

Food Allergy and Anaphylaxis

An Overview of Recent Developments

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Learning Objectives

By the end of this course the learner will be able to:

- ▶ Discuss the definition of anaphylaxis and current anaphylaxis guidelines
- ▶ Evaluate the triggers and clinical manifestations associated with allergic reactions and anaphylaxis in different age groups
- ▶ Identify intervention strategies, treatment protocols, and diverse options for handling allergic reactions and anaphylaxis in both home and acute settings
- ▶ Engage in discussions on the most recent developments in allergy prevention, desensitization, and therapeutic approaches
- ▶ Recognize the significance of emergency management in improving community health outcomes concerning allergic emergencies

Course Overview

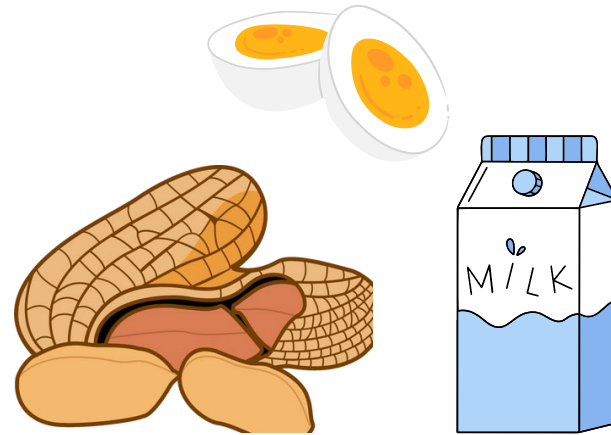
- Food Allergy: Introduction
- Recent Advances in Food Allergy: Prevention
- Recent Advances in Food Allergy: Therapies
- Anaphylaxis: Definitions and Criteria
- Anaphylaxis: Triggers and Clinical Manifestations
- Anaphylaxis: Acute and Long-term Management
- Key Messages on Anaphylaxis Management

Food Allergy

Introduction

Food Allergy Prevalence and Common Triggers

- Currently approximately 8% of children and 10% of adults in the US have a food allergy
- >90% of allergic reactions to food are caused by 9 allergens:
 - Milk
 - Egg
 - Soy
 - Wheat
 - Peanut
 - Tree nuts
 - Sesame
 - Fish
 - Shellfish



Gupta et al, Pediatrics, 2011
Gupta et al, JAMA, 2019

Management of Food Allergy

Traditional approach:

- Complete/strict avoidance of the allergenic food
- Recognizing signs and symptoms of an allergic reaction
- Knowing how to treat allergic reactions
- Education on how to prevent future exposures

Novel management approaches:

- Food immunotherapy
- Biologics

Recent Advances in Food Allergy

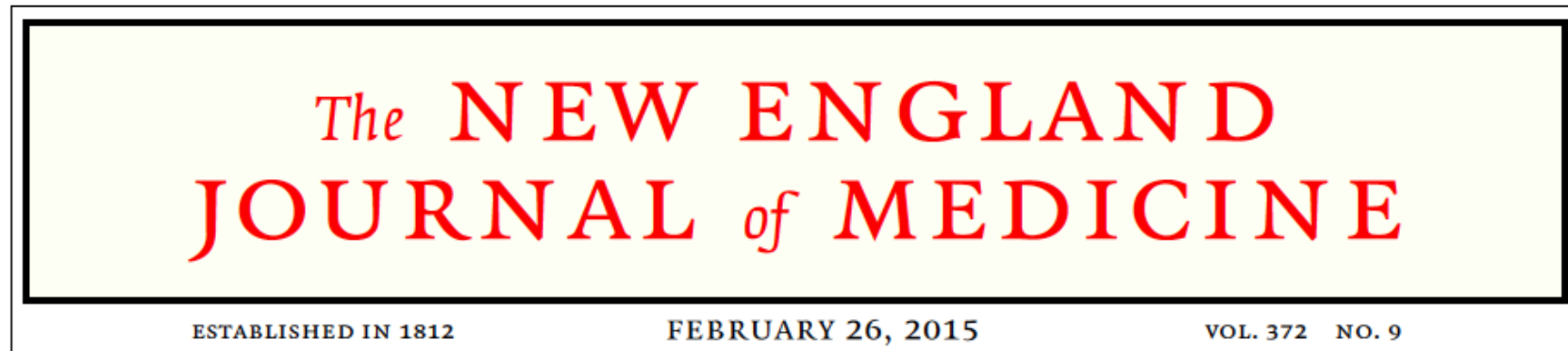
Prevention

Evolution of Recommendations in Timing of Exposure to Allergenic Foods

- 1960s : Introduction by 4 months
- 1970s : Introduction after 4 months
- 1980s-1990s : Delay introduction of allergenic foods
- 2000s-2010s : No good evidence to support delay in allergenic food introduction
- **Currently: Early introduction of allergenic foods is recommended**
(between 4-6 months, when infant developmentally ready)



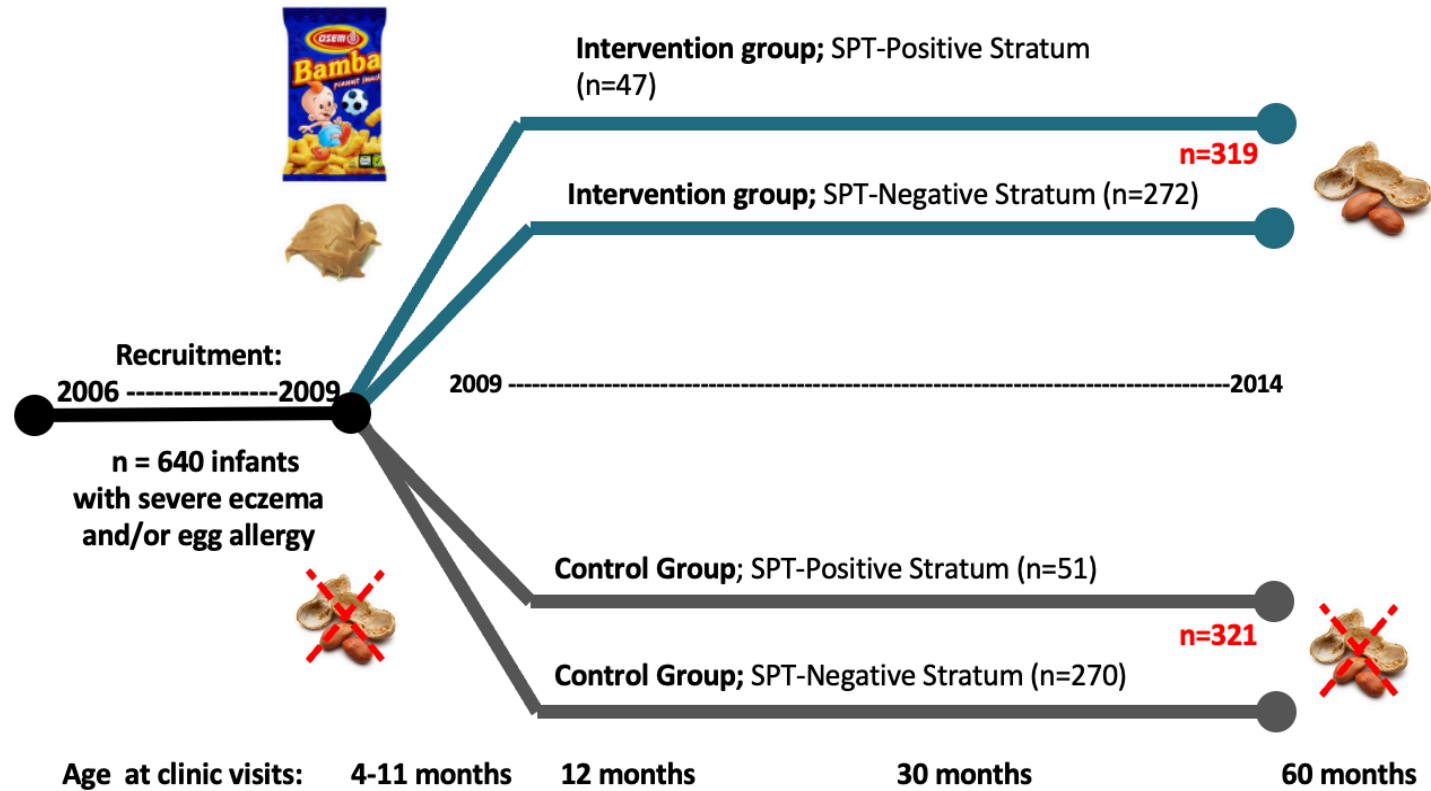
Learning Early About Peanut (LEAP) trial



Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

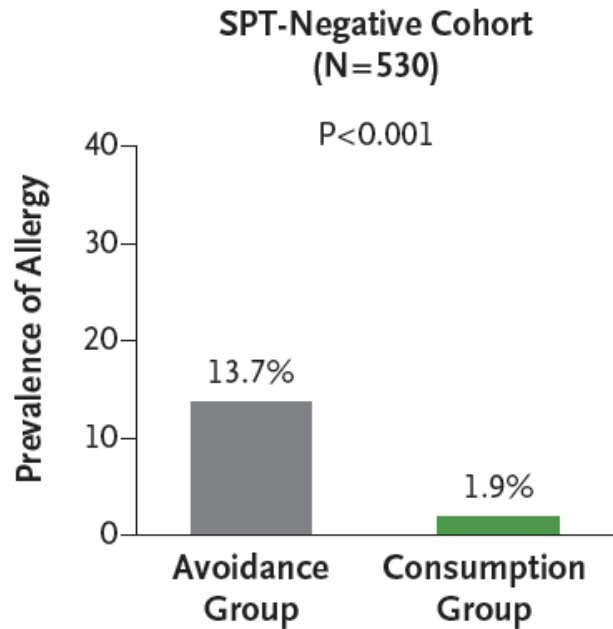
LEAP Study Design



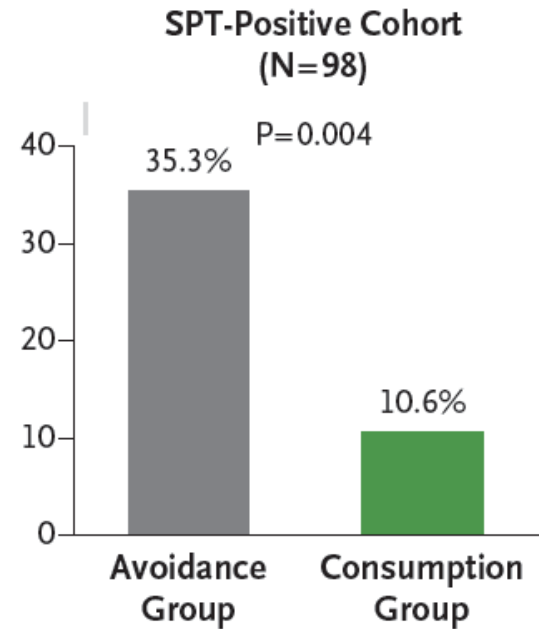
Trial population: High risk cohort = early onset eczema and/or egg allergy

