HASSENFELD CHILDREN'S HOSPITAL AT NYU LANGONE

The emerging epidemiology of FPIES

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Session 0313

Anna Nowak-Wegrzyn, MD, PhD
Professor of Pediatrics
NYU Grossman School of Medicine
Chief, Allergy and Immunology Division

Disclosures (past 24 months)

- Grants: ITN-NIAID, DBV Technologies, Astellas Pharma, Thermofisher, Nutricia, Nestle
- Advisory Board: Merck, Alk-Abello
- Royalties: Up To Date
- Deputy Editor for the Annals of Allergy, Asthma and Immunology
- Chair, medical advisory board, International FPIES Association
- Chair, FAED Interest Section, AAAAI

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Learning objectives

- To describe prevalence of FPIES
- To discuss food triggers of FPIES
- To describe FPIES phenotypes and comorbidities

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Food protein-induced enterocolitis syndrome: definition

FPIES is a non-IgE, cell-mediated food allergic disorder manifesting with predominantly gastrointestinal symptoms of:

- delayed emesis
- lethargy
- pallor
- diarrhea

with notable absence of typical cutaneous and respiratory allergic symptoms

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Studies reporting cumulative incidence of infantile FPIES

	Katz et al 2011	Mehr et al 2017	Bellon-Alonso 2018
Country	Israel	Australia	Spain
Design	Unselected birth cohort	Population based (APSU)	Unselected birth cohort
Diagnosis confirmation	OFC	Case-definition of acute FPIES	OFC
Foods	Cow's milk	Rice, CM, egg	CM, fish, egg yolk
Incidence	0.34% in the first 12 months	0.015% in the first 24 months	0.7% in the first 12 months

5

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FPIES prevalence in the USA: 0.51% in <1-17years old

- A cross-sectional, population-based survey between 10/2015 and 9/2016
- 53,575 US households included
- Primary outcome: **lifetime prevalence of physician-diagnosed FPIES.**
- Participants were asked *"Has your child **ever been diagnosed by a physician** with food protein-induced enterocolitis syndrome (FPIES)? Note, this is a very specific and rare allergic condition"*. Questions about the presence of other chronic atopic comorbidities utilized the same question stem.

Children	
<18 years, N=261	**.51 (.42-.62)**
< 1 year, N=6	.11 (.04-.26)
1 year, N=17	.59 (.32-1.08)
2 years, N=20	.76 (.39-1.47)
3-5 years, N=41	.52 (.29-.93)
6-10 years, N=74	.56 (.40-.78)
11-13 years, N=58	.61 (.43-.88)
14-17 years, N=45	.37 (.24-.57)

Children with FPIES had high rates of other allergic conditions including IgE-FA, EoE, asthma, and seasonal allergies.

Nowak-Wegrzyn…Gupta R
JACI, August 2019

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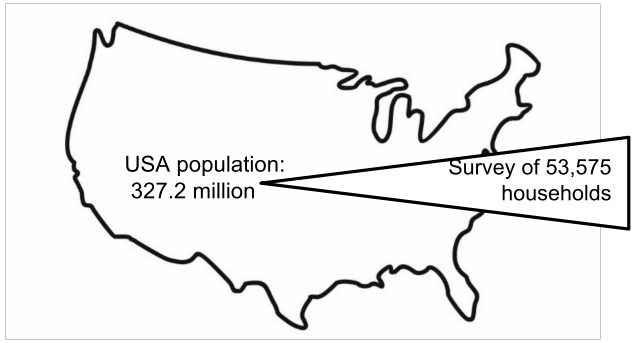
FPIES prevalence in the USA- population-based survey



375,000 Children with FPIES
(0.51% of US Pediatric Population)

550,000 Adults with FPIES
(0.22% of US Adult population)

