Why Everything You Thought You Knew About Allergies May Be Wrong

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Disclosures

- Social Media Medical Editor – American Academy of Allergy, Asthma and Immunology
- Consultant –Before Brands, Kaleo, Novartis
- Associate Editor – Annals of Allergy, Asthma and Immunology
- Honoraria – ACAAI, AAP, AAAAI
- Non-financial:
  - Member – Joint Task Force on Practice Parameters for Allergy and Immunology
  - Member – Board of Regents, American College of Allergy, Asthma and Immunology

Objectives

- Implement evolving evidence into clinical practice
- Understand limitations in use of antihistamines when treating various conditions

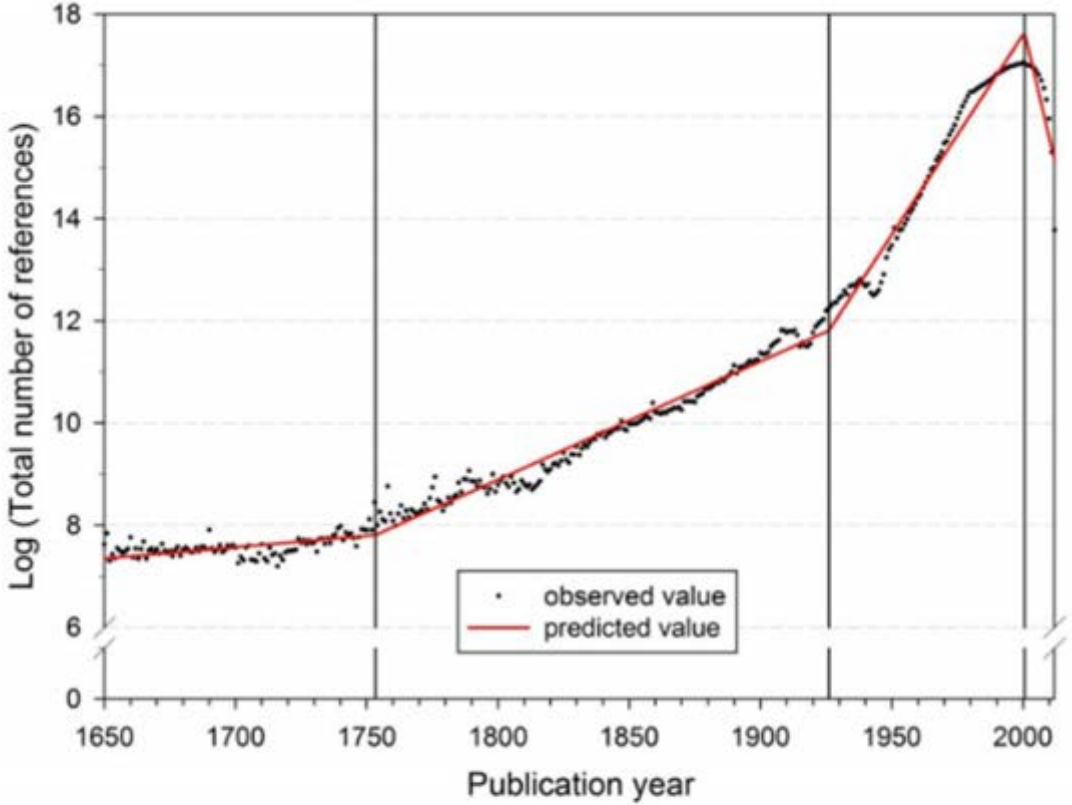
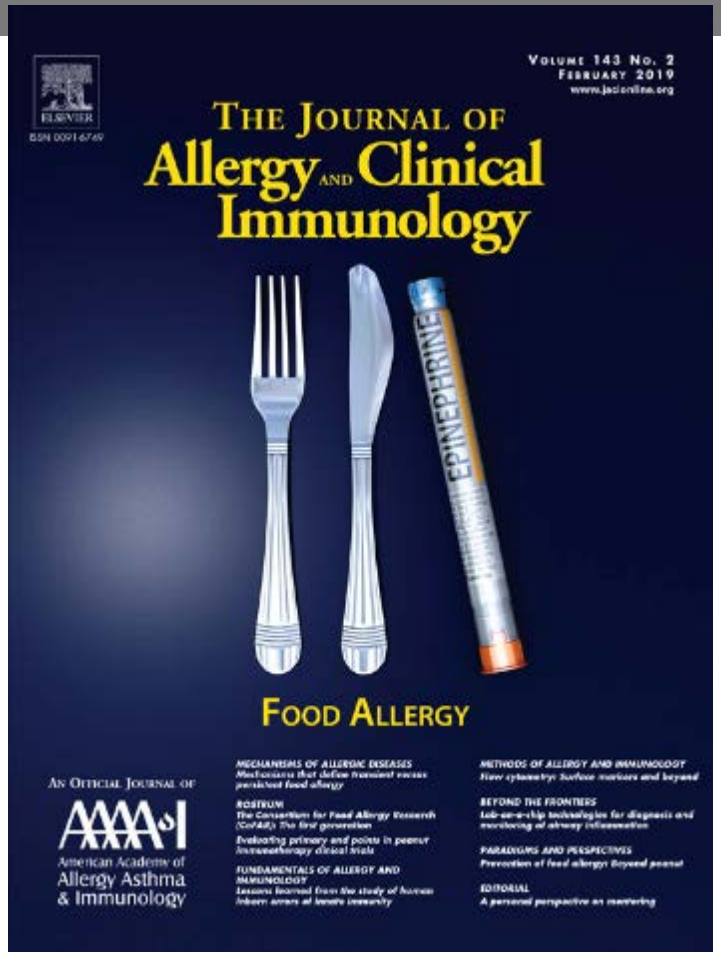
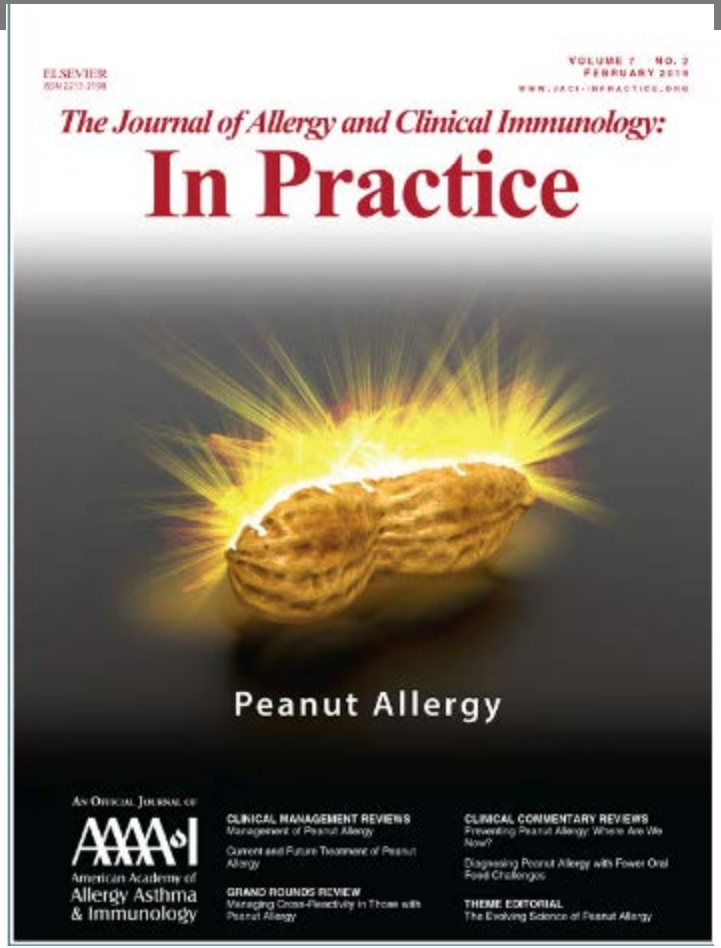


Figure 2. Segmented growth of the annual number of cited references from 1650 to 2012 (citing publications from 1980 to 2012)

Bornmann L, et al. J Assoc Info Sci Tech: arxiv.org/abs/1402.4578





>1,000 articles in 2021

The answer is 17 years, what is the question: understanding time lags in translational research

