Mild Food Allergy and Thresholds

Roxanne C. Oriel, MD, MA

Assistant Professor of Pediatrics

Serena and John Liew Division of Pediatric Allergy and Immunology

Icahn School of Medicine at Mount Sinai

Elliot and Roslyn Jaffe Food Allergy Institute

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Learning Objectives

Upon completion of this learning activity, participants should be able to:

1. Define food allergy severity and thresholds.
2. Discuss management approaches beyond strict avoidance, including risks, benefits, and unknowns.
3. Describe high- and low-threshold phenotypes and how they may be used to individualize management strategies for patients.

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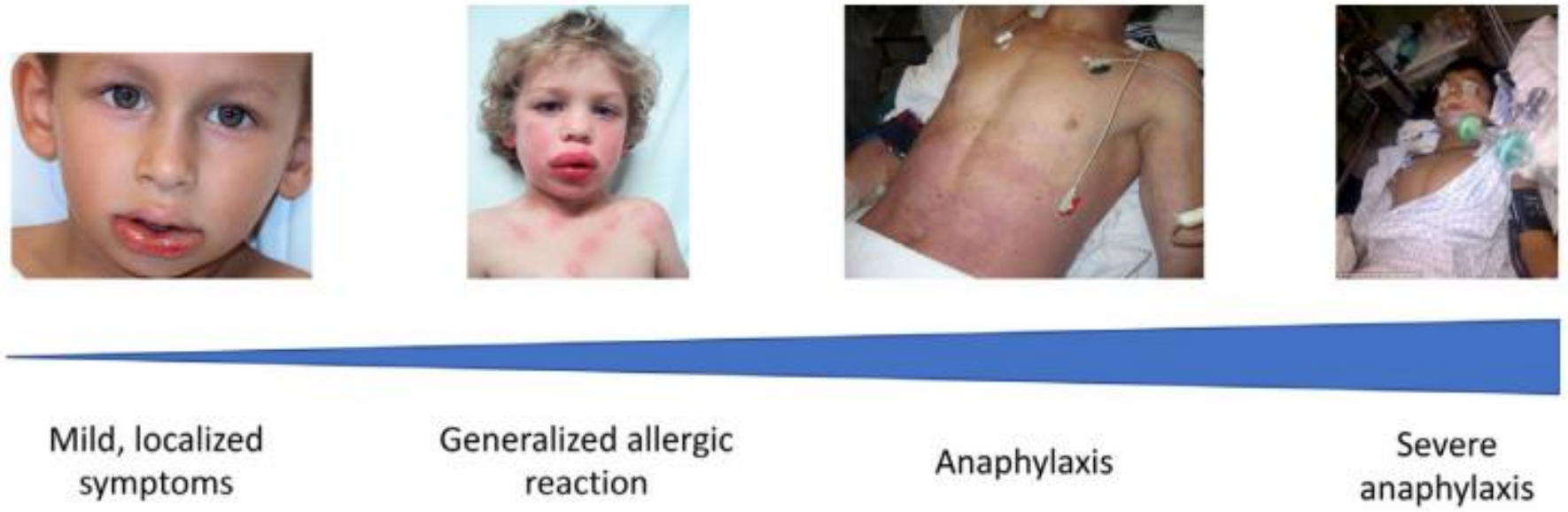
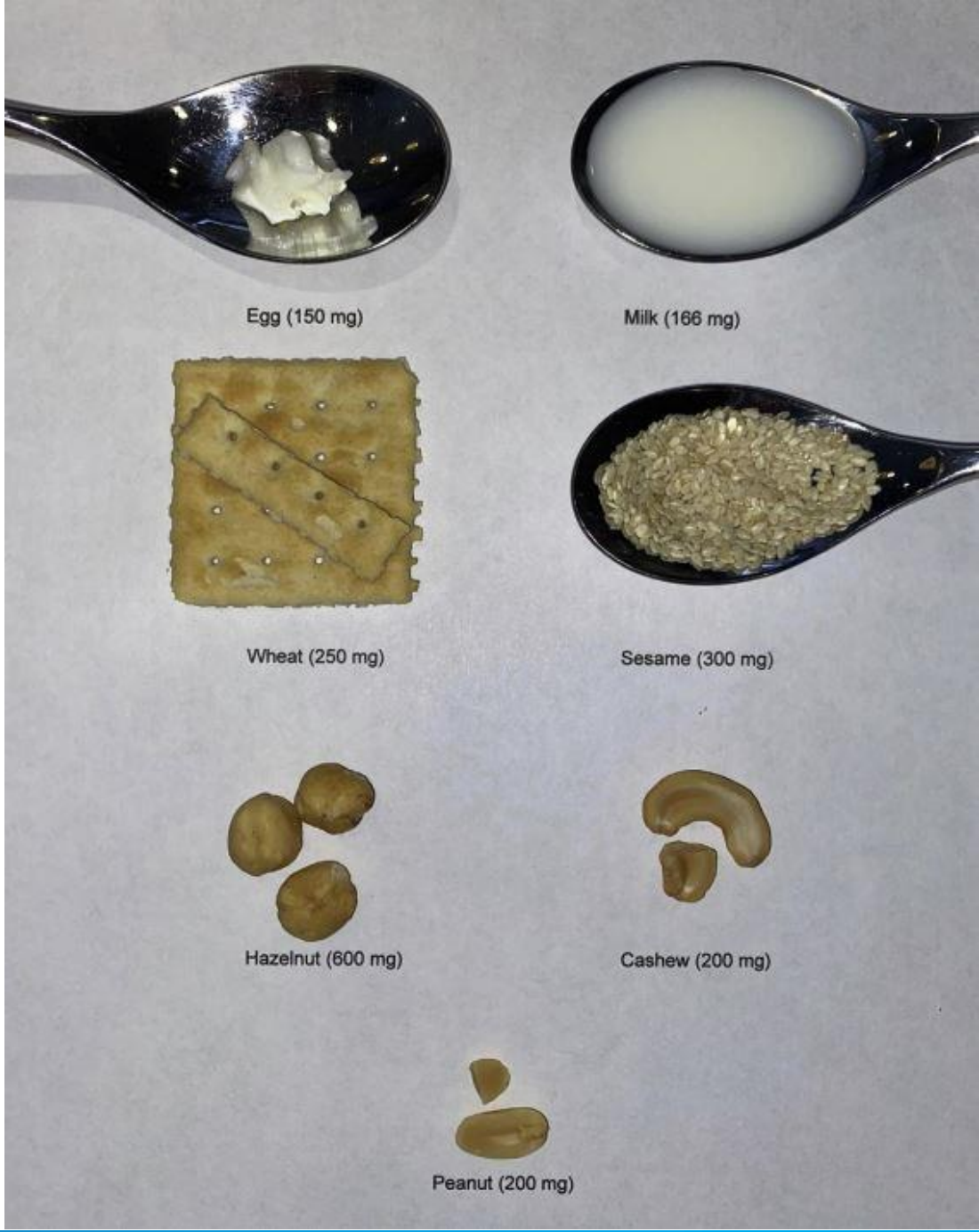
Should all patients with food allergies be managed the same?



Dribin et al., J Allergy Clin Immunol Pract, 2023

Paradigm Shift

- ***Traditional approach:*** strict avoidance for all patients with food allergies
- ***Emerging recognition***
  - Individual thresholds vary considerably
  - Most patients are not “highly allergic”
  - This group with “mild allergy” may not need to strictly avoid allergens
  - 50% of food allergic individuals can consume sizeable portions without reacting
  - **Not all patients react to trace amounts**



Sicherer et al., J Allergy Clin Immunol Pract, 2022
Li et al., Ann Allergy Asthma Immunol, 2024

Patient 1 is an 11-month-old who recently developed **facial hives** within 15 minutes after ingesting hummus containing tahini. Teddy's parents thought the hives were due to skin contact since he has sensitive skin and mild atopic dermatitis. They retried the hummus at home (citing that they felt comfortable doing so since he tolerated sesame seeds and sesame oil last week) and he developed facial hives and swelling. He also became inconsolable. Skin prick testing performed at your office revealed:

Skin test	Wheal (mm)
Saline	0
Histamine	3
Chickpea	0
Sesame	8

What management strategy would you recommend to Teddy's parents?

