Toxic / Intolerance

- Lactose intolerance
- Galactosemia
- Pancreatic insufficiency
- Gallbladder / liver disease
- Gustatory rhinitis
- Dyspesia

Do depend on host factors
Idiosyncratic

Adverse Reactions to Food:

Immunologic

IgE | **IgE / Non-IgE** | **Non-IgE**

Urticaria/angioedema
Rhinitis /Asthma
Anaphylaxis

Oral allergy syndrome

Atopic dermatitis

Eosinophilic gastro-intestinal disorders

Protein-induced proctocolitis/enterocolitis

Celiac disease
Contact dermatitis
Herpetiform dermatitis
Heiner´s syndrome

Adapted from J Allergy Clin Immunol. 1999;103:717-728

Food allergy

- Prevalence in the US is increasing
  - Adults: 1.4% - 2.4%
  - Children < 3 years: ~ 6-8%

- Most commonly perceived cause of urticaria

- 90% of food allergy is caused by:
  - eggs, wheat, milk, soy, peanuts, tree nuts and shellfish

Adapted from Sampson HA. Adverse Reactions to Foods. Allergy Principles and Practice. 2003

Management of Food Allergy.

Table 3. Management of Food Allergy.

Strategy	Standard Management	Additional Strategies
Diet	Strict avoidance of culprit foods	Some limited forms of food (e.g., baked products containing milk and egg) may be safely consumed, but this safety must be confirmed clinically with a medically observed feeding or food challenge
Medication	First-line treatment: epinephrine administered with the use of an autoinjector	Adjunctive treatment: antihistamines, beta-agonists, glucocorticoids
Education	Education on label reading, cross-contamination, cross-contact, access to safe foods, and use of medical-alert jewelry; creation of patient-specific action plan for food allergy anaphylaxis	Information provided in schools, workplaces, restaurants, and the food service industry; change in labeling laws for food industry
Scheduled clinical follow-up	Planned follow-up with provider who has experience in treating food allergies (may include allergist); ongoing education, including review of technique for administering epinephrine and use of anaphylaxis action plan; evaluation for resolution of allergy or change in disease with management of coexisting conditions; review of therapeutic plan	Review of emerging treatment options; consideration of participation in clinical trials if applicable

Jones SM, Burks AW. N Engl J Med 2017;377:1168-1176

The NEW ENGLAND JOURNAL of MEDICINE

Immunotherapies under Investigation in Clinical Trials for Treatment of Food Allergy.

Table 4. Immunotherapies under Investigation in Clinical Trials for Treatment of Food Allergy.

Feature	Oral Immunotherapy	Sublingual Immunotherapy	Epicutaneous Immunotherapy
Form of study product (protein dose)	Allergen powder (300–4000 mg per day)	Allergen extract drops (2–7 mg per day)	Allergen patch (100–500 μg per day)
Clinical effect			
Desensitization	Large effect	Moderate-to-small effect	Variable effect
Sustained unresponsiveness	Occurs in subgroups of persons	Not known (studies under way)	Not known
Side effects	Oral or gastrointestinal; potential for anaphylaxis in persons with fever, infection, or menses and during exercise after receipt of a dose of oral immunotherapy	Oral or pharyngeal (local effects)	Skin (local effects)
Immune modulation: antibody and cellular changes	Substantial	Small or moderate	Small or moderate

Jones SM, Burks AW. N Engl J Med 2017;377:1168-1176

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Food allergy: Prevention

Recent studies have examined the role of :

The timing of food introduction in infants at risk for food allergy

The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.