Zoë Slote Morris[1] • Steven Wooding[2] • Jonathan Grant[2]

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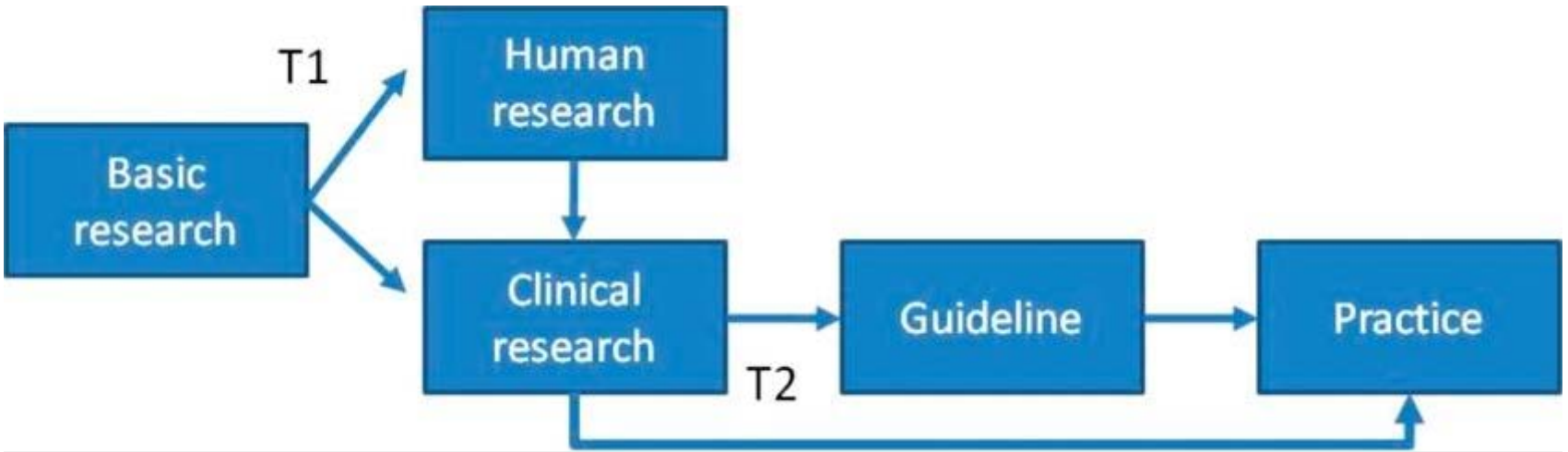
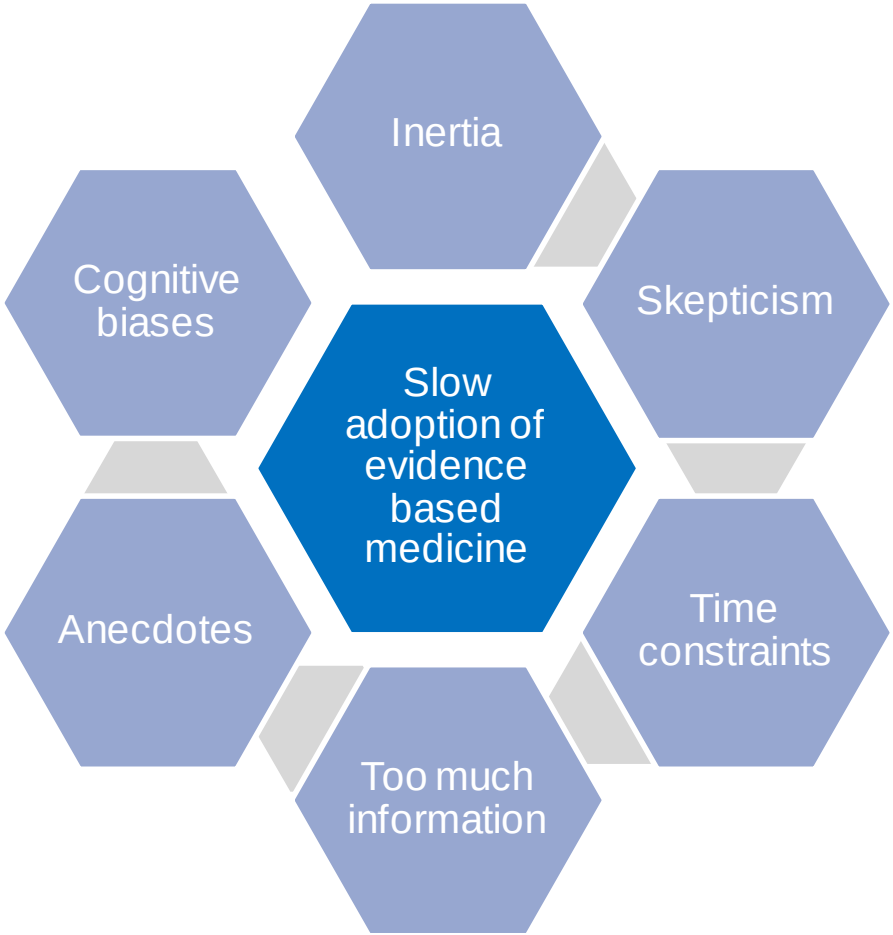
Correspondence to: Jonathan Grant. Email: jgrant@rand.org



J R Soc Med. 2011 Dec; 104(12): 510–520.


Inertia
Skepticism
Time constraints
Too much information
Anecdotes
Cognitive biases
Slow adoption of evidence based medicine

What is an Allergy?

al·ler·gy

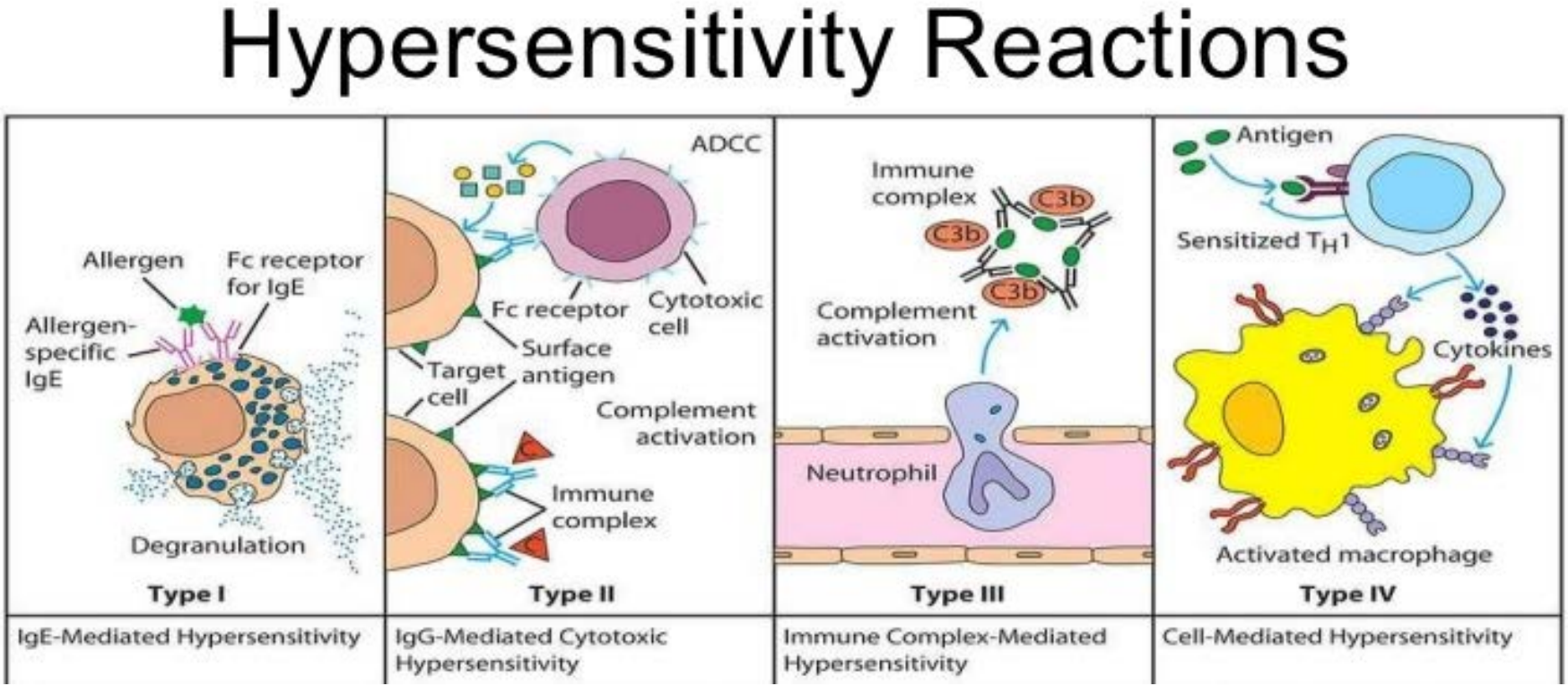
/ˈalərjē/

noun

a damaging immune response by the body to a substance, especially pollen, fur, a particular food, or dust, to which it has become hypersensitive.