A. Strict avoidance of all forms of sesame.

B. Avoid all forms of sesame but allow PAL for sesame.

C. Avoid tahini/sesame paste, but allow sesame seeds, sesame oil, and PAL.

D. Offer OIT to sesame.

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Patient 2 is an 11-month-old who recently developed **difficulty breathing and pallor** within 15 minutes after ingesting hummus containing tahini. Penelope tolerated sesame seeds and sesame oil last week. Skin prick testing performed at your office revealed:

Skin test	Wheal (mm)
Saline	0
Histamine	3
Chickpea	0
Sesame	8

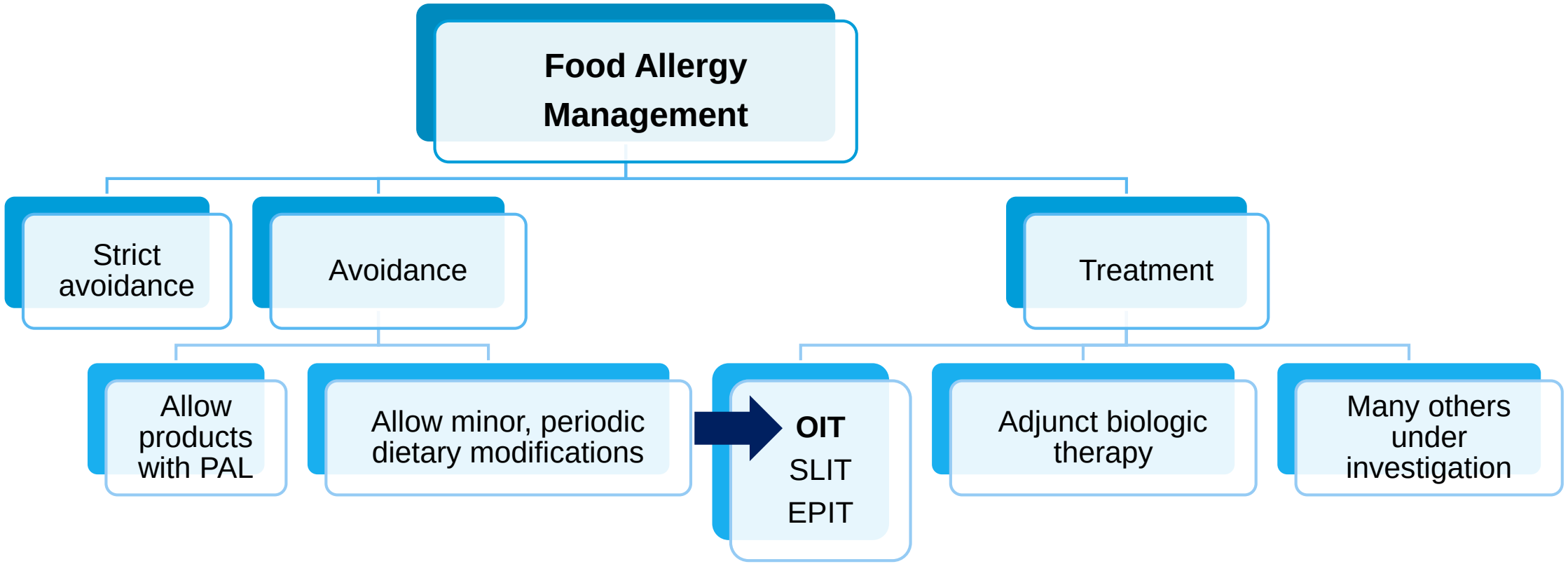
What management strategy would you recommend to Penelope's parents?

A. Strict avoidance of all forms of sesame.

B. Avoid all forms of sesame but allow PAL for sesame.

C. Avoid tahini/sesame paste, but allow sesame seeds, sesame oil, and PAL.

D. Offer OIT to sesame.



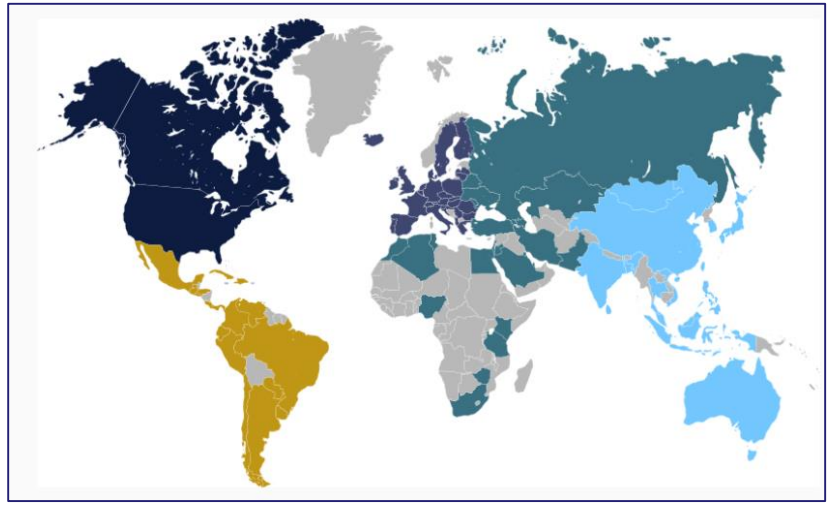
Discuss all of the possibilities with the parents of patients 1 and 2.

Sicherer et al., J Allergy Clin Immunol Pract, 2022

Outline

1. **Food allergy *severity* and *threshold***
2. Food allergy phenotypes - *highly allergic*, *mildly allergic*
3. Management strategies - from *strict avoidance* to *ingestion of sub-threshold amounts*

Food allergy *severity*



DEFASE - DEfinition of **F**ood **A**llergy **Se**verity

The World Allergy Organization (WAO) initiated a project to develop an international definition and classification system of severity associated with food allergy

- Systematic review
- Electronic Delphi survey
- Consensus document
- Validation & implementation

Arasi et al., World Allergy Organ J, 2021

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DOMAINS	MILD (1 point)	MODERATE (2 points)	SEVERE (3 points)
Symptoms/signs with most severe previous reaction	• Only cutaneous • Mild gastrointestinal • Rhinoconjunctivitis	• Lower respiratory • Laryngeal • Gastrointestinal • Cardiovascular	• Respiratory • Circulatory failure
Minimum therapy to treat most severe previous reaction	• No previous need for epinephrine • Only symptomatic therapy	• Reaction(s) have always visibly responded to a maximum of 2 doses of IM epinephrine	*At least 1 of the following*: • More than 2 doses of IM epinephrine needed • Intensive care treatment
Minimal eliciting dose (ED)	> ED20 exposure	ED05 <exposure ≤ ED20	≤ED05 exposure
Food allergy-related quality of life (FA-QoL)	No/minimal impact on FAQoL	Moderate impact on FAQoL	Severe impact on FAQoL
Health economic impact	No/minimal impact	Moderate impact	Severe impact

Arasi et al., World Allergy Organ J, 2021

DEFASE score

- Higher score, increasing severity
- DEFASE score is the first comprehensive grading of food allergy severity
- Considers not only the severity of a single reaction, but the whole disease spectrum
- One estimate of disease severity at a single time point may not be predictive of future severity

Severe ≥ 13

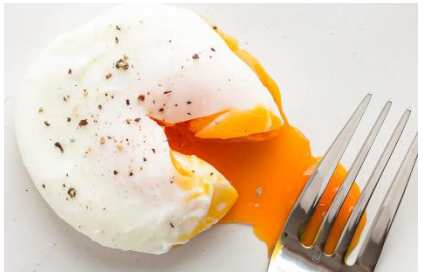
Moderate 7-12

Mild ≤ 6

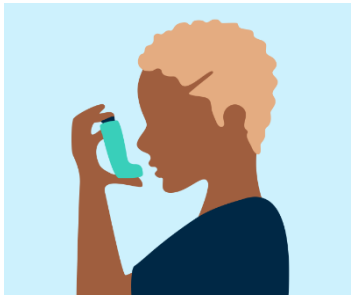
Arasi et al., World Allergy Organ J, 2021

Severity

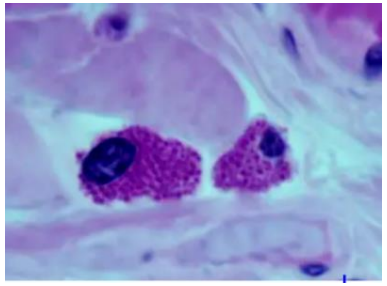
How much allergen ingested

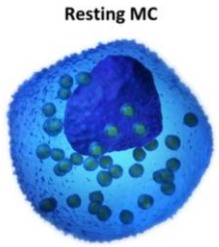


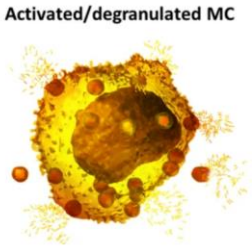
Food (processed, heated, matrix)