Du Toit G et al. N Engl J Med 2015;372:803-813

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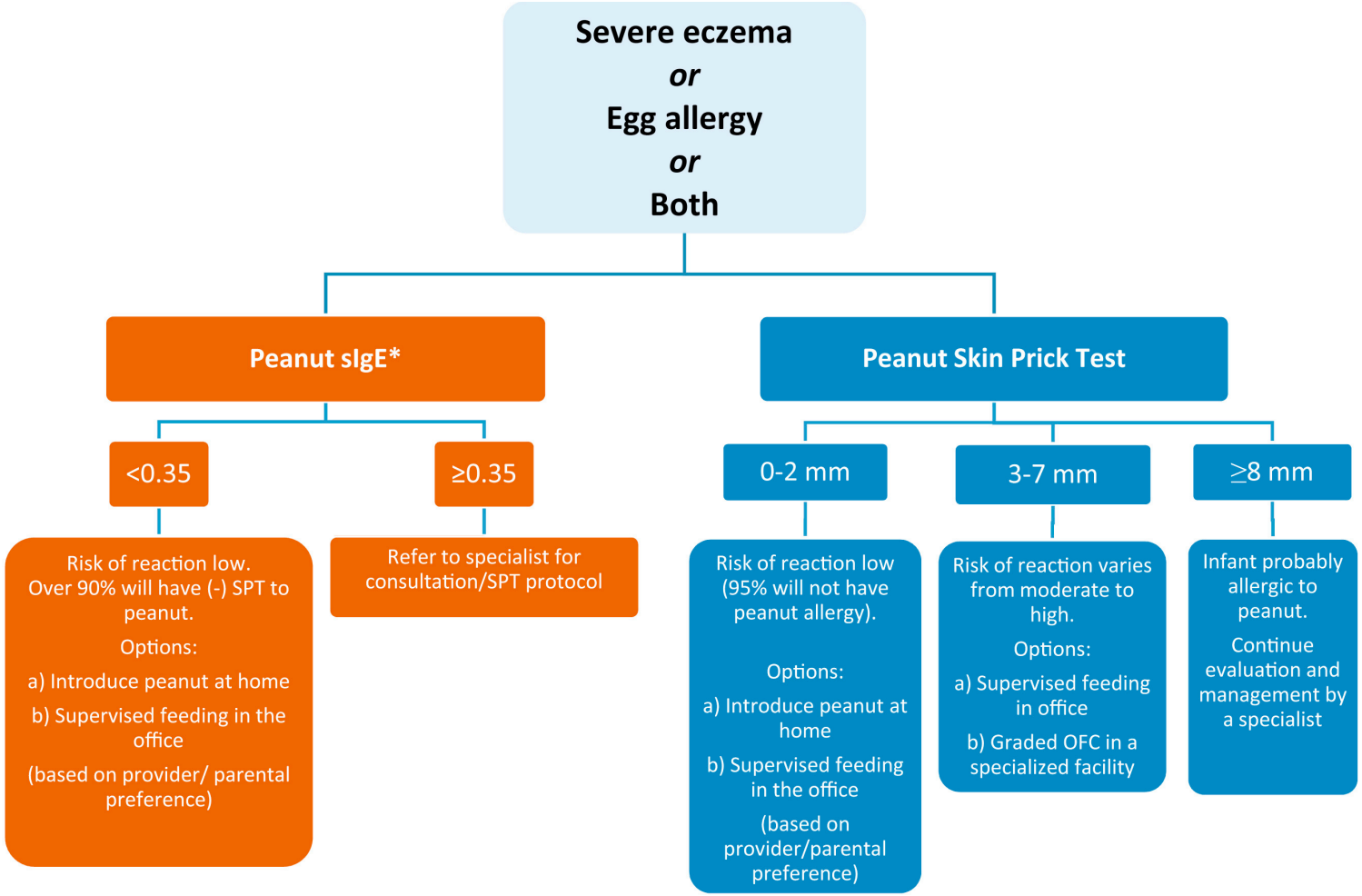


* To minimize a delay in peanut introduction for children who may test negative, testing for peanut-specific IgE may be the preferred initial approach in certain health care settings. Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predictive value.