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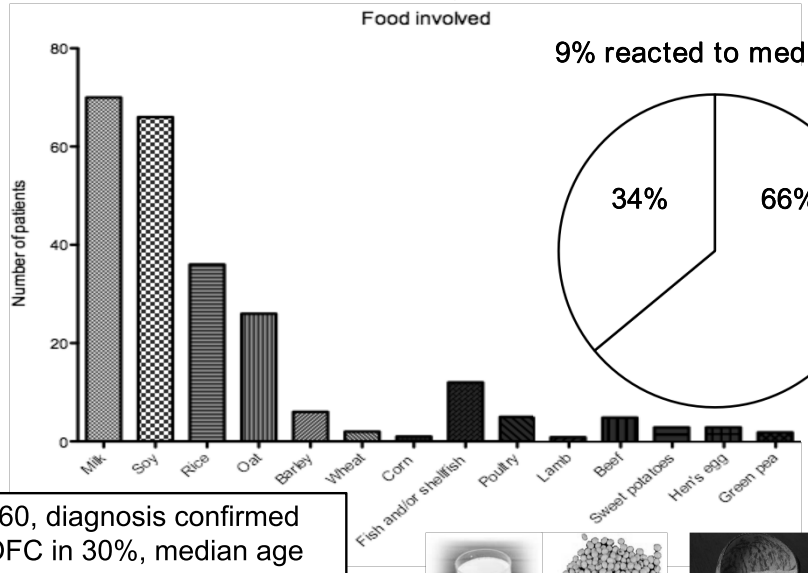
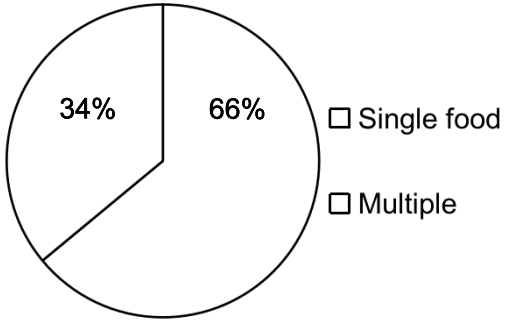
Food allergens in childhood FPIES: Mt Sinai 10-year experience



9% reacted to median 3 foods (3-10)

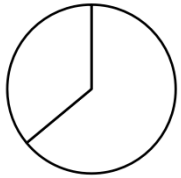


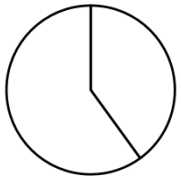
N=160, diagnosis confirmed by OFC in 30%, median age 45 mo

Caubet JC et al, JACI, May 2014

Food allergens in childhood FPIES: referral centers in the US

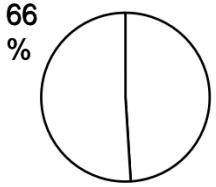
Mount Sinai	CHOP	Baylor
N=160	N=462	N=74
66% single food	40% single food	49% single food

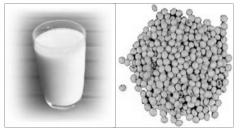




34%

66 %





Caubet JC et al, JACI, May 2014

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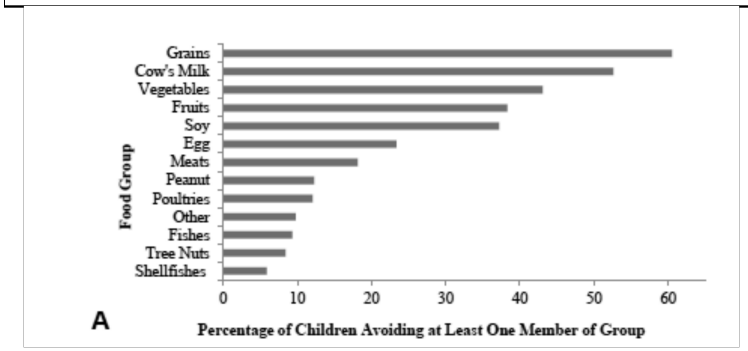
More recent data-USA, 2020

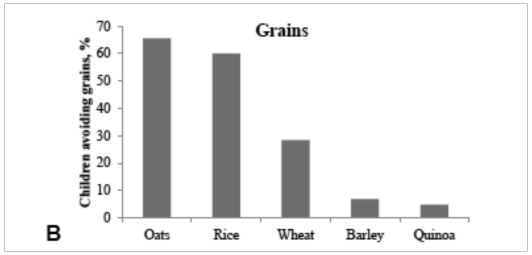
Original Article

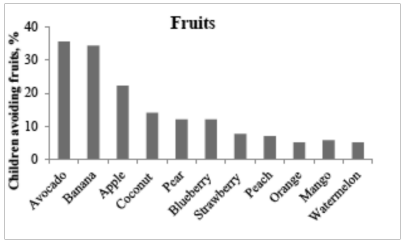
A Slice of Food Protein–Induced Enterocolitis Syndrome (FPIES): Insights from 441 Children with FPIES as Provided by Caregivers in the International FPIES Association