Presence of asthma





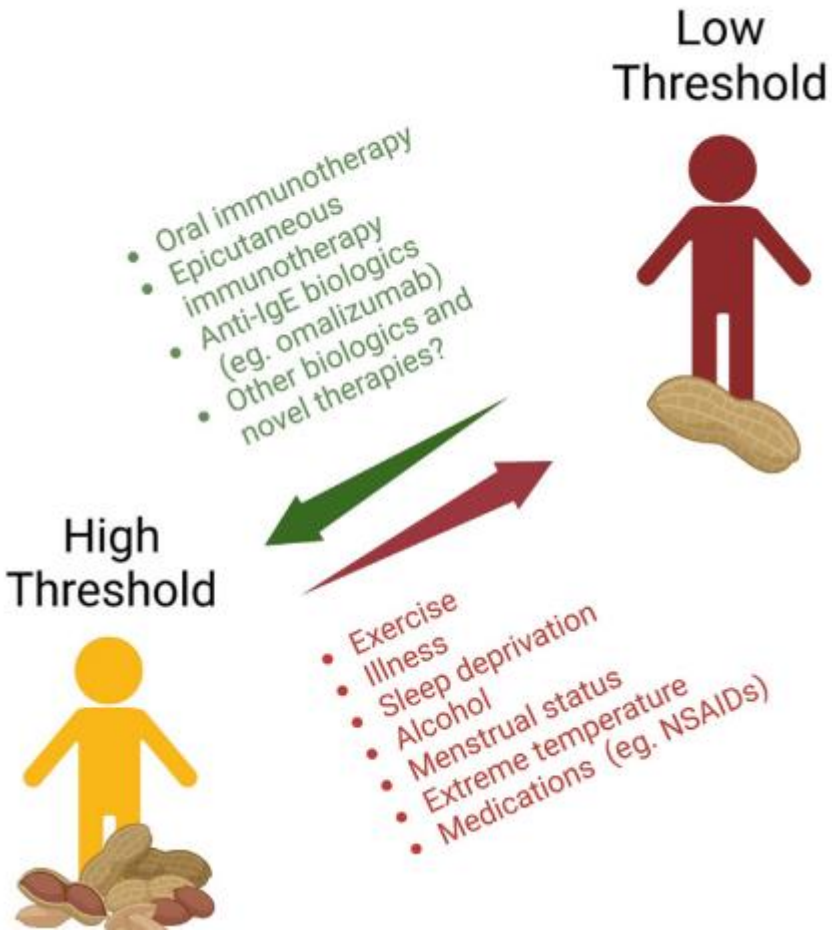


Intrinsic immune features

Augmentation factors

Food allergy *threshold*

- Minimum amount of food protein that triggers objective symptoms
- Determined via OFC
- Stable and reproducible feature of an individual's allergy in the absence of augmentation factors, may change with age
- Population-based thresholds
  - ED01: dose at which 1% of allergic population reacts
  - ED05: dose at which 5% of allergic population reacts



Li et al., Ann Allergy Asthma Immunol, 2024

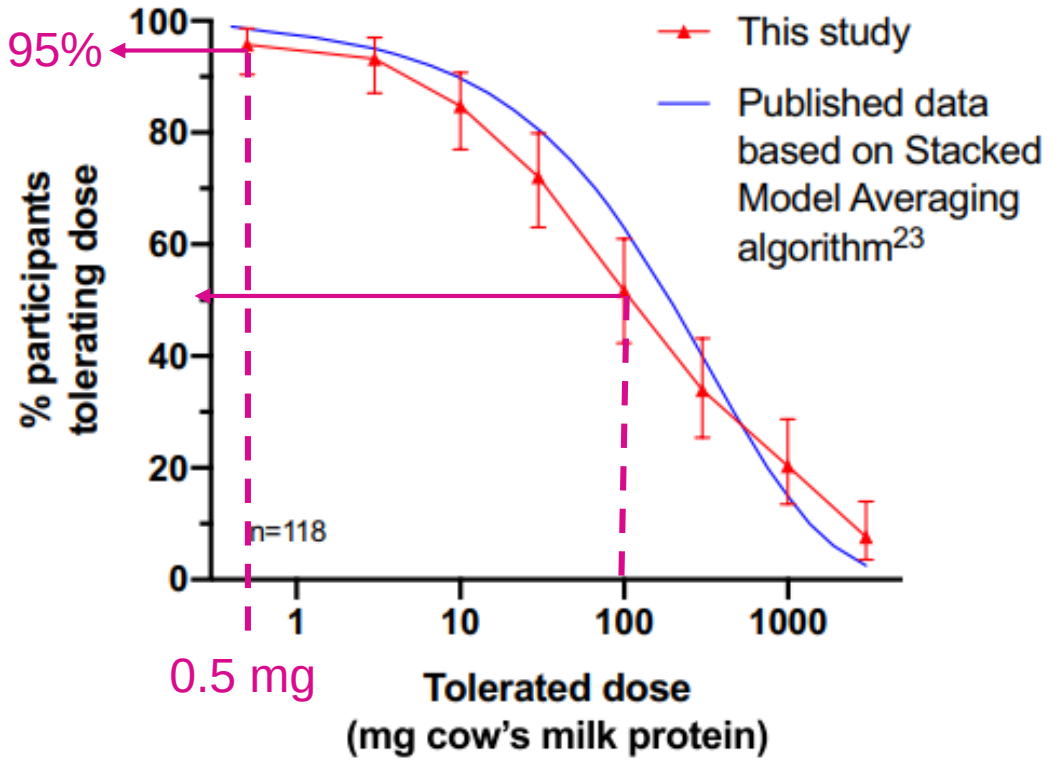
Food allergy *threshold*

Challenge Food	N	Number of subjects (% of total)	Eliciting dose (mg) median (range)	Eliciting dose curves (ED) (mg) (95% CI)		
				ED_5	ED_{10}	ED_{50}
Almond✠	30	29 (7)	25.0 (5–500)	0.86 (0, 1.92)	1.73 (0, 3.60)	20.77 (5.76, 35.78)
Cashew	151	150 (35)	25.0 (0.1–500)	0.07 (0, 0.13)	0.25 (0.05, 0.46)	8.78 (5.40, 12.16)
Egg	63	60 (14)	8.1 (0.1–500)	0.04 (0, 0.12)	0.18 (0, 0.42)	7.07 (2.61, 11.54)
Hazelnut	68	65 (15)	25.0 (1.6–500)	0.07 (0, 0.17)	0.29 (0, 0.68)	14.38 (5.36, 23.39)
Milk	67	66 (15)	32.7 (1.7–500)	0.21 (0, 0.49)	0.74 (0, 1.55)	20.41 (9.73, 31.09)
Peanut	347	330 (77)	75.0 (0.1–500)	0.49 (0.24, 0.73)	1.52 (0.89, 2.15)	29.90 (23.81, 35.98)
Pecan✠	88	88 (21)	25.0 (1.7–500)	0.38 (0.04, 0.71)	0.79 (0.19, 1.39)	10.68 (5.71, 15.64)
Pistachio	60	59 (14)	5.0 (5–275)	0 (0, 0.1)	0.01 (0, 0.04)	1.71 (0, 3.61)
Sesame	30	30 (7)	25.0 (5–500)	0.26 (0, 0.75)	0.88 (0, 2.24)	21.19 (5.28, 37.10)
Walnut	121	120 (28)	25.0 (1.7–500)	0.15 (0, 0.31)	0.56 (0.07, 1.05)	18.01 (10.54, 25.47)
Wheat	13	13 (3)	32.7 (5–500)	0.03 (0, 0.17)	0.16 (0, 0.75)	12.64 (0, 33.20)

Purington et al., Front Immunol, 2018

ED01 and ED05 for Select Food Allergens Reported From Recent Studies

Food	ED01 (discrete)	ED01 (cumulative)	ED05 (discrete)	ED05 (cumulative)	Study (n = participants)
Peanut	0.2 (CI, 0.1-0.4)	0.7 (CI, 0.5-1.3)	2.1 (CI, 1.2-4.6)	3.9 (CI, 2.8-7.1)	Remington et al,[55] 2020 (n = 1306)
Egg		29.7 (CI, 12.1-73)		87.7 (CI, 43-179)	Valluzzi et al,[58] 2022 (n = 49, baked food tolerant)
	0.2 (CI, 0.1-0.5)	0.2 (CI, 0.1-0.5)	2.3 (CI, 1.2-4.7)	2.4 (CI, 1.3-5.3)	Remington et al,[55] 2020 (n = 450)
Cow's milk	1.9 (CI, 1.6-2.4)	1.8 (CI, 1.4-2.3)	5.6 (CI, 4.7-6.6)	6.2 (CI, 5.1-7.6)	Katz et al,[59] 2023 (n = 866)
	0.3 (CI, 0.2-0.7)	0.4 (CI, 0.3-0.9)	3.2 (CI, 1.8-6.4)	4.3 (CI, 2.4-9.0)	Blom et al,[57] 2022 (n = 697)
		1.4 (CI, 0.1-5.5)	4.2 (IQR, 0.9-19.6)	6 (CI, 2.1-17.4)	Valluzzi et al,[58] 2022 (n = 38, baked food tolerant)
	0.2 (CI, 0.1-0.5)	0.3 (CI, 0.2-0.6)	2.4 (CI, 1.3-5.0)	3.1 (CI, 1.6-6.6)	Remington et al,[55] 2020 (n = 450)
Sesame	0.2 (CI, 0.09-1.0)	0.2 (CI, 0.08-1.0)	2.4 (CI, 1.0-7.7)	2.5 (CI, 0.9-9.5)	Turner et al,[56] 2022 (n = 246)
	0.1 (CI, 0.03-2.7)	0.2 (CI, 0.04-4.8)	2.7 (CI, 0.4-33.6)	4.2 (CI, 0.6-57.7)	Remington et al,[55] 2020 (n = 40)



Li JC, et al. Ann Allergy Asthma Immunol 2024;132:321−7.