Du Toit et al, NEJM, 2015

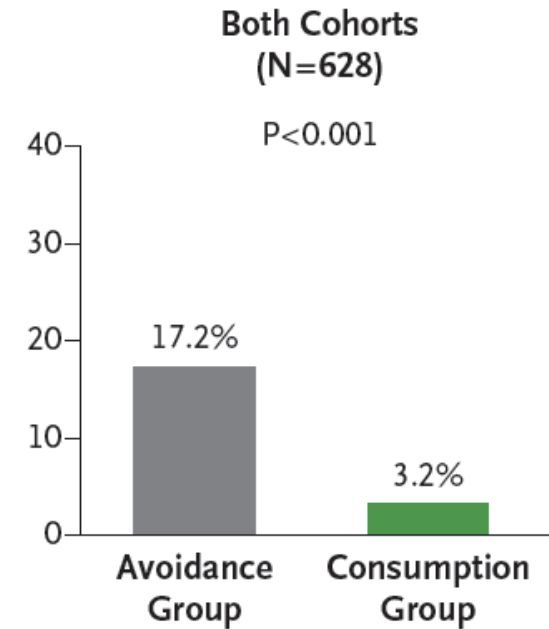
LEAP Results



86% Relative Reduction



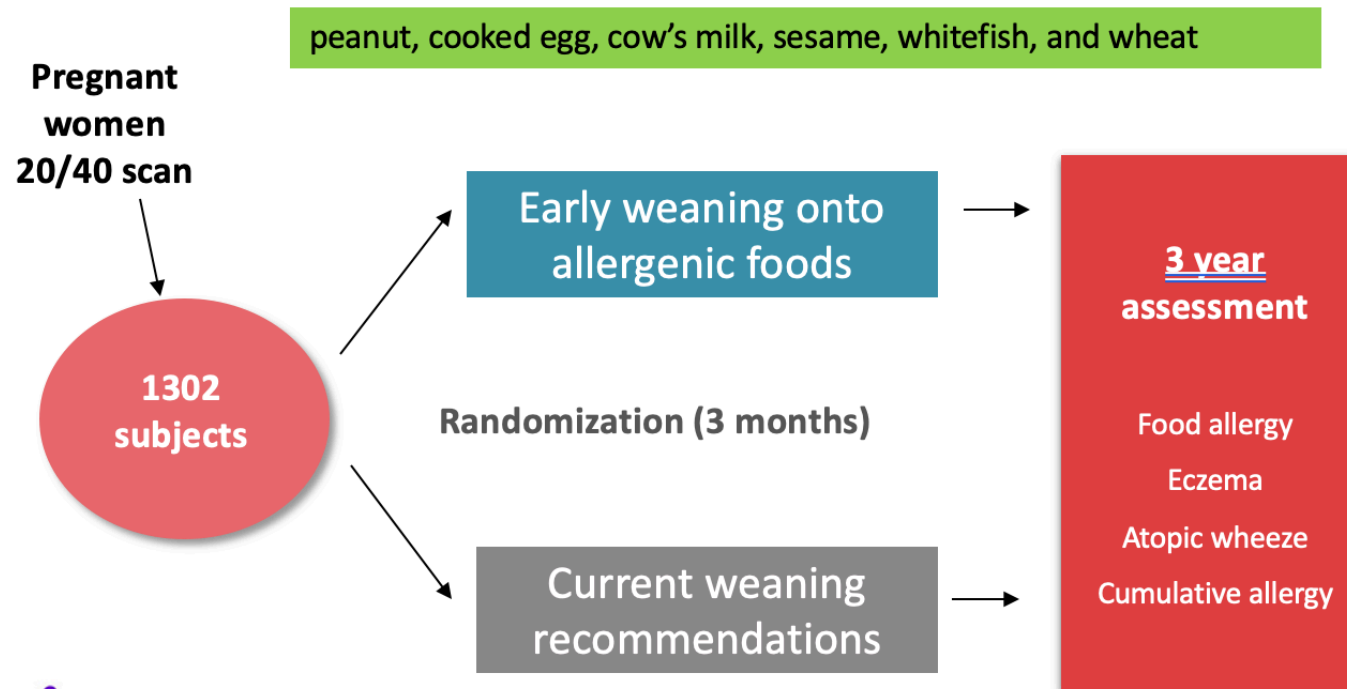
70% Relative Reduction



81% Relative Reduction

EAT Study - Early Weaning Trial

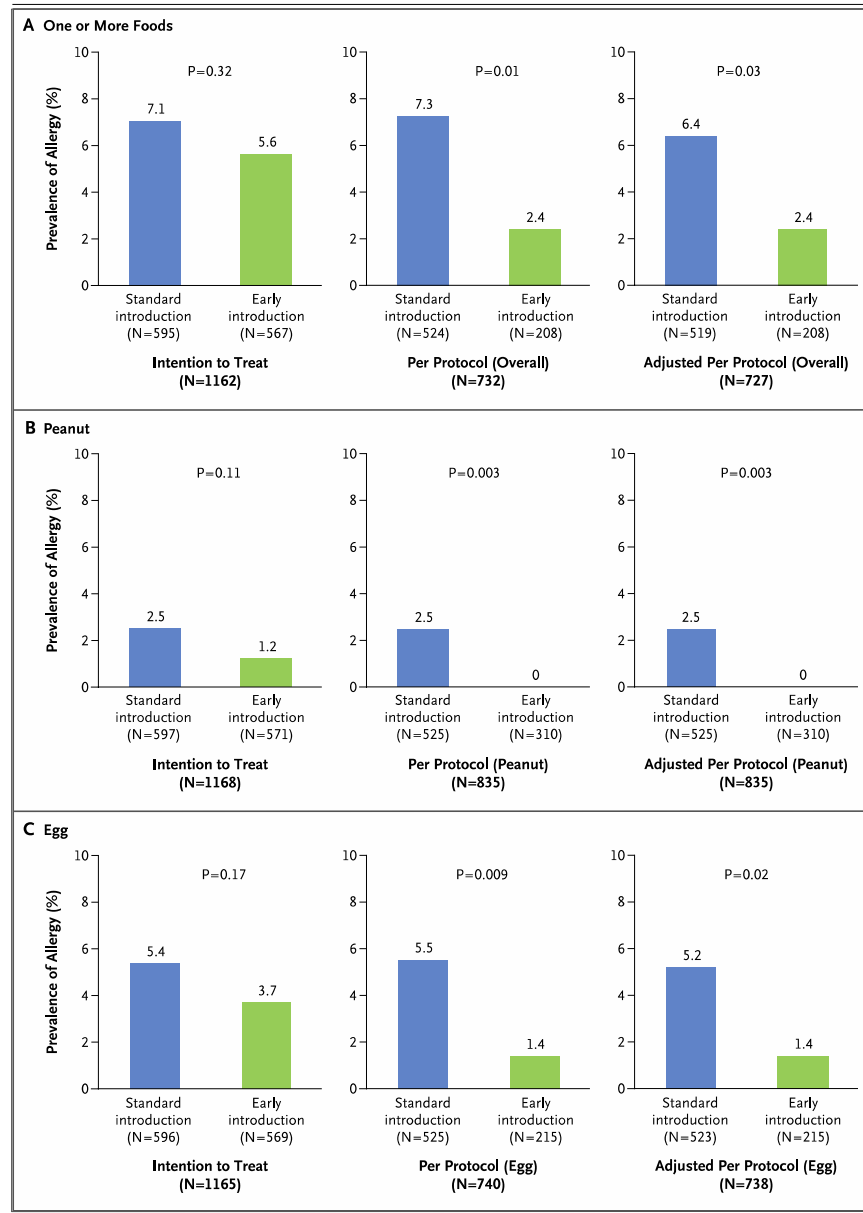
Infants recruited from the general population



EAT Study Results

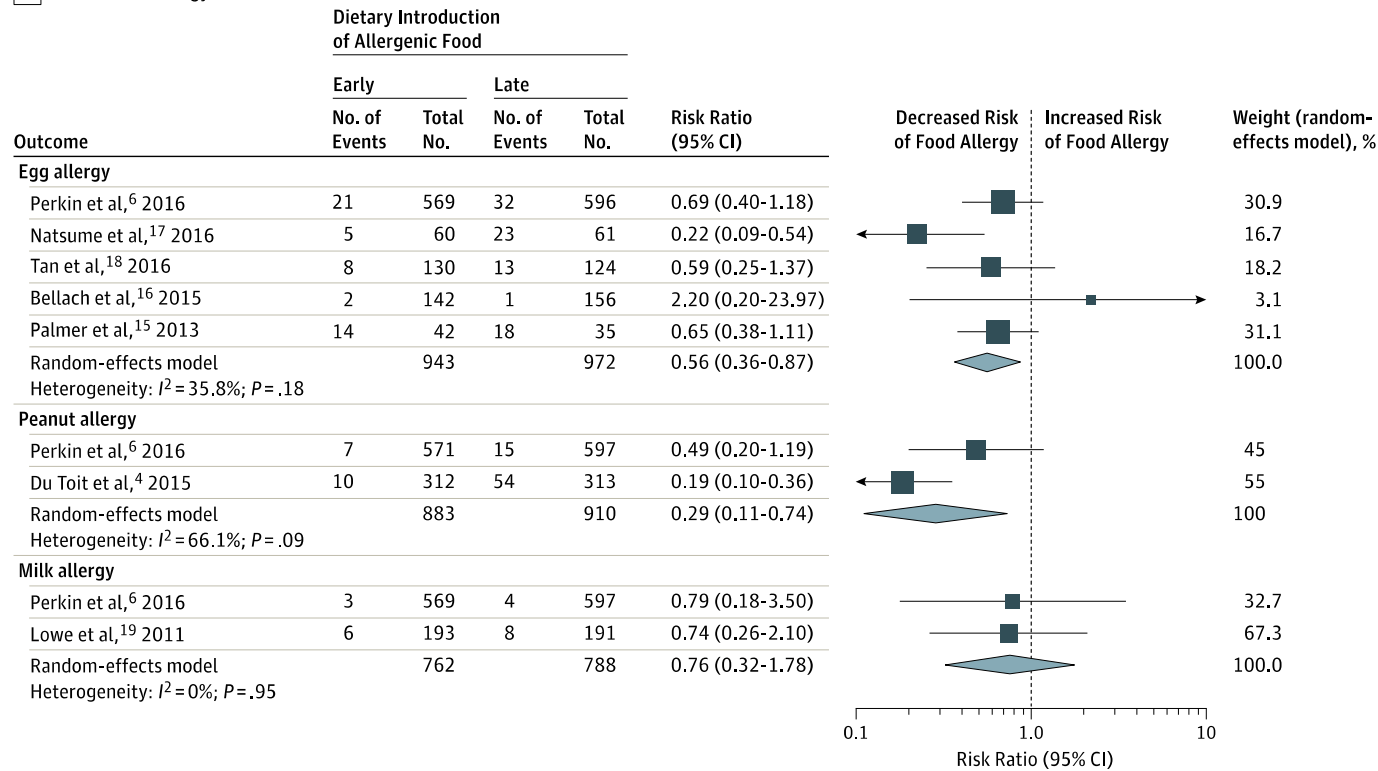
The prevalence of any food allergy was:

- **Significantly lower in the early-introduction group than in the standard-introduction group (2.4% vs. 7.3%, P=0.01)**
- **As was the prevalence of peanut allergy (0% vs. 2.5%, P = 0.003)**
- **And egg allergy (1.4% vs. 5.5%, P = 0.009)**



Can Prevention be Extended to Other Allergenic Foods?

A Risk of food allergy



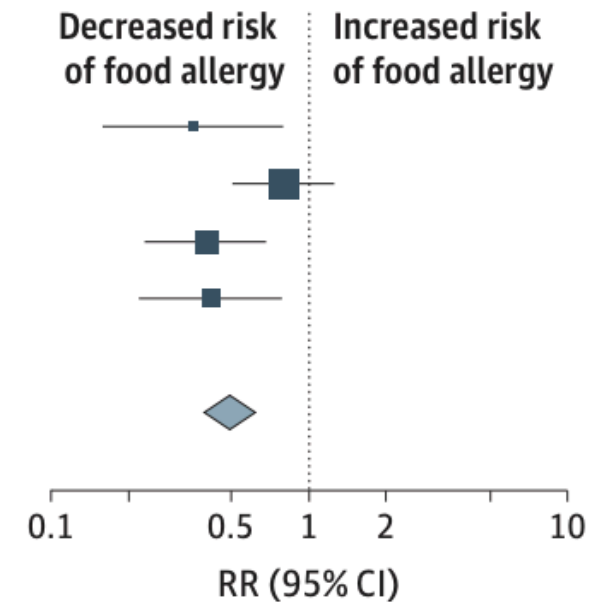
In this systematic review, early egg or peanut introduction to the infant diet was associated with lower risk of developing egg or peanut allergy.

Can Prevention be Extended to Other Allergenic Foods?

