

Síndrome de enterocolitis inducida por proteínas “Food protein-induced enterocolitis syndrome” (FPIES)

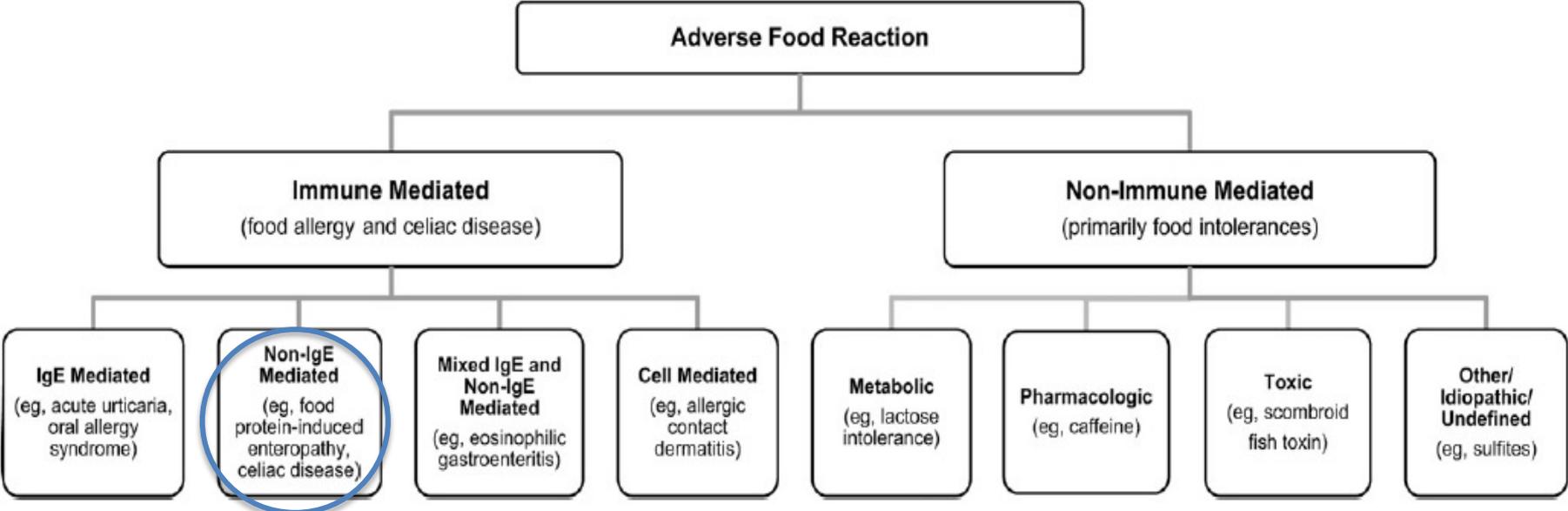
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Enterocolitis inducida por proteínas alimentarias

¿Qué es?

Trastorno alérgico no mediado por IgE
caracterizado por síntomas GI y una
respuesta inflamatoria sistémica

Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel



FPIES

FIG 1. Types of adverse reactions to food

Boyce et al. JCAI, 2010.

Manifestaciones clínicas de la ALERGIA ALIMENTARIA según el tipo de reacción

Reacciones IgE mediadas, inmediatas	
Gastrointestinales	Vómitos, dolor abdominal, y/o diarrea
Cutáneas	Urticaria, angioedema, prurito, exantema morbiliforme
Respiratorias	Rinoconjuntivitis aguda, sibilancias, tos y estridor
Generalizadas	Anafilaxia
Reacciones mixtas: IgE mediadas y mediadas por mecanismo celular, de inmediatas a retardadas	
Cutáneas	Eccema atópico
Mediadas por mecanismo celular	
Gastrointestinal	Síndrome de enterocolitis inducida por proteínas*, proctocolitis*, enteropatía inducida por proteínas*
Respiratorias	Hemosiderosis inducida por proteínas (S. Heiner)*. Muy raro
Mecanismo incierto	
Dismotilidad gastrointestinal	Reflujo gastroesofágico Estreñimiento Cólico infantil

Clinical features of food protein–induced enterocolitis syndrome

Scott H. Sicherer, MD, Philippe A. Eigenmann, MD, and Hugh A. Sampson, MD

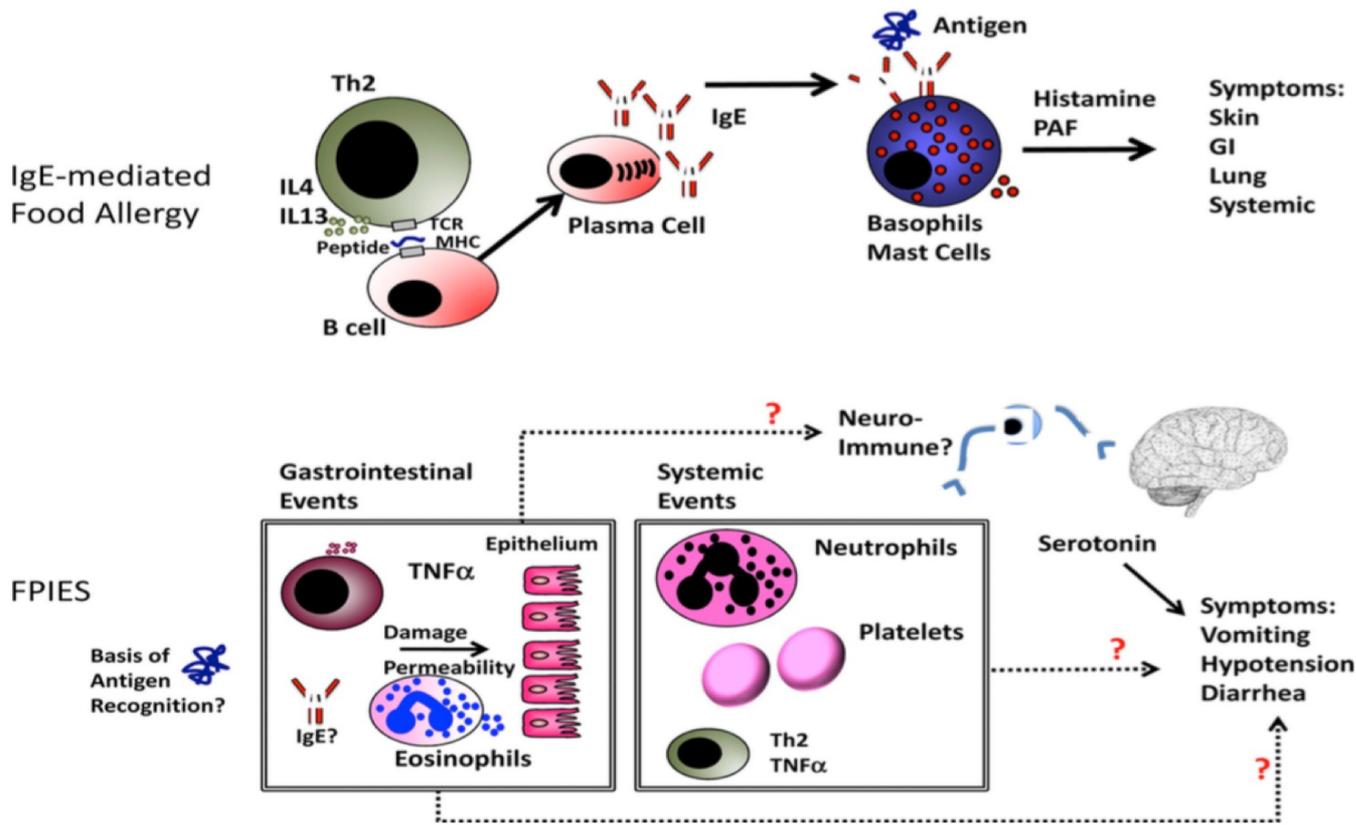
Objective: To describe the clinical characteristics of food protein–induced enterocolitis syndrome (FPIES), a symptom complex of severe vomiting and diarrhea occurring several hours after the ingestion of particular food proteins in infants.