ED05 for milk: 0.5 mg cow's milk protein = 0.015 mL of fresh cow's milk

Turner PJ, et al. Pediatr Allergy Immunol 2021;32:1056-65.

Peanut Allergen Threshold Study (PATS): Novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy

Jonathan O'B. Hourihane, MD, DM,[a] Katrina J. Allen, MD, PhD,[b,c] Wayne G. Shreffler, MD, PhD,[d] Gillian Dunngalvin, PhD,[a,e] Julie A. Nordlee, MS,[f] Giovanni A. Zurzolo, PhD,[b,g] Audrey Dunngalvin, PhD,[a,e] Lyle C. Gurrin, PhD,[h] Joseph L. Baumert, PhD,[f] and Steve L. Taylor, PhD[f]

J Allergy Clin Immunol 2017;139:1583-90.

4 mg

approximately the size of a pencil tip

- Multicenter study, n = 378 children (206 male), single dose of 1.5 mg peanut protein
- 65% - no reaction to single dose of peanut
- 18% - subjective reaction without objective findings
- 15% - signs of a mild/transient nature that did not meet predetermined criteria
- 2.1% - objective and likely related event

- Almost half ignored PAL
- No child experienced more than a mild reaction (4/8 po antihistamines, no epinephrine)
- FA-related QoL improved from baseline to 1 month after challenge regardless of outcome

ED05 for peanut:

1.5 mg of peanut protein = 6 mg whole peanut (1/200 of a peanut)

Single-dose OFC of 1.5 mg peanut could be cost-effective as a decision point for removing PAL restrictions for some children.

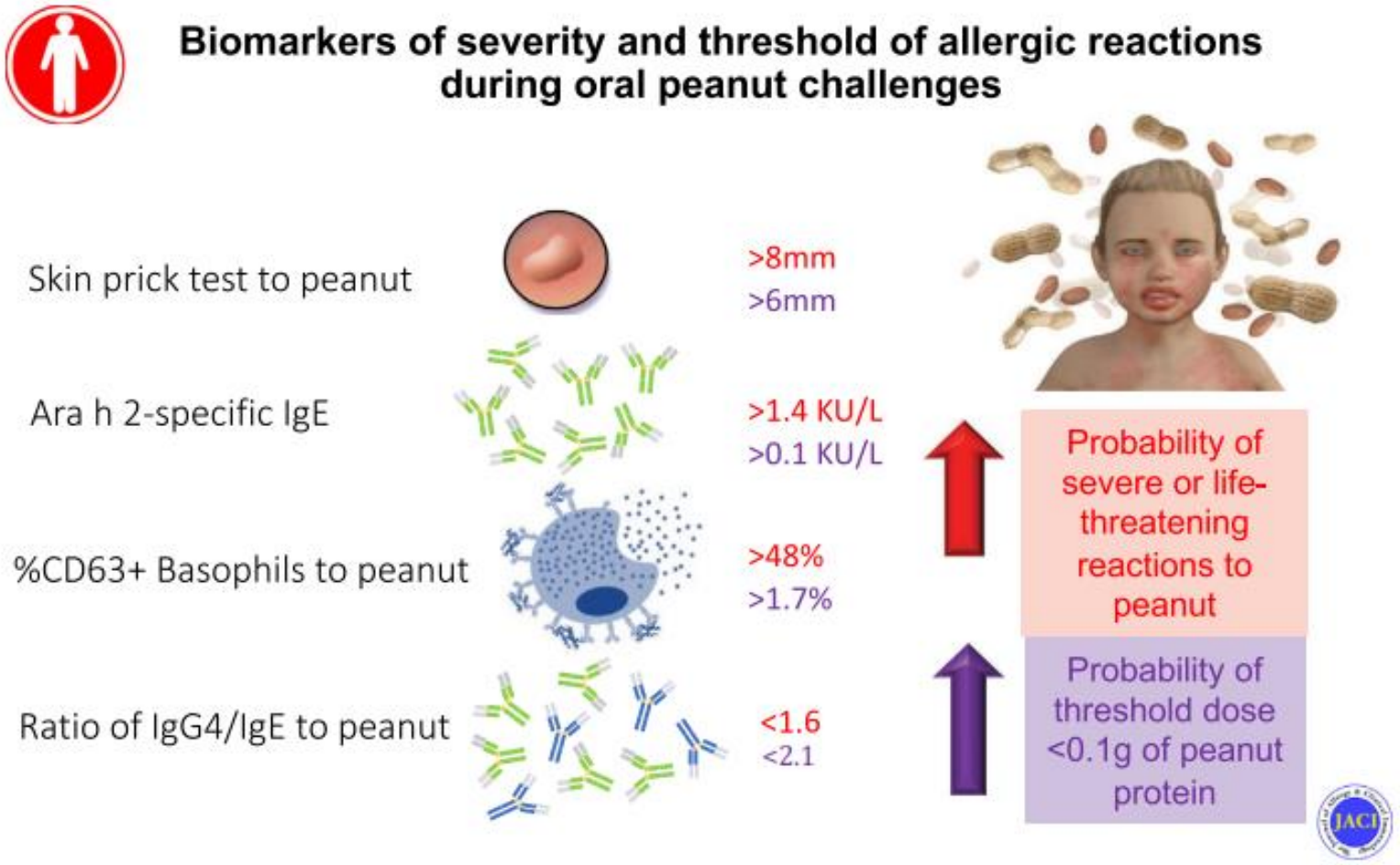
Biomarkers of severity and threshold

Basophil activation test

- Best biomarker for severity
- Can predict threshold, but skin prick test better

Skin prick test

- Best individual predictor for threshold



Santos AF, et al. J Allergy Clin Immunol 2020;146:344-355.

Outline

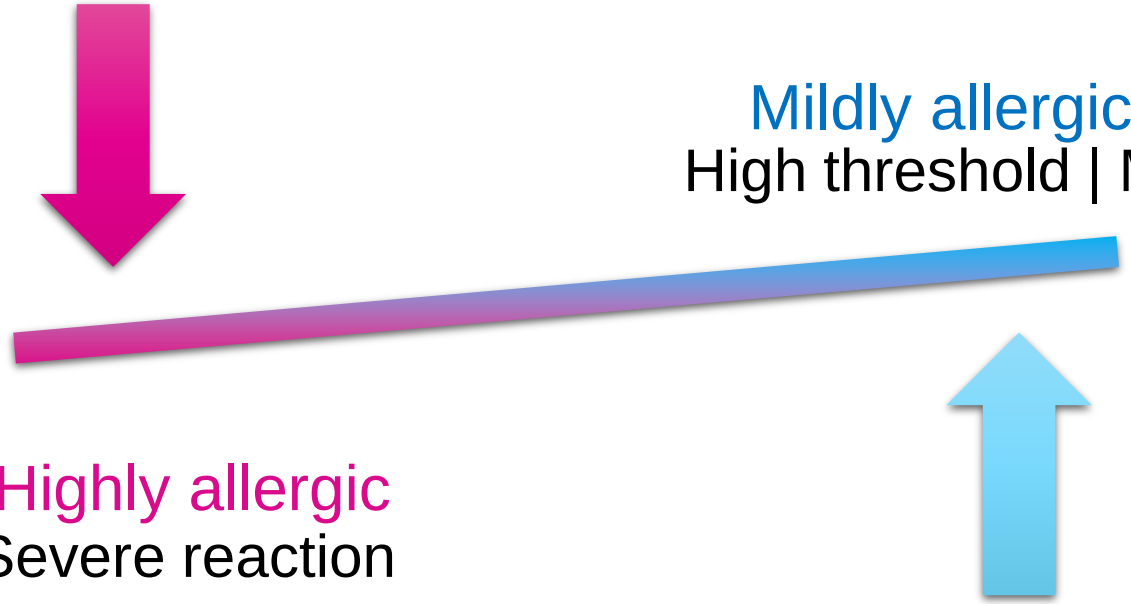
1. Food allergy *severity* and *threshold*
2. **Food allergy phenotypes - *highly allergic*, *mildly allergic***
3. Management strategies - from *strict avoidance* to *ingestion of sub-threshold amounts*

