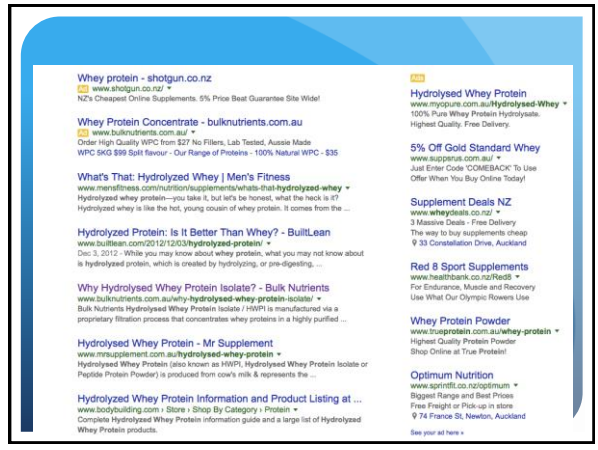
Hydrolysed Protein in infant formula

A/Professor John Sinn

MBBS (Syd), D Paed, DCH, M Med(Clin Epi), FRACP

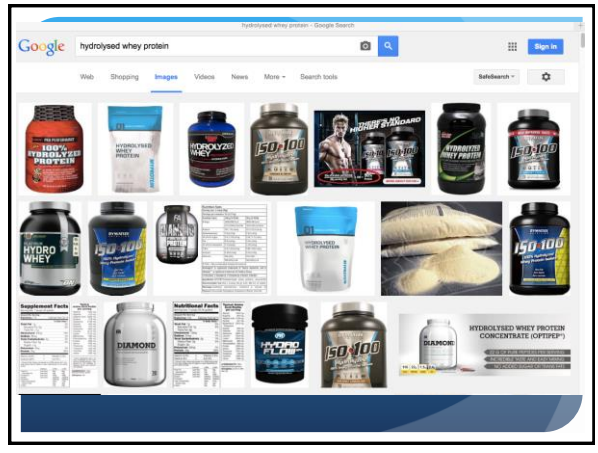
Consultant Neonatologist and Infant Allergist

The University of Sydney
Royal North Shore Hospital
The Paediatric Centre
www.thepaediatriccentre.com.au



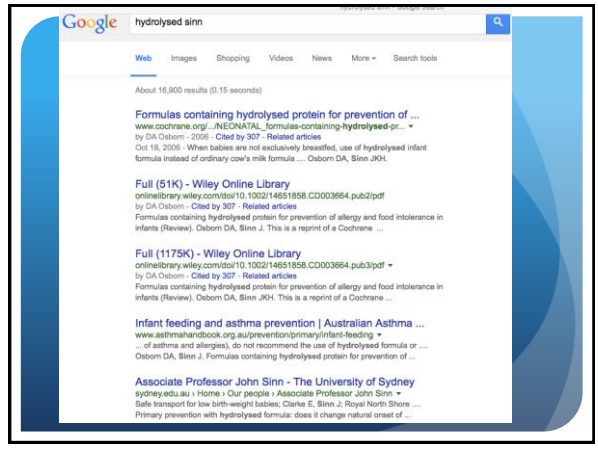
Body Builders

faster absorbed



Hydrolysed Whey Protein

- has been treated with enzymes to break the protein down into smaller peptides and amino acids.
- The very bitter taste comes from the high percentage of peptides and amino acids particularly arginine.
- The percentage of whey hydrolysed varies from 5% to 25% - The higher the percentage, the more amino acids are isolated and the more bitter it will taste.



[1]Department of Post Harvest Engineering and Technology, Aligarh ...

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... Автор(ы): Sinn, G; Reiterer, A (alexander.reiterer@lff.co.at); Stanzl-Tschegg, ... S (nandhini@csrltrd.ren.nic.in); Pavithran, C Название: Effect of hydrolysed ...

