

Alergia a Proteína de Leche de vaca: APLV

Dra. Paola Garcés

**La alergia es una reacción de
hipersensibilidad iniciada por
mecanismos inmunes específicos**

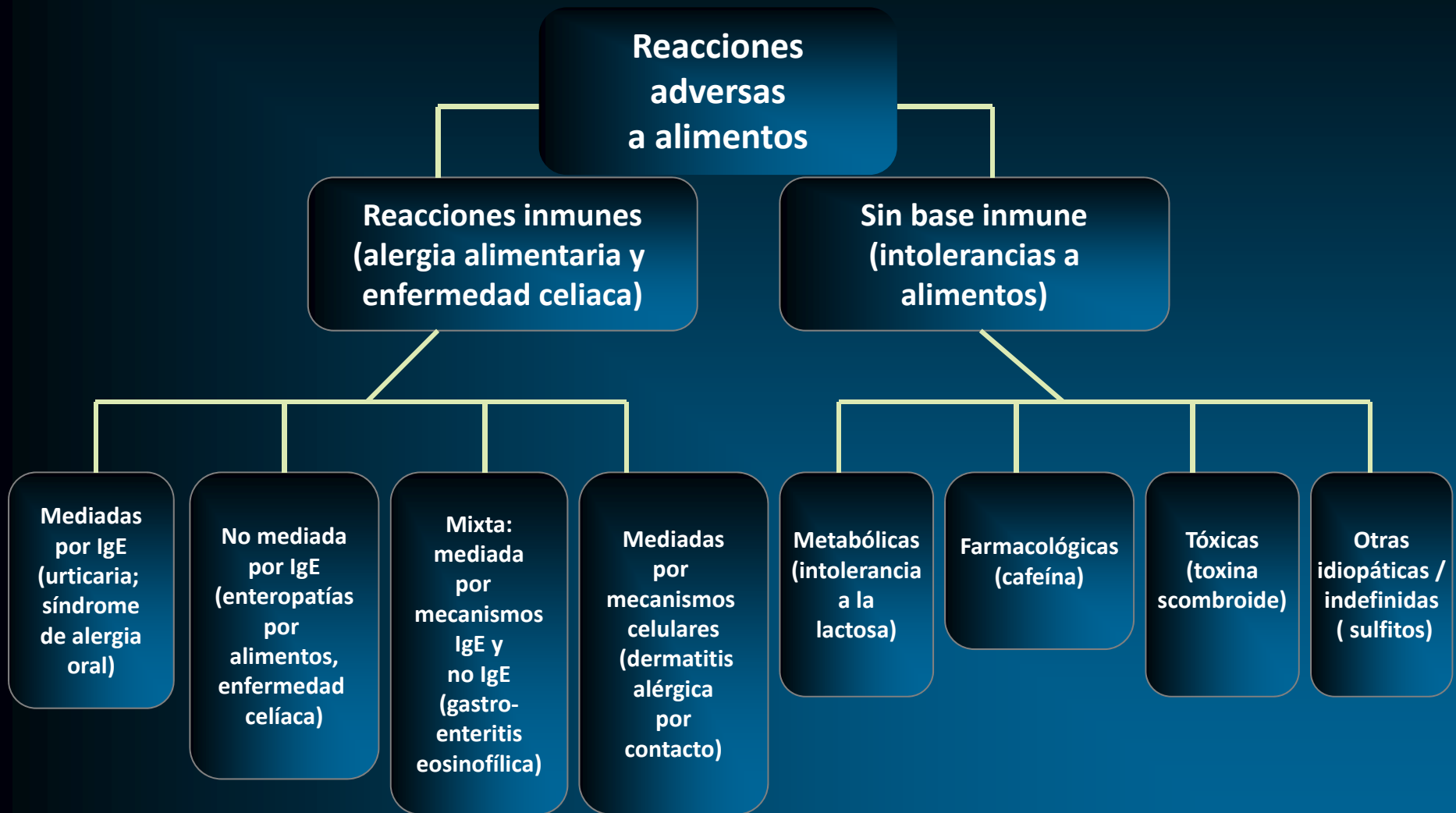
**Las alergias a alimentos son respuestas
inmunes adversas, anormales, a proteínas
de los alimentos mediadas
por IgE, IgG o
mecanismos celulares o mixtos**

Terminología de las reacciones adversas a los alimentos

1. *Intolerancia a los alimentos:* reacción desagradable, reproducible, que se produce frente a algún alimento o ingrediente específico, sin base inmunológica ni psicológica.
2. *Alergia a los alimentos:* intolerancia con evidencias de reacción inmunológica anormal.
3. *Aversión a alimentos:* incluye tanto la aversión como la intolerancia psicológica.
4. *Aversión psicológica:* aversión a un alimento por causas psicológicas.
5. *Intolerancia psicológica:* reacción corporal desagradable desencadenada por emociones asociadas con alimentos.

Tomado de J Br Cell Phys. Lond 1984; 18: 83-123

Reacciones adversas a alimentos



Base familiar de la alergia a proteínas de la leche de vaca

<u>Antecedentes familiares</u>	<u>Riesgo (%)</u>
Ambos padres son atópicos	40 – 60
Ambos padres son atópicos, con igual sintomatología	50 – 80
Uno de los padres es atópico	20 – 40
Un hermano es atópico	20 – 25
No hay antecedentes de atopía en la familia	5 – 15

Tomado de Bousquet J, Kjellman NIM. J Allergy Clin Immunol, 1986;78:1018-22

La restricción de antígenos (leche, huevos)
de la dieta materna durante el embarazo
y/o la lactancia no se asoció con
disminuciones del riesgo de enfermedades
atópicas en el hijo

Kramer MS., Kakuma R., Cochrane Review 2012

La restricción de la dieta materna en el embarazo se asocia con ganancias de peso levemente menores pero estadísticamente significativas y un riesgo algo aumentado, pero significativo, de prematuridad y de disminución del peso de nacimiento.