Food allergy phenotypes

Exquisitely allergic

Anaphylaxis to trace exposure

High-risk of a severe or life-threatening reaction



Highly allergic

Low threshold | Severe reaction

Mildly allergic

High threshold | Mild reaction

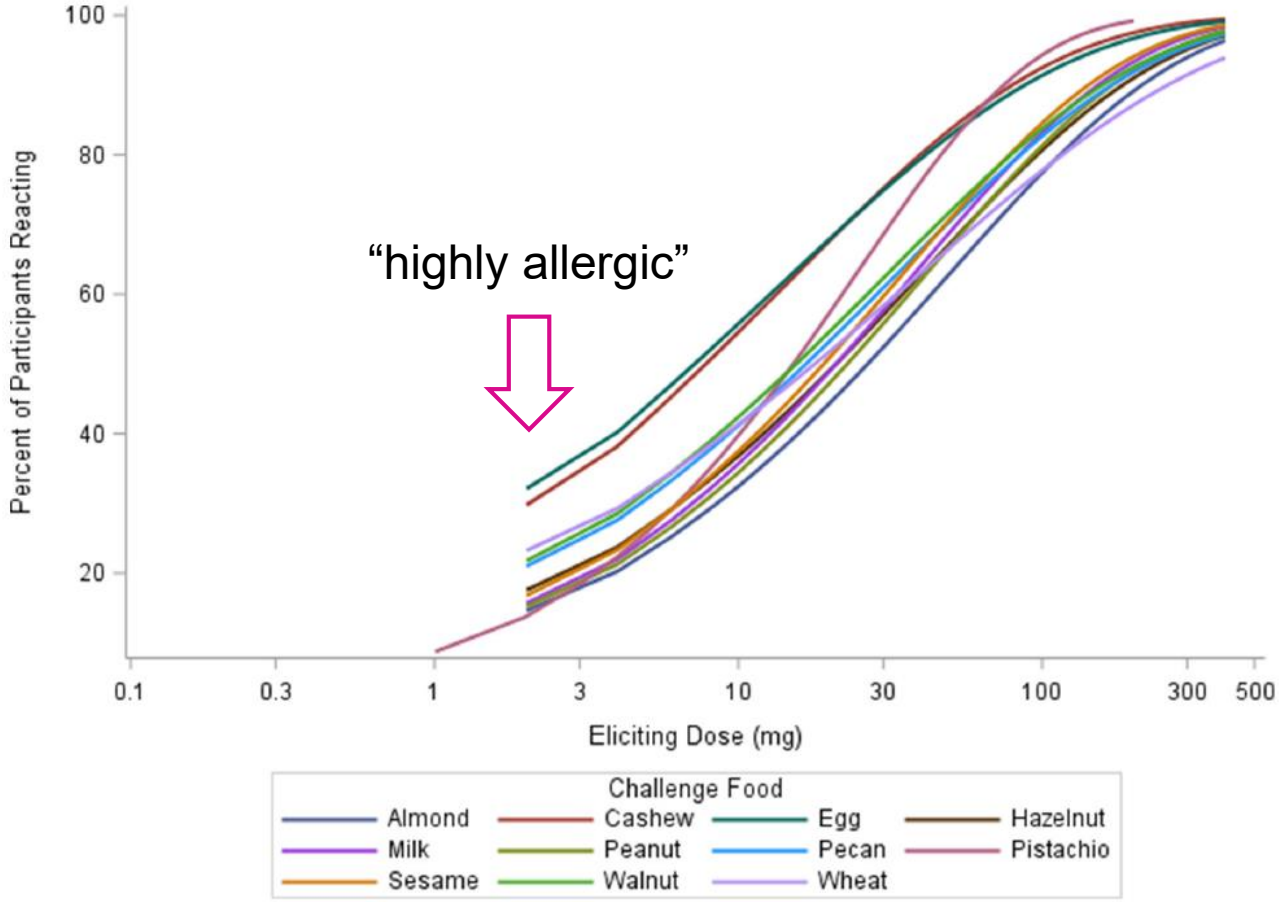
Low dose tolerant

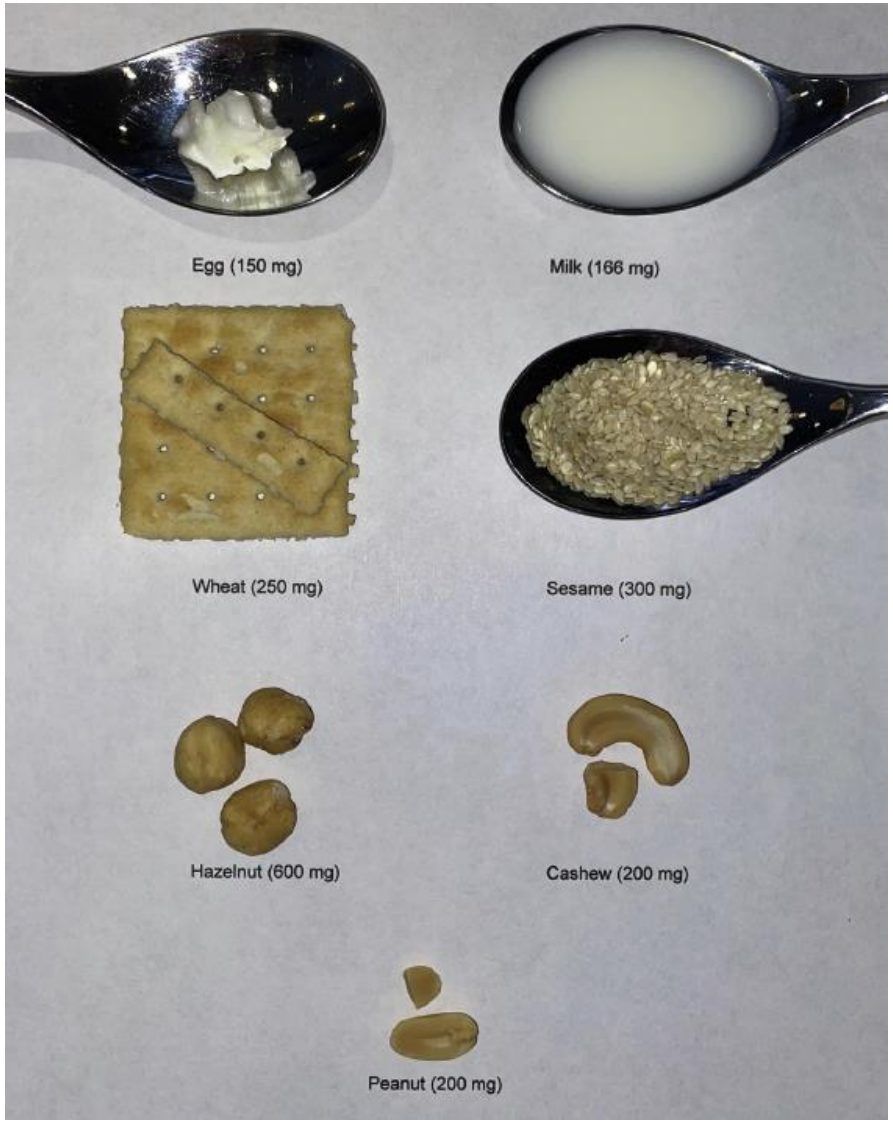
High-dose mild reactors

Mild allergy / almost like absence of allergy

“mildly allergic”

“highly allergic”