Study design: Retrospective review of a referral population.

Results: Sixteen patients had typical FPIES; 11 reacted to milk, 11 to soy, and 7 to both. Mean age at diagnosis was 7 weeks for milk reactivity and 8 weeks for soy reactivity. Two patients also had rice- and pea-induced FPIES. Among 14 patients who were followed up for a median period of 25 months, loss of sensitivity to milk occurred in 6 of 10 patients and loss of sensitivity to soy occurred in 2 of 8. Six additional cases of FPIES were considered atypical: 1 patient had late-onset disease caused by poultry, and in 5 patients IgE antibody to milk or soy developed. During supervised food challenges with milk and soy, the peripheral blood neutrophil count rose over 3500 cells/mm³ in 9 of 10 positive challenges and did not rise above this value in the 7 negative challenges. Emergency treatment was required in 62% of challenges.

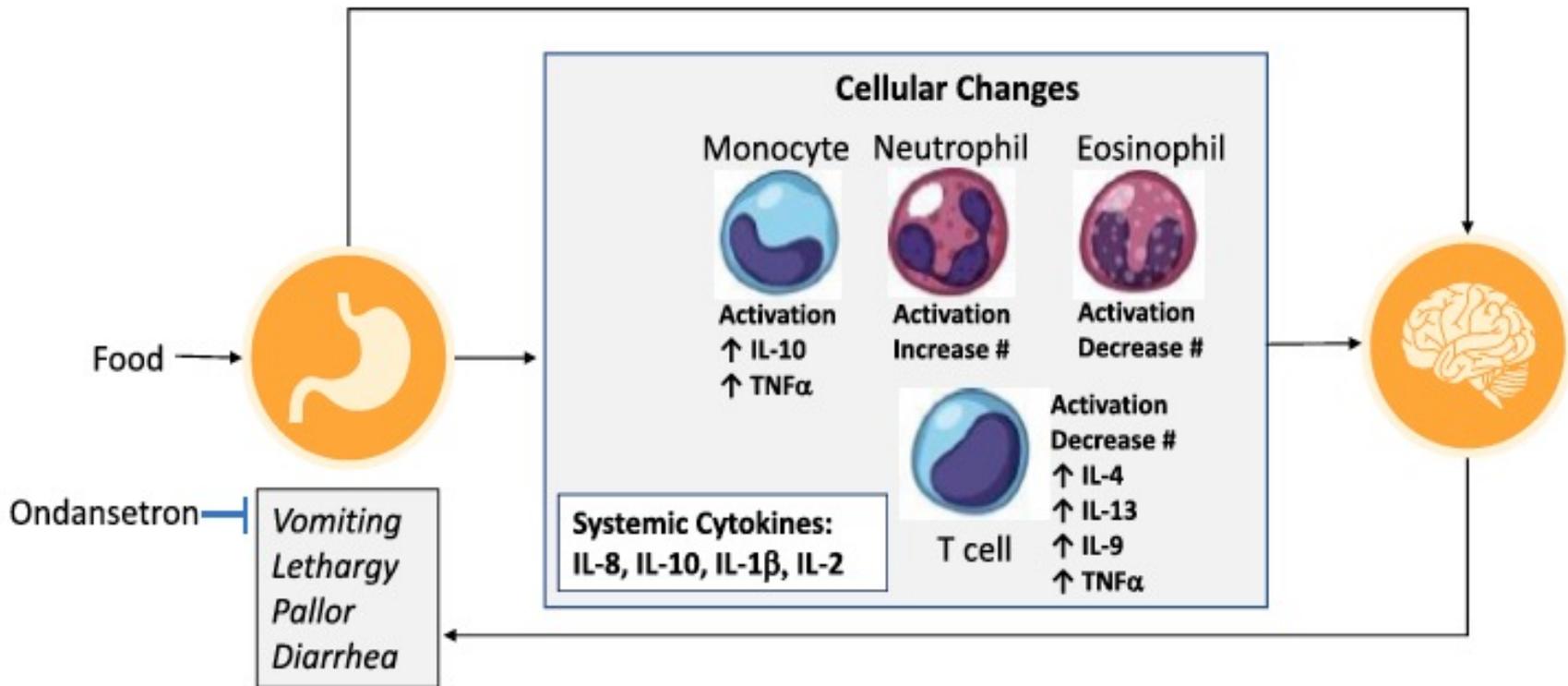
Conclusions: Although most patients with FPIES are infants reactive to milk and/or soy, this diagnosis should be considered in older children and for other foods. Food-specific IgE sensitivity may develop in some patients. Standardized food challenges are helpful for diagnosis and follow-up. (*J Pediatr* 1998; 133:214-9)