Annals of Allergy, Asthma & Immunology 2017 118, 166-173.e7DOI: (10.1016/j.anai.2016.10.004)

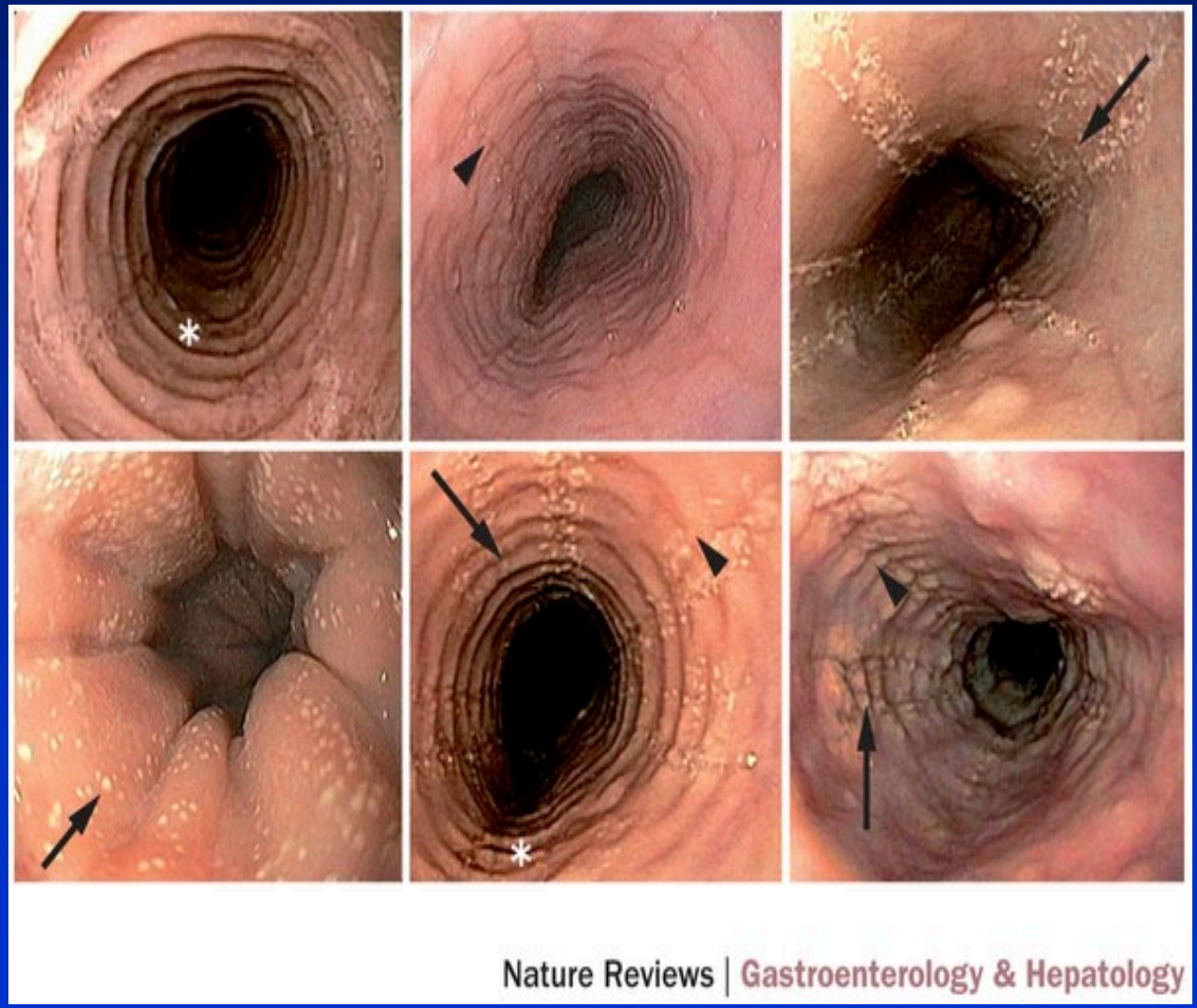
Oral Allergy Syndrome
Pollen-Food Syndrome