A Risk of any food allergy

Study	Earlier introduction	Later introduction	RR (95% CI)
	Events, No./total No.	Events, No./total No.	
Nishimura et al ³⁷	7/82	19/79	0.35 (0.16-0.80)
Perkin et al ⁹	32/567	42/595	0.80 (0.51-1.25)
Quake et al ⁴⁰	17/89	21/44	0.40 (0.24-0.68)
Skjerven et al ¹⁰	13/924	31/915	0.42 (0.22-0.79)
Overall	69/1662	113/1633	0.49 (0.33-0.74)

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 5.86$; $df = 3$ ($P = .12$); $I^2 = 49\%$



Scarpone et al, JAMA, 2023

Early Introduction to Allergenic Foods

- Patient education aims to introduce allergenic foods between 4-6 months of age

Introducing Highly Allergenic Solid Foods

In the past, some experts recommended that dairy products and other highly allergenic foods like eggs, peanuts and fish not be introduced until after an infant's first birthday. More recently, evidence has shown that there is no reason to delay introduction of the highly allergenic foods beyond 4 to 6 months of age. In fact, delaying the introduction of these foods may increase your baby's risk of developing allergies.

Highly allergenic foods can be introduced to your baby between 4 and 6 months of age, just as you would introduce any other solid foods. Highly allergenic foods that you can feed your baby include dairy products such as cheese, yogurt or cow's milk protein formula (not whole cow's milk to drink due to nutrition reasons not related to allergies); egg; soy; wheat; peanut and tree nuts in a form of butter or paste (not whole peanuts or tree nuts due to aspiration risk); and fish and shellfish.

You may want to be cautious when introducing your baby to highly allergenic solid foods. One safe way to do this is to introduce the first tastes at home rather than at day care or a restaurant.

You should introduce highly allergenic foods to your baby after other solid foods have been fed and tolerated, and with the first taste being at home. If no reaction occurs, then you can gradually increase the amount at a rate of one new food every 3 to 5 days.

You should talk to your baby's doctor *before* introducing a highly allergenic food for the following reasons: if your infant has had an allergic reaction to a food or has a known food allergy, or you think your infant has a food allergy; your infant has persistent, moderate to severe atopic dermatitis despite recommended treatment; your infant's sibling has a peanut allergy; or your infant has positive blood tests to food(s).

Your doctor may refer you an allergist/immunologist for evaluation and the development of a personalized plan to introduce solid foods to your infant.



Primary Prevention of Allergic Disease Through Nutritional Interventions. Parent Prevention Guidelines.

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Reference: Fleischer DM, Spergel JM, Assaad AH, Pon-gracic. *J Allergy Clin Immunol: In Practice* 2013;1:29-36.

Preventing Allergies: What You Should Know About Your Baby's Nutrition



Any baby can develop an allergy. It has long been known that allergies tend to run in families. If one or both parents or other siblings have an allergic disease, your infant is more likely to develop an allergic condition, such as food allergy or atopic dermatitis (eczema). Your feeding choices can also make a difference in your baby's likelihood of developing allergies, and your child's nutrition can play a critical role in prevention. *Note: The following recommendations for your baby's nutrition and prevention of allergies are not intended for infants who have already developed an allergic condition.*



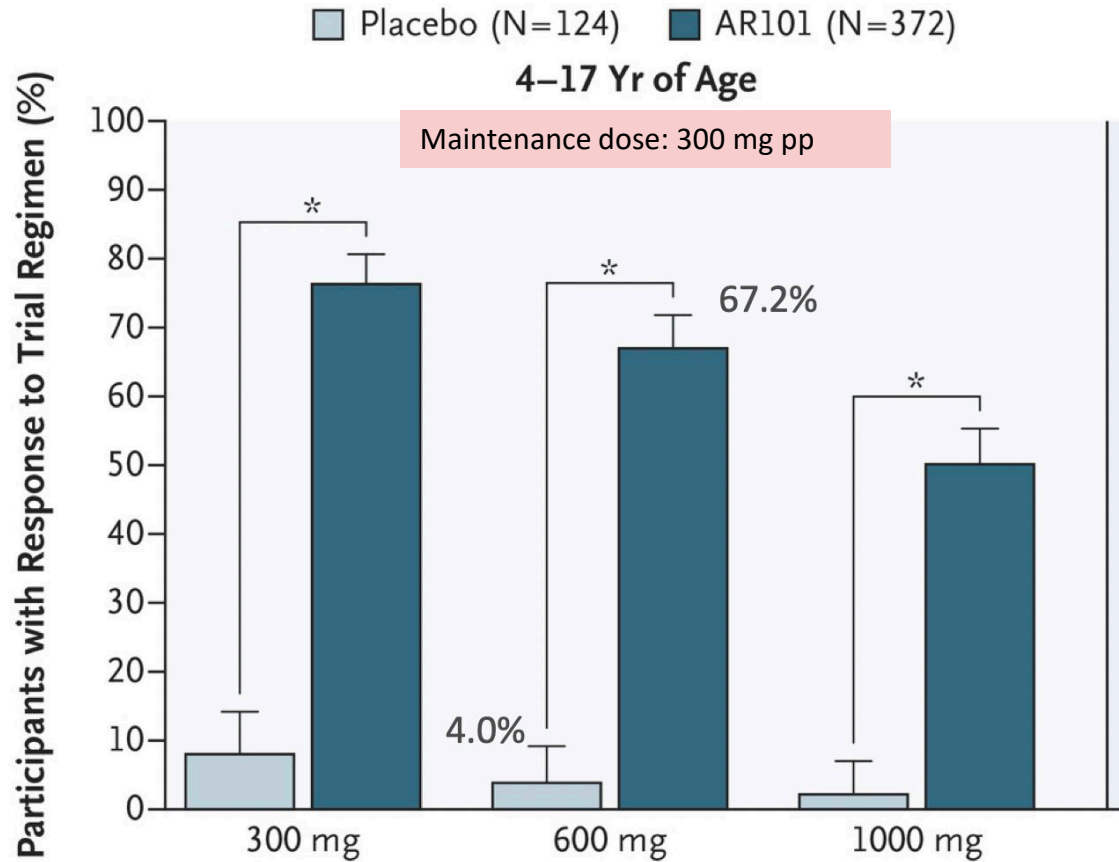


Recent Advances in Food Allergy

Therapies

Peanut

STOP II Trial



PALISADE study – Vickery et al, NEJM, 2018

- 100 peanut-allergic children
- After 6 months of therapy:
 - 40/49 (82%) on maintenance dose 800mg (approx. 5 peanuts)
- OFC to 1400mg (approx. 10 peanuts)
 - 39/49 (80%) underwent, 24/39 (62%) passed

Anagnostou et al, Lancet, 2014

Study 1: IMPACT Trial

Articles

Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study

[Prof Stacie M Jones MD^a](#)  , [Edwin H Kim MD^b](#), [Prof Kari C Nadeau MD^c](#),
[Prof Anna Nowak-Wegrzyn MD^{d,f}](#), [Prof Robert A Wood MD^e](#), [Prof Hugh A Sampson MD^d](#),
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[Sayantani B Sindher MD^c](#), [Mike Kulis PhD^b](#), [Jacqueline Johnson DrPH^g](#), [Katharine Spain MS^g](#),
[Denise C Babineau PhD^g](#), [Hyunsook Chin MPH^g](#), [Joy Laurienzo-Panza RN^h](#), [Rachel Yan MSⁱ](#),
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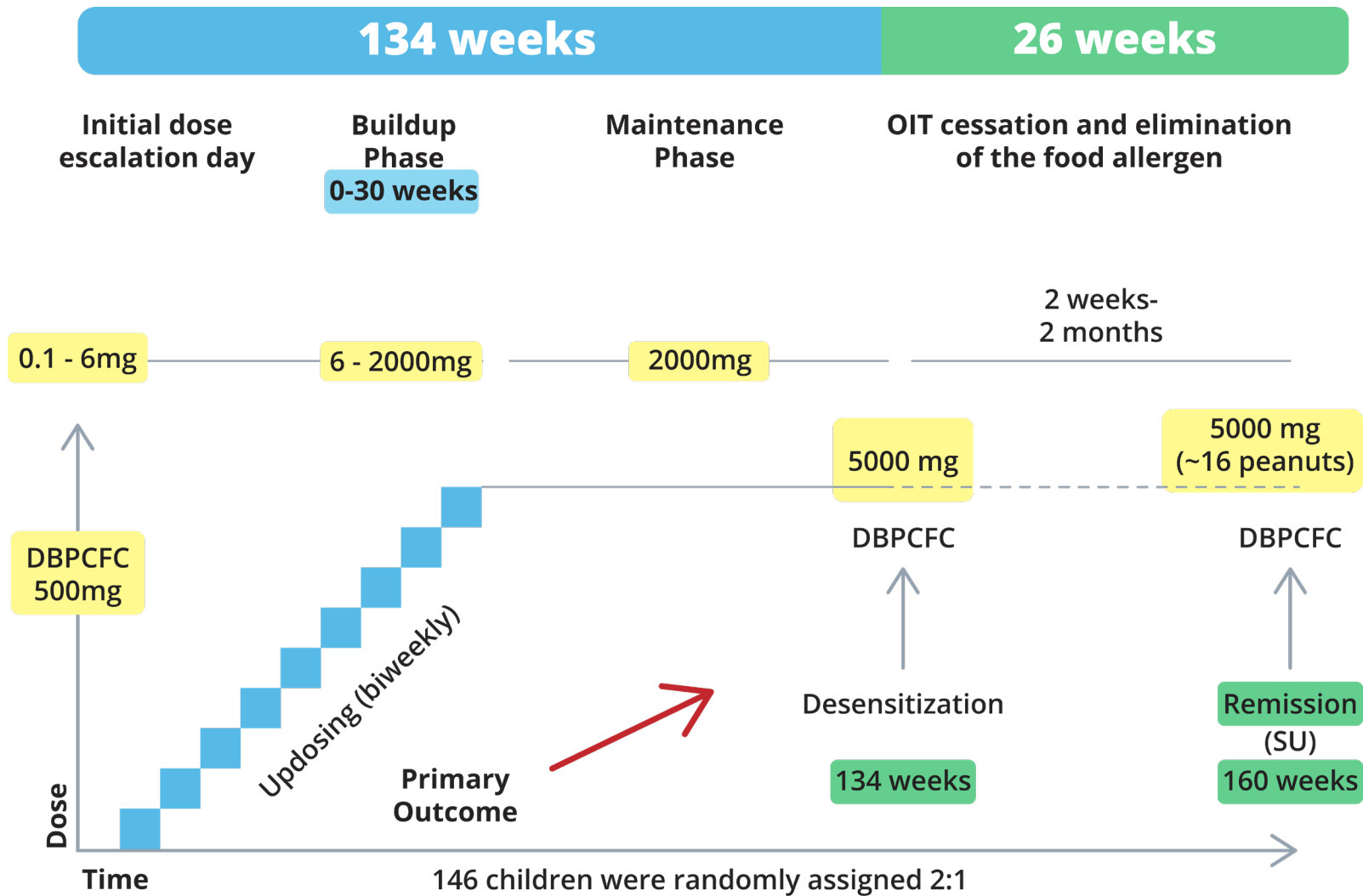
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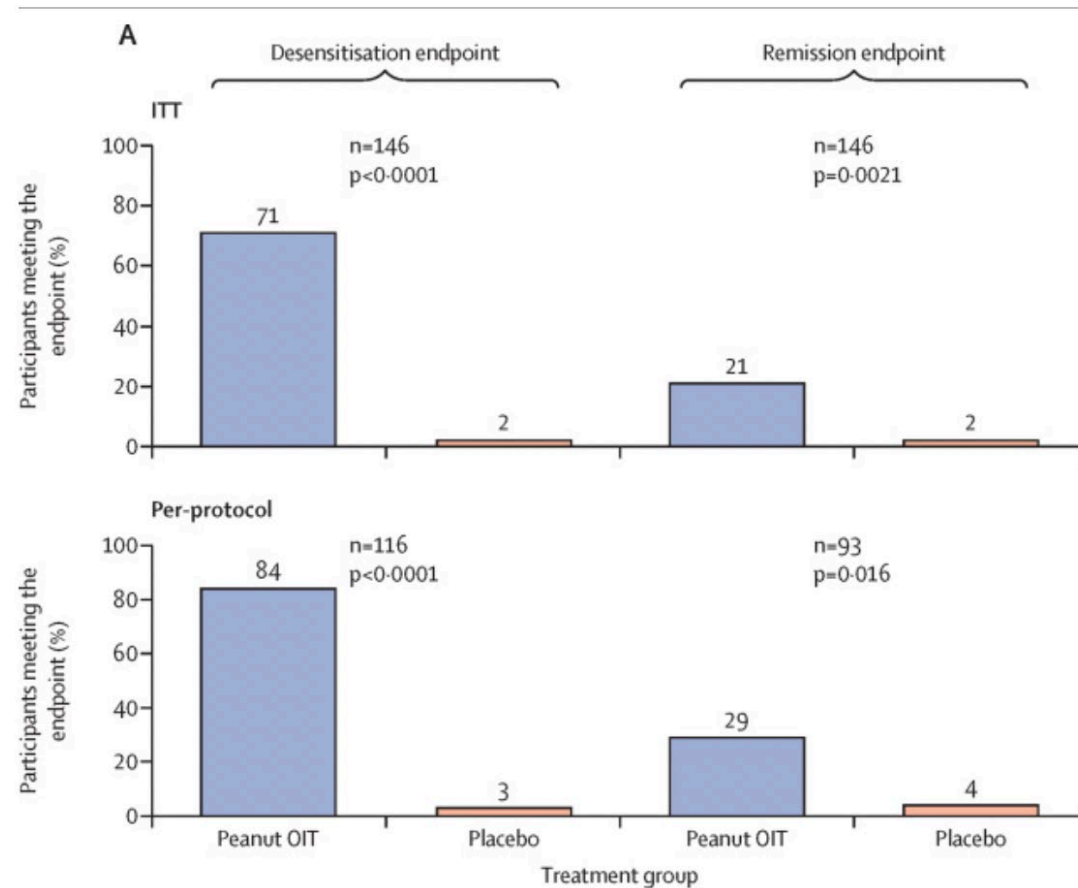
[Prof Stacie M Jones MD^a](#) [👤](#) [✉](#), [Edwin H Kim MD^b](#), [Prof Kari C Nadeau MD^c](#),
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IMPACT Trial: Oral Immunotherapy