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www.wam.go.jp/wamappl/bb16GS70.nsf/.../20070319_2shiryou2_2.pdf
Mar 19, 2007 - Osborn DA, Sinn J. Formulas containing hydrolysed protein for ... Osborn DA, Sinn I. Soy formula for prevention of allergy and food intolerance.

[PDF] Allergy & Nutrition - Drivetime Radio
www.drivetimeradio.com.au/test/resources/.../Allergy_Nutrition-Refs.pdf
Osborn, D.A. and J. Sinn, Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev, ...

ALLERGY UPDATE - Audio-Digest Foundation
www.audio-digest.org/CME-Summary/.../ALLERGY-UPDATE
Feb 7, 2014 - J Allergy Clin Immunol 2008 Feb;121(2):343-7; Osborn DA and Sinn J: Formulas containing hydrolysed protein for prevention of allergy and ...

In order to show you the most relevant results, we have omitted some entries very similar to the 320 already displayed.
If you like, you can repeat the search with the omitted results included.

‹ Goooooooooogle
Previous 23 24 25 26 27 28 29 30 31 32

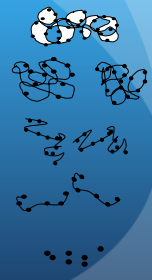
Extensively hydrolyzed rice protein-based formula for cow's milk allergy

- 40 (1-6 months) CMPA confirmed by a food challenge
- All infants tolerated the eRHF
- eRHF allowed a catch-up to normal weight gain
- eRHF was tolerated by more than 90 % of children with proven CMPA

- Eur J Pediatr. 2014 Sep;173(9):1209-16.
- Vandenplas Y1, De Greef E, Hauser B; Paradice Study Group.

Protein breakdown of formula

Potential Antigenicity	Protein Breakdown	Hydrolytic Stages of an antigenic protein molecule
High	Intact protein	
	Incomplete proteins (partially digested)	
	Large peptides	
	Small peptides	
Low		Amino acids



Dalton size

Protein in cow's milk and Dalton size of each protein[1,2]

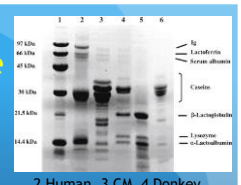
	Protein	Dalton Size (kDA)
Whey proteins	α-lactalbumin	14.2
	immunoglobulins	160.0
	lactoferrin (traces)	800.0
	ß-lactoglobulin	18.2
	bovine serum albumin	67.0
Casein proteins	α-s1-casein	23.6
	α-s2-casein	25.2
	ß-casein	24.0
	γ1-casein	20.6
	γ2-casein	11.8
	γ3-casein	11.6
	K-casein	19.0

Hydrolysed formulas are processed using four main technologies to reduce the molecular weight of CM[3].

HA vs EHF

- partial hydrolysate is in one in which 60% of the protein/peptide population has a molecular weight of less than 1000 Daltons
- extensive hydrolysate is one in which at least 95% of the protein/peptide population has a molecular weight of less than 1000 Daltons

Size of the molecule



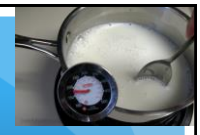
2 Human, 3 CM 4 Donkey

- Allergen 10000-70000 daltons
- Intact Soy 28000 daltons
- Partial hydrolysed 1100-10000 daltons
- Extensive hydrolysed < 1500
- Can be Allergenic if >1300 daltons
- Amino acid < 1000 daltons

Cow milk protein modification

1. Heat treatment - which mainly affects the conformational epitopes and leads to a reduction in allergenicity in particular for whey proteins, but not casein[10].
2. Enzymatic hydrolysis (using trypsin, chymotrypsin and papain) – enzymatic cleavage of polypeptide chains leads to the destruction of sequential epitopes and affects both casein and whey[10,11].
3. Enzymatic hydrolysis under hydrostatic pressure – enzymatic cleavage under pressure has been shown to yield even shorter chain lengths than standard enzymatic hydrolysis[12,13].
4. Ultrafiltration of residual long peptides[1,10].