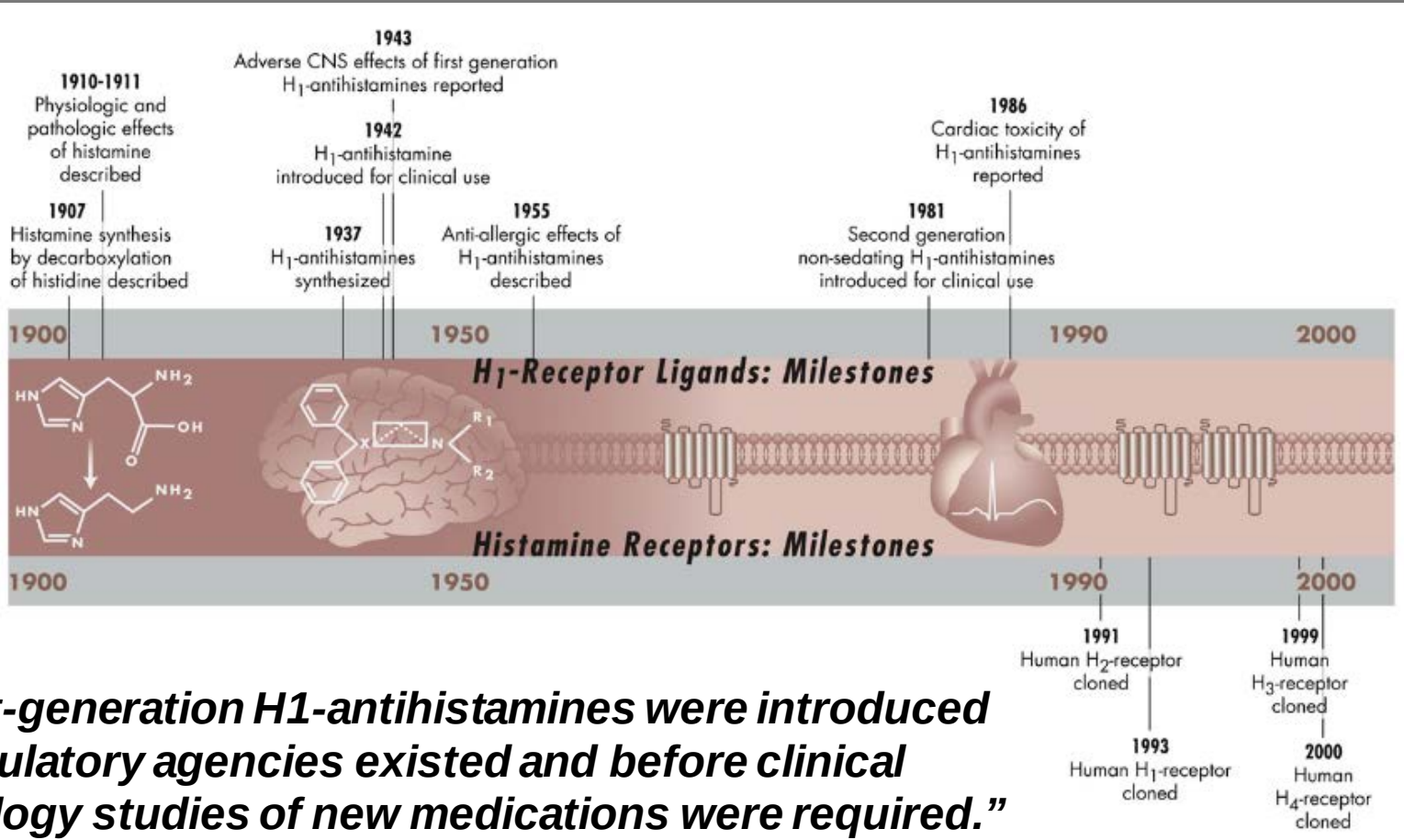
An abnormal response of the immune system to a harmless substance

Gel and Coombs Classification



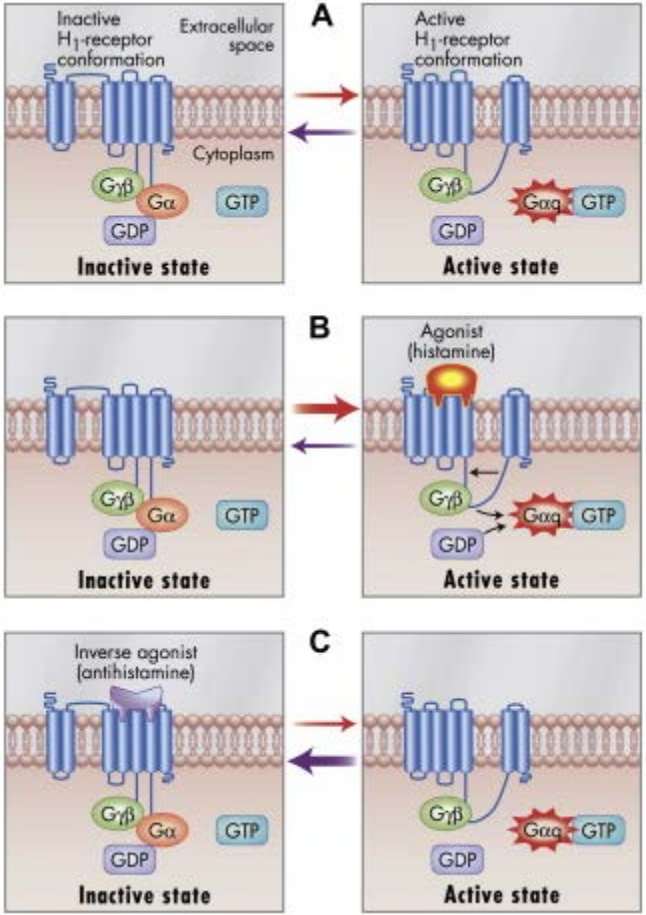
Which Would You Choose?

	Medication A	Medication B
Onset of action	Longer	Shorter
Duration of action	Shorter	Longer
Efficacy	Less	More
Side effects	Very common	Uncommon
Are pilots legally allowed to take this medication before flying an airplane?	No	Yes
	1st generation antihistamines	**2nd generation antihistamines**