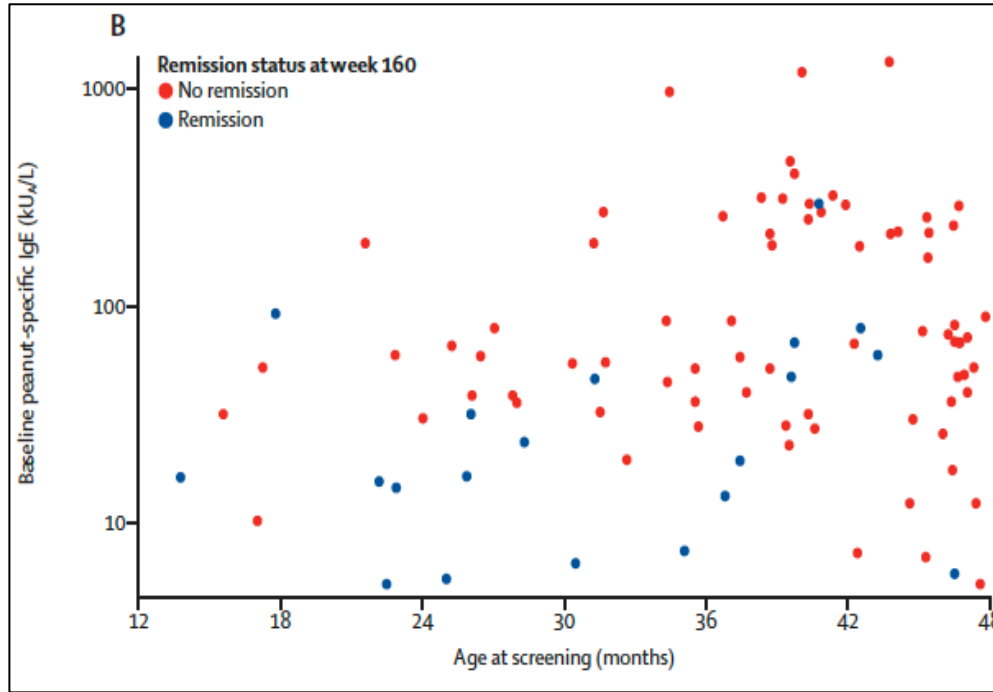
IMPACT Trial Results: Desensitization and Remission

Peanut OIT group vs. Placebo group



IMPACT Trial Results

- INCREASED probability of remission was associated with younger age and lower Specific IgE to peanut



Blue: probability of remission > 50%
 Red: probability of remission < 50%.

Age Group	Peanut OIT
Per protocol sample for remission	N=70
12-23.9 months	5/7 (71)
24-35.9 months	7/20 (25)
36-47.9 months	8/43 (19)

1. For every 10-fold increase in baseline peanut-specific IgE, the odds of remission decreases by 88%
2. For every month increase in age at screening, the odds of remission decreases by 7%

Study 2: OUtMATCH

- Is omalizumab effective and safe as monotherapy in patients with multiple food allergies?
- Primary end point:
 - Ingestion of peanut protein in a single dose of 600 mg or more without dose-limiting symptoms.
- Secondary end points:
 - Consumption of cashew, of milk, and of egg in single doses of at least 1000 mg each without dose-limiting symptoms.

OUTMATCH: Methods

Inclusion:

- 1 to 55 years of age who were allergic to peanuts and at least two other trial-specified foods (cashew, milk, egg, walnut, wheat, and hazelnut) were screened.

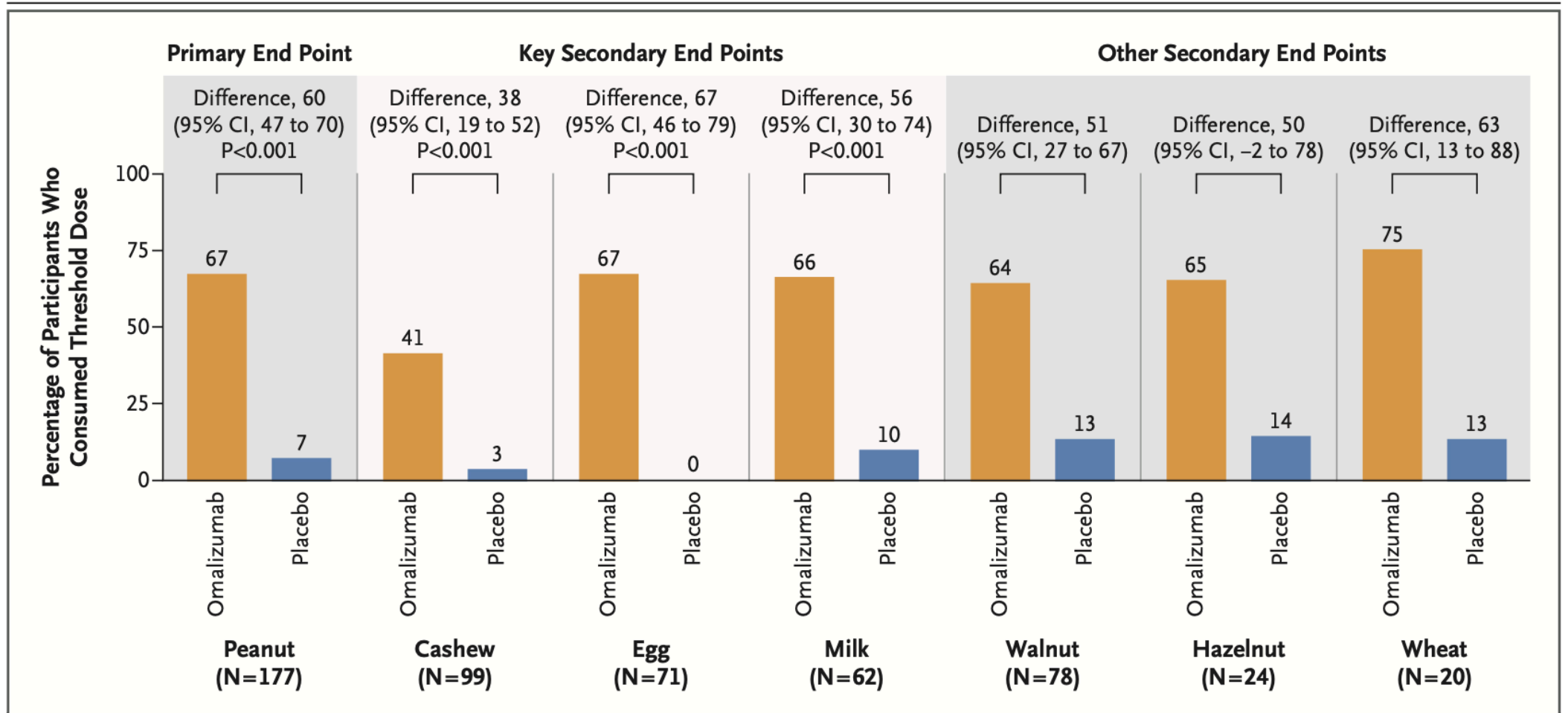
Methods:

- Reaction to a food challenge of 100 mg or less of peanut protein and 300 mg or less of the two other foods.
- Participants were randomly assigned, in a 2:1 ratio, to receive omalizumab or placebo administered subcutaneously (with the dose based on weight and IgE levels) every 2 to 4 weeks for 16 to 20 weeks, after which the challenges were repeated.
- The first 60 participants (59 of whom were children or adolescents) who completed this first stage were enrolled in a 24-week open-label extension.

OUTMATCH: Results

- 462 screened, 180 underwent randomization.
- The analysis population consisted of 177 children and adolescents (1-17 yo) and 3 adult subjects
- 79 of the 118 participants (67%) receiving omalizumab met the primary end-point criteria, as compared with 4 of the 59 participants (7%) receiving placebo (P<0.001).
- Key secondary end points:
 - cashew, 41% vs. 3%
 - milk, 66% vs. 10%
 - egg, 68% vs. 0%(P<0.001 for all comparisons).
- Safety end points did not differ between the groups, aside from more injection-site reactions in the omalizumab group.

OUTMATCH: Results



Wood et al, NEJM, 2024

Epicutaneous food immunotherapy

EPIT

EPIT

- Occlusive patch
- Contains dried allergen in the chamber
- Application of allergen on the skin every 24 hrs
- ‘Targets’ dendritic skin cells

- Single, daily dose, 250 µg Investigational Viaskin™
Peanut patch applied to the child’s back
- Annual exposure amount: ~1/3 of a peanut

PEPITES TRIAL

Analysis	No./Total No. (%)	
	Peanut Patch	Placebo Patch
Intention to treat	84/238 (35.3)	16/118 (13.6)
Full analysis set	84/222 (37.8)	16/109 (14.7)
Per protocol	77/201 (38.3)	14/100 (14.0)
Eliciting dose strata adjusted ^a		
Region adjusted ^a		
Age adjusted ^a		
Multiple imputation ^b	36.4	14.8
Worst case ^c	84/238 (35.3)	25/118 (21.2)

35.3% vs 13.6% after 12 months of therapy
(difference in response rates = 21.7%; p=0.00001; 95% CI = 12.4% - 29.8%).