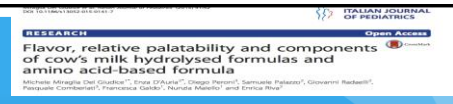
Heating



- CMP:
  - No effect on antigenicity for CM
  - Boiling milk for no difference in weal size for SPT
  - Super heat 121C may increase immunological response

Cow's Milk Antigens

- More than 25 proteins in cow's milk can induce antibody production in humans
- β-lactoglobulin (in whey), casein, and bovine serum albumin are the most important antigens
- Casein antigens include:
  - α_{s1} ; α_{s2} ; β ; κ
- Clinical reactions have occurred to all the major cow's milk antigens



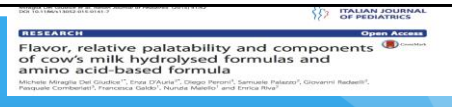
ITALIAN JOURNAL OF PEDIATRICS

RESEARCH Open Access

Flavor, relative palatability and components of cow's milk hydrolysed formulas and amino acid-based formula

Michele Miraglia Del Giudice[1*], Enza D'Auria[1*], Diego Peroni[1], Samuele Pelazza[1], Giovanni Radaelli[1], Pasquale Comberiati[1], Francesca Galdo[1], Nunzia Melello[1] and Enrica Riva[2]

- RCT 150 < 30 year old university staff: Control is Cow Milk
- Palatability: PHF > eHF and AAF
- Smell: whey-eHFs better smell > casein eHF and AAFs
- The aftertaste less Whey vs Casein hydrolysed and AAF
- palatability decreased with increasing PUFA
- improved with increasing levels of
  - saturated fatty acids
  - alfa- linoleic acid
  - Lactose
- Casein hydrolysed and the AAF having the worst taste of



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- Lactose enhances the absorption and the retention of the calcium and other minerals, such as magnesium and zinc
- Lactose beneficial bacteria population in the lower part of the gut
- lactose continues to be excluded from the majority of the cow's milk based-hydrolysed formulas.
- linolenic acid is preferred over oleic acid
- linolenic acid is preferred over linoleic acid

Tastes and tolerability

Adults are not infants : infants generally prefer higher concentrations of sweet solutions than adults) and greater aversion for bitter, influence by cultural differences

- infants exposed <4 month of age to hydrolysed formulas, more wiling to accept them than older infants
- Taste depends on
  - peptides content
  - molecular weight
  - lipids
  - lactose content.

Method for decreasing bitterness and improving taste of protein-free and hydrolyzed infant formulas: PATENT PENDING

- using a combination of casein and whey protein instead of the 100% whey protein may improve the taste of hydrolyzed formulas.
- INCREASE the pH TO 6.5 -7.2.
  - hydrolyzed have a pH range of about 4.5 to 6.0
- If not pH adjusted was more acidic and had a stronger fish taste, with more brothy and beany characteristics.

Improve taste

- Start early with AAF and EHF
- Add vanilla: license for > 1year
- Golden Syrup
- For CMA:
- Maternal exclusion of CMP
- If FTT: add EHF or AAF to breast milk could make refuse breast milk but starting early may allow tolerability.

EHF

- IgE-mediated CMA: 10% react to an EHF
- non IgE mediated CMA: 30% react to EHF
- Due to residual intact proteins (i.e. ß-lactoglobulin)
- six different EHFs as follows:
  - EHF-casein (Nutramigen, Pregestimil)
  - EHF-whey (Alfare, Pepti
  - EHF based on casein having the least allergenic potential[19].
- However, as with the Dalton size, none of the above in vitro studies can predict a clinical reaction in a child with a proven CMA.