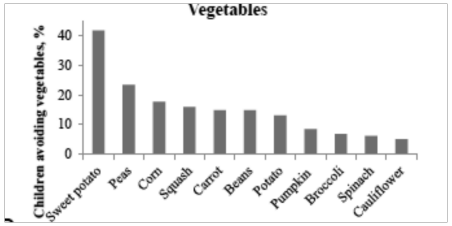
Michelle C. Maciag, MD[a,b], Lisa M. Bartnikas, MD[a,b], Scott H. Sicherer, MD[c], Linda J. Herbert, PhD[d], Michael C. Young, MD[a,b], Fallon Matney, MSW, LCSW, CAM[a], Amity A. Westcott-Chavez, MA, MFA[a], Carter R. Petty, MA[a,b], Wanda Phipatanakul, MD, MS[a,b], and Theresa A. Bingemann, MD[a] *Boston, Mass; New York, NY; Washington, DC; Point Pleasant Beach, NJ; and Rochester, NY*

JACIIP 2020, 1702-9









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10

FPIES phenotype: acute

- Ingestion following a period of avoidance (at least several days)
- Onset of emesis: **1- 4 hours**
- Lethargy, limpness (“septic appearance”)
- Elevated PMN with left shift, elevated platelets
- 20% go into **shock**
- 15% with methemoglobinemia
- 6-8 hours later: diarrhea
- Symptoms resolve within 24 hours
- Onset: usually under 12 months; F/SF children, adults

FPIES phenotypes: chronic

Food aversion and poor weight gain in food protein–induced enterocolitis syndrome: A retrospective study

Kuan-Wen Su, MD,[a,b,c,d] Sarita U. Patil, MD,[a,b,e,f] Jennifer L. Stockbridge, MSN, CNP, FNP-BC,[a,b] Victoria M. Martin, MD, MPH,[a,e,g] Yamini V. Virkud, MD, MA, MPH,[a,b,e,f] Jing-Long Huang, MD,[h] Wayne G. Shreffler, MD, PhD,[a,b,e,f] and Qian Yuan, MD, PhD[a,e,g]
Boston, Mass, and Keelung and Taoyuan, Taiwan

(J Allergy Clin Immunol 2020;145:1430-7.)

Results: Two hundred three patients with FPIES were identified, including 180 only with acute FPIES, 8 with chronic FPIES, and 15 with both. Oat (34.5%), rice (29.6%), and cow's milk (19.2%) were the most common food triggers. The

13% of cases were chronic FPIES

TABLE III. Logistic regression analysis for patients with FPIES with food aversion and poor body weight gain

Variables	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis* OR (95% CI)	*P* value
Food aversion				
Multiple triggers (≥3)	3.46 (1.59-7.51)	**.002**	3.07 (1.38-6.82)	**.006**
FPIES to wheat	7.26 (1.74-30.40)	**.007**	2.60 (0.50-13.56)	.26
Family history of food allergy	1.91 (0.94-3.90)	.08	1.79 (0.86-3.73)	.12
Poor body weight gain				
Multiple triggers (≥3)	3.61 (1.32-9.79)	**.01**	2.05 (0.63-6.61)	.23
FPIES to cow's milk	3.19 (1.19-8.59)	**.02**	3.41 (1.21-9.63)	**.02**
FPIES to banana	7.10 (2.05-24.62)	**.002**	7.63 (2.10-27.80)	**.002**
Chronic FPIES	4.07 (1.37-12.11)	**.01**	1.96 (0.44-8.83)	.38

Variables in the multivariate analysis for poor body weight gain: sex, birth mode, prematurity, perinatal antibiotics exposure, bread-feeding, multiple trigger, FPIES to cow's milk/banana, and chronic FPIES. Boldface indicates $P < .05$.
OR, Odds ratio.
*Variables in the multivariate analysis for food aversion: sex, birth mode, prematurity, perinatal antibiotics exposure, bread-feeding, multiple trigger, FPIES to wheat, and family history of food allergy.