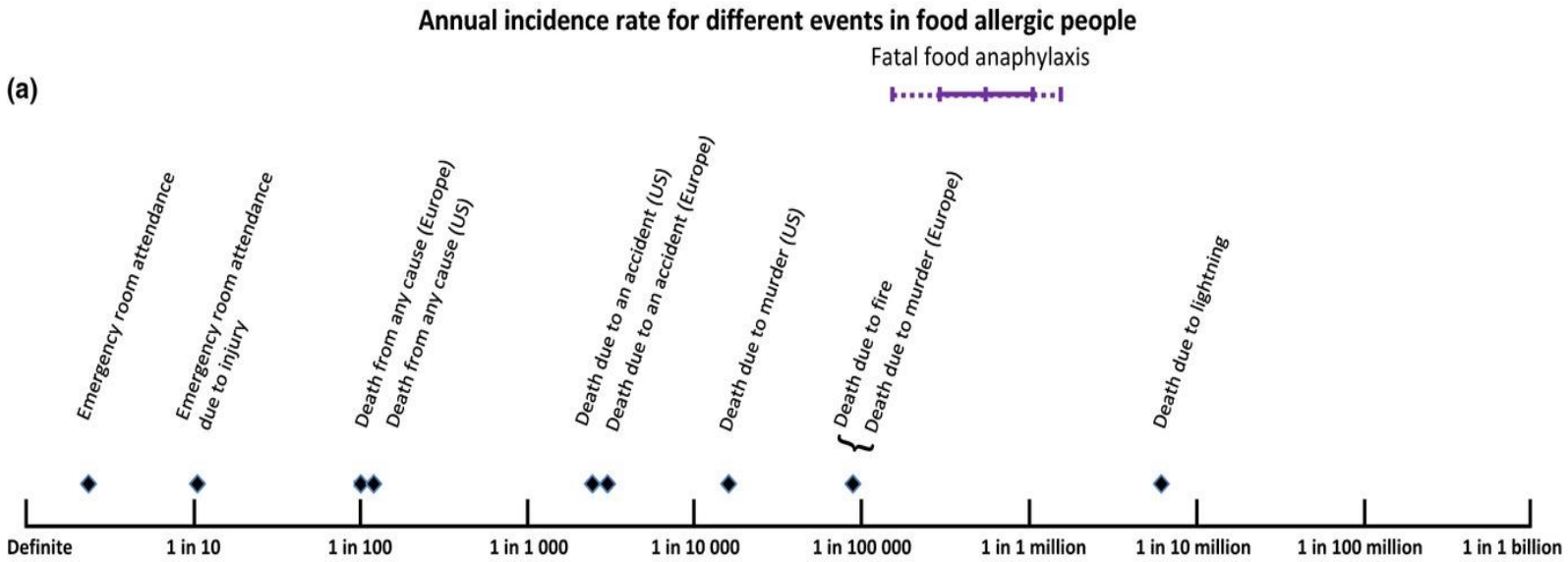


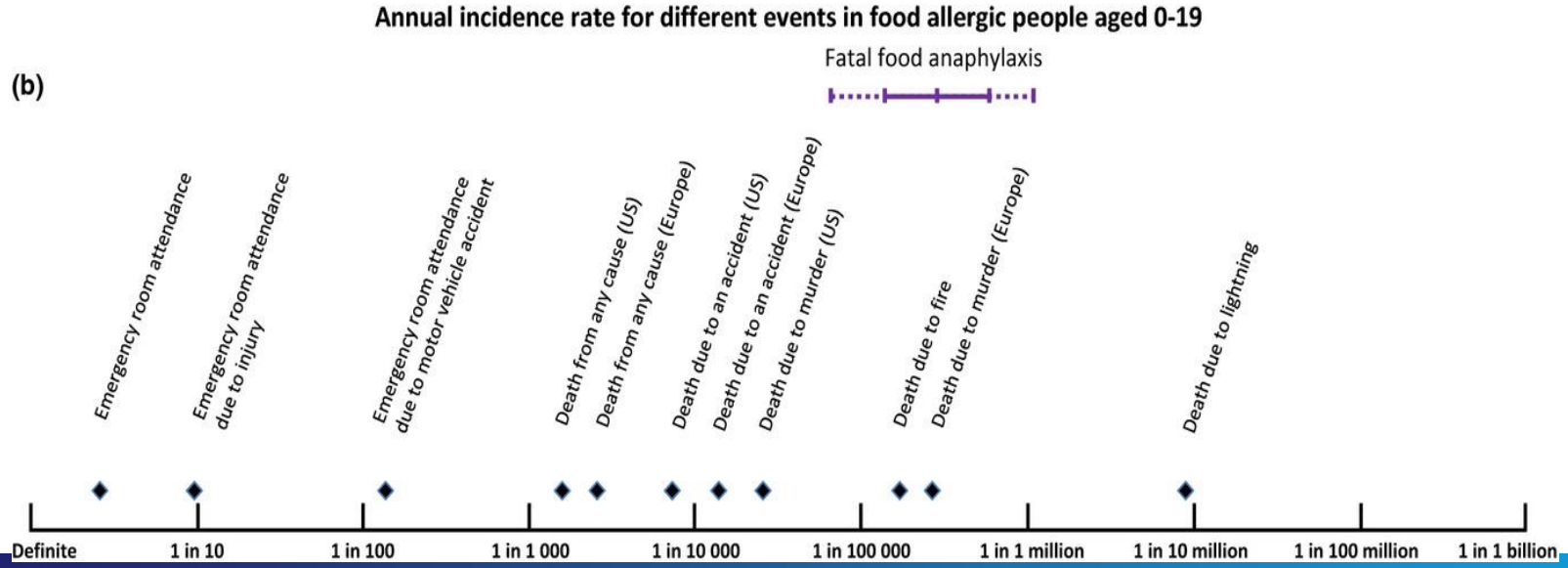
Purington et al., Front Immunol, 2018

Sicherer et al., J Allergy Clin Immunol Pract, 2022

Incidence of fatal food anaphylaxis in people with food allergy: *a systematic review and meta-analysis*

Umasunthar T, et al. Clin Exp Allergy 2013;43:1333-41.





Fatal allergic reactions due to food under any ingestion circumstances are ***rare*:**

1.81 per million person-years

(# of events that occur in a population of one million individuals over the course of one year)

Outline

1. Food allergy *severity* and *threshold*
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3. **Management strategies - from *strict avoidance* to *ingestion of sub-threshold amounts***

Managing Food Allergy When the Patient Is Not Highly Allergic

J Allergy Clin Immunol Pract 2022; 10:46-55.

Scott H. Sicherer, MD[a], Elissa M. Abrams, MD[b,c], Anna Nowak-Wegrzyn, MD, PhD[d,e], and Jonathan O'B. Hourihane, FRCPI[f,g]

Approach	Intention	Example	Benefit	Risk	Research needs†
Avoidance	Reduce reaction risk, no judgment needed	Avoid all milk, peanut, and products with PAL	Reduce risk	Impair HRQOL	Which has greater impact on HRQOL, avoidance or nonavoidance with risks?

- Appropriate for a patient with severe reaction to trace exposure.
- Difficult to achieve
- Concerns of medical liability may be one reason this is the only strategy offered to families/patients.

- Check ingredient labels for allergen(s) and avoid PAL.
- Avoid ingestion of foods that may have had cross-contact with allergen(s).
- Discuss how to safely dine out at restaurants.

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Avoidance	Reduce reaction risk, no judgment needed	Avoid all milk, peanut, and products with PAL	Reduce risk	Impair HRQOL	Which has greater impact on HRQOL, avoidance or nonavoidance with risks?
Allow products with precautionary labeling	Reduce restrictions to improve HRQOL	Allow peanut- allergic patient to use PAL products	Reduced restrictions, improved HRQOL	Allergic reaction	- Improved PAL - Real-word PAL risks

May contain ...	May contain traces of...	Packed in an environment where ... may be present	Made in a facility that also processes ...
Produced in a factory which handles ...	Produced on shared equipment which also processes ...	Made on the same production line as...	Made in a production area that also uses ...
No nuts in ingredients, but cannot guarantee to be nut-free	Not suitable for ... allergy sufferers	Due to methods used in the manufacture of this product, it may occasionally contain...	May be present: ... (used by VITAL™ 2.0)

Allen KJ, et al. World Allergy Organ J 2014;7:10.