EHF IgE against Whey vs Caesin

Specific IgE and positive SPT according to several studies using a variety of different patients (adjusted from Halken S and Host A)[20,21]

	Specific IgE against EHF			SPT ≥3mm against EHF				
EHF	Oldeaeus *et al.*[19]	Halken *et al.*[22]	Ragno *et al.*[23]	Oldeaeus *et al.*[19]	Sampson *et al.*[24]	Halken *et al.*[22]	Ragno *et al.*[23]	Giampietro *et al.*[20]
Nutramigen (EHF-casein)	6/45	-	-	1/45	11/25	-	-	-
Alimentum (EHF-casein)	3/45	-	3/20	1/45	7/25	-	3/20	-
Profylac (EHF-whey)	6/45	3/66	4/20	5/34	-	3/66	3/20	4/26
Nutrilon (Aptamil) Pepti (EHF-whey)	-	-	-	-	-	-	-	6/31

EHF challenges Whey vs Caesin

	Outcome of CMP Challenge					
EHF	Oldeaeus *et al.*[19]	Sampson *et al.*[24]	Ragno *et al.*[23]	Halken *et al.*[22]	Hill *et al.*[25]	Giampietro *et al.*[20]
Nutramigen (EHF-casein)	0/7	0/23	0/8	0/16	4/5	-
Pregestimil (EHF-casein)	-	-	0/8	-	0/1	-
Alimentum (EHF-casein)	1/11	0/23	-	-	-	-
Profylac (EHF-whey)	-	-	-	0/66	-	2/26
Alfare (EHF-whey)	-	-	2/8	-	2/4	-
ExpHA (EHF-whey)	-	-	4/8	-	-	-
Pregomin (EHF-whey)	-	-	1/8	-	-	-
Nutrilon (Aptamil) Pepti (EHF-whey)	-	-	-	-	-	1/31

EHF

- Positive SPT and specific IgE results in both EHF-C and EHF-W with different peptide lengths.
- majority of peptides < 1.5 kDa, some < 1 kDa.
- ß-lactoglobulin can be detected in the breast milk of 95% of lactating women at a level of 0.9-150 lg/l (median 4.2 lg/l).
- Similarly low amounts (0.84-14.5 lg/l) of residual ß-lactoglobulin have been found in EHFs and different caseins, (i.e. α-casein or γ-casein)

Hypoallergenic formula

- EAACI and the AAP: tolerated by at least 90% of infants with documented CMA.
- A hypoallergenic formula needs to comply with the following two definitions: an in vitro content of < 1% immunoreactive protein of total nitrogen containing substances, or that at least 90% of children with a proven CMA tolerate the feed with a 95% confidence interval.
- Both EHF-casein and EHF-whey formulas exist with a variety of peptide lengths (all with the majority < 1.5 kDa) complying with the suggested definition.
- Peptide length does not allow for the prediction of clinical reactivity.
- Other factors outside of peptide length may lead to reactions (i.e. residue of B-lactoglobulin).
- EHFs should be recommended not on their peptide length, but on the basis of clinical studies in CMA children.

CMA resolution

- - 56% by 4 years of age
- - 78% by 6 years of age
  Of milk-allergic children studied:
- Prognosis
- 28% of milk allergic infants tolerated milk by 2 years of age
- - 50% were also allergic to egg and soy - 30% to peanut
- [Bishop, 1990]

Ezcema:

Atopic Eczema: Ig E mediated
Eczema: Non - IgE Mediated

Associated: asthma, hay fever,
Food allergies

Allergies to
animal dander, rough fabrics, and dust can also trigger the condition in some people.

