

Plenary Session 4: Anaphylaxis through the Life Cycle

> October 17, 2015; 9.00-10.30 Coex CC, Hall D2

Does the relative importance of anaphylaxis triggers differ from infancy to old age?

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CONTENT

- Common triggers of anaphylaxis
- Age trends in etiology of anaphylaxis
- Triggers in infancy
- Unmet needs

IMMUNOLOGIC MECHANISMS (IgE dependent)



Simons FER, Ardusso LRF, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. J Allergy Clin Immunol 2011;127:587-93.

IMMUNOLOGIC MECHANISMS (IgE independent)



J Allergy Clin Immunol 2011;127:587-93.

Variation of Anaphylaxis Triggers with Age

- In children, adolescents, and young adults, foods are the most common trigger.
- In middle-aged and older adults, medications and stinging insects are important considerations, as is idiopathic anaphylaxis.

Lieberman PL. Anaphylaxis. Middleton's Allergy: Principles and Practice. 7th ed. St Louis: Mosby 2009;p. 1027–1049.



Relative percentages of the most frequent trigger groups related to a age Worm M, et al. Dtsch Arztebl Int. 2014;111:367-75.



The ten most common food allergens as triggers in various age groups Worm M, et al. Dtsch Arztebl Int. 2014;111:367-75.



Causes of anaphylaxis admissions by age group, Australia 1994–2005

Laemmle-Ruff I, O'Hehir R, Ackland M, Tang ML. Anaphylaxis - identification, management and prevention. Aust Fam Physician 2013;42(1-2):38-42.

Triggers of Anaphylaxis in Children

Despite differences between studies, food allergy is the most common cause of anaphylaxis in children:

- Foods (33%), insect stings (19%), and medications (14%)
- Less common triggers include cats, latex, cleaning agents, environmental allergens, and exercise.
- For about a quarter of cases, the trigger is unknown.

Dinakar C. Curr Allergy Asthma Rep 2012;12:641-9.

Anaphylaxis in Latin American children and adolescents: the Online Latin American Survey on Anaphylaxis (OLASA)

Solé D, et al. Allergol Immunopathol (Madr) 2012;40:331-5

- Triggers of severe allergic reactions (SAR) were traced in children and adolescents (n=191, up to 18 years of age) registered in the Online Latin American Survey of Anaphylaxis
- The etiological agent was identified in 85.5% of subjects including foods (36.1%), drugs (27.7%), and insect stings (26.2%)



Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes.

Huang F, et al. J Allergy Clin Immunol 2012;129:162-8.



Type of trigger	Total, no (%)	0-6 y	7	-18 y	р	value	
Drugs	19 (9)	7		12		0.83	
Unknown	32 (15)	9		23		0.13	
Other	10 (5)	3		7		0.66	
Food	152 (71)	70		82		0.07	
Specific food trigge	ers no (%)						
Seafood	22 (26)	2		20	().001	
Peanut	17 (20)	12		5		0.06	
Tree nuts	17 (20)	11		6		0.16	
Fruits/vegetables	9 (11)	4		5		0.8	
Cow's milk	6 (7)	6		0		0.02	
Chicken egg	4 (5)	3		1		0.5	
Wheat	4 (5)	3		1		0.5	
Meat/poultry	3 (4)	1		2		0.9	
Seeds	2 (2)	2		0		0.4	
Soy	1 (1)	1		0		0.9	

Anaphylaxis triggers in infancy

- Typical culprits are cow's milk, egg, and peanut, but any food can be implicated, including tree nuts, soy and other legumes, fish, vegetables, fruits, and grains, such as wheat and rice.
- Food-induced anaphylaxis can occur after direct ingestion or indirect ingestion through breast milk; rarely, it is triggered by skin contact with food or vomitus, or inhalation of vapors from cooking food.

Simons FE, Sampson HA. J Allergy Clin Immunol 2015;135:1125-31.

Anaphylaxis triggers in infancy (Cont'd)

- Cow's milk is one of the first foreign proteins ingested by infants.
- Several foods may contain cow's milk in a hidden form.

Cantani A. J Investig Allergol Clin Immunol 1999;9:141-5.

 Contamination of probiotic preparations with milk allergens can cause anaphylaxis in children with cow's milk allergy.

Lee TT, et al. J Allergy Clin Immunol 2007;119:746-7.

Anaphylaxis triggers in infancy (Cont'd)

- In infants, sensitization to one or more foods is common and is not necessarily accompanied by any symptoms.
- However, in one population-based sample, more than 10% of 1-year-olds had oral challenge-proven clinical reactivity to uncooked egg, peanut, or sesame.
 Simons FE, et al. Curr Opin Allergy Clin Immunol 2012;12:389-99.

Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes.

Huang F, et al. J Allergy Clin Immunol 2012;129:162-8.

Age (mo)/sex	Trigger	Symptoms	Severity
4 M	Amoxicillin	Hives, mild wheezing, swelling of hands and feet	Mild
6 F	Rice cereal and formula	Rash, wheezing	Moderate
7 M	Breast-feeding (after mother ate smoked fish for the first time)	Hives, swelling, cough	Mild
11 M	Peanut butter	Eye and facial swelling, perioral cyanosis, hives	Severe
11 M	Egg	Vomiting, eye and periorbital swelling, mild wheezing, urticaria	Mild
11 F	Unclear	Vomiting, cough, rash, mild dyspnea, swelling	Mild



Anaphylaxis triggers in infancy (Cont'd)

- Drug triggers include antibiotics, antipyretics, and neuromuscular blockers.
- Insect stings and bites are more likely to trigger large local reactions or urticaria than anaphylaxis.
- Natural rubber latex (NRL) remains a potential trigger in health care and community settings

Simons FE, Sampson HA. J Allergy Clin Immunol 2015;135:1125-31.

Anaphylaxis triggers in infancy (Cont'd)

- Vaccination.
- topical agents, including soaps and creams.
- Non-immune triggers, such as cold exposure.
- In infants with apparent idiopathic anaphylaxis, novel allergens and antigens, and the possibility of a mast cell activation syndrome, should be considered.

Simons FE, Sampson HA. J Allergy Clin Immunol 2015;135:1125-31.

Food Triggers

 In contrast to older patients, foods are consistently reported to be the most common trigger of anaphylaxis in children and teenagers

Simons FE, et al. Curr Opin Allergy Clin Immunol 2012;12:389-99.

 The most common food allergens are milk products (19 and 29%), peanuts (9-36%), tree nuts (9-19%), eggs (5-22%), shellfish (4-17%), and fruits and vegetables (9%)

Dinakar C. Curr Allergy Asthma Rep 2012;12:641-9.

Food triggers (cont'd)

- Regional differences most likely account for the differences between studies.
- In the United States, shellfish is the most common food allergen in persons aged ≥5 years, whereas eggs, fruits, peanuts, and tree nuts are more common in those aged <5 years.

Dinakar C. Curr Allergy Asthma Rep 2012;12:641-9.

Food triggers (cont'd)

- Peanut and tree nuts are the most common food triggers in North America and in some European countries
- Fruits such as peach are the most common trigger in some other European countries
- In Asia, chickpeas, buckwheat, and bird's nest top the list.

Simons FER. J Allergy Clin Immunol 2009;124:625-36.



Paediatric anaphylaxis in a Singaporean children cohort: changing food allergy triggers over time

Liew WK, et al. Asia Pac Allergy. 2013;3:29-34.



Barzegar S, et al. Common causes of anaphylaxis in children: the first report of anaphylaxis registry in Iran. World Allergy Organ J 2010;3:9-13.

Frequency of FEIAn and EIAn in junior-high-school students attending 130 schools in Yokohama

	Boys (%)	Girls (%)	Total (%)
Subjects	39,697	36,550	76,229
FEIAn	11* (0.027)	2* (0.005)	13 (0.017)
EIAn	12 (0.030)	12 (0.033)	24 (0.031)
* <i>P</i> < .05.			

EIAn: Exercise induced anaphylaxis FEIAn: Food-dependent exercise induced anaphylaxis

Povesi Dascola C, Caffarelli C. Ital J Pediatr 2012;38:43.



Anaphylaxis from passive transfer of peanut allergen in a blood product

Jacobs JF, et al. N Engl J Med 2011;364:1981-2.

- A 6-year-old boy with acute lymphoblastic leukemia had an anaphylactic reaction while receiving a leuko-reduced pooled buffy-coat product with ABO-identical platelets.
- The patient's mother stated that her son had a similar reaction after eating peanuts at the age of 1 year.
- IgE antibodies reactive to both Ara h2 and DRP–Ara h2 were detected.
- Consumption of peanuts by the donors provided the trigger for this patient's transfusion reaction



Medications as Triggers of Anaphylaxis

- Beta-lactam and other antibiotics e.g. penicillin in areas were rheumatic fever is still prevalent.
- NSAIDs: aspirin, ibuprofen, and others.
- Anti-tuberculosis drugs in some parts of the world.

Simons FER. J Allergy Clin Immunol 2010;125:S161-81.