PEPITES TRIAL

Anaphylaxis rate: 3.4% vs 0.8%

System Organ Class Preferred Term	Peanut Patch, 250 µg (n = 238)			Placebo Patch (n = 118)		
	No. (%)	No. of Events	Exposure-Adjusted Event Rate ^b	No. (%)	No. of Events	Exposure-Adjusted Event Rate ^b
Any TEAE considered related to patch ^c	142 (59.7)	569	2.413	41 (34.7)	157	1.363
General disorders and administration site conditions	137 (57.6)	510	2.163	32 (27.1)	138	1.198
Administration site conditions	137 (57.6)	508	2.154	32 (27.1)	138	1.198
Pruritus ^d	82 (34.5)	152	0.645	14 (11.9)	30	0.26
Erythema ^d	67 (28.2)	118	0.5	20 (16.9)	54	0.469
Swelling ^d	38 (16)	86	0.365	2 (1.7)	18	0.156
Eczema	25 (10.5)	29	0.123	6 (5.1)	18	0.156
Application site reaction	21 (8.8)	29	0.123	2 (1.7)	5	0.043
Urticaria	15 (6.3)	23	0.098	0 (0)	0	0
Dermatitis	10 (4.2)	27	0.115	0 (0)	0	0
Irritation	8 (3.4)	10	0.042	2 (1.7)	3	0.026
Rash	6 (2.5)	6	0.025	0 (0)	0	0
Edema	5 (2.1)	7	0.03	1 (0.8)	5	0.043

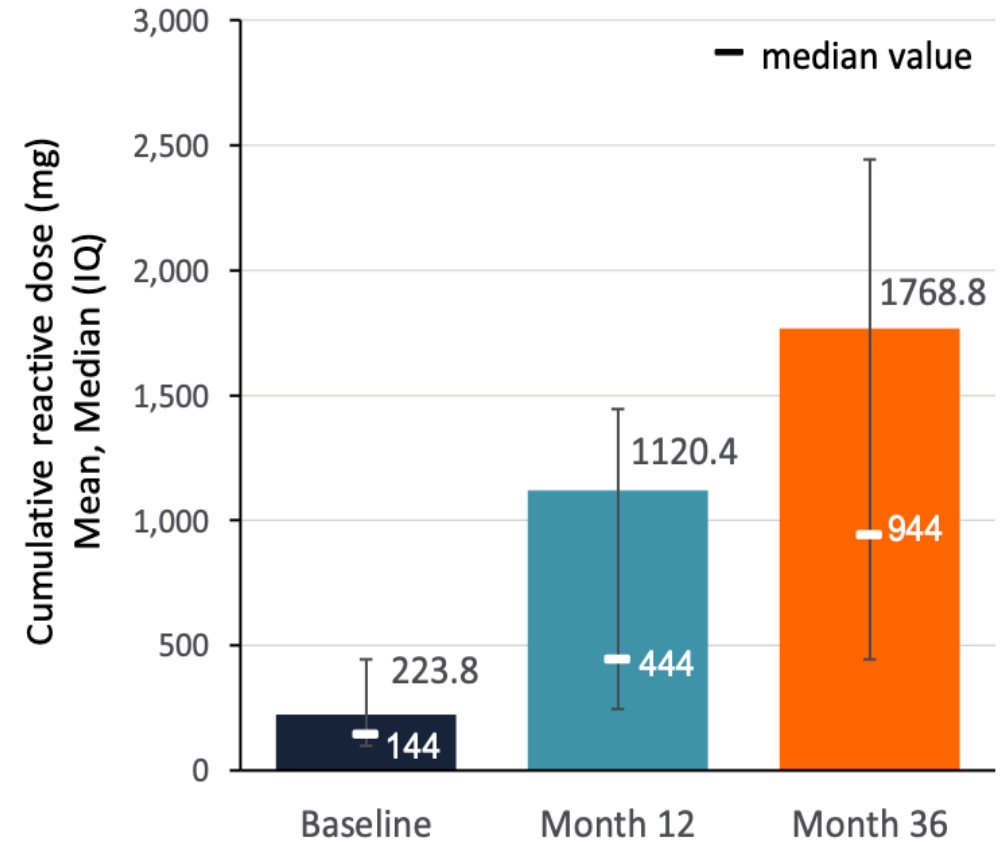
PEOPLE TRIAL

3-year interim analysis (141 subjects):

At month 36:

- **75.9%** demonstrated increased eliciting dose compared with baseline
- **67% of the most sensitive patients** (ED \leq 10 mg at baseline) reached an **ED \geq 300 mg**
- **51.8%** of subjects reached an eliciting dose of \geq 1000 mg, versus 40.4% at month 12;
- **13.5%** tolerated full challenge dose of **5444 mg**.

Median cumulative reactive dose increased from **144** to **944 mg**.



Special Consideration

Individuals who are concerned about food allergies or experience an allergic reaction to food should be referred to an allergist.

Anaphylaxis Definitions

2020-2023

Anaphylaxis Definitions

Source	Date	Definition	Reference
WAO	2019 2020	Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation and may occur without typical skin features or circulatory shock being present.	Turner et al 2019 and Cardona et al 2020
EAACI	2020	Anaphylaxis is a severe allergic reaction. [Defined in the context of when to use epinephrine autoinjectors]	Kraft et al 2020

Anaphylaxis Definitions

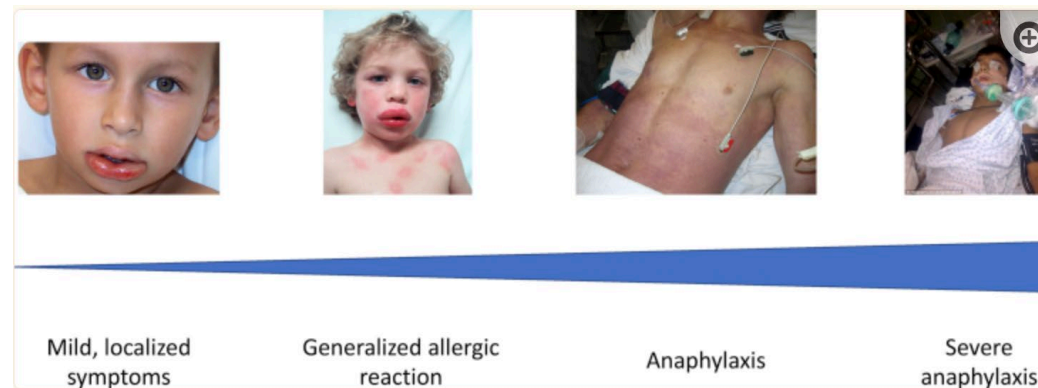
Source	Date	Definition	Reference
ASCIA	2021	Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), plus involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms ; or. any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.	ASCIA 2021

Anaphylaxis Definitions

Source	Date	Definition	Reference
Brighton Collaboration Working Group	2022	Anaphylaxis presents acutely and leads to a marked change in an individual's previous stable condition and is characterized by the following: Rapid progression of symptoms and signs which typically affects multiple body systems (skin/mucosa / respiratory / cardiovascular / gastrointestinal) at the same time or sequentially but occurring over a short period of time (within 1 hour of onset of the first symptoms or signs).	Gold et al, 2022
US Anaphylaxis Practice Parameter update (open for comments)	2023	Anaphylaxis is a systemic, usually multi-organ, potentially life-threatening syndrome.	Golden et al, 2023

Common Terms Used Across Guidelines and Literature

- Generalized
 - Systemic
 - Serious
 - Severe
 - Rapid onset/rapidly evolving
 - Potentially life-threatening
- May occur without typical skin/mucosal symptoms
 - Usually/typically multi-organ/multi-system
 - 2+ organ systems OR *single* organ system with major involvement that causes more physiological disruption than others (predominantly cardiovascular or respiratory)



Turner, World Allergy Organ J., 2019

Anaphylaxis Criteria

Examining Different Criteria for the Diagnosis of Anaphylaxis

1. National Institute of Allergy and Infectious Diseases (NIAID) criteria 2006
2. World Allergy Organization (WAO) criteria 2020
3. Brighton Collaboration criteria (2007 & 2022) – specific for vaccine-associated anaphylaxis

National Institute of Allergy and Infectious Diseases Criteria

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

- 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips- tongue-uvula)**

And at least one of the following:

- a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)**
- b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, dizziness, syncope, incontinence)**

Sampson et al, J Allergy Clin Immunol. 2006

National Institute of Allergy and Infectious Diseases Criteria

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 (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
- b.** Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- c.** Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
- d.** Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

Sampson et al, J Allergy Clin Immunol. 2006

National Institute of Allergy and Infectious Diseases Criteria

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

- a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
- b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Patient Case

- 40 year old man
- Stung by a bee at a picnic
- Within 5 minutes: developed generalized hives, felt dizzy, became short of breath and wheezy
- **Is this anaphylaxis? Why?**



Sussman, CMAJ, 2016

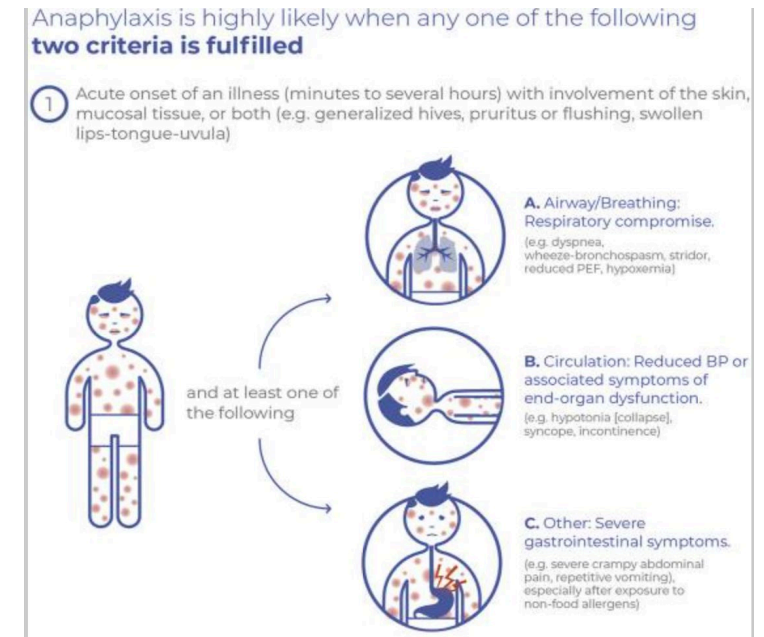
WAO 2020

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:

- 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg generalized hives, pruritus or flushing, swollen lips-tongue-uvula)**

AND AT LEAST ONE OF THE FOLLOWING:

- a. Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- b. Reduced BP or associated symptoms of end-organ dysfunction (eg hypotonia [collapse], syncope, incontinence)
- c. Severe gastrointestinal symptoms (eg severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens

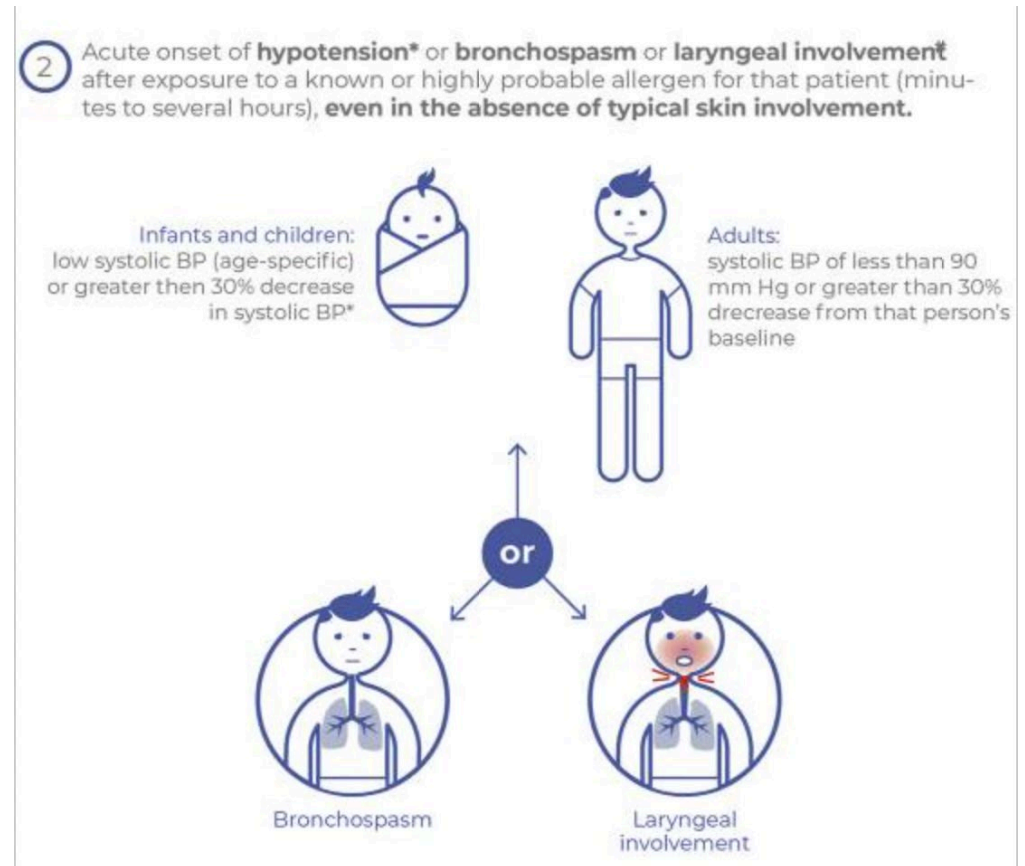


Cardona et al, WAO, 2020

WAO 2020

2. Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement.