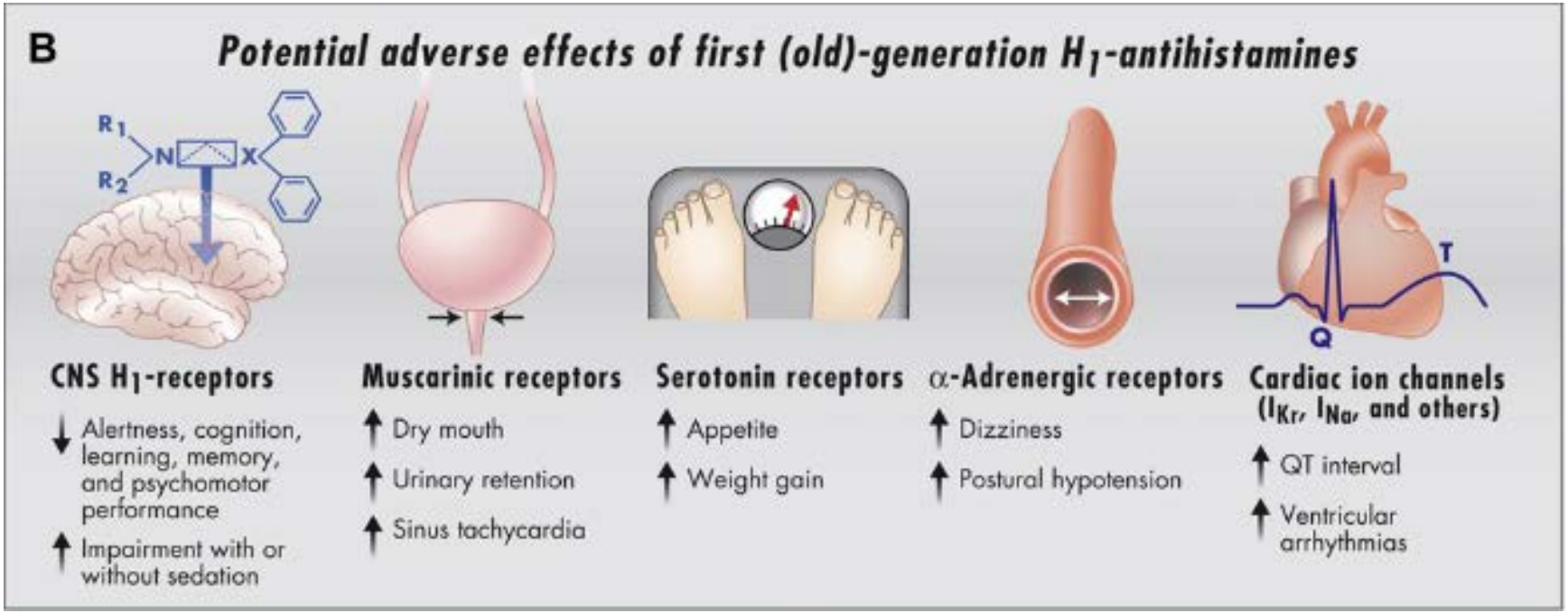
"Most first-generation H1-antihistamines were introduced before regulatory agencies existed and before clinical pharmacology studies of new medications were required."

Simons FE, Simons KJ. J Aller Clin Immunol. 2011;128(6):1139-1150



Antihistamines act as inverse agonists

Simons FE, Simons KJ. J Aller Clin Immunol. 2011;128(6):1139-1150



Simons FE, Simons KJ. J Aller Clin Immunol. 2011;128(6):1139-1150

Conditions currently treated with H_1-antihistamines

Strong evidence base for second (new)-generation H_1-antihistamine use

Allergic rhinitis

Allergic conjunctivitis

Urticaria

Weak evidence base for H_1-antihistamine use

- Atopic dermatitis
- Asthma
- Anaphylaxis
- Non-allergic angioedema
- Upper respiratory tract infections (colds)
- Otitis media
- Sinusitis
- Nasal polyps
- Non-specific cough
- Non-allergic, non-specific itching

Weak evidence base for first (old)-generation H_1-antihistamine use in CNS and vestibular disorders

- Insomnia
- Conscious sedation
- Perioperative sedation
- Analgesia
- Anxiety
- Serotonin syndrome
- Akathisia
- Migraine
- Motion sickness
- Vertigo

Simons FE, Simons KJ. J Aller Clin Immunol. 2011;128(6):1139-1150

HEALTH

Canadian allergists' group wants Benadryl behind the counter due to side-effects

Michelle Ward
The Canadian Press

Published Wednesday, November 13, 2019 8:24PM EST
Last Updated Thursday, November 14, 2019 6:34PM EST

https://www.ctvnews.ca/health/canadian-allergists-group-wants-benadryl-behind-the-counter-due-to-side-effects-1.4684745

Fein *et al.*
Allergy Asthma Clin Immunol (2019) 15:61
https://doi.org/10.1186/s13223-019-0375-9

Allergy, Asthma & Clinical Immunology

REVIEW Open Access

CSACI position statement: Newer generation H_1-antihistamines are safer than first-generation H_1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria

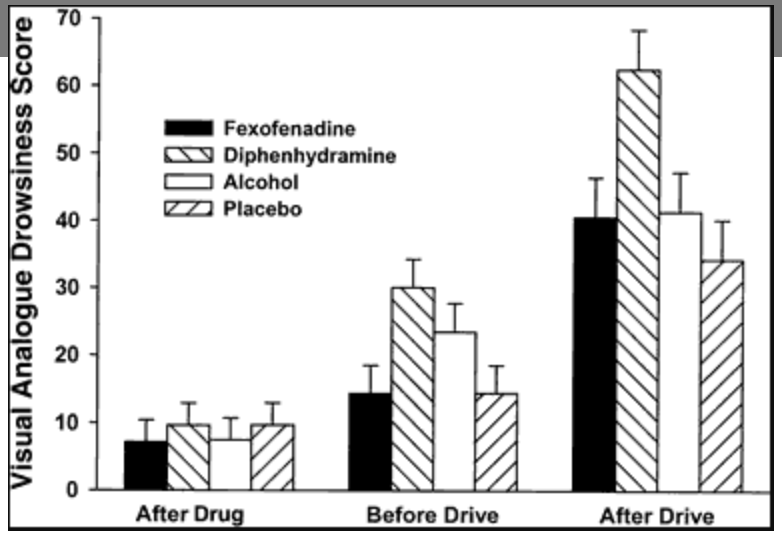
Michael N. Fein[1], David A. Fischer[2,3*], Andrew W. O'Keefe[4] and Gord L. Sussman[5]

Fein MN, et al. Allergy Asthma Clin Immunol (2019) 15:61

Table 1 H1 Antihistamines: pharmacokinetics and pharmacodynamics in healthy adults. Reproduced with permission [5]

Orally administered H1-antihistamines	Time to maximum plasma concentration (h) after a single dose	Terminal elimination half-life (h)	Clinically relevant drug–drug interactions[a]	Onset of action (h)[b]	Duration of action (h)[b]
First (old) generation					
Chlorpheniramine[c]	2.8 ± 0.8	27.9 ± 8.7	Possible	3	24
Diphenhydramine[c]	1.7 ± 1.0	9.2 ± 2.5	Possible	2	12
Doxepin[c]	2	13	Possible	NA	NA
Hydroxyzine[c]	2.1 ± 0.4	20 ± 4.0	Possible	2	24
Second (new) generation					
Bilastine	1.2	14.5	Unlikely	2	24
Cetrizine	1.0 ± 0.5	6.5–10	Unlikely	0.7	≥ 24
Desloratidine	1.0–3.0	27	Unlikely	2–2.6	≥ 24
Fexofenadine[a]	1.0–3.0	11.0–15.0	Unlikely	1.0–3.0	24
Levocetirizine	0.8 ± 0.5	7 ± 1.5	Unlikely	0.7	> 24
Loratidine (metabolite: descarboethoxyloratidine)	1.2 ± 0.3 (1.5 ± 0.7)	7.8 ± 4.2 (24 ± 9.8)	Unlikely	2	24
Rupatadine	0.75–1.0	6 (4.3–14.3)	Unlikely	2	24

Fein MN, et al. Allergy Asthma Clin Immunol (2019) 15:61



Conclusions: Participants had similar performance when treated with fexofenadine or placebo. After alcohol use, participants performed the primary task well but not the secondary tasks; as a result, overall driving performance was poorer. After participants took diphenhydramine, driving performance was poorest, indicating that diphenhydramine had a greater impact on driving than alcohol did. Drowsiness ratings were not a good predictor of impairment, suggesting that drivers cannot use drowsiness to indicate when they should not drive.

Weiler JM, et al. Ann Intern Med. 2000;132(5):354-363.

Take Home Points

- Newer generation antihistamines:
  - Are readily available
  - Have shorter onset of action
  - Have longer duration of action
  - Have less side effects
  - Are MORE effective!

Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis

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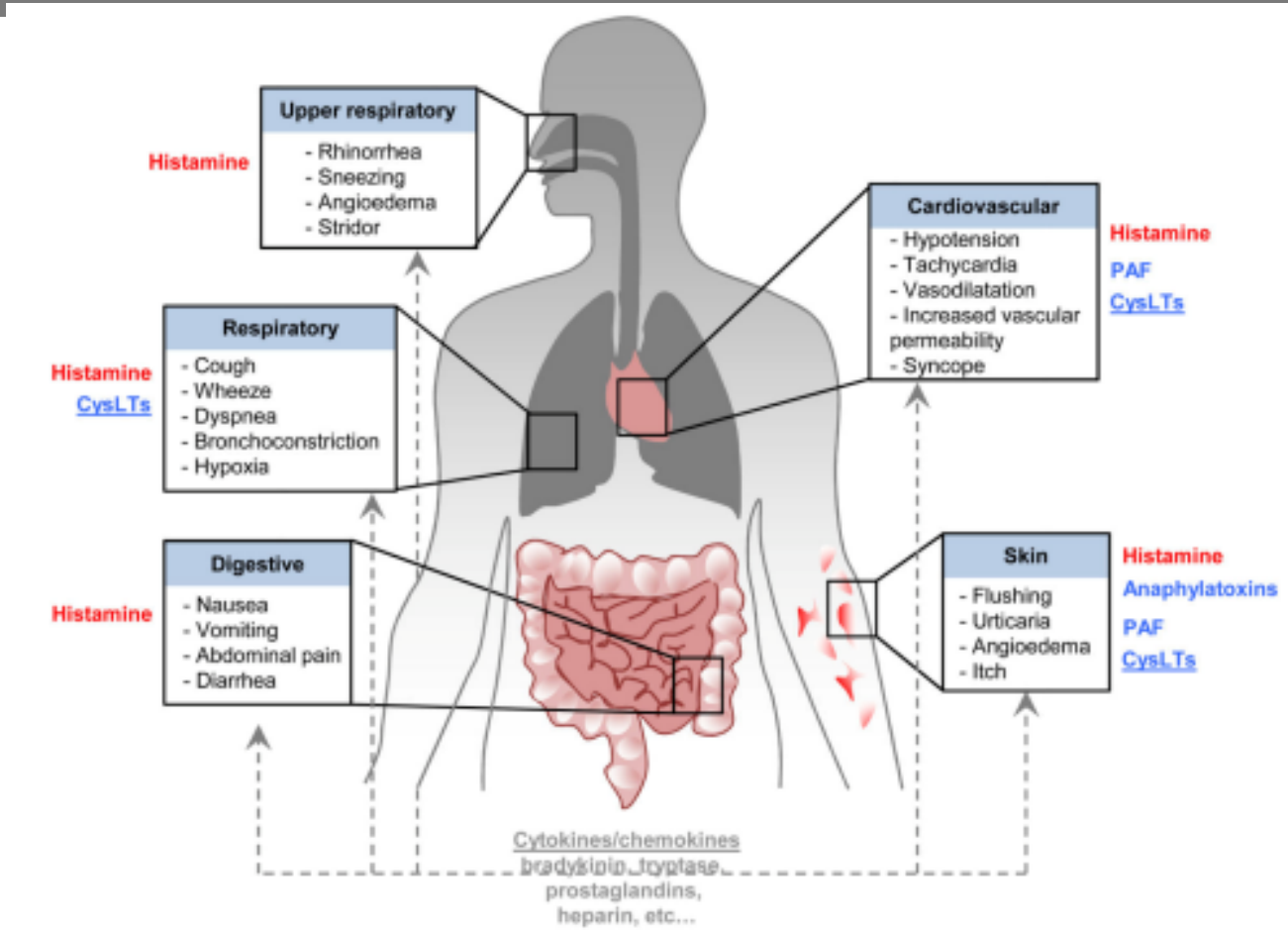
Chief Editors: Marcus S. Shaker and Dana V. Wallace

https://www.aaaai.org/practice-resources/statements-and-practice-parameters/practice-parameter-guidelines



Reber LL, et al. JACI. 2017;140(2):335-348.

Supplemental Therapies to Prevent Biphasic Anaphylaxis

Question 2	Recommendation: **The guideline suggests against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis**

Conditional Recommendation; Very Low Certainty Evidence

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

What Does This Actually Mean?

- Epinephrine is the only effective treatment for anaphylaxis
- Antihistamines & steroids do not treat anaphylaxis or prevent biphasic anaphylaxis

- Antihistamines may be indicated to help with itching or other symptoms
- Steroids have a very limited role in anaphylaxis (if any)


KEEP
CALM
AND
GIVE
EPI

There’s No Need to Be Rash about Rashes

Most people eat food throughout the day

Chronic skin conditions wax and wane over time

People will have eaten something when their chronic skin condition flares

Human minds are programmed to ask then find answers to questions

Anticipate Concerns and Reassure!

Table 5. Contact Urticaria

Meats, fruits, vegetables, and other foodstuffs		Spices	Additives
Apple	Liver	Caraway seed	Acetic acid
Apricot	Lupin seed	Cayenne pepper	Amaranth
Almond	Maize	Cinnamon	Benzic acid
Artichoke	Malt	Coriander	Butyric acid
Arugula	Mango	Curry	Cinnamic acid
Asparagus	Melon	Dill	Cinnamic aldehyde
Banana	Milk	Garlic	Cellulase
Barley	Mushroom	Mustard	Caraway
Beans	Oatmeal	Onion	Benzaldehyde
Beef	Onion	Paprika	Balsam of Peru
Beer	Orange	Parsley	Ethyl, butyl, isopropyl, acetyl alcohol
Brazil nut	Parsnip	Thyme	Methanol
Buckwheat	Peach		Neocaoccine
Cabbage	Peanut		Sorbic acid
Carrot	Pear		Sodium benzoate
Cauliflower	Pickles		Sunset Yellow
Celery	Pineapple		Tartrazine (FD & C no. 5)
Chamomile	Plum		
Cheese	Pomegranate		
Chicory	Pork		
Chicken	Potato		
Chives	Rice		
Coffee bean (Green)	Rutabaga		
Corn	Seaweed		
Cucumber	Sesame seeds		
Egg	Shallots		
Endive	Shellfish		
Fennel	Soybean		
Fig	Spinach		
Fish	Strawberry		
Flour	Sesame seeds		
Frog's legs	Sunflower seeds		
Garlic	Tofu		
Grapefruit	Tomato		
Green pepper	Turkey		
Honey	Venison		
Kiwi lamb	Watercress		
Leek	Watermelon		
Lemon	Wheat		
Lettuce	Wheat bran		
Lime	Winged bean		
Litchi			

Brancaccio RR. Dermatol Ther. 2004;17(4):302-13.

Eczema

What Causes Eczema?

- Strong genetic component leads to altered skin barrier/epidermis
  - Filaggrin loss of function mutations
  - SPINK5
- Leads to → increased transepidermal water loss → increased entry of allergens, irritants, chemicals → ***inflammation***

Cork M et al. J Allergy Clin Immunology. 2006;118(1):3-21.