Medications (Cont'd)

- Chemotherapeutic agents
- monoclonal antibodies
- contaminants in medications, for example, oversulfated chondroitin sulfate in heparin

Herbal formulations

Simons FE, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J 2011;4(2):13-37.

Causes of Drug-Induced Anaphylaxis in 313 Patients by Age Group

Drugs	All Patients (n=313)	Patients <18 y (n=26)	Patients 18-65 y (n=250)	Patients ≥65 y (n=37)
NSAIDs	150 (47.9)	11 (42.3)	124 (49.6)	15 (40.5)
Antibiotics	111 (35.5)	12 (46.2)	91 (36.4)	8 (21.6)
Anesthetic agents	19 (6.1)	0	15 (6)	4 (10.8)
Cytostatics (carboplatin, 4; oxaliplatin, 3; docetaxel, 1; tamoxifen, 1)	9 (2.9)	1 (3.8)	4 (1.6)	4 (10.8)
Corticosteroids (hydrocortisone, 2; methylprednisolone, 2; betamethasone, 1)	5 (1.6)	1 (3.8)	3 (1.2)	1 (2.7)
Analgesics (clonixin)	5 (1.6)	0	5 (2)	0
PPIs (lansoprazole, 1; omeprazole 1; pantoprazole, 1; esomeprazole, 1)	4 (1.3)	0	4 (1.6)	0
Vitamins (vitamin B ₁₂ , 3; vitamin D ₃ , 1)	4 (1.3)	0	2 (0.8)	2 (5.4)
Iodinated contrast media	3 (0.96)	0	1 (0.4)	2 (5.4)
Vaccines (anti-tetanus in 1 adult; MMR and anti-meningococcal in 1 child)	2 (0.6)	1 (3.8)	1 (0.4)	0
Others ^b	10 (3.2)	0	8 (3.2)	2 (5.4)

Faria E, et al. J Investig Allergol Clin Immunol 2014;24:40-8.

Insect Stings

 Systemic allergic reactions to insect stings affect up to 5% of the population during their lifetime, and up to 32% of beekeepers

Ludman SW, Boyle RJ. J Asthma Allergy 2015;8:75-86.

 Although insect sting-induced admissions peaked between 5 and 9 years of age, most insect sting-induced anaphylaxis deaths occurred between 35 and 84 years of age

Dinakar C. Curr Allergy Asthma Rep 2012;12:641-9.

Insects (cont'd)

- Hymenoptera venoms (bee, wasp, yellow-jacket, hornet, fire ant): contain enzymes such as phospholipases and hyaluronidases as well as other proteins
- less commonly, saliva from a biting insect (e.g. order Diptera [flies and mosquitoes] or Hemiptera [kissing bugs])

Simons FER. J Allergy Clin Immunol 2009;124:625-36.



Natural rubber latex (NRL)

- It is widely used in infants and children.
- Infant pacifiers, balloons, toys, sports equipment, and other articles
- Medical procedures, e.g., internal examinations, surgery, and catheterization.
- In some NRL-sensitive children, cross-reacting foods also trigger anaphylaxis.



Foods associated with latex allergy

High association	Moderate association	Low association
Avocado	Apple	Apricot
Banana	Carrot	Buckwheat
Chestnut	Celery	Castor Bean
Kiwi	Melons	Cayenne pepper
	Papaya	
	Potato	
	Tomato	

Pollart SM, et al. Am Fam Physician 2009;80(12):1413-8.

Elective medical procedures

The risk of systemic reactions with SPT is remote but cannot be totally excluded! Liccardi G, et al. J Investig Allergol Clin Immunol 2006;16:75-8.



Systemic reactions associated with subcutaneous allergen immunotherapy: timing and risk assessment

DaVeiga SP, et al. Ann Allergy Asthma Immunol 2011;106:533-7.



- Rate of systemic reaction from SCIT was 0.28% (46/16,375) per injection visit.
- Twenty patients had 46 systemic reactions.
- All severe reactions occurred within 30 minutes.
- The estimated odds of systemic reaction were almost 6 times higher for patients with more than 3 to 4+ positive skin tests.
- For each additional 4+ skin test, the estimated odds for systemic reaction increased by 17% (P = .020)

Anaphylaxis during anesthesia in France: an 8-year national survey

- In adults: neuromuscular blocking agents (58%), latex (20%), or antibiotics (13%)
- In children: latex (42%), neuromuscular blocking agents (32%), or antibiotics (9%)





Mertes PM, et al. J Allergy Clin Immunol 2011;128:366-73.