FPIES phenotypes: atypical

Cow milk-FPIES
1 in 4 develop +CM-IgE
(atypical FPIES)

⇩

1 in 3 progress to immediate IgE- CMA

FPIES & IgE-mediated allergy can occur in the same child

Overall 1 in 3 have IgE-FA to another food

Caubet JC, et al. JACI, 2014

FPIES phenotypes: adult onset

- Anecdotal reports of FPIES with an onset in adulthood
- Natural history largely unknown
- **Scallop**--Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. J Allergy Clin Immunol. 2012
- **Shrimp**--Gleich GJ, Sebastian K, Firszt R, Wagner LA. J Allergy Clin Immunol Prac. 2015 Nov
- **Shellfish, dairy, wheat, egg**--Du Y, Nowak-Wegrzyn A, Vadas P. Annals of Allergy Asthma and Immunology 2018
- **Fish, Crustaceans, egg**--Tan JA, Smith WB JACI in Practice 2014
- **SYMPTOMS:** dramatic, severe abdominal pain, nausea, vomiting, LOC

FPIES in adults

Shrimp--Gleich GJ, Sebastian K, Firszt R, Wagner LA. J Allergy Clin Immunol Prac. 2015 Nov

38 adults with allergy to shrimp

8/38 **(21%)** exclusively GI sxs, neg sIgE; **7/8 F!**

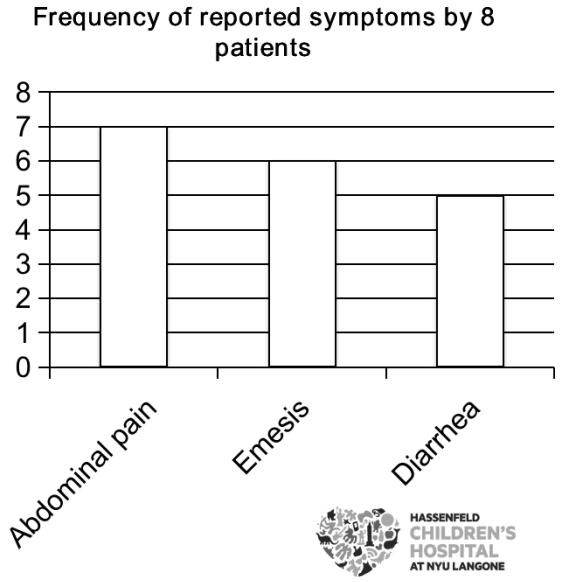
Age at evaluation 23-69 years

Age at onset: <12-62 years

Past reactions: 2-6 (1 pt >100)

5 reported reactions to 2 or more SF

(e.g., crab, scallop, clam); Retrospective, no OFC



15

FPIES COMORBIDITIES: EoE

	% among those with EoE	% among those without EoE	*P* value
Children			
Lifetime			
IgE-FA	32.44 (20.48-47.22)	7.59 (7.11-8.10)	<.001
FPIES	19.11 (9.32-35.20)	0.48 (0.39-0.59)	<.001
Asthma	26.83 (14.92-43.41)	12.17 (11.37-13.01)	.008
Atopic dermatitis/ eczema	27.53 (15.81-43.44)	5.8 (5.25-6.48)	<.001
Allergic rhinitis	43.48 (28.62-59.61)	12.74 (11.97-13.56)	<0.001
Insect sting allergy	2.83 (0.69-10.85)	2.23 (1.93-2.57)	.74
Medication allergy	3.94 (1.57-9.58)	4.15 (3.71-4.65)	.91
Biological parental reported history of atopy			
IgE-mediated food allergy	59.54 (44.52-72.96)	19.32 (18.24-20.46)	<.001
Asthma	36.17 (23.37-51.28)	18.30 (1719-19.46)	.003
Atopic dermatitis/ eczema	41.31 (27.50-56.64)	15.54 (14.50-16.63)	<.001
Allergic rhinitis	59.73 (4.47-73.31	40.02 (38.52-41.54))	.009

Allergy EAACI WILEY

DOI: 10.1111/all.14148

Eosinophilic esophagitis and allergic comorbidities in a US-population-based study

Antonella Cianferoni[1]
Christopher M. Warren[2]
Terri Brown-Whitehorn[1]
Fallon Schultz-Matney[3]
Anna Nowak-Wegrzyn[4,5]
Ruchi S. Gupta[2]