Note: This is excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause “inhalational” reaction in the absence of ingestion.



Cardona et al, WAO, 2020

Patient Case

- **Part 1**

- 2 year old girl
- Ate a small piece of walnut pie
- Within 5 minutes complained of tongue itching, developed lip swelling
- **Is this anaphylaxis? Why?**

- **Part 2**

- Within 10 minutes developed generalized hives & wheeze
- Vomited three times
- **Is this anaphylaxis? Why?**

Differential Diagnosis of Anaphylaxis

Skin or mucosal

- Chronic remittent or physical urticaria and angioedema
- Pollen food allergy syndrome (just oral symptoms)

Respiratory diseases

- Acute laryngotracheitis
- Laryngeal, tracheal or bronchial obstruction (eg foreign substances, intermittent laryngeal obstruction or vocal cord dysfunction)
- Status asthmaticus (without involvement of other organs)

Cardiovascular diseases

- Vasovagal syncope
- Pulmonary embolism
- Myocardial infarction
- Cardiac arrhythmias
- Cardiogenic shock

Fig. 1: Typical presentation of urticaria.



Kolchir, Nature Reviews Disease Primers, 2022

Muraro et al, Allergy, 2022

Differential Diagnosis of Anaphylaxis

Pharmacological or toxic reactions

- Ethanol
- Histamine, eg scombroid fish poisoning
- Opiates

Neuropsychiatric diseases

- Hyperventilation syndrome
- Anxiety and panic disorder
- Somatoform disorder (eg psychogenic dyspnoea)
- Dissociative disorder and conversion (eg globus hystericus)
- Epilepsy
- Cerebrovascular event
- Psychoses
- Factitious disorder

Endocrinological Diseases

- Hypoglycemia
- Thyrotoxic crisis
- Carcinoid syndrome
- Vasointestinal polypeptide tumours
- Pheochromocytoma

Triggers and Clinical Manifestations of Anaphylaxis

Common Triggers

- Foods
- Drugs
- Insect venom
- Idiopathic/unknown cause
- Food-induced anaphylaxis more common in children
- Drug- and venom-induced anaphylaxis more common in adults



Cardona et al, WAO, 2020

Examples of Anaphylaxis Elicitors Worldwide

FOOD:

Cow's milk, hen's egg, peanut, tree nuts, seeds, wheat, fish, shellfish

INSECT VENOM:

Bee, wasp, fire ant

DRUGS:

Antibiotics, analgesics, chemotherapeutics, biologics

ADAPTED FROM: Cardona et al, WAO, 2020

PATIENT CASE

- 6-month-old infant
- Receiving peanut butter on toast for the first time
- Ate approximately a teaspoonful
- Within 5 minutes parents notice: fussiness, facial erythema, widespread hives and multiple episodes of severe, persistent vomiting.
- **Is this anaphylaxis? Why?**



Allen, DermNet, 2019



Hassan, Case Rep Pediatr., 2016

Why Do We Need to Discuss Infant & Toddler Anaphylaxis?

- Recognizing anaphylaxis in infants & toddlers can be challenging for physicians and caregivers.
- Infants are non-verbal, symptoms difficult to interpret, symptoms common in healthy infants or non-specific for anaphylaxis
- Strict avoidance of triggers (usually food) difficult to achieve
- New prevention guidelines with earlier food introduction
- Novel therapies such as oral immunotherapy

Anaphylaxis: Unique aspects of clinical diagnosis and management in infants (birth to age 2 years)

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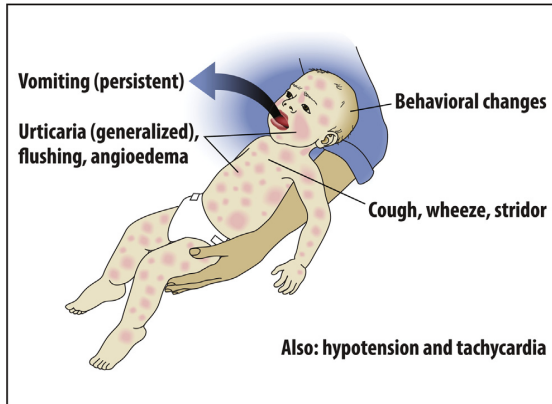
Special Article

Guiding Principles for the Recognition, Diagnosis, and Management of Infants with Anaphylaxis: An Expert Panel Consensus



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Anaphylaxis in infants: Potential symptoms and signs



AAAAI Work Group Report

Conducting an Oral Food Challenge to Peanut in an Infant



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INFANT/TODDLER ANAPHYLAXIS EMERGENCY ACTION PLAN

This plan is intended for infants and toddler (0-3 years of age) with a diagnosis of anaphylaxis.



PATIENT NAME _____ DOB _____ AGE _____ DATE OF PLAN _____
 HEIGHT _____ inches (____ cm) WEIGHT _____ lbs. (____ kg)

CHILD DEVELOPMENT: APPROPRIATE FOR AGE DELAYED VERBAL YES NO

KNOWN ALLERGENS: Tree nut, specify _____
 Peanuts, specify _____ Fish/shellfish, specify _____
 Milk, specify _____ Grains, specify _____
 Egg, specify _____ Other _____

PREVIOUS ALLERGIC SYMPTOMS TO KNOWN ALLERGENS:
 Skin _____ Breathing _____
 Stomach/intestinal _____ Tongue/throat _____
 Heart _____ Other _____

IF THE CHILD SHOWS ANY OF THE FOLLOWING SYMPTOMS WITHIN MINUTES TO A FEW HOURS AFTER EXPOSURE TO A KNOWN ALLERGEN, GIVE EPINEPHRINE.

- Skin: raised red rash in more than one small area; swelling of the lips/mouth; blue skin around the mouth/lips
- Breathing: difficulty breathing (wheezing, coughing, gasping, turning blue)
- Stomach/intestinal: repeat vomiting; persistent diarrhea
- Tongue/throat: pushing out the tongue; drooling, scratching at mouth
- Heart: unconscious, weak pulse, sweating, pale color, fast heart beat (greater than 120-130 beats per minute)
- Symptoms that can look like normal behaviors but may not be if exposed to known allergen: behavioral changes such as fussiness, clinginess, sleepiness and unable to wake

HOW TO ADMINISTER EPINEPHRINE TO THE INFANT/TODDLER:

1. Place the child in a secure position (reverse hug in lap if possible)
2. Hold the child's legs from moving before to using their prescribed epinephrine auto-injector
3. Use the child's prescribed epinephrine auto-injector in the outer thigh muscle
4. Assess child, and if necessary, call 911 (discuss when to call 911 with your child's allergist)
5. Contact others in the order listed here:
 Parent's # _____; Pediatrician's # _____; Allergist's # _____

PRESCRIBED MEDICATIONS*

0.1 mg epinephrine auto-injector[†] Auvi-q 0.1 mg
 0.15 mg epinephrine auto-injector[†] Generic 0.15 mg EpiPen, Jr 0.15 mg Auvi-q 0.15 mg
 Other medications to administer: _____
 Instructions: _____

*For anaphylaxis, epinephrine is always the first choice of therapy. [†]Consider alternative forms of epinephrine for children weighing less than 16.5 lbs., since this device is indicated for infants and toddlers 16.5 lbs. to 33 lbs. [‡]If the child weighs more than 33 lbs., consider using a 0.15-mg epinephrine auto-injector.

PARENT NAMES/NUMBERS _____
 PEDIATRICIAN NAME/NUMBER _____
 ALLERGIST NAME/NUMBER _____

FIGURE E1. Sample infant anaphylaxis action plan.

Study 1: Infantile Anaphylaxis in Korea

- The true prevalence of infant & toddler anaphylaxis is unknown
- Infants represent 3-22% of anaphylaxis cases presenting to the ED
- An increase in infant anaphylaxis was reported over a 5-year period (2009-2013) in a Korean study with case numbers nearly quadrupling.

Study 2: Prehospital Treatment and Emergency Department Outcomes in Children

- Retrospective case series from review of ED records (01/2016 – 12/ 2018)
- Study population:
 - 1,518 children younger than 5 years presenting to the ED with food-induced allergic reactions
 - Infants <12 months: 448 (30%)
 - Toddlers 12 months to <2 y: 494 (32%)
 - Preschoolers 2 y to <5 y : 576 (38%)

Study 2: Prehospital Treatment and Emergency Department Outcomes in Children

- Common symptoms:
 - Mucocutaneous 99% , GI 32%, Respiratory 7%, CV 0.9% (Hypotension 0.2%)
 - Mucocutaneous symptoms more common in infants and toddlers compared with preschoolers (P < .001)
- Common triggers:
- Egg 34%, Peanut 22%, Cow's milk 16%,
 - Tree nuts 8%, Seeds 4%, Fish 3%
- Hen's egg (P < .001) and cow's milk (P 1/4 .02) more likely in infants compared with other age groups



Mundasad, BBC, 2014

Study 2: Prehospital Treatment and Emergency Department Outcomes in Children

- Presented with Anaphylaxis:
 - 32% of infants, 30% of toddlers, 42% of preschoolers
- Treated with epi:
 - In the ED: Infants 10% Toddlers 12% Preschoolers 16%
 - Prehospital: Infants 4% Toddlers 12% Preschoolers 13%

Key Messages for Infant & Toddler Anaphylaxis

From Infant Studies:

- Prevalence of preschool anaphylaxis varies between 3-22% of ED admissions.
- Most common trigger is food, with egg & cow's milk being the most frequent.
- Cutaneous, respiratory and gastrointestinal symptoms are the most frequent. Cardiovascular symptoms are rare.
- Most episodes are not severe.
- Epinephrine is under-prescribed and under-used in this age group.