Precautionary Allergen Labeling (PAL)

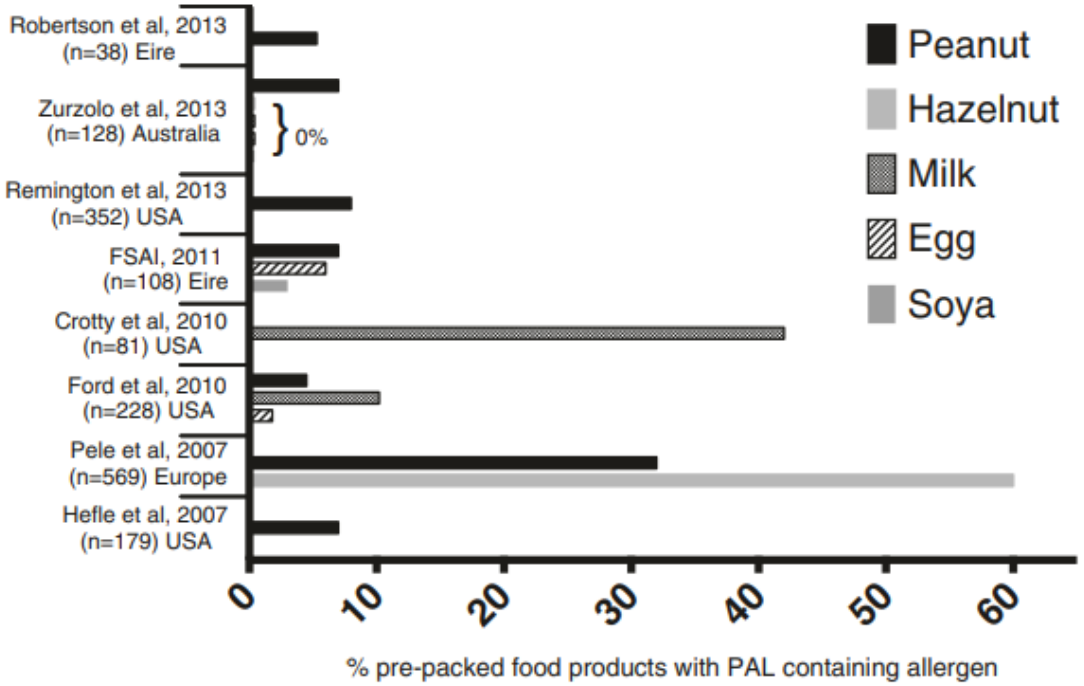

TABLE II. Respondents' purchasing practices based on food labeling

Variable	Frequency, % (n)			
	All respondents (United States and Canada)	United States	Canada	Significance
Purchase processed food				
Yes	95.9% (6391)	96.0% (5287)	95.6% (1104)	
No	4.1% (271)	4.0% (220)	4.4% (51)	.511
Purchase product with the following label:				
"May contain allergen"				
Never	87.7% (5574)	89.9% (4730)	77.2% (844)	
Sometimes	11.3% (716)	9.4% (492)	20.5% (224)	
Always	1.0% (63)	0.7% (37)	2.4% (26)*	.000
"Manufactured in a facility that also processes allergen"				
Never	59.7% (3795)	58.9% (3098)	63.5% (697)	
Sometimes	34.2% (2174)	35.0% (1841)	30.4% (333)	
Always	6.1% (389)	6.1% (322)	6.1% (67)	.011
"Manufactured on shared equipment with products containing allergen"				
Never	83.3% (5301)	83.0% (4375)	84.7% (926)	
Sometimes	14.2% (904)	14.5% (762)	13.0% (142)	
Always	2.5% (160)	2.6% (135)	2.3% (25)	0.376
"Good manufacturing practices used to segregate ingredients in a facility that also processes allergens"				
Never	25.2% (1596)	23.8% (1259)	32.2% (347)	
Sometimes	41.2% (2611)	42.0% (2209)	37.5% (402)	
Always	33.6% (2124)	34.2% (1800)	30.2% (324)*	.000

*$P < .01$.

Allen KJ, et al. World Allergy Organ J 2014;7:10.

Marchisotto MJ, et al. J Allergy Clin Immunol Pract 2017;5:345-351.

Precautionary Allergen Labeling (PAL)

Allen KJ, et al. World Allergy Organ J 2014;7:10.

Table 2 Presence and regulation of additional/precautionary allergen labelling on prepacked foods

	Precautionary allergen labelling			"Contains…" labelling permitted	Legislation on allergen disclosure implemented
	In use?	Is use regulated?	Risk-based approach, using thresholds?		
Argentina [11]	NO	USE IS PROHIBITED	NO	YES and may be used as an alternative to precautionary labelling to indicate potential cross-contamination	2010
Australia/New Zealand[12]	✓	No	Voluntary. Thresholds vary with allergen	✓	2002
Canada [14]	✓ (specific phrasing recommended)	No	No	✓	1994
Chile [28]	✓	No	No	YES and can be used to indicate risk from cross-contamination. NB free-from labels prohibited	2010
China [15]	✓	No	No	✓	2012
European Union [16,26]	✓	No*	No	No longer permitted from Dec 2014	2003
Hong Kong [17]	✓	No	No	✓	2004
Japan [18]	NO	USE IS PROHIBITED	>10 ppm requires mandatory disclosure for all allergens	YES, only for allergen present in >10 ppm	2002
Kuwait/Gulf [19]	✓	No	No	✓	2008
Malaysia [20]	✓	No	No	✓	2009
Mexico [21]	✓	No	No	✓	2010
Singapore [22]	✓	No	No	✓	2011
South Africa [23]	✓	Yes**	No	✓	2012
South Korea [24]	✓	No	No		2004
Switzerland [29]	✓	Precautionary statements can only be use for non-ingredients above 1 g/kg	Any allergen (whether 'ingredient' or not) above 1000 ppm requires disclosure	✓	2002
USA [25]	✓	No	No	✓	2006

*Indiscriminate use of PAL might be construed as misleading and is therefore prohibited by EU legislation. However, no risk assessment is mandated prior to use of PAL therefore suspicion of any risk of contamination (however minimal) can be used to justify use of PAL.

**Legislation requires use of precautionary labelling to be substantiated by a documented risk assessment demonstrating adherence to GMP.

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Allow minor, periodic dietary modifications	Improve HRQOL	Permit sesame seeds but not tahini, peas but not pea soup, low- concentration hazelnut spread but not hazelnuts	Reduced restrictions, improved HRQOL	Allergic reaction	- Stability of threshold and severity - Determination of threshold/severity - Defining aspects of threshold and severity - Identification of amounts/food types to allow

Managing Food Allergy When the Patient Is Not Highly Allergic

J Allergy Clin Immunol Pract 2022; 10:46-55.

Scott H. Sicherer, MD[a], Elissa M. Abrams, MD[b,c], Anna Nowak-Wegrzyn, MD, PhD[d,e], and Jonathan O'B. Hourihane, FRCPI[f,g]

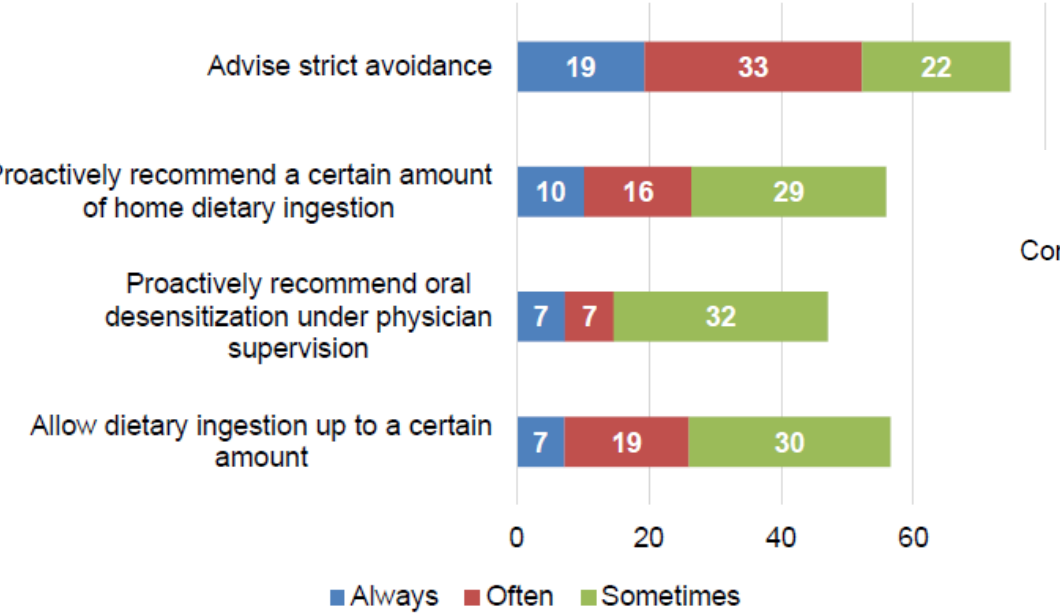
Approach	Intention	Example	Benefit	Risk	Research needs†
Avoidance	Reduce reaction risk, no judgment needed	Avoid all milk, peanut, and products with PAL	Reduce risk	Impair HRQOL	Which has greater impact on HRQOL, avoidance or nonavoidance with risks?
Allow products with precautionary labeling	Reduce restrictions to improve HRQOL	Allow peanut- allergic patient to use PAL products	Reduced restrictions, improved HRQOL	Allergic reaction	- Improved PAL - Real-word PAL risks
Allow minor, periodic dietary modifications	Improve HRQOL	Permit sesame seeds but not tahini, peas but not pea soup, low- concentration hazelnut spread but not hazelnuts	Reduced restrictions, improved HRQOL	Allergic reaction	- Stability of threshold and severity - Determination of threshold/severity - Defining aspects of threshold and severity - Identification of amounts/food types to allow
Prescribe subthreshold ingestion	Therapeutic	Instruct ingestion of 10 mL milk, provide OIT precautions, schedule periodic increases	Increasing threshold, desensitization, potential remission	Acute allergic reactions, chronic allergic inflammation	Safety and efficacy of daily ingestion of subthreshold OIT for any and all starting thresholds for multiple foods

American Academy of Allergy Asthma & Immunology

Food Allergy Management Practices Utilizing Individual Patient Thresholds: A Work Group Report of the AAAAI Adverse Reactions to Foods Committee

J Allergy Clin Immunol Pract 2023; 11:1083-6.