- Symptoms of oral itching, throat swelling, GI symptoms after ingestion of certain fruits or vegetables
- Occurs in pollen allergic patients:
  - Birch pollen allergic patients: *e.g. pitted fruits, hazelnut, walnut, almond, celery and carrot*
  - Ragweed allergic patients: *e.g. melons and bananas*
- Pollen proteins share structural homology with the food proteins
- Allergic antibodies to the pollen proteins cross react with the food proteins and elicit the oral symptoms
- Immunotherapy for treating the pollen-induced rhinitis may reduce/eliminate oral allergy symptoms

Eosinophilic Esophagitis (EoE)

- Characterized by infiltration of the esophagus, stomach and/or intestinal walls with eosinophils
- EoE can occur in children and adults.
- Children: vomiting, FTT, GERD symptoms
- Adults refractory GERD, dysphagia and food impaction
- Almost 50% of patients have other atopic diseases
- Diagnosis is based on endoscopic findings and biopsy (>15-20 eosinophils per HPF)
- Treatment involves either dietary restrictions and or swallowed topical steroids

Eosinophilic Esophagitis



Esophageal rings
“Felinization”

Linear furrows

White plaques

Alpha-gal allergy a.k.a. Mammalian Meat Allergy

- Affected individuals develop IgE antibodies to galactose-alpha,1,3 galactose (alpha-gal)
- The allergic antibodies develop after being bitten by the lone star tick
- A typical reaction occurs 3-8 hours after eating mammalian meat (delayed onset)
- Reactions can include:
  - Hives /angioedema
  - Wheezing
  - GI symptoms
  - Anaphylaxis

Carrier

Tick bite

IgE to alpha gal ↑
(1-3 months)