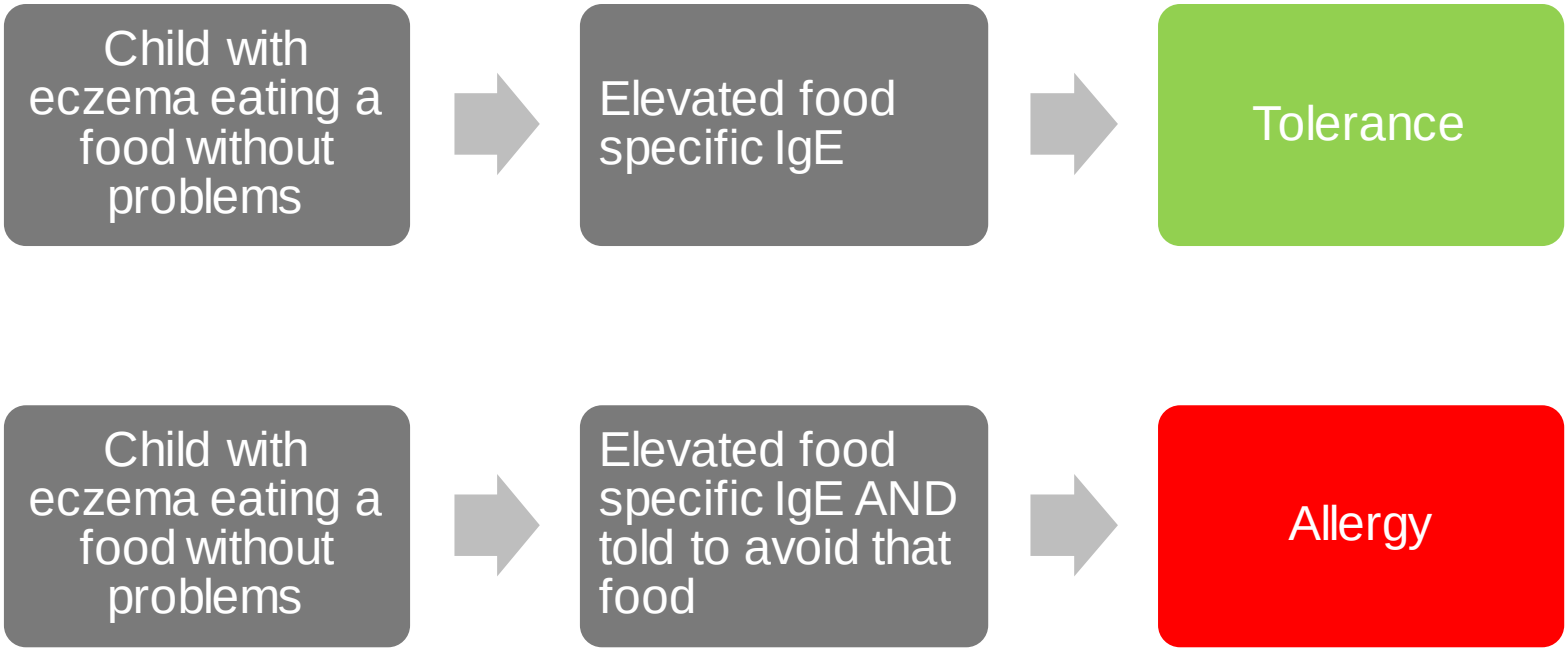
Role of Allergens and Eczema

- History is often unreliable in identifying potential food or environmental allergen triggers
  - Symptoms may not appear for hours to days after ingestion

- IgE testing is often unreliable in identifying potential food allergen
  - High rate of false positive testing
  - May be T cell mediated response (negative IgE testing)

Eigenmann P et al. Ped Allergy Immunol. 2000;11:95-100.

Primum non nocere (First, do no harm)



Spergel J, et al. Pediatrics 2015;136(6):e1530-e1538

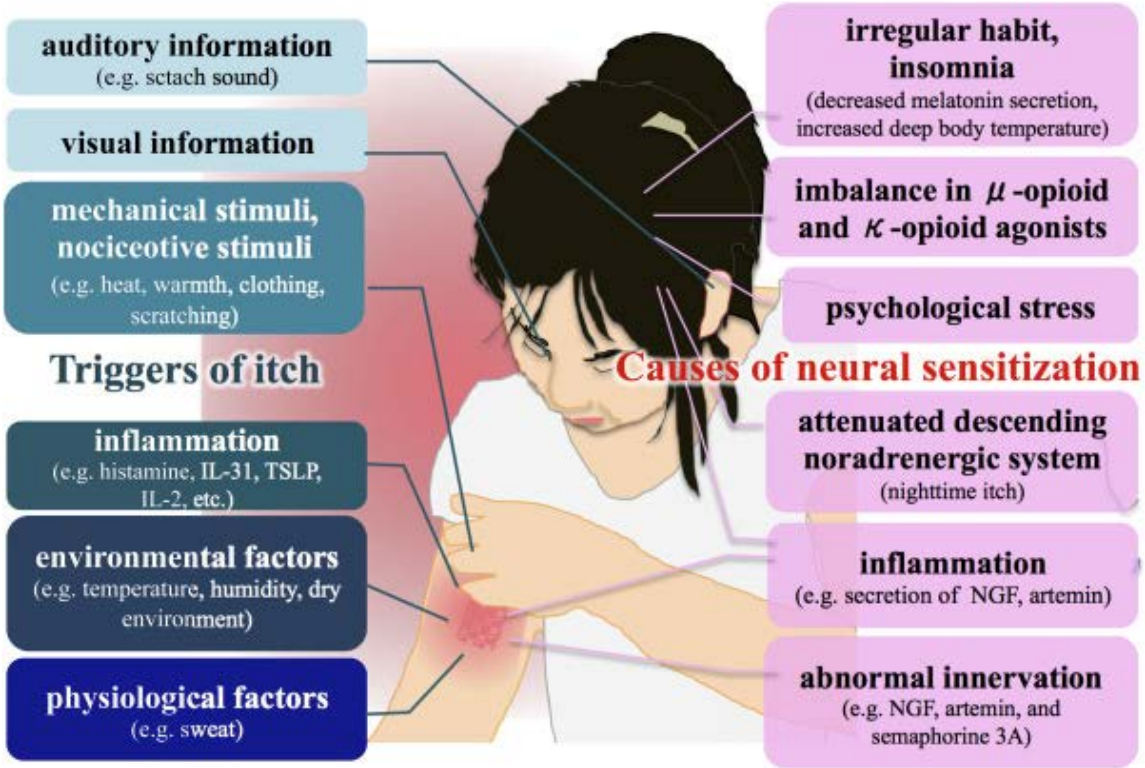
Role of Allergens and Eczema

- A subset of infants (< 2 years of age) with **refractory** moderate-severe eczema may have food allergy contributing
  - **Only consider after thorough regimen of skin care**
  - Egg, milk, peanut most commonly implicated
- Sensitization to aeroallergens can lead to chronic or seasonal flares of eczema lesions
  - Dust mite, pet dander, pollen

Role of Other Factors in Eczema

- **# 1 cause of poorly controlled eczema:**
  - Lack of understanding regarding:
    - Chronic nature of the underlying condition
    - Knowledge/avoidance of triggers
    - Need for frequent application of moisturizer

Severe Itch in Atopic Dermatitis



Allergol Int. 2017;66(1):8-13.

Case

- 2 year old boy with frequent episodes of generalized hives
- Parents report hives after he eats dairy, egg, wheat, soy, peanut, tomato, strawberry
- Avoiding all these foods… but hives still occur

Case

- Allergist evaluates with skin prick testing
- Parents told he has > 20 food and environmental allergies
  - Told to administer epinephrine if hives ever “cover more than his chest”
  - He has received epinephrine 7 times in 2 months
- Referred for 2nd evaluation of mastocytosis

One Test…

Case

ALLERGEN: ALMONDS IGE	<0.10
ALLERGEN: CASHEWS IGE	<0.10
ALLERGEN: COD IGE	<0.10
ALLERGEN: CORN IGE	<0.10
ALLERGEN: CRAB IGE	<0.10
ALLERGEN: EGG WHIT...	2.69 ▲
ALLERGEN: HAZELNUT...	<0.10
ALLERGEN: LOBSTER IGE	<0.10
ALLERGEN: MILK (CO...	0.17
ALLERGEN: PEA IGE	0.40 ▲
ALLERGEN: PEANUT IGE	2.40 ▲
ALLERGEN: PECAN NU...	<0.10
ALLERGEN: PISTACHI...	<0.10
ALLERGEN: SALMON IGE	<0.10
ALLERGEN: SHRIMP IGE	<0.10
ALLERGEN: TUNA IGE	<0.10
ALLERGEN: WALNUTS IGE	<0.10

History *NOT* Suggestive of IgE-mediated Food Hypersensitivity

- Long list of suspected triggers
- Suspected trigger is not recognized as a common or highly allergenic item
- No identifiable trigger
- Delayed symptom onset after exposure (> 3 hrs)
- Symptoms not reproducible with each exposure
- Able to tolerate allergen in other forms
- Symptom duration >24 hours in acute urticaria
- ***Chronic urticaria***

The Stukus Rule of Hives

- The longer the list of suspected items grows, the less and less likely it is that multiple different IgE-mediated allergies to those items are present
- Key question:
  - “What causes your child’s hives?”