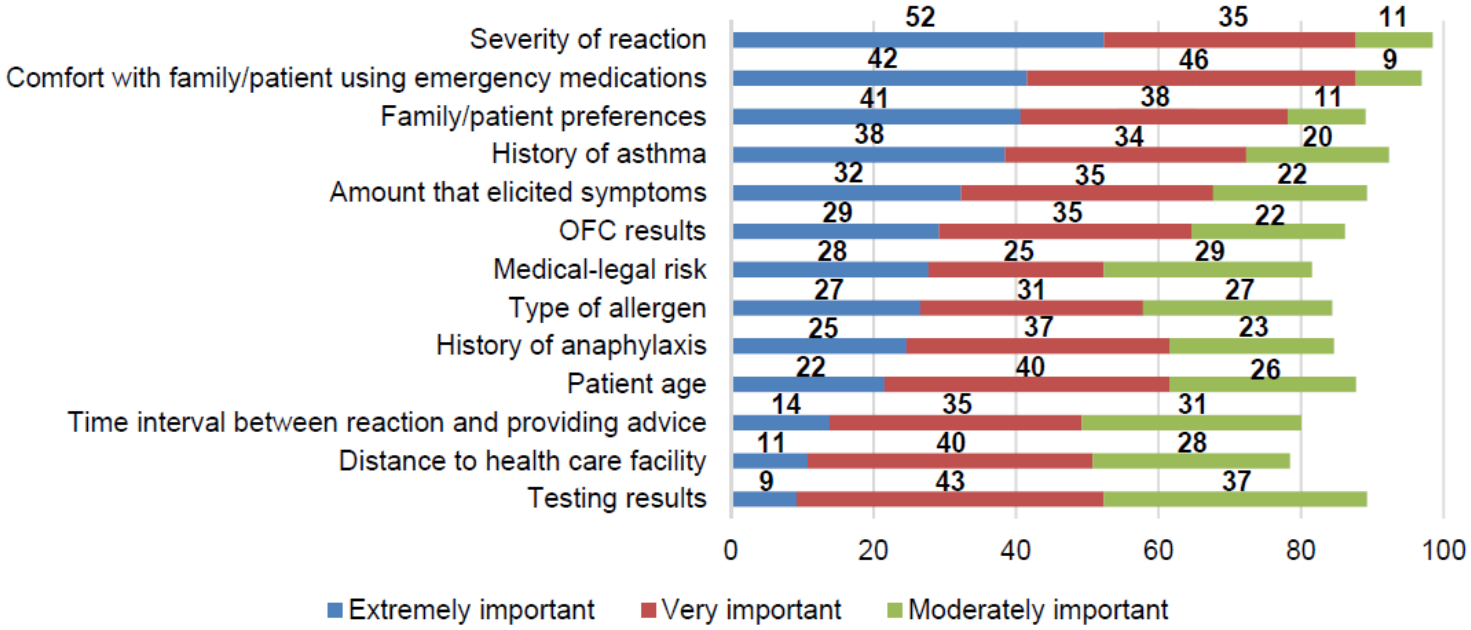
Roxanne C. Oriel, MD[a,*], Ami Shah, MD[a,*], Aikaterini Anagnostou, MD[b], Matthew Greenhawt, MD[c], Fatima Khan, MD[d], Stephanie Leeds, MD[e], Mayuran Ravindran, MD[f], Guillaume Stoffels, MA, MS[g], Brian P. Vickery, MD[h], Yamini V. Virkud, MD, MA, MPH[i], and Scott H. Sicherer, MD[a]



81% reported management strategies other than strict avoidance

Respondent and practice characteristics	Value
Country of practice	
United States	56 (87.5)
Canada	8 (12.5)
Type of practice	
Private	33 (51.6)
Academic	24 (37.5)
Other	7 (10.9)
Years in practice, median (range)	19 (2-51)
Food allergy patients per month, median (range)	30 (1-150)
OFC per month, median (range)	5 (0-65)
OFC per month for children younger than 5 y, median (range)	3 (1-90)
Percent of patients counseled to avoid PAL, median (range)	50 (0-100)
Oral immunotherapy	
Offered, to multiple foods	17 (26.6)
Offered, but only FDA-approved product	20 (31.3)
Not offered, but plans to start	13 (20.3)
Not offered with no plans to start	14 (21.9)

FDA, Food and Drug Administration; *PAL*, precautionary allergen labeling.
Values are n (%) unless otherwise indicated.



Options for management

Actively increase exposure

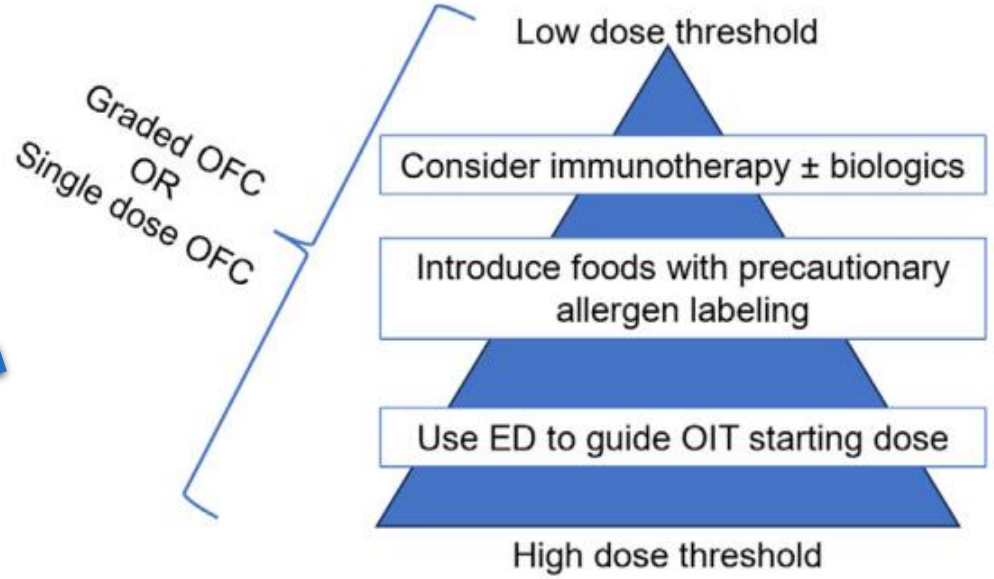
Allow small amounts of exposure

Allow ingestion of PAL

Continue strict avoidance

Not highly allergic

Highly allergic



Li JC, et al. Ann Allergy Asthma Immunol 2024;132:321−7.

Other important things to consider when individualizing management

- Severity of reaction and threshold are independent variables
- Low thresholds do not necessarily correlate with severe reactions
- Quality of life impact should be taken into consideration
- Risk stratifying patients improves daily management

Li et al., Ann Allergy Asthma Immunol, 2024

Conclusions

- Most individuals with food allergies do not react to very low doses of allergen.
- There is a range of phenotypes. There is variability in eliciting doses and clinical manifestations.
- The one-size-fits-all approach to food allergy management is no longer the only strategy offered to patients and their families.
- Historically, “highly allergic” and “mildly allergic” individuals would be advised to avoid their allergen(s) strictly. We now have the opportunity to individualize management plans. Management is no longer binary (ie, avoid vs ingest)

Conclusions

- DEFASE is a tool to define severe allergic reactions systematically – patient perspectives is also one of the domains due to lack of biomarkers for severity.
- PAL is not well standardized, and most food products with such labeling contain none to only trace levels of allergen residue.
- Understanding a patient's threshold level could help in shared decision-making to determine the optimal treatment options for patients (eg, starting dose for OIT and/or the use of biologics).

Thank you for your attention!

Email

roxanne.oriel@mssm.edu

Icahn School of Medicine at Mount Sinai

Elliot and Roslyn Jaffe Food Allergy Institute