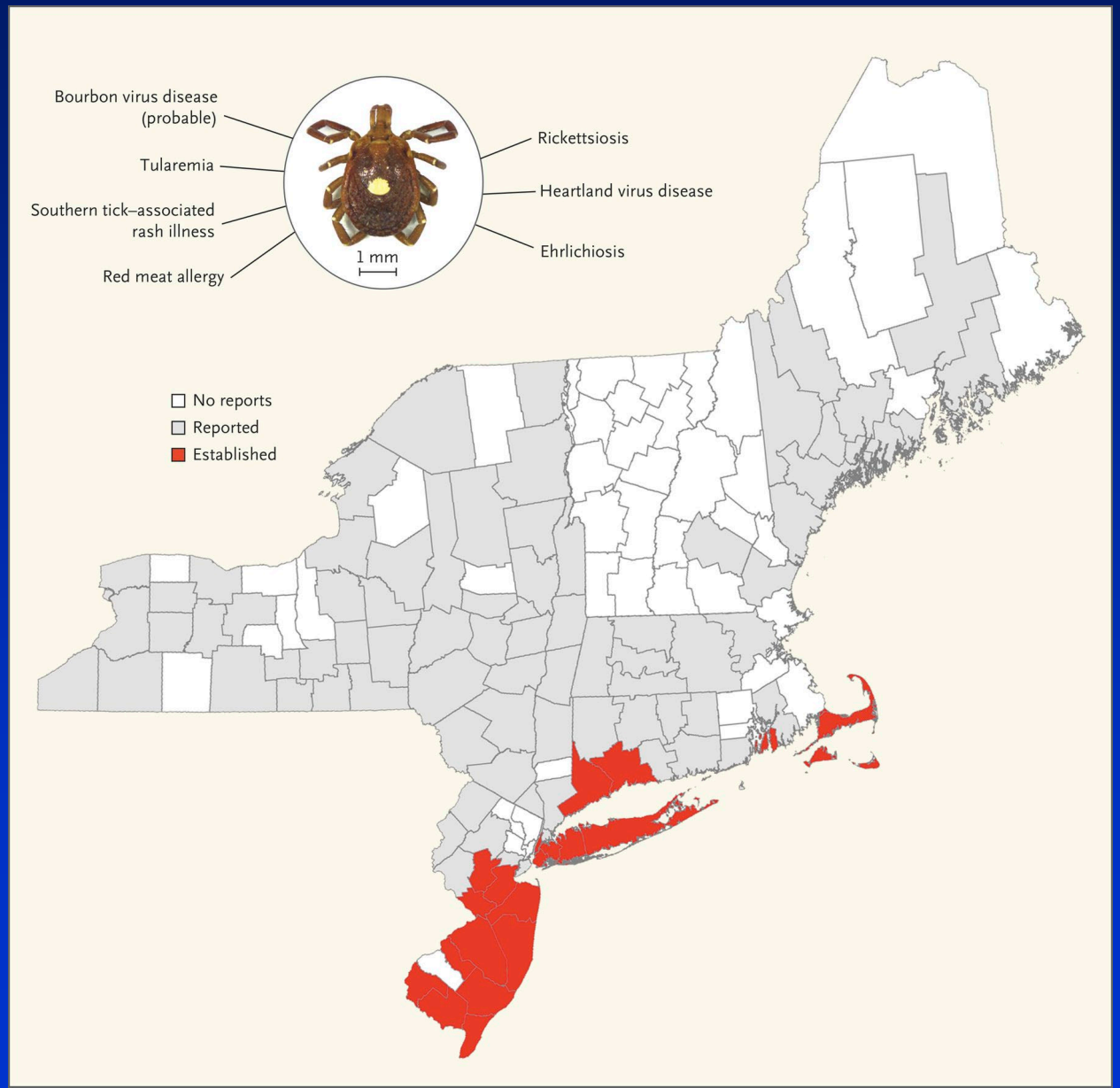
Ingestion mammalian products

2-6 hrs

Urticaria
Angiodema
Anaphylaxis

J Allergy Clin Immunol. 2015 Mar; 135(3): 589–597

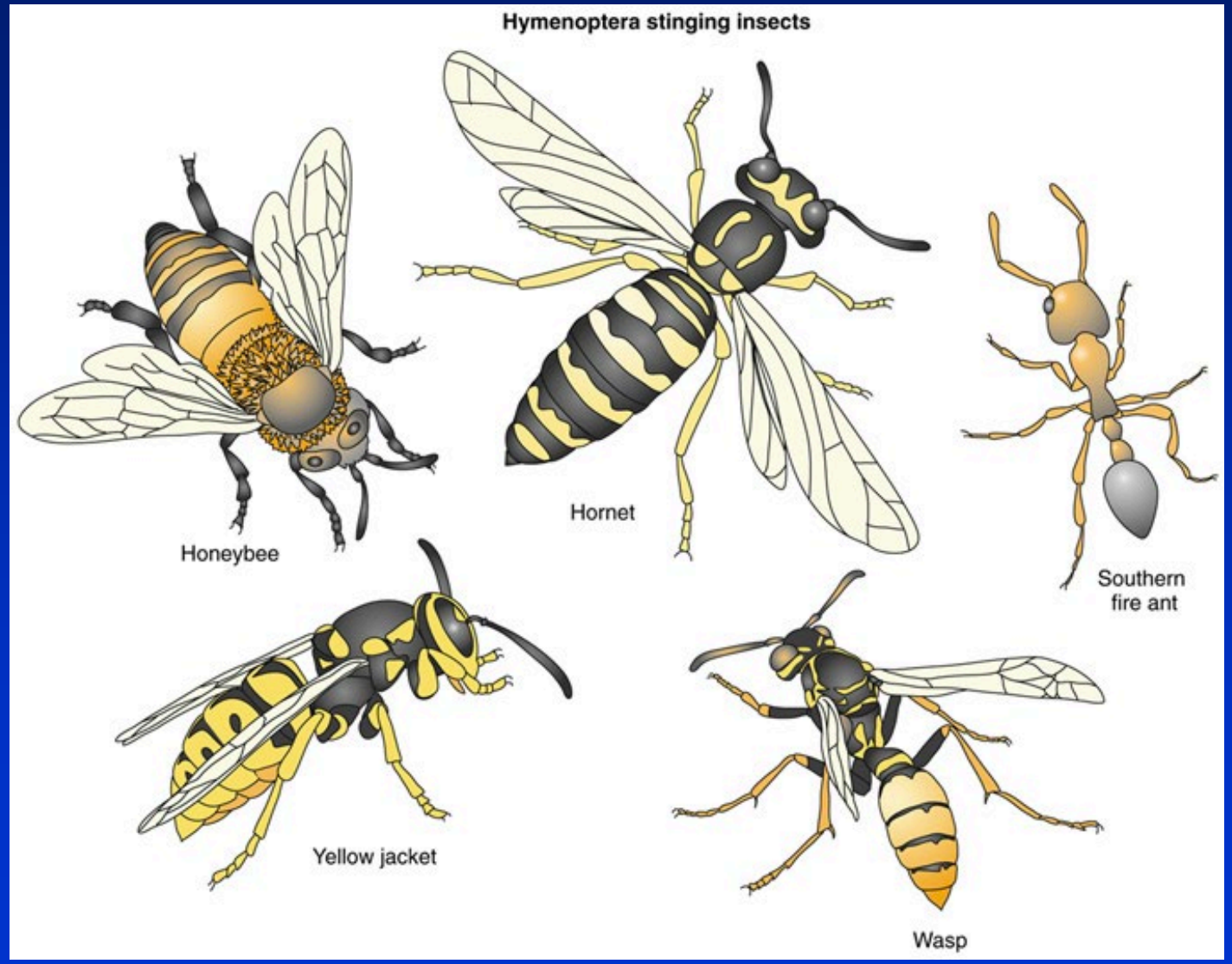
Bracing for the Worst — Range Expansion of the Lone Star Tick in the Northeastern United States