Prognosis

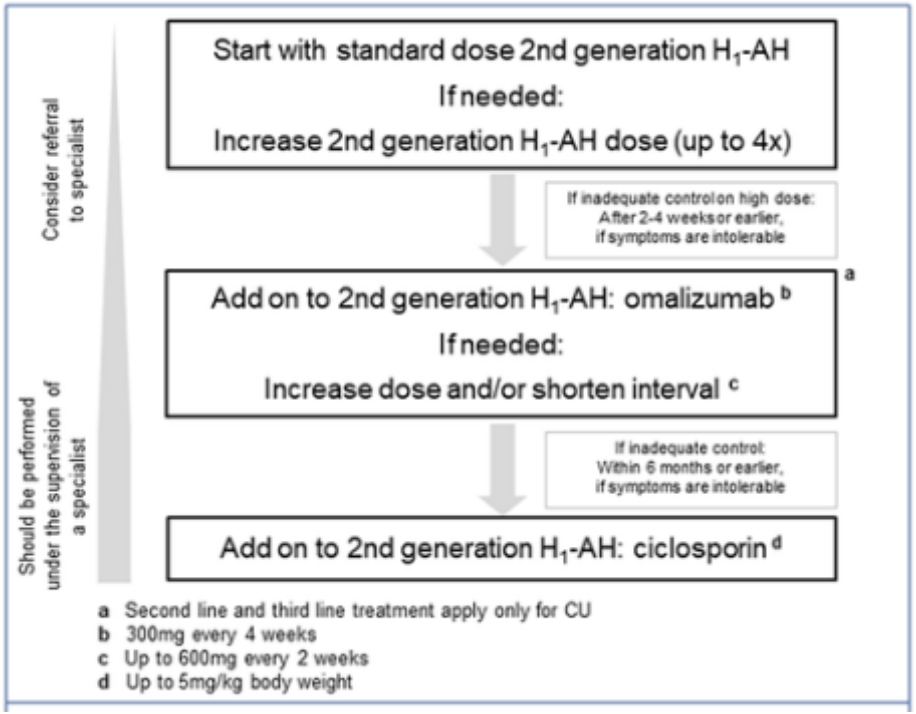
- Acute urticaria is self limited
  - By definition, lasts < 6 weeks
- Chronic urticaria
  - Episodic
  - Self limited
  - 30-50% resolve within one year
  - ~20% persist longer than 5 years
  - Can be debilitating in refractory cases

Treatment of Urticaria

- Reassurance and realistic expectations
- No need to change diet or environment
- Daily or twice daily 2nd generation antihistamines
- Skip the benadryl!!!!!!
- Higher than standard doses – up to 4x normal dose
- H2 blockers, montelukast not very effective
- Avoid using steroids, but may be necessary during severe exacerbations

Allergy. 2018 Jul;73(7):1393-1414.

International Urticaria Guidelines



Allergy. 2021. PMID: 34536239

Biologics for Urticaria

- Omalizumab approved in 2014
  - Targets IgE → downregulates receptors → dissociates IgE from receptor → suppress mast cell and basophil responsiveness
- Recommended ages ≥ 12 years for urticaria
  - ≥ 6 years for mod-to-severe asthma
  - ≥ 18 years for nasal polyposis
- Recommended for use as 3rd step in therapy AFTER patients fail consistent use of low-moderate then high dose non-sedating antihistamines

J Allergy Clin Immunol Pract 2021;9:1067-78

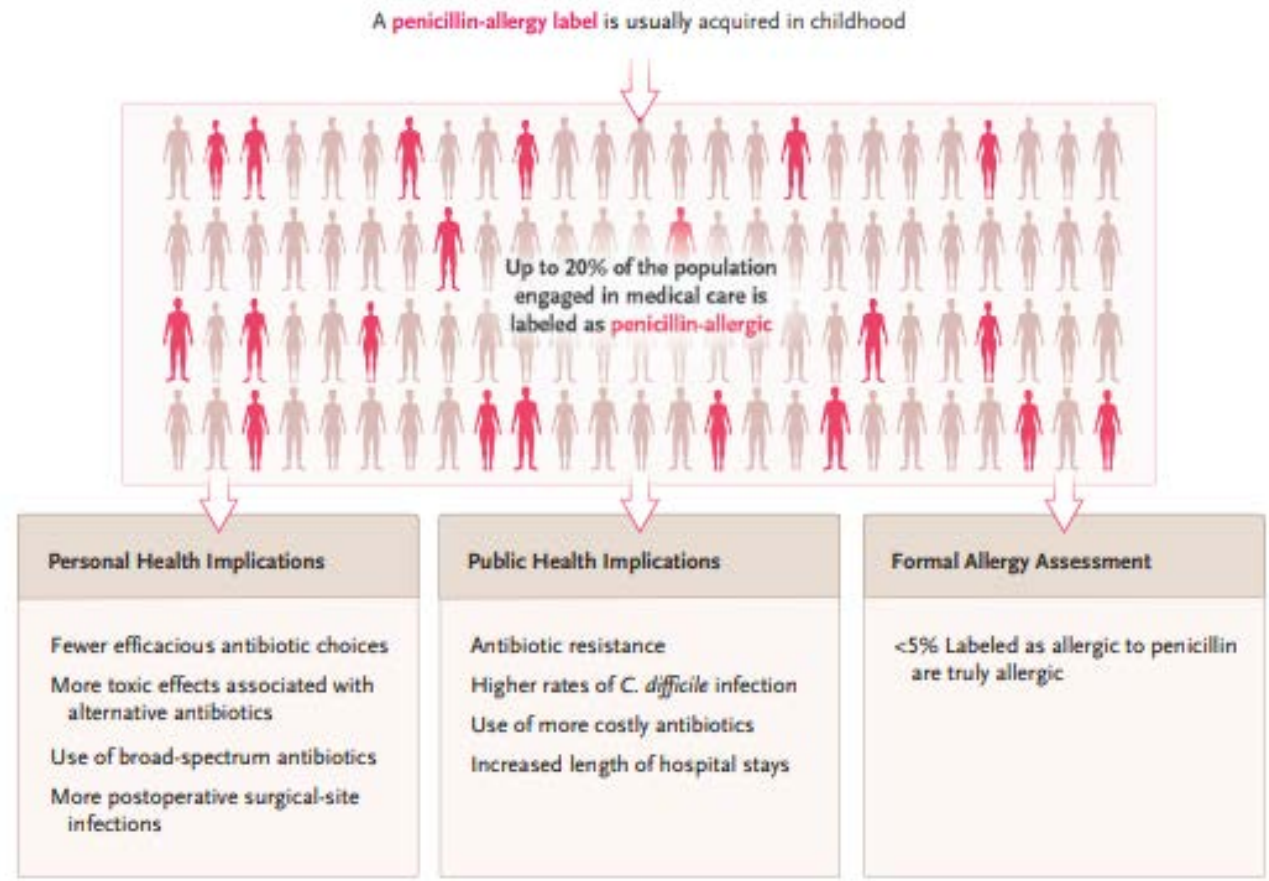

HELP ME HELP YOU

Penicillin Allergy

10% of the general population

reports having a penicillin allergy…

…BUT >95% of those individuals
are NOT actually allergic to penicillin.



Castells M, et al. N Engl J Med 2019;381:2338-51.

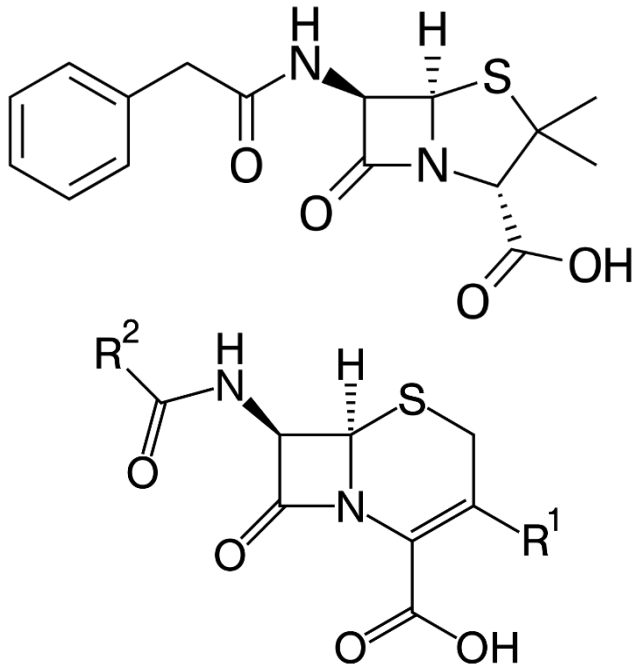
Use the History to Determine if There is LOW Likelihood of Drug Allergy

What Can YOU Do to Clarify a Patient's Drug Allergy Status?