Patogenia



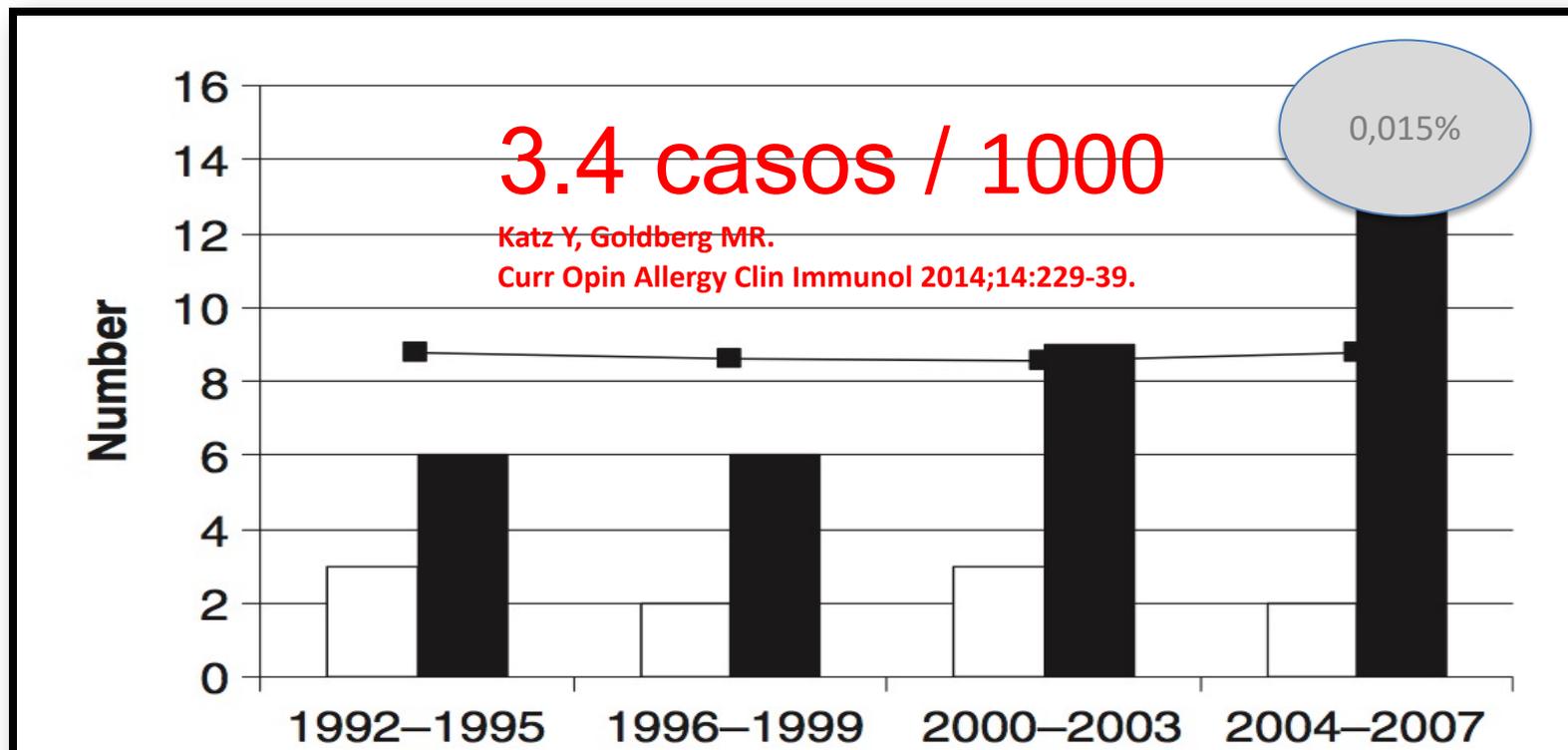
Bering et al. *J Allergy Clin Immunol.* 2015 May ; 135(5): 1108–1113.

Patogenia



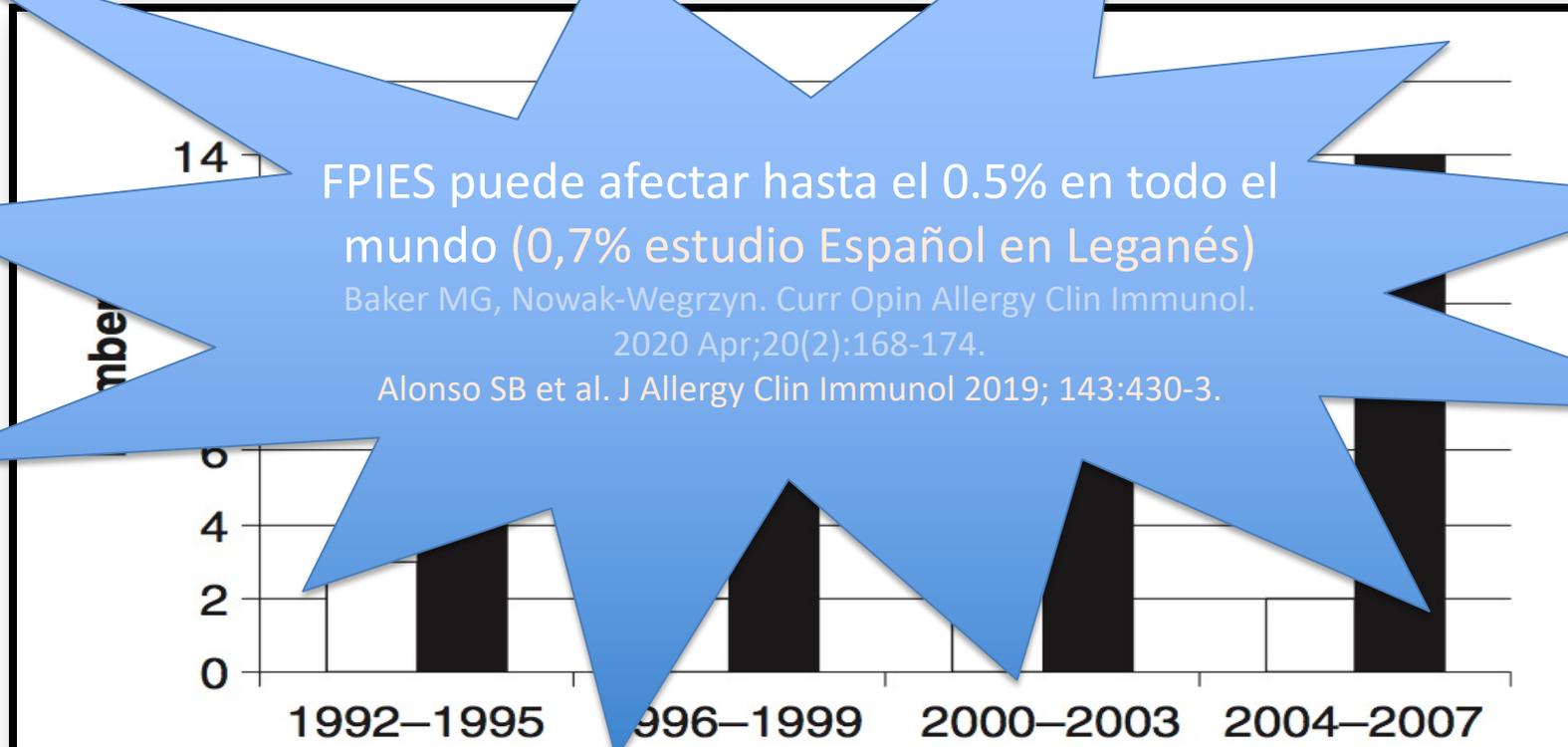
Nowak et al. J Allergy Clin Immunol Pract 2020;8:24-35)