Atopic eczema

- Associated with high levels of IgE to
  - milk, egg and peanut
- 10% of cases are not IgE associated.
- Sleep disturbances
- For severe eczema 35 % would benefit from Food elimination

Atopic Ezcema and Food Allergy

- NESS study: n 1400 Severe vs Mild to moderate
- Severe is more associated with Ig E mediated allergy
  - CMP 1.3x
  - Egg 1.2x
  - Peanuts 1.5x

  Infant with Atopic ezcema should have a skin prick test or RAST test for CMP, Egg, peanut

Food sensitisation < 4/12 of age

- Children with eczema
- 36% have egg IgE > 0.35kU/L
- 15% have egg IgE of > 2KU/L
- Prior to starting solids
- 29% react to egg
- 1.2% anaphylaxis
- Palmer JACI 2013

Strategies

- Breast feeding longer
- Probiotics
- Prebiotics
- HA formula
- Vit D
- Decrease in use of Proton pump inhibitor
- Solid introduction: window period

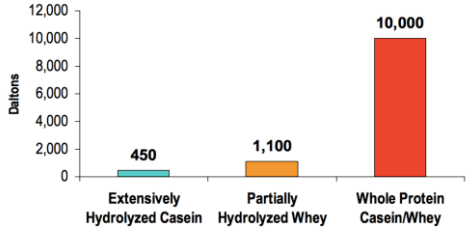
THE COCHRANE COLLABORATION®

Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants

David A Osborn, John KH Sinn

RPA Newborn Care, Royal Prince Alfred Hospital
Neonatal Unit, Royal North Shore Hospital
Australian Satellite of the Cochrane Neonatal Review Group, Australia

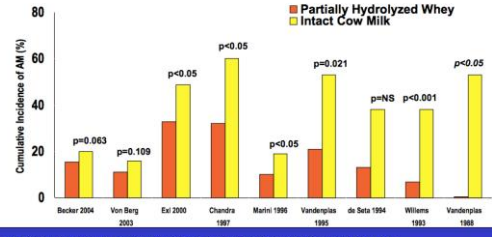
Hydrolysis Can Reduce Allergenicity of Cow Milk Proteins



Median Molecular Weight of Infant Formulas

Cumulative Incidence of Atopic Manifestations < 12 months of age

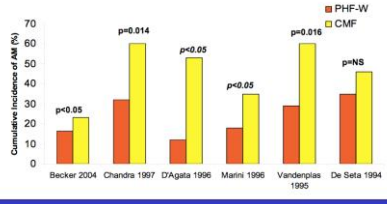
100% Whey Protein Partially Hydrolyzed Formula vs Cow Milk Formula in Prevention Studies



* Graph depicts only published, peer-reviewed, prospective trials with data collection at timepoints ≤12 months.
** For all studies except Becker 2004, AM includes AD as one of the allergic outcomes assessed; for Becker 2004, AM refers to asthma alone.
*** 4 months: Vandenplas 1988; 6 months: Exl 2000, De Seta 1994; 12 months: Becker 2004, Von Berg 2003, Chandra 1997, Marini 1996, Vandenplas 1995, Willems 1993
**** p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and CI

Cumulative Incidence of Allergic Manifestations > 12 mo of Age

100% Whey Protein Partially Hydrolyzed Formula vs Cow Milk Formula in Prevention Studies



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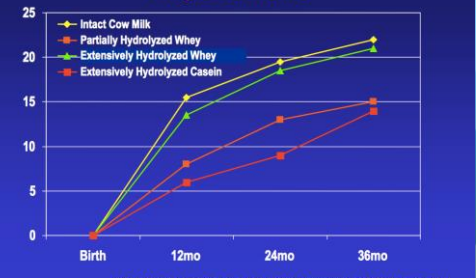
•For all studies except Becker 2004, AM includes AD as one of the allergic outcomes assessed; for Becker 2004, AM refers to asthma alone.
•2 years: Becker 2004, De Seta 1994; 3 years: Marini 1996; 4 years; D'Agata 1996; 5 years: Chandra 1997, Vandenplas 1995
•p-values in italics indicate that no p-value is reported in publication; p-value is based on calculated OR and 95% CI
•Chan 2002 not included. Wheezing reported exclusively, not inclusive of other AM at 30 months.