1. Address with every patient at every visit
2. Make it a part of the culture
3. Ask clarifying questions
4. Take the easy 'wins'
5. Refer patients for testing/challenge when appropriate
6. **Remove the label** if they're not allergic!!!

Penicillin Cross Reactivity

- Beta lactam antibiotics all share common beta lactam ring
  - This causes **a minority** of type I allergic reactions
  - Cross reactivity comes from similarity in side chains



Middleton's Allergy: Principles and Practice, 7th Edition. Chapter 68. Elsevier 2012.

Penicillin: Rates of Cross Reactivity

- Penicillin + 1st gen Cephalosporins = 4%
- Penicillin + 2nd, 3rd, 4th gen Cephalosporins = 0%
- Penicillin + Carbapenems = <1%
- Penicillin + Aztreonam = 0%

Frumin J et al. Annal of Pharmacology. 2009;43:304-315.

Penicillin Allergy Evaluation

- We can perform skin testing for penicillin
  - Pre-pen
  - Penicillin G
  - Negative skin prick and intradermal testing associated with 97-99% negative predictive value
- Low cost
  - 2016 US $ = $220/patient

Blumenthal KG, et al. J Allergy Clin Immunol Pract. 2018;6(3):1019-1027.

Amoxicillin Graded Dose Challenge

- 1 step:
  - Amoxicillin 250 mg or 500 mg PO x 1, 60 minutes observation
- 2 step:
  - Amoxicillin 50 mg PO x 1, 30-60 minutes observation
  - Amoxicillin 500 mg PO x 1, 60 minutes observation

Solensky R, et al. Ann Allergy Asthma Immunol. 2010;105(4):259-273.

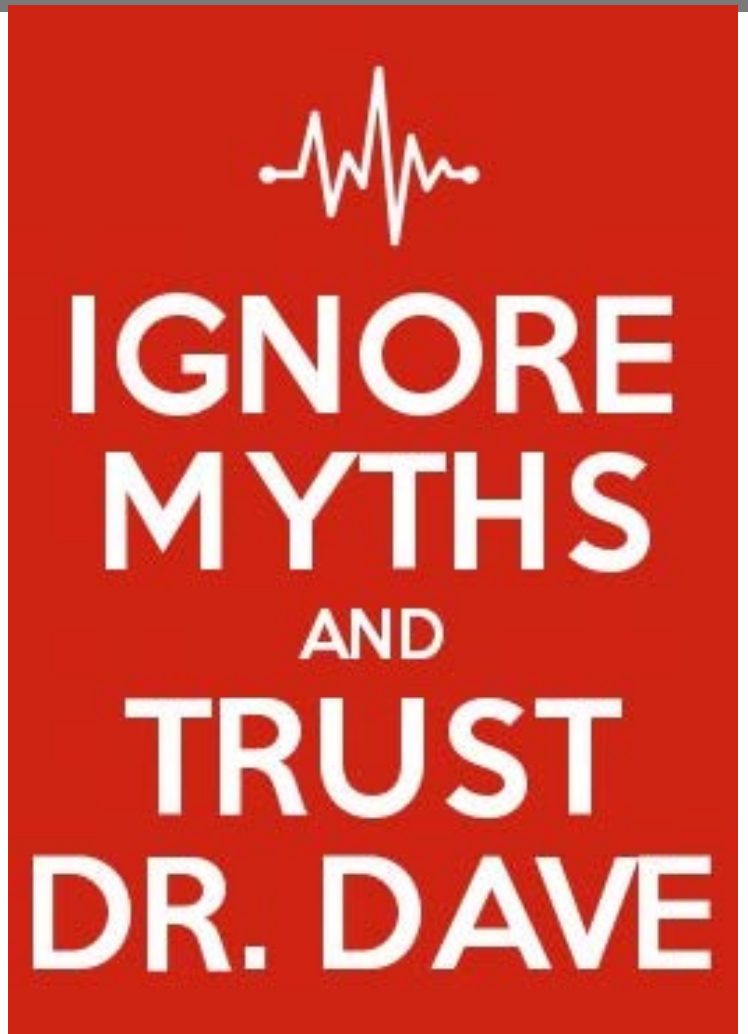
It Starts at Home

Who is “Allowed” to Remove a Listed Drug Allergy from a Chart?

Conclusion

- Misperceptions about allergic conditions are common among patients and medical professionals
- Utilize current guidelines to provide the best evidence based care and answer patient questions
- When in doubt, call your friendly neighborhood allergist!

Thank You

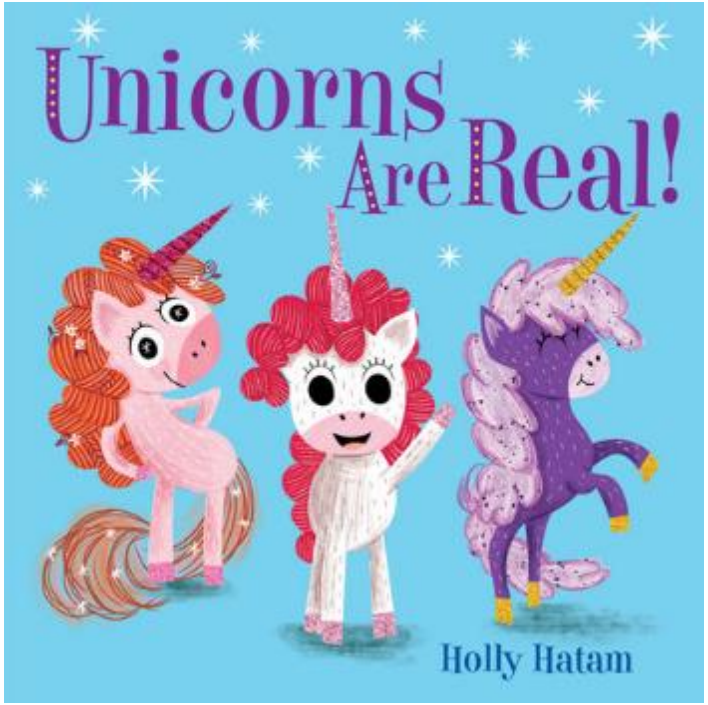


Rapid Fire Myth Busting

700 Children's® – A Blog by Pediatric Experts

The Myth of the Hypoallergenic Dog

Nov 25, 2020



https://www.nationwidechildrens.org/family-resources-education/700childrens/2020/11/myth-hypoallergenic-dog

Milk, mucus and myths

Ian M Balfour-Lynn

CONCLUSIONS

While certainly the texture of milk can make some people feel their mucus and saliva is thicker and harder to swallow, there is no evidence (and indeed evidence to the contrary) that milk leads to excessive mucus secretion. Milk is an important source of calories, calcium and vitamins for children. The milk–mucus myth needs to be rebutted firmly by healthcare workers.

https://adc.bmj.com/content/104/1/91
Balfour-Lynn IM. Arch Dis Child 2019;104:91–93.

Article

November 22, 1995

The Effect of Sugar on Behavior or Cognition in Children

A Meta-analysis

Mark L. Wolraich, MD; David B. Wilson, PhD; J. Wade White, MD

› Author Affiliations

JAMA. 1995;274(20):1617-1621. doi:10.1001/jama.1995.03530200053037

Conclusion. —The meta-analytic synthesis of the studies to date found that sugar does not affect the behavior or cognitive performance of children. The strong belief of parents may be due to expectancy and common association. However, a small effect of sugar or effects on subsets of children cannot be ruled out.(*JAMA*. 1995;274:1617-1621)

Does “Local” Honey Treat Allergies???

- Bees collect large non-wind borne pollen from flowers & plants.
- The small wind-borne pollen that **causes allergy symptoms** comes from trees, grasses, & weeds.
- Honey **does not** contain the same pollen that causes allergy symptoms.
- If someone with pollen allergies ate honey that contained the pollen they are allergic to, **they would have a reaction**, not relief.
- Honey is yummy. It can help soothe sore throats or relieve nighttime cough for some. **It does not treat allergies.**
- Honey should never be given to children < 12 months old due to risk for botulism.

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The Relationship of Radiocontrast, Iodine, and Seafood Allergies: A Medical Myth Exposed

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