FPIES: incidencia en aumento



Cases of FPIES according to year of diagnosis. Black bars indicate the total number of children diagnosed as having FPIES, white bars indicate the median number of FPIES episodes before a correct diagnosis was made, and the black line indicates the total population of children <12 months of age ($\times 10^4$) in New South Wales.²²

FPIES: incidencia en aumento



FPIES puede afectar hasta el 0.5% en todo el mundo (0,7% estudio Español en Leganés)

Baker MG, Nowak-Wegrzyn. Curr Opin Allergy Clin Immunol. 2020 Apr;20(2):168-174.

Alonso SB et al. J Allergy Clin Immunol 2019; 143:430-3.

Cases of FPIES according to year of diagnosis. Black bars indicate the total number of children diagnosed as having FPIES, white bars indicate the median number of FPIES episodes before a correct diagnosis was made, and the black line indicates the total population of children <12 months of age ($\times 10^4$) in New South Wales.²²



Figure 1. Estimated prevalence of food protein-induced enterocolitis syndrome.

FPIES : Consenso Internacional 2017

Position paper

International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology



Anna Nowak-Węgrzyn, MD, Mirna Chehade, MD, Marion E. Groetch, MS, RDN, Jonathan M. Spergel, MD, PhD, Robert A. Wood, MD, Katrina Allen, MD, PhD, Dan Atkins, MD, Sami Bahna, MD, PhD, Ashis V. Barad, MD, Cecilia Berin, PhD, Terri Brown Whitehorn, MD, A. Wesley Burks, MD, Jean-Christoph Caubet, MD, Antonella Cianferoni, MD, PhD, Marisa Conte, MLIS, Carla Davis, MD, Alessandro Fiocchi, MD, Kate Grimshaw, PhD, RD, RNutr, Ruchi Gupta, MD, Brittany Hofmeister, RD, J. B. Hwang, MD, Yitzhak Katz, MD, George N. Konstantinou, MD, PhD, MSc, Stephanie A. Leonard, MD, Jennifer Lightdale, MD, Sean McGhee, MD, Sami Mehr, MD, FRACP, Stefano Miceli Sopo, MD, Giovanni Monti, MD, PhD, Antonella Muraro, MD, PhD, Stacey Katherine Noel, MD, Ichiro Nomura, MD, Sally Noone, RN, MSN, Hugh A. Sampson, MD, Fallon Schultz, MSW, LCSW, CAM, Scott H. Sicherer, MD, Cecilia C. Thompson, MD, Paul J. Turner, MD, Carina Venter, RD, PhD, A. Amity Westcott-Chavez, MA, MFA, and Matthew Greenhawt, MD, MBA, MSc

J Allergy Clin Immunol 2017;139:1111-26.)

FPIES: fenotipos

TABLE I. Proposed defining features for clinical phenotyping of FPIES

FPIES subtypes	Defining features
Age of onset	
Early	Younger than age 9 mo
Late	Older than age 9 mo
Severity	
Mild-to-moderate	Repetitive emesis with or without diarrhea, pallor, mild lethargy
Severe	Repetitive projectile emesis with or without diarrhea, pallor, lethargy, dehydration, hypotension, shock, methemoglobinemia, metabolic acidosis
Timing and duration of symptoms	
Acute	Occurs with intermittent food exposures, emesis starts usually within 1-4 h, accompanied by lethargy and pallor; diarrhea can follow within 24 hours, with usual onset of 5-10 h. Usual resolution of symptoms within 24 h after elimination of the food from the diet. Growth is normal, and child is asymptomatic during food trigger elimination.
Chronic	Occurs with daily ingestion of the food (eg, feeding with CM- or soy-based formula in an infant); symptoms include intermittent emesis, chronic diarrhea, poor weight gain, or FTT. Infants with chronic FPIES usually return to their usual state of health within 3-10 d of switching to a hypoallergenic formula, although in severe cases temporary bowel rest and intravenous fluids might be necessary. <u>Subsequent feeding of the offending food after a period of avoidance results in acute symptoms.</u>
IgE positivity	
Classic	Food specific, IgE negative
Atypical	Food specific, IgE positive

FPIES agudo: Criterios diagnósticos

Criterio mayor:

Vómitos en el período de 1 a 4 horas después de la ingestión del alimento y ausencia de síntomas clásicos de piel o respiratorios mediados por IgE

Criterios menores:

1. Un segundo (o más) episodio de vómitos repetitivos después de ingerir el mismo alimento
2. Episodios repetidos de vómito 1-4 h después de comer un alimento diferente
3. Extremo letargo con cualquier sospecha de reacción
4. Palidez marcada con cualquier sospecha de reacción
5. Necesidad de acudir al servicio de urgencias con cualquier sospecha de reacción
6. Necesidad de soporte de líquidos intravenosos con cualquier sospecha de reacción
7. Diarrea en 24 h (normalmente 5-10 h)
8. Hipotensión
9. Hipotermia termometrada 35°C

FPIES crónico: Criterios diagnósticos

Cuando el alimento es ingerido regularmente. Se desarrollan vómitos intermitentes pero progresivos y diarrea (ocasionalmente con sangre), a veces con deshidratación y acidosis metabólica.