Key Messages for Infant & Toddler Anaphylaxis

From the US 2023 anaphylaxis practice parameter

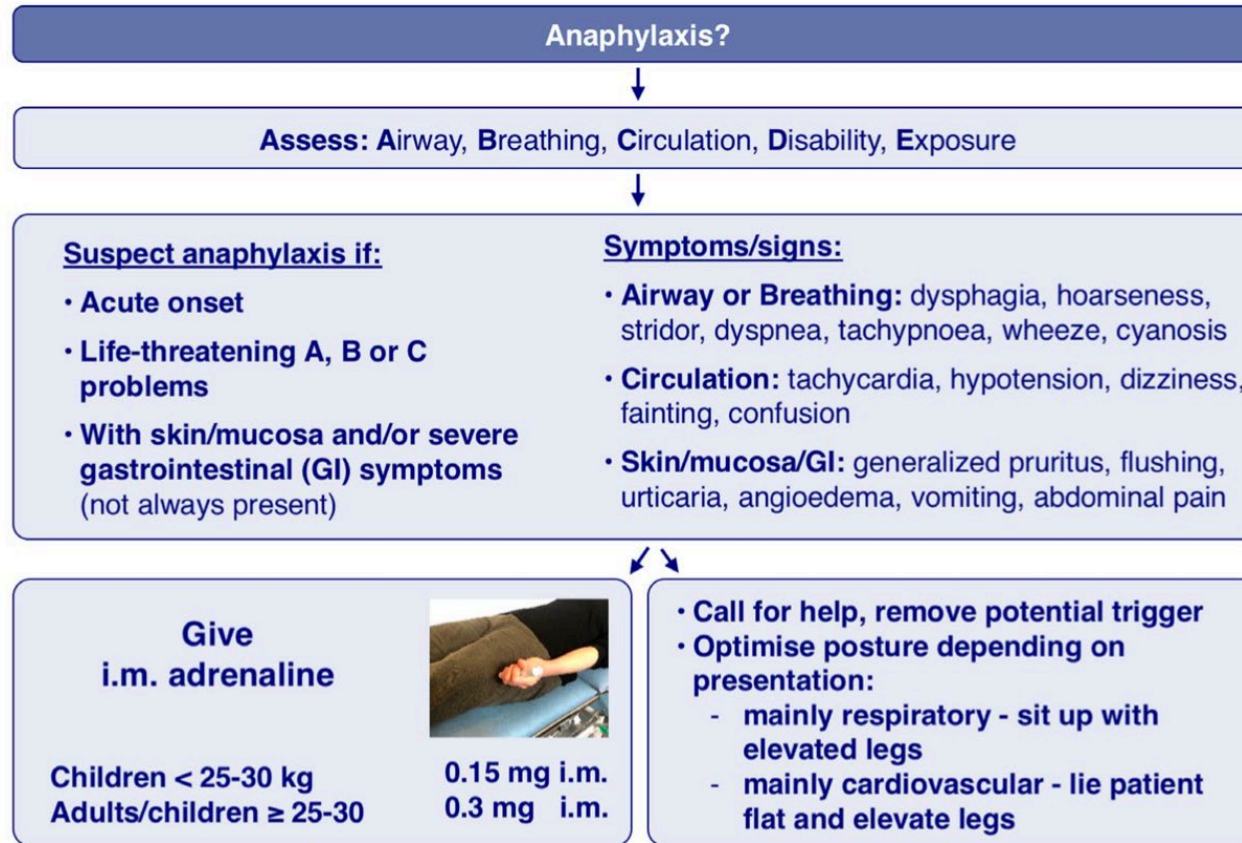
- We suggest clinicians be aware that anaphylaxis is unlikely to be the initial reaction to a food or medication upon first exposure.
- We suggest clinicians be aware that parents of infants and toddlers may report age-specific symptoms that are less often reported by older children and adults.
- We suggest clinicians prescribe either the 0.1 mg or the 0.15 mg epinephrine auto-injector (EAI) dose for infants/toddlers weighing less than 15 kg.

Golden et al, Annals of Allergy, Asthma Immunol., 2024

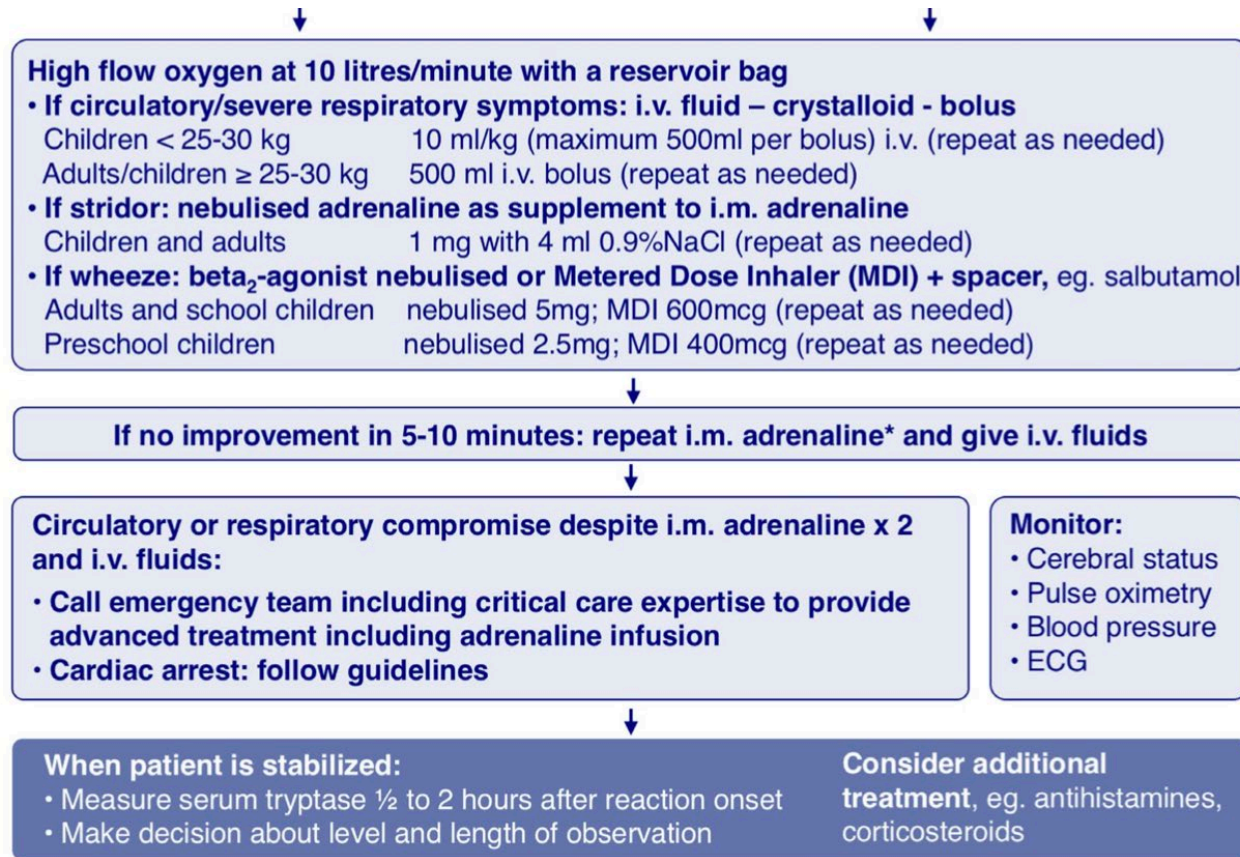
Anaphylaxis Management

"Anaphylaxis is not a fluke. Even though there were no reactions to many previous exposures (eg, bee sting, shellfish, penicillin), once it occurs, it will likely happen again if exposed again. The number one risk factor for anaphylaxis is a history of previous anaphylaxis (to anything)." David Golden, MD

Acute Management I



Acute Management II



*Consider (i) giving second dose by needle and syringe in case of autoinjector failure and (ii) using 0.5mg dose for adolescents or adults.

Modified from the 2020 Danish National Anaphylaxis guideline (12.06.21)

Long-term Management

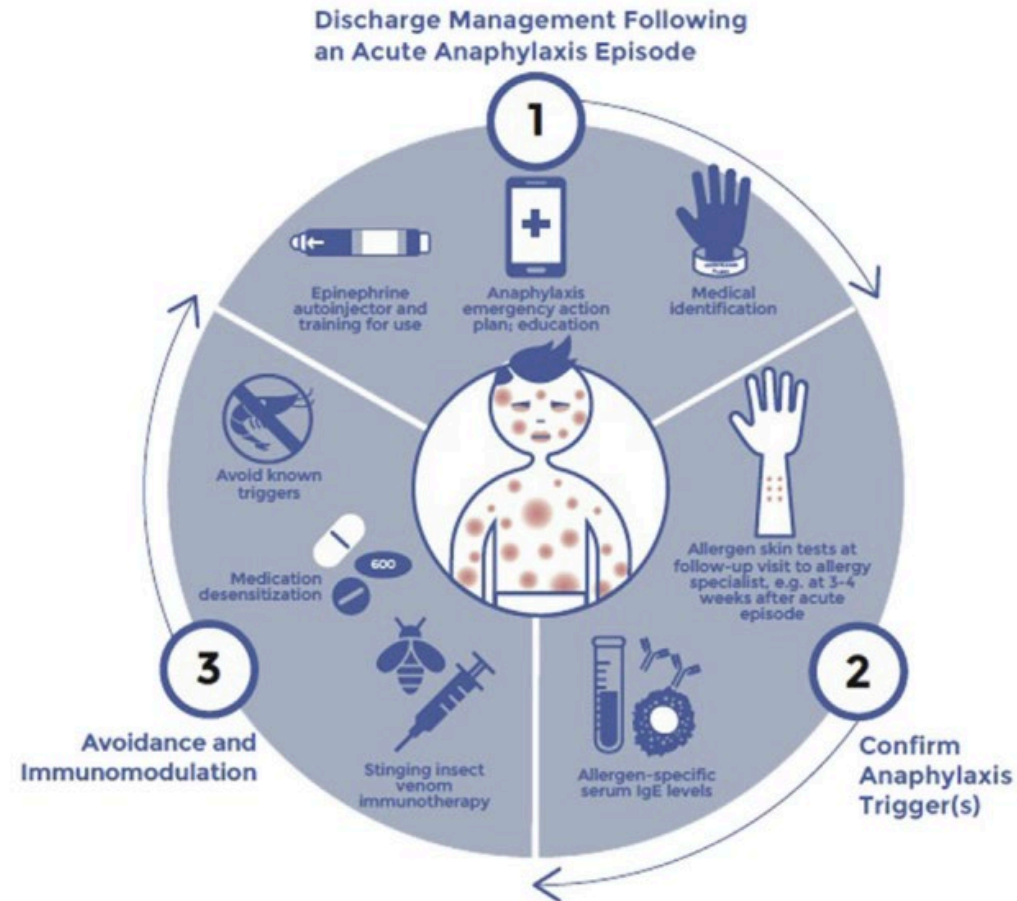


Fig. 5 Long-term management of anaphylaxis

Managing Food Allergies & Anaphylaxis in the Community

- Create a safe environment
- Employ prevention and avoidance strategies
- Be prepared to handle an allergic reaction
- Address bullying

Golden et al, Annals of Allergy, Asthma Immunol, 2024
Muraro et al, Allergy, 2022

Managing Food Allergies & Anaphylaxis in the Community

- **Students to:**

- Not share food, utensils, or containers
- Wash hands before and after meals
- Communicate

- **Patients and Caregivers to:**

- Provide written medical documentation
- Work with school to develop a plan
- Provide medication
- Keep emergency contact information up to date
- Provide the classroom teacher with approved allergen free items

- **Teachers to:**

- Know their students with food allergies
- Be familiar with handling allergic reactions
- Notify classroom parents
- Beware of classroom animals and projects
- Wipe tables and chairs
- Educate substitute teachers and volunteers

Golden et al, Annals of Allergy, Asthma Immunol, 2024

Muraro et al, Allergy, 2022

Managing Food Allergies & Anaphylaxis in the Community

Food Allergy Action Plan

Emergency Care Plan

Place Student's Picture Here

Name: _____ D.O.B.: ____/____/____

Allergy to: _____

Weight: _____ lbs. Asthma: Yes (higher risk for a severe reaction) No

Extremely reactive to the following foods: _____

THEREFORE:

If checked, give epinephrine immediately for ANY symptoms if the allergen was *likely* eaten.

If checked, give epinephrine immediately if the allergen was *definitely* eaten, even if no symptoms are noted.

Any SEVERE SYMPTOMS after suspected or known ingestion:

One or more of the following:

LUNG: Short of breath, wheeze, repetitive cough

HEART: Pale, blue, faint, weak pulse, dizzy, confused

THROAT: Tight, hoarse, trouble breathing/swallowing

MOUTH: Obstructive swelling (tongue and/or lips)

SKIN: Many hives over body

Or combination of symptoms from different body areas:

SKIN: Hives, itchy rashes, swelling (e.g., eyes, lips)

GUT: Vomiting, diarrhea, crampy pain

1. INJECT EPINEPHRINE IMMEDIATELY

2. Call 911
3. Begin monitoring (see box below)
4. Give additional medications:*
-Antihistamine
-Inhaler (bronchodilator) if asthma

*Antihistamines & inhalers/bronchodilators are not to be depended upon to treat a severe reaction (anaphylaxis). USE EPINEPHRINE.