Factores que regulan el balance entre la tolerancia (supresión) y la sensibilización

- Genética
- Naturaleza y dosis del antígeno
- Frecuencia de la administración
- Edad al primer contacto
- Estado inmunitario previo del huésped
- Vía de transmisión del antígeno (leche materna, tubo digestivo, piel, etc.)

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Tomado de Bousquet J, Kjellman NIM. J Allergy Clin Immunol, 1986;78:1018-22

**La APLV se manifiesta generalmente
durante los 2 primeros
meses de vida.**

**Intensidad máxima al año de edad.
Después disminuye paulatinamente.**

Cuadros clínicos mediados por Ig asociados con reacciones inmunes a leche de vaca.

- I. Reacciones sistémicas mediadas por IgE (anafilaxia).**
 - A. Reacciones inmediatas.**
 - B. Reacciones retardadas.**

- II. Reacciones gastrointestinales mediadas por IgE.**
 - A. Síndrome de alergia oral.**
 - B. Alergia gastrointestinal inmediata.**

- III. Reacciones respiratorias mediadas por IgE.**
 - A. Asma y rinitis secundarias a la ingestión de leche.**
 - B. Asma y rinitis secundarias a la inhalación de leche (asma ocupacional).**

- IV. Reacciones cutáneas mediadas por IgE.**
 - A. Reacciones de comienzo inmediato.**
 - 1. Urticaria aguda ó angioedema.
 - 2. Urticaria por contacto.
 - B. Reacciones de comienzo retardado.**

- V. Dermatitis atópica**

Diversidad de cuadros asociados con reacciones por mecanismos mixtos o no mediados por IgE

- I. Dermatitis atópica.**
 - A. Reacciones de comienzo inmediato.**
 - B. Reacciones de comienzo tardío.**

- II. Reacciones gastrointestinales no mediadas por IgE.**
 - Reflujo gastroesofágico
 - Espasmo cricofaríngeo
 - Estenosis pilórica
 - Esofagitis eosinofílica alérgica
 - Enteropatía inducida por proteínas de la leche de vaca
 - Constipación
 - Cólico (irritabilidad intensa)
 - Gastroenteritis y proctocolitis inducidas por proteínas de alimentos

- III. Reacción del aparato respiratorio no mediada por IgE.**
 - Síndrome de Heiner.

Terminación de la APLV en relación con la edad

Edad (años)	% terminación
-------------	---------------

1	56
2	77
3	87
5	92
10	92
15	97

Höst A et al. Pediatr Allergy Immunol 2002; 3: 23-28.

Table 2. Typical Compositions of the Major Proteins in Human and Cow's Milk.

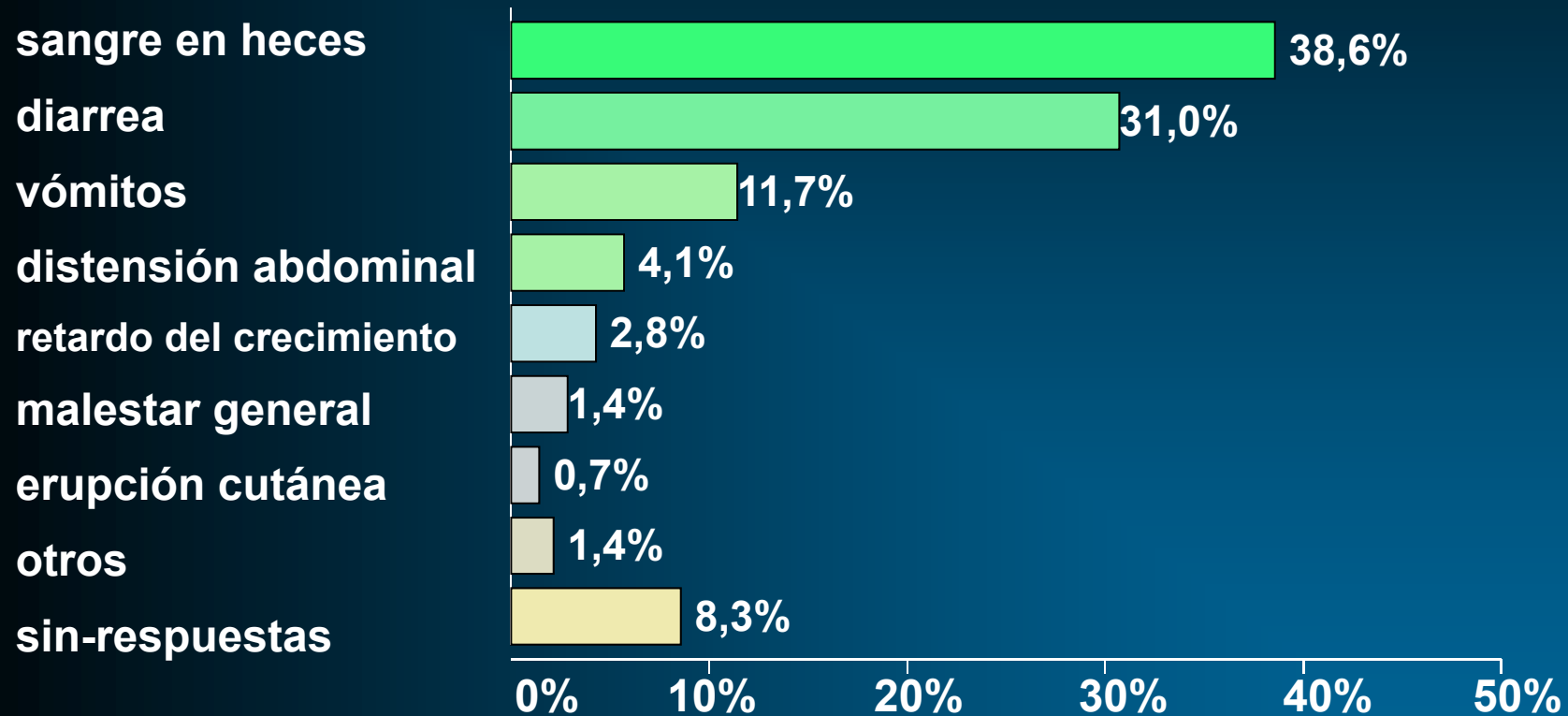
Protein	Human (mg/mL)	Cow (mg/mL)
α -lactalbumin	2.2	1.2
α -s1-casein	0	11.6
α -s2-casein	0	3.0
β -casein	2.2	9.6
κ -casein	0.4	3.6
γ -casein	0	1.6
immunoglobulins	0.8	0.6
lactoferrin	1.4	0.3
β -lactoglobulin	0	3.0
lysozyme	0.5	trace
serum albumin	0.4	0.4
other	0.8	0.6