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FPIES COMORBIDITIES: Atopy

TABLE II. Cumulative incidence of atopic comorbidity in FPIES

	Cohort %			
	Primary care (n = 158,296)	FPIES (n = 214)	*P* value	Odds ratio [95% CI]
Atopic dermatitis	11.7%	20.6%	<.001	2.0 [1.5-2.7]
IgE-food allergy	4.0%	23.8%	<.001	7.6 [5.5-10.4]
Asthma	18.4%	26.6%	<.01	1.6 [1.2-2.2]
Allergic rhinitis	16.7%	28.0%	<.001	1.9 [1.4-2.6]

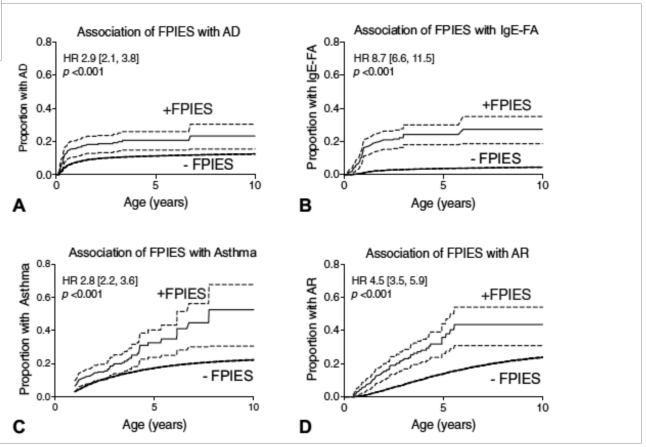
Cumulative incidence of atopic comorbidities at 10 years of follow-up in patients with and without FPIES. *P* value is shown from the χ^2 test, followed by the Woolf-logit method to compute the unadjusted odds ratio.
CI, Confidence interval; *FPIES*, food protein–induced enterocolitis syndrome.

Original Article

Elevated Atopic Comorbidity in Patients with Food Protein–Induced Enterocolitis

Melanie A. Ruffner, MD, PhD[a,b], Kathleen Y. Wang, MD[c], Jesse W. Dudley, MS[d], Antonella Cianferoni, MD, PhD[a,b], Robert W. Grundmeier, MD[d], Jonathan M. Spergel, MD, PhD[a,b], Terri F. Brown-Whitehorn, MD[a,b], and David A. Hill, MD, PhD[a,b] *Philadelphia, Pa; and Chapel Hill, NC*

(J Allergy Clin Immunol Pract 2020;8:1039-46)



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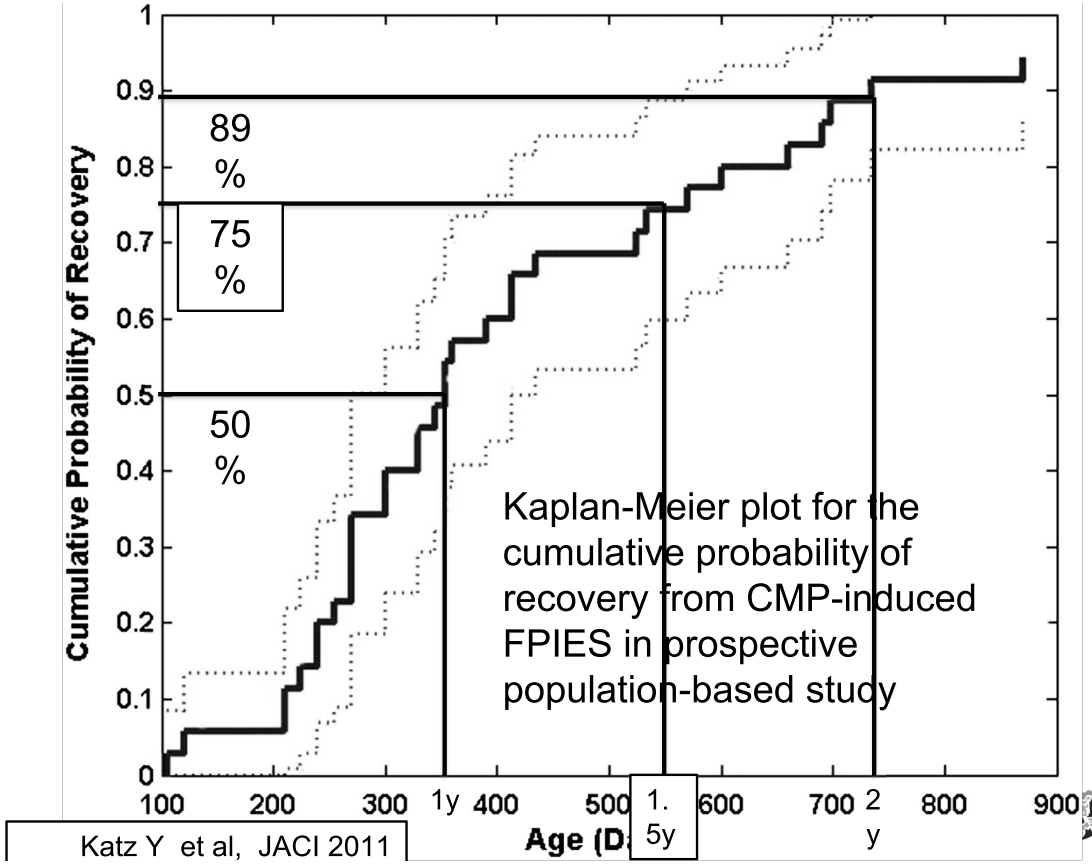