MILD SYMPTOMS ONLY:

MOUTH: Itchy mouth

SKIN: A few hives around mouth/face, mild itch

GUT: Mild nausea/discomfort

1. GIVE ANTIHISTAMINE

2. Stay with student; alert healthcare professionals and parent
3. If symptoms progress (see above), USE EPINEPHRINE
4. Begin monitoring (see box below)

Medications/Doses

Epinephrine (brand and dose): _____

Antihistamine (brand and dose): _____

Other (e.g., inhaler-bronchodilator if asthmatic): _____

Monitoring

Stay with student; alert healthcare professionals and parent. Tell rescue squad epinephrine was given; request an ambulance with epinephrine. Note time when epinephrine was administered. A second dose of epinephrine can be given 5 minutes or more after the first if symptoms persist or recur. For a severe reaction, consider keeping student lying on back with legs raised. Treat student even if parents cannot be reached. See back/attached for auto-injection technique.

Parent/Guardian Signature _____

Date _____

Physician/Healthcare Provider Signature _____

Date _____

TURN FORM OVER Form provided courtesy of the Food Allergy & Anaphylaxis Network (www.foodallergy.org) 9/2011

- **Healthcare Professionals to:**
 - Prepare medical treatment plan
 - Educate students, families, and school community about food allergies
 - Provide updated Food Allergy/Anaphylaxis Action Plan

Golden et al, Annals of Allergy, Asthma Immunol, 2024
Muraro et al, Allergy, 2022

What Advice Do We Give to Patients Based on Current Evidence?

- Communicate their food allergies to others in your community.
- Engage with their community to create a safe environment for their food allergies.
- Anaphylaxis is serious and requires prompt treatment. Delay in epinephrine administration is associated with more severe reactions, more prolonged ED or hospital stay, and increased risk of fatal anaphylaxis.
- First line treatment for anaphylaxis is epinephrine.
- Epinephrine is a safe treatment.
- Education on how to recognize and treat anaphylaxis remains key.
- Anaphylaxis is rarely fatal.



Anaphylaxis Severity & Fatalities

Severe Anaphylaxis and Fatalities

- Up to 5% of the US population has suffered anaphylaxis.
- Fatal outcome is rare.
- For people with known venom or food allergy, fatal anaphylaxis constitutes <1% of total mortality risk.
- The incidence of fatal anaphylaxis has not increased in line with hospital admissions for anaphylaxis.

Turner et al, JACI IP, 2017

Annual incidence of fatal anaphylaxis in an unselected population

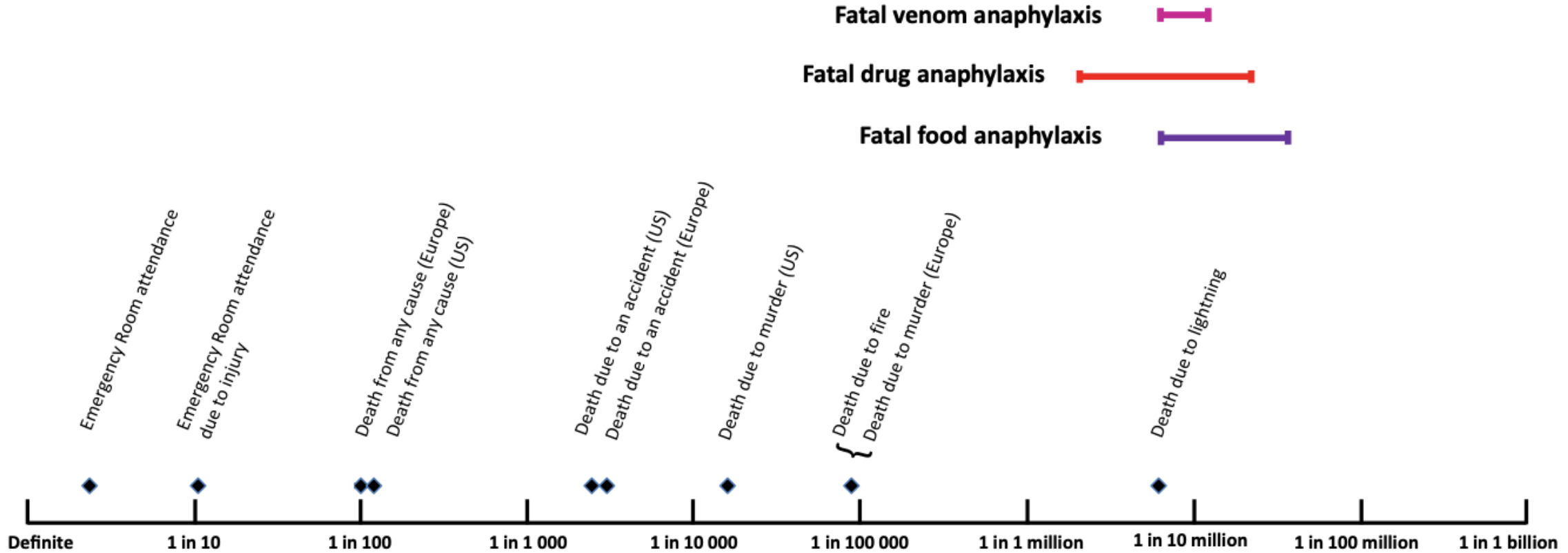


Figure 1. Estimated rates of fatal drug, food, and venom anaphylaxis compared with other risks for the general population. Reference risks are for the US population, unless otherwise stated. Bars represent the range of estimates from recent population-based studies of fatal anaphylaxis

Turner et al, JACI IP, 2017

Risk Factors for Fatal Anaphylaxis Vary

- Risk factors for fatal anaphylaxis vary according to cause:
 - **Fatal drug anaphylaxis:** previous cardiovascular morbidity, older age; beta-lactam antibiotics, general anesthetic agents, and radiocontrast injections are the most common triggers.
 - **Fatal food anaphylaxis:** delayed epinephrine administration; common triggers are nuts, seafood, and in children, milk.
 - **Fatal venom anaphylaxis:** middle age, male sex, white race, cardiovascular disease, and mastocytosis.

Co-Factors that Amplify Anaphylaxis*



* Age-related factors, concomitant diseases, and concurrent medications potentially contribute to severe or fatal anaphylaxis. Co-factors potentially amplify anaphylaxis. Multiple factors and co-factors likely contribute to some anaphylactic episodes.

** ACE, angiotensin-converting enzyme.

*** NSAIDs, Non-steroidal anti-inflammatory drugs

Turner et al, JACI IP, 2017

Understanding Biphasic, Persistent, Refractory Anaphylaxis

- **Biphasic anaphylaxis** is highly likely when the patient develops anaphylaxis after initial signs and symptoms have completely resolved for at least one hour before the onset of repeated anaphylaxis within 48 hours without re-exposure to an allergen trigger.
- **Persistent anaphylaxis** is highly likely when anaphylaxis persists for at least 4 hours.
- **Refractory anaphylaxis** is highly likely when anaphylaxis continues despite appropriate epinephrine dosing and symptom-directed medical management (eg, intravenous fluid bolus for hypotension).

Golden et al, Annals of Allergy, Asthma Immunol,, 2024



2023 US Anaphylaxis Practice Parameter

Key Messages

Key Messages for Anaphylaxis Management

Patient Education Recommendations

- Clinicians counsel patients at high-risk of anaphylaxis to always carry self-injectable epinephrine and teach patients proper indications and use.
- Clinicians educate patients on avoidance of potential exposure to their allergen(s).
- Clinicians educate patients that the main route of food-induced anaphylaxis is by ingestion and not contact or inhalation.

Key Messages for Anaphylaxis Management

Community Management Recommendations

- Child-care centers and schools implement staff training for allergy and anaphylaxis management.
- Child-care centers and schools not implement site-wide food specific prohibition, because current research does not support consistent benefits.
 - Special circumstances: It might be appropriate to implement allergen-restricted zones (eg, milk-free table) when there are students who lack the capacity to self-manage.
- Child-care centers and schools stock undesignated EAs that can be used to treat any individual on school grounds who experiences anaphylaxis.

Key Messages for Anaphylaxis Management

Community Management Recommendations

- Clinicians counsel patients on safe practices for dining outside of the home.
- Clinicians counsel patients that although US regulations require disclosure of major allergens on labels of prepackaged foods, restaurants are not required to declare ingredients or provide allergy warnings for non-prepackaged foods.
- Advising individuals at risk of anaphylaxis to wear or carry medical identification (e.g., jewelry or wallet card) be considered optional. If worn or carried, the wording on medical alert jewelry or wallet cards should be verified for accuracy by a healthcare professional.
- Stock epinephrine in community settings should be encouraged, if feasible.

Golden et al, Annals of Allergy, Asthma Immunol, 2024

Key Messages for Anaphylaxis Management

Epinephrine Auto-Injectors & EMS Recommendations

- Clinicians counsel patients and caregivers to give epinephrine at the first sign of suspected anaphylaxis.
- In general, clinicians counsel patients or caregivers to not give epinephrine preemptively to an asymptomatic patient
- Clinicians counsel patients that immediate activation of EMS may not be required if the patient experiences prompt, complete, and durable response to treatment with epinephrine, provided that additional epinephrine and medical care are readily available, if needed.
- Clinicians counsel patients to always activate EMS following epinephrine use, if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens following a first dose of epinephrine.

Key Messages for Anaphylaxis Management

Epinephrine Auto-Injectors (EAI) & EMS Recommendations

- Serious adverse reactions to intramuscular (IM) epinephrine are very rare and should not pose a barrier to the prescription or early administration of EAIs when indicated.
- To manage the risk of adverse events, we recommend that clinicians counsel patients and caregivers on the proper use of EAIs, the common side effects, and the need for immediate evaluation and treatment when signs or symptoms of serious adverse events develop.

Individuals who have experienced anaphylaxis should be referred to an allergist for diagnosis, management, and counselling.

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QUESTION 1

The parents of a 3-month-old infant with mild eczema seek advice on when to introduce allergenic foods. Which advice matches current evidence based recommendations:

- A. To delay introduction of allergenic foods until after 3 years of age
- B. To delay introduction of allergenic foods until after 2 years of age
- C. To start early introduction of allergenic foods between 4-12 months of age depending on developmental readiness
- D. To start early introduction of allergenic foods before 4 months of age

QUESTION 2

The parents of a 4-year-old peanut allergic child are interested in peanut oral immunotherapy and asking for your advice. You explain that peanut oral immunotherapy:

- A. Is the traditional management approach for food allergies
- B. Is a safe and effective management approach for food allergies
- C. Is associated with severe and frequent anaphylaxis
- D. May only be used to treat adults

QUESTION 3

The most common triggers of anaphylaxis in children are:

- A. Foods
- B. Drugs
- C. Venom
- D. Idiopathic

QUESTION 4

Epinephrine should be used:

- A. Promptly, as first line treatment, when anaphylaxis occurs
- B. Pre-emptively even if no symptoms are present
- C. After other medications, such as antihistamines, are given
- D. In selective cases of anaphylaxis only

QUESTION 5

Choose the one correct statement below with regards to anaphylaxis:

- A. Fatalities due to anaphylaxis are common
- B. Delay in administering epinephrine is associated with severe anaphylaxis and an increased risk of fatal anaphylaxis
- C. Exercise is not a co-factor for anaphylaxis
- D. Anaphylaxis is slow onset and always involves the cardiovascular system

QUESTION 6

A 2-year-old child has a history of anaphylaxis to peanut. During an accidental exposure at daycare, they develop hives, vomiting, and wheeze. Which of the following is the most appropriate next step for the daycare provider?

- A. Administer the patient's epinephrine immediately and call emergency services
- B. First give antihistamines and observe for improvement
- C. Bring the child to the emergency room without treating first
- D. Have the child rinse their mouth out and monitor symptoms

QUESTION 7

A 10-year-old with multiple food allergies asks about ways to prevent anaphylaxis reactions when going to parties or restaurants. Which of the following would be an appropriate recommendation?

- A. Avoid all restaurants and parties to completely eliminate risk
- B. Ask about ingredients and food preparation details when dining out
- C. Only eat prepackaged foods with labeled ingredients when away from home
- D. Carry epinephrine auto-injectors, but do not need to ask about food allergens

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