Incidencia de alergia neonatal a la proteína de leche de vaca

Peso nacimiento (g)	Lactantes hospitalizados	Alergia neonatal a PLV (n)	%
< 1000	4.034	14	0,35
1000-1500	5.848	11	0,19
1500-2500	26.294	45	0,17
>2500	33.620	75	0,22
TOTAL	69.676	145	0,4

Miyazawa T. Pediatr Int 2009;51:544-47

Los síntomas más frecuentes en casos de alergia neonatal a la leche



n = 145

Miyazawa T. et al. Pediatr Int. 2009; 51: 544-47

Retrospective Multicenter Survey on Food-Related Symptoms Suggestive of Cow's Milk Allergy in NICU Neonates

Tokuo Miyazawa¹, Kazuo Itabashi¹ and Takanori Imai^{1,2}

ABSTRACT

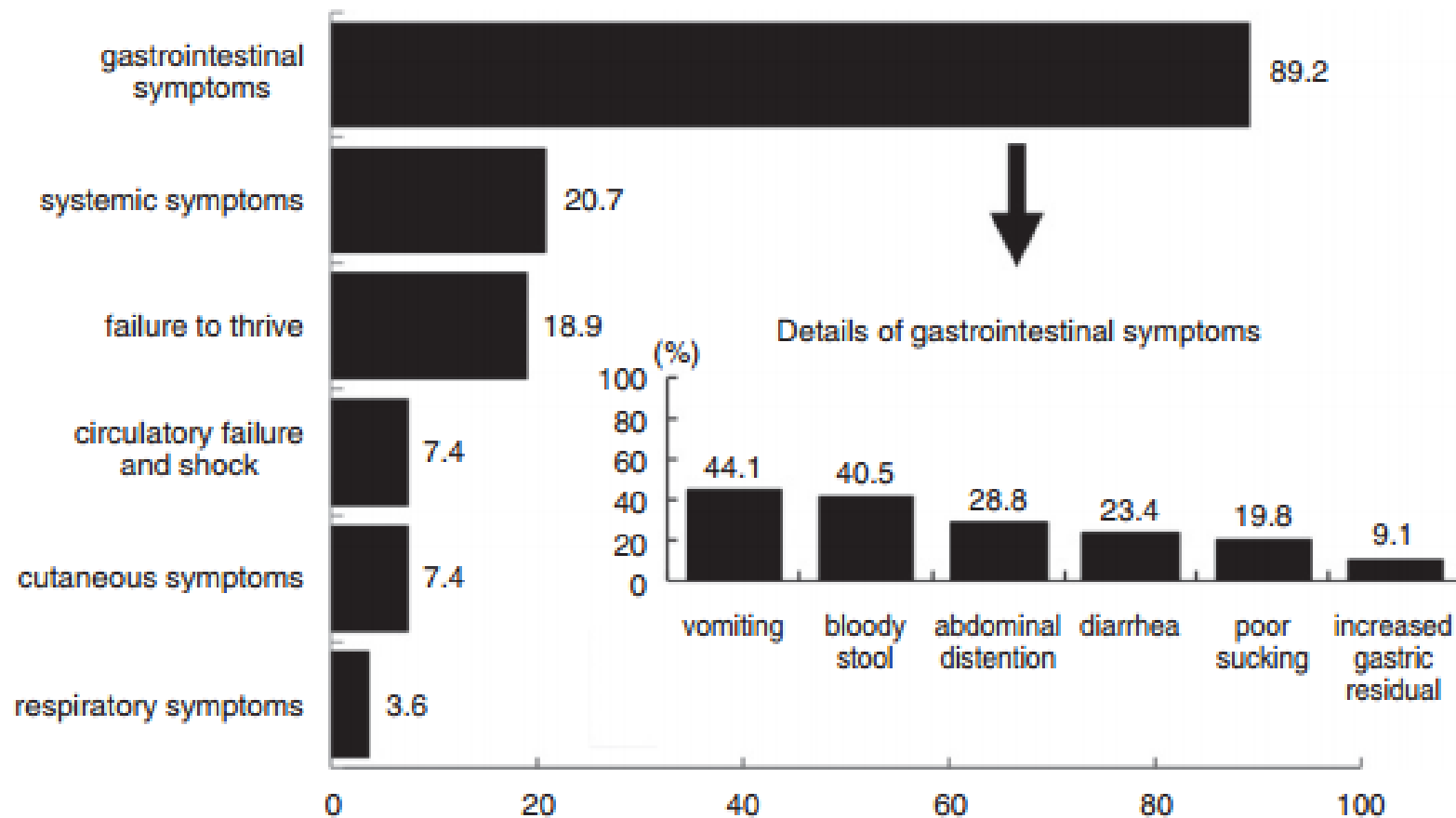
Background: Cow's milk allergy (CMA) is one of the causes of gastrointestinal symptoms in neonates. A relationship between non-immunoglobulin (Ig) E mediated allergic reactions and CMA in early infancy has been proposed, but the clinical features and pathogenesis have not been established. The objective of this study is to determine the clinical characteristics of the neonates found in the earlier study to have food-related symptoms that suggested CMA.