Stinging Insect Allergy

- Reaction may be local or systemic
- Severe reactions & fatalities more common in adults than children
  - fatalities in patients <16 yo are rare
- Distinguish biting (mosquitoes) from stinging insects
- Skin testing is diagnostic test of choice
- Immunotherapy for systemic reactions only
  - 97% effective!
- EpiPen

Insect Sting Allergy



Chronic and Recurrent Urticaria / Angioedema

Physical Urticarias

Urticarias that occur from physical stimulation of the skin

- Symptomatic dermatographism
- Cold-induced
- Cholinergic urticaria (heat)
- Exercise-induced
- Delayed pressure urticaria
- Solar
- Aquagenic
- Vibratory

Features of Physical Urticaria

Type	Age (yrs)	Clinical Features	Angio-edema	Diagnostic Test
Dermatographism	20-50	Linear lesions	No	Light stroking of skin; + transfer factor
Cold	10-40	Itchy, pale lesions (5% with cryos)	Yes	5-10 minute ice-cube test; + transfer factor
Cholinergic	10-50	Itchy, monomorphic pale or pink lesions	Yes	Exercise or hot shower; + transfer factor
Pressure	20-50	Large painful or itchy lesions	No	Dermographometer; application of pressure to skin or Sand bag test 15 lb weight for 15 minutes
Solar	20-50	Itchy pale or red swelling	Yes	Irradiation by a solar simulator;+ transfer factor