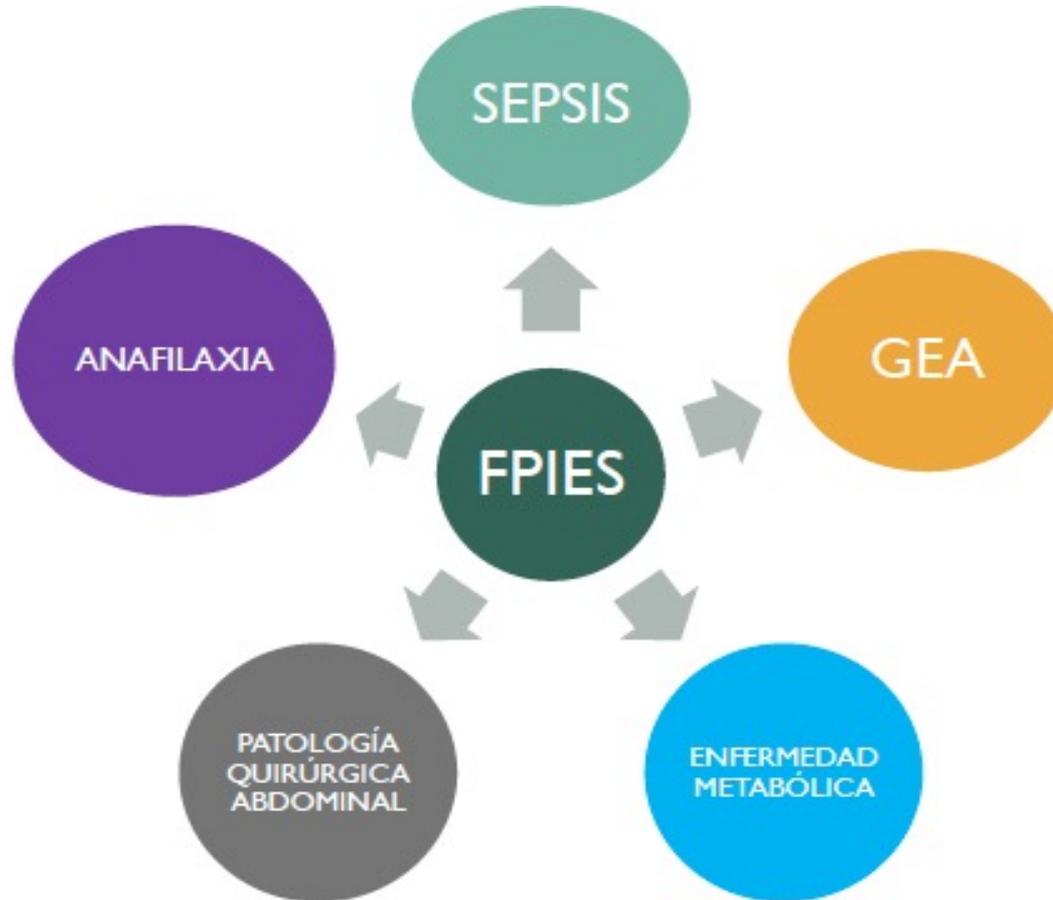
- 2 casos pediátricos de FPIES crónico por pescado. Ingesta 1 vez por semana!!

J Allergy Clin Immunol Pract. 2020 Jan 29. Infante S et al

Resolución de los síntomas en los días o incluso semanas posteriores a la eliminación del alimento y la recurrencia aguda de los síntomas cuando se reintroduce el mismo, el inicio del vómito en 1-4 h, la diarrea en 24 h (5-10 h).

J Allergy Clin Immunol 2017;139:1111-26.