En este estudio...

We previously reported that the incidence of cases with food-related symptoms that suggested CMA was 0.21% (145/69,796) in neonatal care units (NICUs) in Japan and that most NICUs currently make a diagnosis and establish treatment strategies based on observation of the clinical course, rather than performing an OFC.⁵ In this study, we retrospectively evaluated clinical data for these identified neonates presenting with food-related symptoms suggestive of CMA.

- 0.21% APLV-UCIN Japón
- Se evalúa en forma retrospectiva síntomas relacionados.

Food-Related Symptoms in Neonates



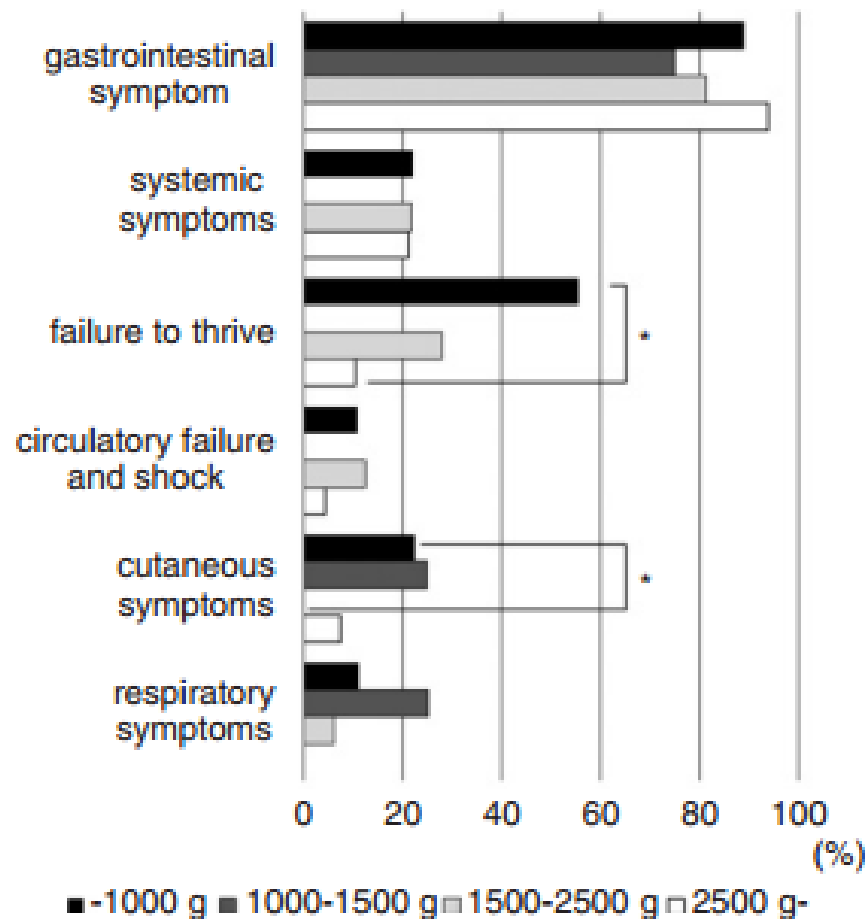
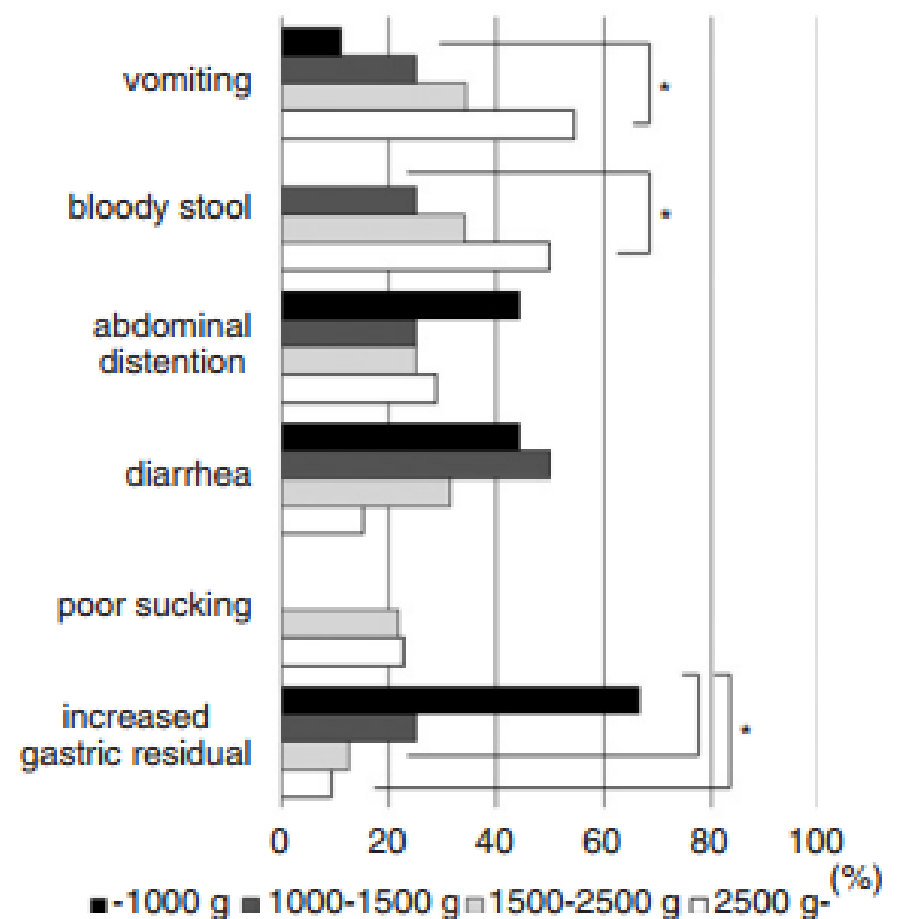
A**B**