Dermatographism

Ice Cube Test

Chronic urticaria

As a sign of systemic illness

- Infections: bacterial, fungal, viral, helminthes
- Thyroid disease

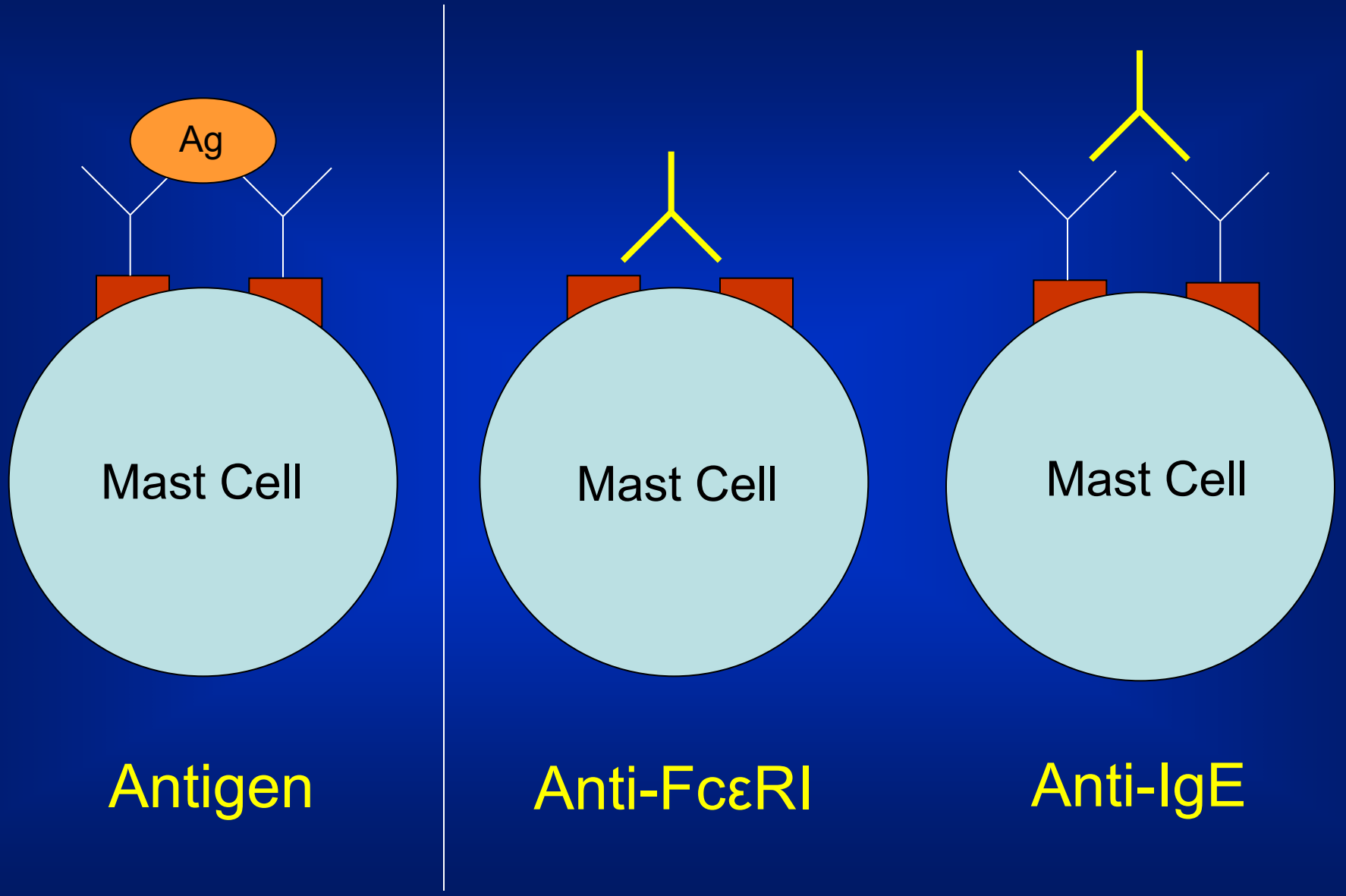
- Connective tissue diseases
- Complement (C1 inhibitor) deficiencies
- Urticaria pigmentosa / mastocytosis

- Chronic urticaria as an autoimmune disease

Chronic Idiopathic Urticaria

- ~ 95% of urticaria is “idiopathic”
- 2:1 female:male
- rarely life-threatening, often disabling
- often resistant to conventional treatment

- Latest research suggests it is an autoimmune illness with auto antibodies directed against the mast cell


Ag
Mast Cell
Mast Cell
Mast Cell
Antigen
Anti-FcεRI
Anti-IgE

Management of allergies

- Avoid or remove inciting agents or triggers
  - e.g. drugs, foods, pets
- Medications
  - Antihistamines
  - Corticosteroids
  - Immune modulators