Diagnóstico diferencial FPIES



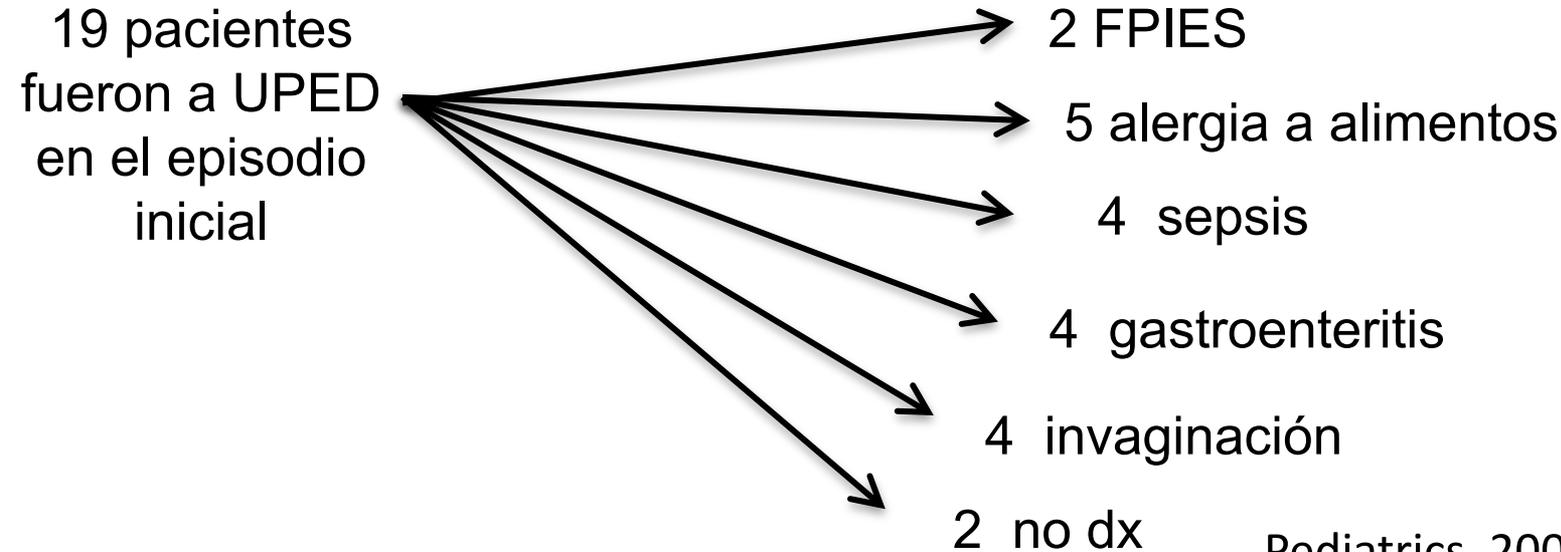
Diagnóstico diferencial FPIES

Patología	Características
Gastroenteritis infecciosa	Fiebre, ambiente epidémico, síntomas duran días no horas.
Sepsis	Resucitación con fluidoterapia sola no es efectiva
Anafilaxia	Síntomas respiratorios o cutáneos, respuesta a adrenalina, test alérgicos positivos
Obstrucción intestinal	No relacionado con ingesta de ningún alimento específico, evidencia de obstrucción en las pruebas de imagen
Enterocolitis necrotizante	Neonatos y lactantes pequeños, rápida progresión de los síntomas, sangre en heces, shock, gas intramural en las radiografías abdominales
Errores innatos del metabolismo	Retraso en el desarrollo, manifestaciones neurológicas, organomegalia, reacción a frutas
Alteraciones neurológicas (vómitos cíclicos...)	No relacionado con ingesta de ningún alimento específico
Intoxicación alimentaria	Otros afectados que han ingerido el mismo alimento

Adaptado de Nowak-Wegrzyn et al. (J Allergy Clin Immunol Pract 2020;8:24-35)

FPIES: Diagnóstico diferencial

- Estudio retrospectivo australiano de 35 niños con FPIES (66 episodios) en 16 años
- 71% ≥ 2 episodios antes del dx (20% 4 episodios)
- 1 niño laparotomía



FPIES : Pruebas de laboratorio

IgE

Hemograma

Albúmina

RFA

Gasometría

Estudio fecal



No necesarias para el diagnóstico!!!!

Estudio del inflammasoma, microbioma y metaboloma fecal en lactantes con síndrome de enterocolitis inducida por proteínas de leche de vaca (FPIES)

Grupo de Trabajo de Alergia Gastrointestinal de la SEGHNPE

Hospital Universitario Central de Asturias, Oviedo.

Hospital Universitario de Cabueñes en Gijón

Hospital Universitario San Agustín de Avilés

Hospital Alvarez Buylla de Mieres

Hospital Universitario Vall d'Hebron de Barcelona

Hospital Infantil Universitario Niño Jesús de Madrid

Hospital Universitario Virgen del Rocío de Sevilla

Centro de Salud la Eria

Centro de Salud Vallobín-Concinos

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Prueba de provocación

Cuándo:

- Para confirmar el diagnóstico inicial si historia no clara
- Para evaluar su resolución (18-24 meses)
- Pescado, retrasarlo a los 5 años

Dónde: siempre en el hospital

Cómo:

- El acceso IV periférico debe asegurarse antes en pacientes con antecedentes de reacciones graves y/o acceso difícil anticipado.
- IgE específica previa
- Hemograma previo recomendado

FPIES: desencadenantes más frecuentes

- **LV**
- **Soja**
- **Cereales** (arroz , avena, cebada, maíz)
- Carnes (ternera, pollo, pavo),
- Verduras y legumbres (boniato, patata, guisante, lentejas ...)
- Fruta (tomate, pera, plátano)
- Huevo de gallina
- Pescado y Mariscos