Fig. 2 Comparison of clinical manifestations (A) and gastrointestinal symptoms (B) according to birth weight. The incidences of symptoms are shown as percentages. * $p < 0.05$ by Fisher exact test.

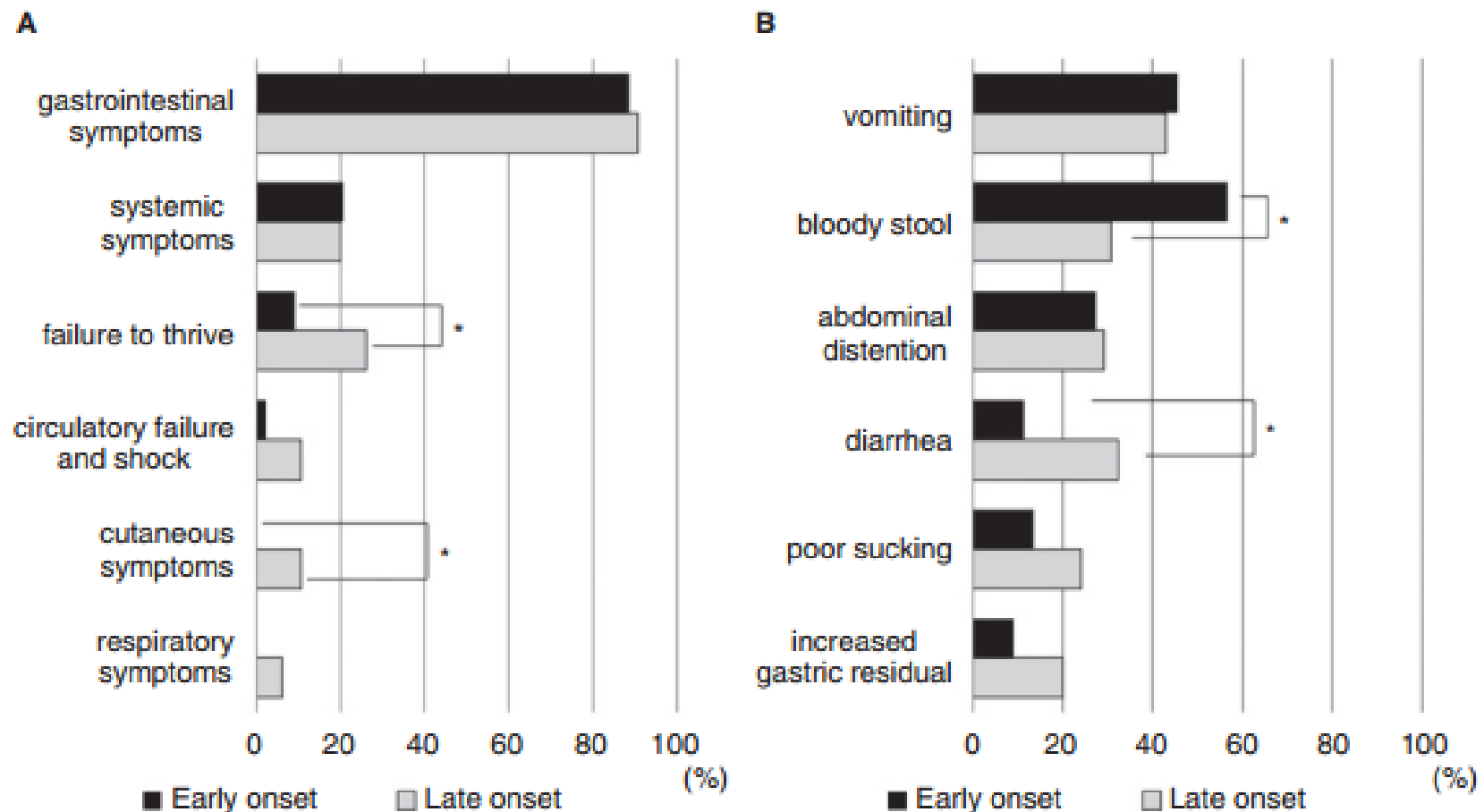


Fig. 3 Comparison of clinical manifestations (**A**) and gastrointestinal symptoms (**B**) according to onset age in days. The incidences of symptoms are shown as percentages. Early onset, development of symptoms ≤ 6 days after birth; Late onset, development of symptoms ≥ 7 days after birth. * $p < 0.05$ by Fisher exact test.