11

Cumulative Incidence of Atopic Dermatitis



3 Yr. GINI study : Findings not published. Results presented at ESPACI Meeting, 2003
Absolute cumulative incidence shown.

13

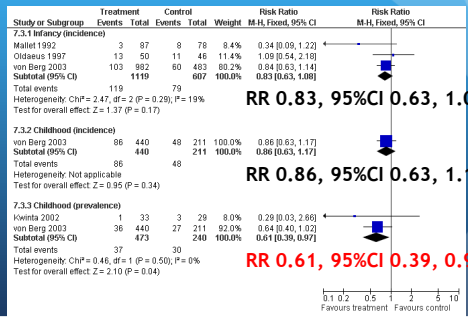
8 Prolonged feeding: Extensively hydrolysed formula versus cow's milk formula

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Any allergy	3		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
8.1.1 Infancy (incidence)	2	1561	Risk Ratio(M-H, Fixed, 95% CI)	0.87 [0.68, 1.13]
8.1.2 Childhood (incidence)	1	651	Risk Ratio(M-H, Fixed, 95% CI)	0.89 [0.71, 1.13]
8.1.3 Childhood (prevalence)	1	62	Risk Ratio(M-H, Fixed, 95% CI)	1.76 [0.76, 4.09]
8.2 Asthma	3		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
8.2.1 Infancy (incidence)	1	96	Risk Ratio(M-H, Fixed, 95% CI)	0.61 [0.18, 2.04]
8.2.2 Childhood (prevalence)	2	713	Risk Ratio(M-H, Fixed, 95% CI)	1.15 [0.76, 1.72]
8.3 Eczema	4		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
8.3.1 Infancy (incidence)	3	1726	Risk Ratio(M-H, Fixed, 95% CI)	0.83 [0.63, 1.08]
8.3.2 Childhood (incidence)	1	651	Risk Ratio(M-H, Fixed, 95% CI)	0.86 [0.63, 1.17]
8.3.3 Childhood (prevalence)	2	713	Risk Ratio(M-H, Fixed, 95% CI)	0.61 [0.39, 0.97]
8.4 Rhinitis	2		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
8.4.1 Infancy (incidence)	1	96	Risk Ratio(M-H, Fixed, 95% CI)	2.76 [0.12, 66.22]
8.4.2 Childhood (prevalence)	1	62	Risk Ratio(M-H, Fixed, 95% CI)	1.32 [0.53, 3.26]
8.5 Food allergy	1		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
8.5.1 Infancy (incidence)	1	96	Risk Ratio(M-H, Fixed, 95% CI)	1.15 [0.33, 4.02]

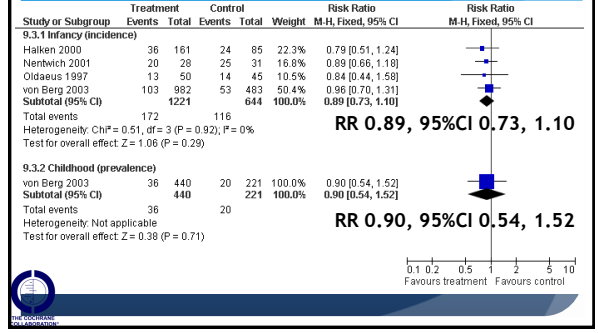
7 Prolonged feeding: Partially hydrolysed formula versus cow's milk formula