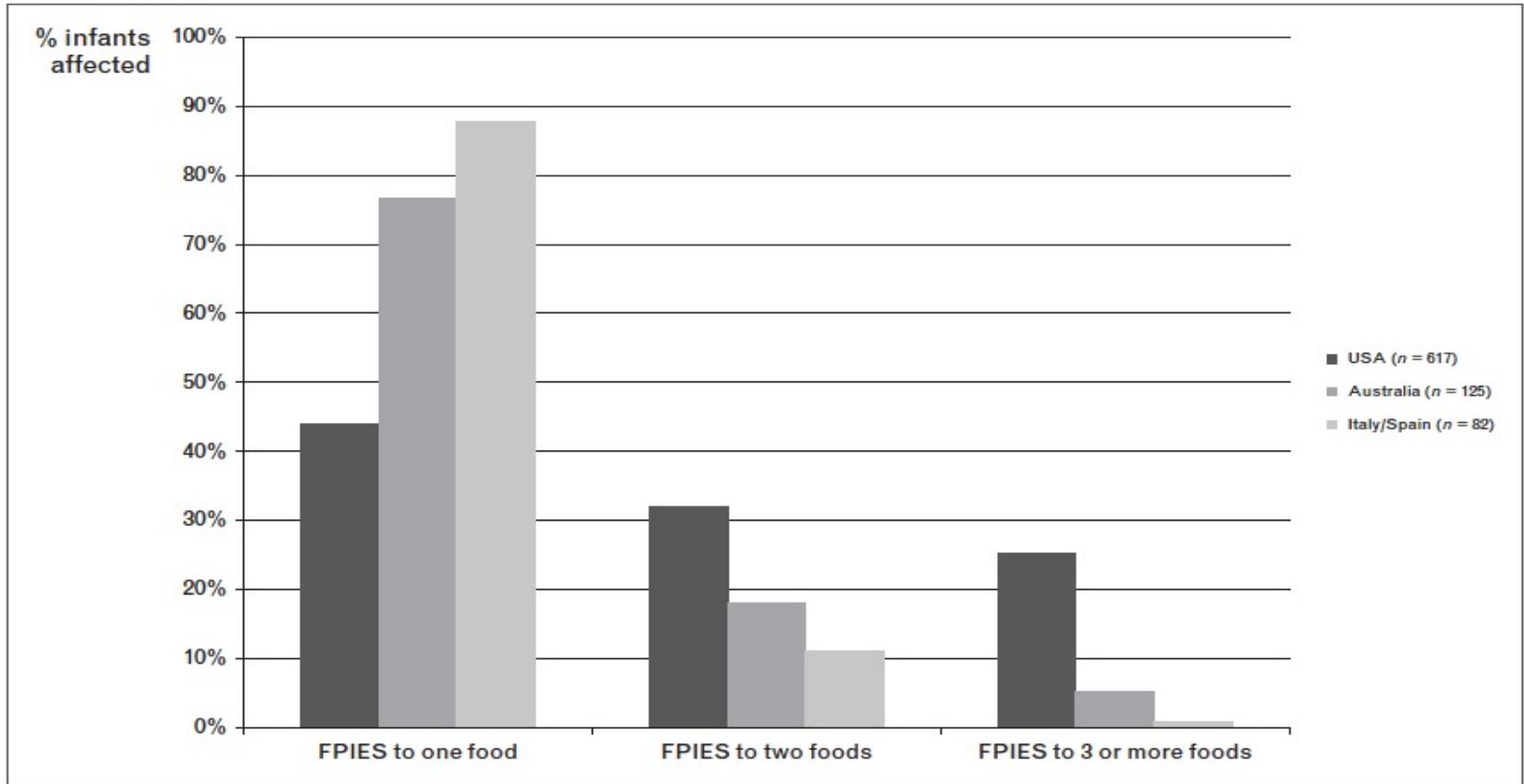


FPIES: Diferencias geográficas

	US	AU	UK	Israel	S. Korea	Spain	Italy
CM	Red	Red	Red	Red	Red	Red	Red
Soy	Red	Yellow	Yellow	Yellow	Red	Yellow	Yellow
Rice	Red	Red	Orange	Yellow	Yellow	Yellow	Yellow
Fish	Yellow	Yellow	Orange	Yellow	Yellow	Red	Red

Figure. Geographic differences in FPIES triggers. Red, most common trigger foods; orange, less common trigger foods; yellow: the least common trigger foods. FPIES indicates food protein–induced enterocolitis syndrome. AU, Australia.

FPIES a múltiples alimentos



FPIES: coalergias frecuentes

TABLE VIII. Common food coalergias in children with FPIES

FPIES to:	Clinical cross-reactivity/ coalergy	Observed occurrence*
CM	Soy	<30% to 40%
	Any solid food	<16%
Soy	CM	<30% to 40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	CM or soy	<25%
Legumes*	Soy	<80%
Grains: rice, oats, etc*	Other grains (including rice)	About 50%
Poultry*	Other poultry	<40%

*Note: where a child already tolerates a food type in a particular group (eg, beans), clinical reactions to other members of the same group (eg, other legumes) are unlikely. Caution is warranted in interpreting these data because they were derived from single centers and from patient populations skewed toward the more severe phenotype of FPIES and might overestimate the actual risk of coalergy.

FPIES: Manejo hospitalario

- Bolos de SSF
- Ondansetrón 0.15 mg/kg en >6 m oral o iv
- Metilprednisolona IV en casos graves
- Corrección desequilibrios electrolitos
- UCI: hipotensión persistente, shock, letargia extrema, distress respiratorio

FPIES: Manejo a largo plazo

- ✓ Eliminación del alimento responsable
- ✓ Planes para avanzar en la alimentación del lactante
- ✓ Tratamiento de los síntomas ante exposición accidental
- ✓ Monitorizar la resolución

FPIES y lactancia materna



Summary Statement 21: Do not recommend routine maternal dietary elimination of offending triggers while breast-feeding if the infant is thriving and remains asymptomatic. [Strength of recommendation: Moderate; Evidence strength: III-IV; Evidence grade: C]

FPIES: Fórmula de sustitución

EAACI, BSACI: Fórmulas elementales

DRACMA, **ESPGHAN**, Guías latinoamericanas: FEH

The official guidelines¹ recommend a hypoallergenic formula for the treatment of FPIES based on several studies demonstrating that most children tolerated extensively hydrolyzed formula, although there are selected children who exclusively tolerate AAFs.^{7,8,80-82} AAFs are the only completely nonallergenic formulas and can be effective in patients not responding to extensively hydrolyzed formulas and those with FTT. Soy formula might be an acceptable alternative, especially in infants older than 6 months; however, cautious introduction is warranted because of the potential for coreactivity between patients with soy-induced FPIES and those with CM-induced FPIES.

FPIES: Manejo nutricional

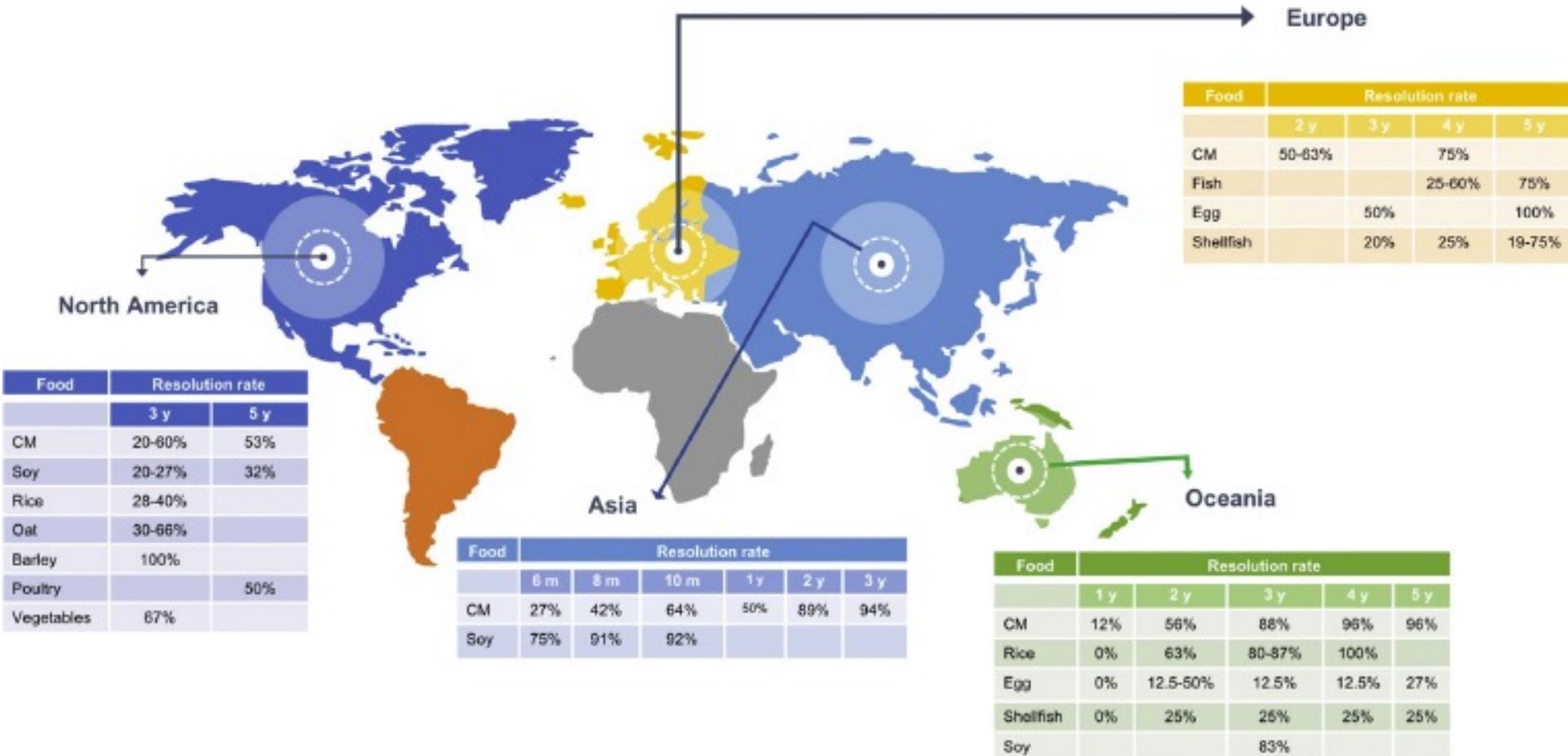
- ✓ Consejo nutricional adecuado para evitar dietas deficitarias en proteínas, Vit A y D, Ca, Fe y Zn
- ✓ Recomendar alimentos que favorezcan la adquisición de habilidades oromotoras para prevenir TCA
- ✓ Introducir alimentos de 1 en 1
- ✓ Espaciar introducción entre 4-7 días
- ✓ Empezar por frutas y vegetales, seguir con carnes y finalizar con cereales