Fig. 1 Clinical manifestations in 111 neonates. The incidences of symptoms are shown as percentages. The vertical bar chart shows the incidence of each gastrointestinal symptom.

Table 1 Results of blood tests

Item	<i>n</i>	Median	Range
White blood cells (/μl)	99	12100	2900-51100
Eosinophils (/μl)	98	814	0-10000
CRP (mg/dl)	100	0.54	0.00-15.00
AST (IU/l)	85	30	9-413
ALT (IU/l)	86	11	1-482
γGTP (IU/l)	25	179	36-689

Table 2 Onset age of symptoms (days)

Birth weight	<i>n</i>	Average (±SD)	Median (range)
<1000 g	9	22.2 ± 13.4	14.5 (9-47)
1000-1500 g	4	15.0 ± 8.2	13.5 (7-26)
1500-2500 g	31	10.7 ± 10.2	7 (1-43)*
>2500 g	65	9.6 ± 13.1	6 (0-67)*
Total	109	11.2 ± 12.6	7 (0-67)

Neonates with birth weight <1000 g tended to develop symptoms significantly later than those with birth weight >1500 g or >2500 g.

**p* < 0.05 (Mann-Whitney U test) vs. birth weight <1000 g.

Hallazgos de laboratorio

LABORATORY FINDINGS

Specific IgE for milk allergens were tested in 98 cases (88%). Of these cases, 25 (26%) and 29 (30%) had specific IgE values of >0.70 UA/ml ($>$ class 2) and >0.35 UA/ml ($>$ class 1), respectively. A lymphocyte stimulation test (LST) was performed in 25 cases (23%) and the positive rate was 84% (21/25). Specific IgE was negative in 20 of these 21 cases and not tested in the remaining case; that is, no neonates were identified who were positive in a LST and a specific IgE test. A fecal eosinophil test was performed in 61 cases (55%) and was positive in 46 (75%). Among 98 cases in which food-related symptoms developed within 1 month after birth, an OFC was conducted in 25 (26%) to confirm the diagnosis.

- 111 casos
- IgE específicas a 98
- 25 casos mayor 0.7
- 29 casos mayor a 0.35
- Test de estimulación linfocitaria a 25, de los cuales 21 fueron positivos
- 25% fueron sometidos a TPO

Relación con la cirugía...

A high incidence of CMA after gastroenterological surgery has been reported,⁹ and we also found 10 cases in which gastroenterological surgery was performed prior to development of symptoms. Because the recurrence of symptoms was not confirmed by OFC, these symptoms cannot be clearly distinguished from transient symptoms caused by surgical stress. However, interestingly, these cases showed a high positive rate for specific IgE, which suggests their sensitization mechanism may differ from that in cases of common CMA. The mechanistic link between gastroenterological surgery and CMA development is unknown, but may be associated with dysfunction of the gastrointestinal tract resulting from primary diseases, surgical invasion of the gastrointestinal tract, and atrophy in the intestinal mucosa caused by extended fasting before and after surgery.⁹

- En 10 casos la cirugía se realizó previamente al dg de APLV
- Estos pacientes , post QX, mostraron valores elevados de IgE específicas a PLV.
- ¿Disfunción del tracto gastrointestinal?

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PEDIATRIC RESEARCH

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Antigen Absorption by the Jejunal Epithelium of Children with Cow's Milk Allergy

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Jussieu, Paris [R.D.]*

Table 1. *Clinical results of children with CMA at different stages of disease*

Patients	Age* (mo)	Diarrhea	Fecal blood loss	Wt loss	Vomiting	Paroxysmal, systemic adverse reactions	Clinical response to cow's milk challenge	Histology	IgE to cow's milk
Group I									
LY	1	+		+	+		+	†Plasmocytes	—
NM	1	+		+	+		+	† Eosinophils	
MJ	4	+		+	+	+	+	Normal	—
LO	4½	+		+	+		+	† Plasmocytes	
								Eosinophils	
LA	7	+	+		+	+		Partial villus atrophy	+
								† Plasmocytes	(α-lactalbumin and β-lactoglobulin)
OD	1	+	+			+		† Mast cells	
MS	2	+		+	+		+	† Lymphocytes	—
								† Plasmocytes	
Group II									
MA	17	+	+	+			+	Normal	
MS‡	6	+	+	+	+		++	Normal	—
MS‡	14	+	+		+		+++	Normal	
MAB	14	+		+	+	+	+	Normal	—
MQ	24	+		+				Normal	
DB	9	+		+	+		+	Partial atrophy	—
Group IIIa									
MS	6	+	+		+		++	Normal	—
DE	9	+	+		+		+	Slight villus atrophy	+
									(LT§ to β-lactoglobulin)
MJ	16	+					+	Normal	
MS	14	+	+		+		+++	Normal	—
DB	9	+		+	+		+	Partial atrophy	—
Group IIIb									
MQ	24						—	Inflammation	
MAB	14						—	Normal	—
AM	9						—	Normal	
ME	14						—	Normal	—

* At biopsy.

† Increased mucosal inflammation.

‡ Same child biopsied twice before each of two positive challenges. Clinical results of group II infants are those obtained after the milk challenge, except histological results that are those of the biopsy taken before the milk challenge.

§ Lymphoblastic stimulation test.