Journal of Allergy and Clinical Immunology 2011 128, 366-373DOI: (10.1016/j.jaci.2011.03.003) Copyright © 2011 American Academy of Allergy, Asthma & Immunology Terms and Conditions

Elective medical procedures (cont'd)

Omalizumab (anti-lgE therapy)

- Anaphylaxis-reporting rate of 0.09%
- 61% of the reactions occurred in the first 2 hours after one of the first 3 doses.
- Wait periods were suggested after administration.

AAAAI/ACAAI Joint Task Force Report on omalizumabassociated anaphylaxis. J Allergy Clin Immunol 2007;120:1373-7.

Vaccine induced anaphylaxis

- Anaphylaxis after vaccination is rare
- Anaphylactic reactions are estimated to occur at a rate of approximately 1 per million
- Recent evidence indicates the safety of MMR and LIV in patients with egg allergy
- In patients with severe egg allergy, a single dose of LIV can be administered without any additional precautions beyond proper equipment

Kelso JM, et al. J Allergy Clin Immunol 2012;130:25-43.

Recommendations regarding influenza vaccination for persons who report allergy to eggs

CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP): United States, 2012-13 influenza season. Morb Mortal Wkly Rep 2012;61:613-8



Risk of anaphylaxis after vaccination in children and adults

Age group (y)	No. of cases	Doses administered	Rate (/10 ⁶ doses)	Lower 95% Cl	Upper 95% Cl
0-17	18	12,403,201	1.45	0.86	2.29
18-49	9	5,063,802	1.78	0.81	3.37
≥50	6	7,706,962	0.78	0.29	1.69

McNeil MM, et al. J Allergy Clin Immunol 2015 in press.

Risk of anaphylaxis after vaccination in children and adults

Vaccine (administered alone)	No. of cases (n = 18)	Doses administered alone	Rate (/10 ⁶ doses)	Lower 95% CI	Upper 95% Cl
τιν	10	7,434,628	1.35	0.65	2.47
ΜΙν	2	1,090,279	1.83	0.22	6.63
Tdap	1	1,951,153	0.51	0.01	2.86
PPSV23	1	403,803	2.48	0.06	13.80
HAV	1	296,271	3.38	0.09	18.81
HZV	2	208,407	9.60	1.16	34.67
Rabies	1	11,619	86.1	2.18	479.43

McNeil MM, et al. J Allergy Clin Immunol 2015 in press.

Vaccine induced anaphylaxis (Cont'd)

- Almost all the vaccine components can be considered as potential triggers
- Of particular importance are culture derived proteins from egg, gelatin and yeast
- Other sources of allergic reaction are antibiotics and vaccination antigens

Chung EH. Clin Exp Vaccine Res 2014;3:50-7.

Idiopathic Anaphylaxis

- Up to 59% of cases of anaphylaxis; more in females.
- Hidden triggers and Mast cell disorders should be excluded
- If the basal tryptase level is > 20 ng/ml, a bone marrow biopsy is indicated, even if cutaneous manifestations of mastocytosis are absent

Simons FE. J Allergy Clin Immunol 2009;124:625-36.

Breakdown of total pediatric anaphylaxis events by allergen triggers, median age on presentation

Allergen	Number (%)	Median age (interquartile range) (years)
Total	108 (100)	7.79 (3.60 - 10.78)
Food	68 (62.9)	4.92 (1.97 - 10.29)
Drugs	32 (29.6)	10.46 (6.63 - 13.09)
ldiopathic	8 (7.4)	7.82 (7.57 - 10.37)

Adapted from: Liew WK, et al. Asia Pac Allergy 2013;3:29-34.

Idiopathic anaphylaxis (Cont'd)

- It accounts for around 10% of cases of anaphylaxis in children
- The discovery of episodes of anaphylaxis caused by galactose-alpha-1,3-galactose in the past decade solved some of its mysteries
- Fortunately, the majority of such patients exhibit a diminishing frequency of reactions over time

Greenberger PA, Lieberman P. J Allergy Clin Immunol Pract 2014;2:243-50.

Unmet Needs in Trigger Information

- High resource countries need improved standardization of allergens, better reporting novel triggers, and standardize protocols for skin tests and challenge tests
- Limited resource countries need more comprehensive information about allergens in some geographic areas, and certain groups of allergens, e.g. reptile venoms and helminths

Simons FE, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J 2014;7(1):9.



- Paucity of information about anaphylaxis triggers in some parts of the world alters proper management
- The key to successful management involves recognition of populations at risk (e.g., children with food allergies)
- Knowledge of the variation in triggers with age helps suspecting the culprit allergen.