Kaplan-Meier plot for the cumulative probability of recovery from CMP-induced FPIES in prospective population-based study

Katz Y et al, JACI 2011

Selected studies of infantile FPIES natural history

Study, country	Study design, number of patients	Study population; foods	Rates of resolution by age
Hwang et al, 2009[28], South Korea	Prospective; n=23; OFCs were performed at 6 months of age and every 2 months thereafter	Cohort of infants with FPIES evaluated by pediatric gastroenterologist practice CM, soy	CM: 27.3% by age 6 months, 100% by age 2 years Soy: 75% by age 6 months, 100% by age 14 months
Katz et al, 2011[3] Israel	Prospective, FPIES diagnosed by an OFC in 44 infants	Unselected population-based cohort (n=13,019), single center CM	90% resolution rate by age 3 years
Caubet et al, 2014[7] USA	Retrospective, single-center, n=160	Cohort of patients evaluated in a referral allergy center CM, soy, rice, oat, other	Median age (years) at resolution was: CM 5.1; soy 6.7; rice 4.7; oat 4.0
Ruffner et al, 2013[8] USA	Retrospective, single center, n=462	Cohort of patients evaluated in a referral allergy center CM, soy, cereal grains, fruits and vegetables	Resolution rates: by age 2 years: 35%; 3 years: 70%; 4 years: 80%; 5 years: 85%
Lee et al, 2017[32], Australia	Retrospective, single center, n=69	Cohort of patients evaluated in a referral allergy center CM, egg, rice, fish, other	Resolution rates by age 3 years: CM: 88%; Rice: 87%; Egg: 12.5%; Fish: 25%
Vila et al, 2015 [35], Spain	Retrospective, single center, n=21	Cohort of patients evaluated in a referral allergy center Fish, other	Median age of tolerance: Fish: 30% by a median age 4 years (range 1 to 17 years. Other solid foods (fruit, rice, corn): 3 years (range, 1 to 4 years)
Gonzalez-Delgado et al, 2016[25], Spain	Retrospective, single center, n=16	Cohort of patients evaluated in a referral allergy center Fish	Fish: 18.75%resolution by mean age 4.5 years
Miceli-Sopo, et al, 2012[36], Italy	Retrospective, multi-center, n=66	Cohort of patients evaluated in a referral allergy centers CM, other foods*	Overall 48% resolved by a mean age 29 months (SD 17 months). Age of resolution: CM: 24+8 months; Other foods 53 ± 17 months, (P < 0.0006).

Nowak-Wegrzyn, Berin, Mehr. JACI in Practice, 2020

19

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SUMMARY

- FPIES is a non-IgE, cell-mediated GI food allergic disorder
- Prevalence estimates in the USA:0.51% children, 0.22% adults
- Infantile FPIES food triggers generally reflect the first foreign food proteins introduced into the diet: CM, cereal grains
- FPIES has different phenotypes: acute, chronic, atypical, adult-onset
- Adult FPIES is usually triggered by seafood with anecdotal reports of other foods (eggs, soy, dairy, wheat)
- FPIES is frequently associated with IgE-comorbidities (FA, A, AR) and EoE, AD

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