FPIES: guía de introducción alimentaria

Lower-risk foods*	Moderate-risk foods*	Higher-risk foods*
Vegetables Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
Fruits Blueberries, strawberries, plum, watermelon, peach, avocado	Apple, pear, orange	Banana
High-iron foods Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Higher-iron foods: fortified, infant rice and oat cereals
Other Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

FPIES: Pronóstico

J.A. Bird et al. / Ann Allergy Asthma Immunol 126 (2021) 506–515



Tasas variables de resolución de FPIES publicadas en todo el mundo

Clinical presentation and acute management of FPIES reactions among 120 patients in Spain in 2017

	Acute FPIES N=111	Chronic FPIES N=9
Age at diagnosis (months) mean (SE)	15 (1.7)	19 (9.4)
Symptoms		
Vomiting	111 (100%)	9 (100%)
Pallor	99 (89.2%)	6 (66%)
Lethargy	98 (88.3%)	5 (55%)
Diarrhea	60 (54.1%)	7 (78%)
Hypotension	22 (19.8%)	1 (11%)
Hypothermia	7 (6.3%)	-
Abdominal distention	10 (9%)	3 (33%)
Dehydration	35 (31.5%)	4 (44.%)
Blood in stools	11 (9.9%)	4 (44.%)
Acute Treatment		
IV fluids	51 (45.9%)	5 (55.6%)
Antibiotics	6 (5.4%)	1 (11.1%)
Ondansetron	40 (36%)	1(11.1%)
Ranitidine	12 (10.8%)	1(11.1%)
Steroids	5 (4.5%)	1(11.1%)
Antihistamines	5 (4.5%)	-
Epinephrine	6 (5.4%)	-
ORS	7 (6.3%)	-

Díaz JJ et al. J Pediatr Gastroenterol Nutr. 2019 Feb;68(2):232-236.

Characteristic	Overall		Acute		Chronic	
	N (%)		N (%)		N (%)	
Number of cases (male/female)	120 (64/56)		111 (58/53)		9 (6/3)	
Median age (IQR)	11,2 months (9.3)		11.2 (9.2)		11.2 (16.2)	
Severity						
Mild	48 (40%)		45 (40.5%)		3 (33%)	
Moderate	44 (36.7%)		40 (36%)		4 (44.4%)	
Severe	28 (23.3%)		26 (23.4%)		2 (22.2%)	
Food involved						
Cow's milk	44 (36.7%)		35 (31.5%)		9 (100%)	
Fish	39 (32.5%)		39 (35.1%)		-	
Hen's egg	13 (10.8%)		13 (11.7%)		-	
Rice	12 (10%)		12 (10.8%)		-	
Lentils	3 (2.5%)		3 (2.7%)		-	
Squid	2 (1.7%)		2 (1.8%)		-	
Poultry	2 (1.7%)		2 (1.8%)		-	
Soy	1 (0.8%)		1 (0.9%)		-	
Potato	1 (0.8%)		1 (0.9%)		-	
Beef	1 (0.8%)		1 (0.9%)		-	
Gluten cereals	1 (0.8%)		1 (0.9%)		-	
Banana	1 (0.8%)		1 (0.9%)		-	
Number of foods involved						
One	101 (84.2%)		92 (82.9%)		9 (100%)	
More than one	19 (15.8%)		19 (17.1%)		-	
Positivity in IgE tests	SIgE	SPT	SIgE	SPT	SIgE	SPT
Cow's milk	11/44	3/44	9/35	2/35	2/9	1/9
Hen's egg	1/13	2/13	1/13	2/13	-	-
Fish	0	0	0	0	-	-
Rice	0	0	0	0	-	-

Características epidemiológicas de FPIES en España

- ✓ Edad: mediana 11 meses
- ✓ Moderadas/graves 60%; graves 23%
- ✓ Causa más frecuentes: PLV, pescado, huevo y arroz.
- ✓ Más de 1 alimento: 15%
- ✓ Dx en el primer episodio 7%, 22% necesitaron 4 ó más.

Díaz JJ et al. J Pediatr Gastroenterol Nutr. 2019 Feb;68(2):232-236.

Mensajes para llevar a casa

- ✓ La clave para el diagnóstico FPIES es un elevado índice de sospecha
- ✓ Un paciente con una historia clara de FPIES no precisa provocación para confirmar el diagnóstico inicial
- ✓ Las causas más frecuentes en España son las proteínas de leche de vaca, pescado, huevo y arroz
- ✓ Las provocaciones siempre en medio hospitalario. Reacciones potencialmente muy graves
- ✓ Uso de fórmulas hidrolizadas en el FPIES por PLV, reservando las elementales para FPIES más graves o en casos de fallo de las anteriores

GRACIAS!