Conclusión del estudio

- 33 niños, de 1 a 24 meses, 18 controles y 15 con APLV.
- Los resultados de este estudio indican que en la infancia hay una permeabilidad basal a las proteínas de la dieta, intactas y degradadas.
- Esto parece constante desde los 2 meses de edad.
- En esta serie, los niños con APLV muestran una mayor absorción de ambas, proteínas intactas y degradadas, probablemente a causa de la inflamación.
- Este proceso está asociado con la enfermedad ya que en la medida que se trata la alergia con una dieta libre de proteína de leche de vaca, la permeabilidad fue restaurada.



Cow's milk protein allergy presenting with Hirschsprung's disease–mimicking symptoms

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Conclusiones de este estudio

Abstract

Background: Pediatric surgeons often encounter neonates who present with Hirschsprung's disease (HD)-like symptoms and plain x-ray findings, but respond well to conservative treatment. During our investigation of the etiology of "transient nonorganic ileus of neonates" (BTNIN), we noted that many cases were caused by cow's milk allergy (CMA). Therefore, a prospective study of the idiopathic transient nonorganic ileus of neonates was conducted.

Methods: Cow's milk allergy, Hirschsprung's disease, and a drug-induced lymphoproliferative disorder were the main differential diagnoses. The study included 26 neonates who presented with HD-like symptoms after oral feeding, and a drug-induced lymphoproliferative disorder was ruled out. The study included 26 neonates who presented with HD-like symptoms after oral feeding, and a drug-induced lymphoproliferative disorder was ruled out. The study included 26 neonates who presented with HD-like symptoms after oral feeding, and a drug-induced lymphoproliferative disorder was ruled out.

Materials: Of 38 neonates who presented with HD-like symptoms after oral feeding, 11 were excluded by plain x-ray in 9, intestinal atresia was diagnosed in 3, and the remaining 26 were enrolled in this study.

Results: Of 26 cases, 9 were diagnosed as HD by manometric studies and 17 as CMA. Thirteen of 17 CMA cases had been fed with breast milk and 4 with formula milk.

Conclusion: The proportion of CMA in the cases presenting with HD-like symptoms in the neonatal period is much higher than what we expected, and most cases of BTNIN are caused by CMA. If HD is ruled out, CMA should be considered.

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De 26 pacientes,
17 tenían APLV

El efecto sobre el huésped de la exposición alergenos de la leche depende de:

- a) La naturaleza y dosis del antígeno.
- b) La eficiencia de la digestión.
- c) La inmadurez del huésped.
- d) La velocidad de transporte de las proteínas de la leche.
- e) El procesamiento de los antígenos en el intestino.
- f) El ambiente inmunosupresor de las placas de Peyer.

Pediatr Surg Int (2006) 22:935–938
DOI 10.1007/s00383-006-1761-1

ORIGINAL ARTICLE

Massive bloody stools in two neonates caused by cow's milk allergy

**Ryuichiro Hirose · Takaharu Yamada ·
Yutaka Hayashida**

Published online: 24 August 2006
© Springer-Verlag 2006

La base del tratamiento de la alergia alimentaria es evitar el contacto con el alérgeno.
Además sirve para el diagnóstico

Tratamientos clásicos disponibles para la alergia

- Suprimir totalmente el contacto con el alergeno
 - Leche materna (eliminar estrictamente de la dieta materna la proteína causal)
 - Fórmulas con la proteína extensamente hidrolizada (eHF)
 - Fórmulas en base a mezclas de aminoácidos
-

Proteínas de la leche de vaca

Fracción	Proteína	g/L	% total proteína	PM (K/Da)	pI
Caseína	~ 30	80			
α_{s1} caseína	12-15	29	23,6	199	4,9 - 5,0
α_{s2} caseína	3 - 4	8	25,2	207	5,2 - 5,4
β -caseína	9 - 4	27	24,0	209	5,1- 5,4
γ_1 -caseína	-	-	20,6	180	5,5
γ_2 -caseína	1 - 2	6	11,8	104	6,4
γ_3 -caseína	-	-	11,6	102	5,8
κ -caseína	3 - 4	10	19,0	169	5,4 - 5,6
Proteínas del suero	~ 5.0	20	-	-	-
α -lactoalbúmina	1 - 1,5	5	14,2	123	4,8
β -lactoglobulina	3 - 4	10	18,3	162	5,3
Inmunoglobulina G	0,6 - 1,0	3	160,0	-	-
Seroalbúmina	0,1 - 0,4	1	67,0	583	4,9 - 5,1
Lactoferrina	0,09	Traza	800,0	703	8,7

El tratamiento de las proteínas de la leche para producir fracciones hipoalergénicas incluye:

- Calentamiento
- Hidrólisis enzimática
- Ultrafiltración

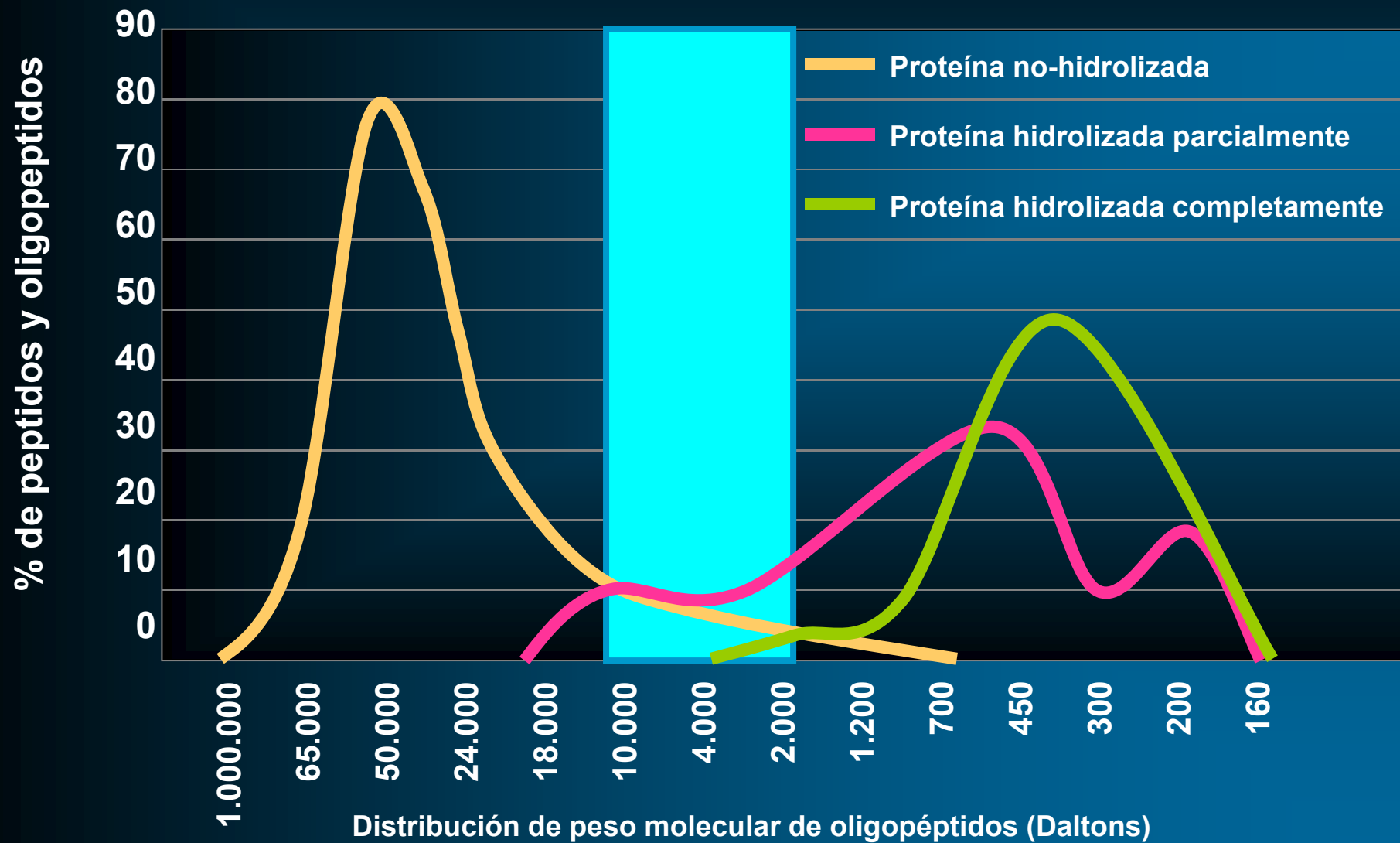
Fórmulas con proteína altamente hidrolizada (eHP)

El proceso de digestión usa tripsina/quimotripsina (triptasa) de cerdo y proteasas de bacterias o mohos

(alcalasa, *Bacillus licheniformis*).

La cantidad de proteína inmuno-reactiva que persiste es <1:1.000.000 (1µg/g N total)

Margen de tamaños moleculares de los péptidos inmunomoduladores de una fórmula parcialmente hidrolizada



El 90% de los niños con manifestaciones de
atopia responde a la fórmula altamente
hidrolizada (eHP)

AAP. Pediatrics 2000; 106 (pt 1): 346-49.

Y si existe sólo riesgo de...

¿Podemos hacer algo?

Fórmulas con proteína parcialmente hidrolizada (pHP)

No son fórmulas para el tratamiento de la alergia sino para prevención primaria en individuos en riesgo.

AAP. Pediatrics 2000; 106 (pt 1): 346-49.

Fórmulas con proteína parcialmente hidrolizada (pHP)

Estudios DBPCFC han demostrado a lo largo del tiempo una incidencia acumulativa de atopia inferior al grupo alimentado con fórmula convencional.

Von Berg A et al. J Allergy Clin Immunol 2007; 119: 718-25.

Von Berg A et al. J Allergy Clin Immunol 2008; 121: 1472-77.

Probióticos

Proceedings of the Nutrition Society (2005), **64**, 465–469
© The Author 2005

DOI:10.1079/PNS2005466

Probiotics and allergy

Department of Immunology

UK

**Lactobacillus rhamnosus
GG**

Allergy is caused by a...
Classical allergy is a type...
(and eosinophils) coat...
logical outcome is in...
diarrhoea, depending on the route of allergen entry. In extreme reactions anaphylactic shock can result that may lead to death. Chronic allergic responses most commonly present themselves as asthma and eczema. All these symptoms are the consequence of an imbalanced immune system making an unsuitable response to an environmental or food antigen. On bacterial colonisation of the colon after birth the appropriate microbiological stimuli is essential to redress the balance of the skewed T-helper 2 immune response present in the newborn. This normal interaction between baby and microbes is thought to be compromised in the Western world, with a reduction in bifidobacteria and an increase in clostridial species, particularly in bottle-fed infants. The use of probiotic therapy to prevent allergic disease has been demonstrated in two studies using a probiotic *Lactobacillus rhamnosus* GG in neonates. A long-term reduction in allergy has been shown in the test group, with lactobacillus reducing the incidence of atopic eczema. Management of allergy through probiotics has also been demonstrated in infants, using lactobacilli to control atopic eczema and cow's milk allergy. Unfortunately, these positive results have not been repeated in studies with older children and young adults.

Probiotics: Management of allergy: Prevention of allergy: Infants

gracias