H1 Antihistamines

- First generation H_1 antagonists
  - Chlorpheniramine, diphenhydramine, hydroxyzine , cyproheptadine

- Second-generation H_1 antagonists (low sedating)
  - OTC: Claritin (loratadine), Allegra (fexofenadine), Zyrtec (cetirizine),
  - Clarinex (desloratadine), Xyzal (levocetirizine)

H2 Antihistamines

- If H_1 is adequately blocked, adding H_2 may be helpful
- Typical use is for GERD
- H_2 antagonists
  - Tagamet (cimetidine), Zantac (ranitidine), Pepcid (famotidine), Axid (nizatidine)

Leukotriene (LT) antagonists

- Well tolerated, few side effects
- Not particularly potent
- Used in asthma, allergic rhinitis and urticaria

- LT Receptor Antagonists
  - Accolate (zafirlukast) 20 mg b.i.d.
  - Singulair (montelukast) 10 mg daily

- LT Synthesis Inhibitor
  - Zyflo (zileuton) 600 mg 2-4 times daily

Systemic Corticosteroids

- Systemic corticosteroids are frequently used in patients with chronic urticaria refractory to antihistamine therapy

- "Systemic corticosteroids should be avoided for long-term treatment of urticaria, since dosages necessary to suppress symptoms are usually high with significant adverse effects" (International Consensus Meeting on Urticaria)

Allergy 2009;64:1427-43.

TABLE 12-1—Evidence for Therapies in Chronic Urticaria

Drug	Level of Evidence	Quality & Amount of Evidence	Potential for Serious Adverse Effects	Cost
H1 antihistamines	Ia	High	Low	Low
H2 antihistamines	Ib	Low	Low	Low
doxepin	Ib	Moderate	Low	Low
Systemic corticosteroids	IV	Low	High	Low
Leukotriene modifiers	Ib	Moderate	Low	Moderate
dapsone	IIb	Low	Moderate	Low*
sulfasalazine	III	Low	Moderate	Low*
hydroxychloroquine	Ib	Low	Low	Low
colchicine	III	Low	Low	Low
Calcineurin inhibitors	Ib	Moderate	High	High*
mycophenolate	IIb	Low	Moderate	High*
omalizumab	Ib	Low	Moderate	High
IVIG	IIb	Low	Moderate	High*
Beta-agonists	Ib (no effect) III (effect)	Moderate Low	Moderate	Low
NSAIDs	III	Low	Moderate	Low
Methylxanthines	Ib	Moderate	Moderate	Low*
Phototherapy	Ib	Moderate	Moderate	High
Androgens	Ib	Low	Moderate	Moderate*
Methotrexate	III	Low	High	Low*
Anticoagulants	III	Low	High	Low*

Khan DA. In: Maibach HI, Gorouhi F ed. Evidence Based Dermatology 2nd ed. 2011

Biologic agents for the treatment of allergic disease

1. Anti-IgE (Omalizumab – Xolair)
   - Approved for moderate to severe asthma
   - Approved for chronic idiopathic urticaria
   - Possible adjunct role in oral immunotherapy for food allergies

2. Anti-IL-5 (Mepolizumab; Reslizumab ; Benralizumab)
   - Approved for severe eosinophilic asthma
   - under investigation for the treatment of atopic dermatitis, hyper-eosinophilic syndrome, nasal polyps, eosinophilic granulomatosis with polyangiitis (Churg Strauss)

3. Anti-IL4R (Dupilumab)
   - Blocks the IL4-R alpha which is shared by IL-4 and IL-13
   - Approved for atopic dermatitis.
   - Approved for moderate to severe asthma
   - Approved chronic rhino-sinusitis with nasal polyps

N Engl J Med 2013; 368:924-935; March 7, 2013; JACI In Press 2016
Dupilumab versus Placebo in Atopic Dermatitis. NEJM Oct 2016

Questions?