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Any allergy	8		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.1.1 Infancy (incidence)	8	1820	Risk Ratio(M-H, Fixed, 95% CI)	0.83 [0.72, 0.96]
7.1.2 Childhood (incidence)	2	510	Risk Ratio(M-H, Fixed, 95% CI)	0.86 [0.67, 1.10]
7.2 Asthma	7		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.2.1 Infancy (incidence)	4	268	Risk Ratio(M-H, Fixed, 95% CI)	0.54 [0.28, 1.04]
7.2.2 Childhood (incidence)	1	78	Risk Ratio(M-H, Fixed, 95% CI)	0.38 [0.08, 1.84]
7.2.3 Childhood (prevalence)	3	789	Risk Ratio(M-H, Fixed, 95% CI)	1.20 [0.91, 1.58]
7.3 Eczema	9		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.3.1 Infancy (incidence)	8	1699	Risk Ratio(M-H, Fixed, 95% CI)	0.89 [0.75, 1.06]
7.3.2 Childhood (incidence)	2	510	Risk Ratio(M-H, Fixed, 95% CI)	0.85 [0.61, 1.19]
7.3.3 Childhood (prevalence)	3	788	Risk Ratio(M-H, Fixed, 95% CI)	0.82 [0.61, 1.09]
7.4 Rhinitis	5		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.4.1 Infancy (incidence)	3	206	Risk Ratio(M-H, Fixed, 95% CI)	0.40 [0.09, 1.70]
7.4.2 Childhood (incidence)	1	78	Risk Ratio(M-H, Fixed, 95% CI)	0.47 [0.04, 5.03]
7.4.3 Childhood (prevalence)	2	357	Risk Ratio(M-H, Fixed, 95% CI)	1.14 [0.78, 1.67]
7.5 Food allergy	2		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.5.1 Infancy (incidence)	2	429	Risk Ratio(M-H, Fixed, 95% CI)	1.00 [0.62, 1.63]
7.6 Cow's milk allergy	2		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
7.6.1 Infancy (incidence)	2	405	Risk Ratio(M-H, Fixed, 95% CI)	0.38 [0.16, 0.86]

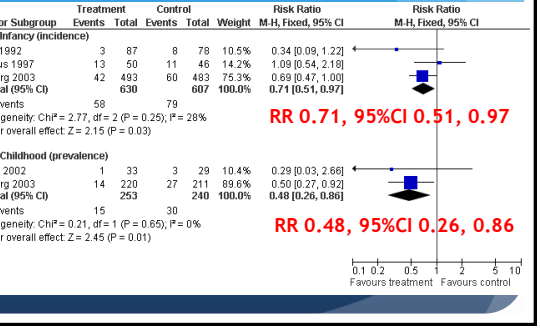
Subgroup analyses: **Eczema** - Extensively hydrolysed formula versus cow's milk formula



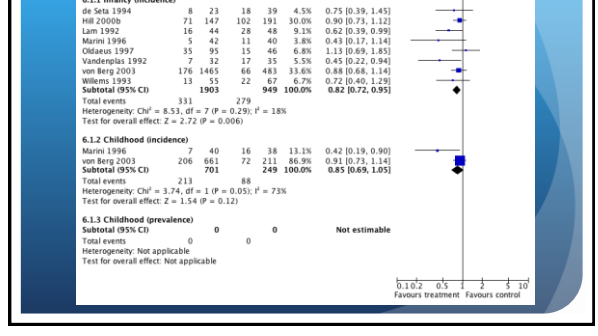
Subgroup analysis: **Eczema** - Extensively hydrolysed formula versus partially hydrolysed formula



Post hoc subgroup analysis: **Eczema** - Extensively hydrolysed casein formula versus cow's milk formula



PHF vs CMF: Any allergy high risk infants



Subgroup analysis: **Eczema** - Partially hydrolysed formula versus cow's milk formula

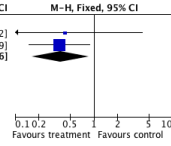
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 Infancy (incidence)						
Chirico 1997	0	21	2	14	1.5%	0.14 [0.01, 2.64]
de Seta 1994	3	23	5	39	1.9%	1.02 [0.27, 3.87]
Hill 2000b	93	191	83	193	42.9%	1.13 [0.91, 1.41]
Lam 1992	13	44	15	48	7.4%	0.95 [0.51, 1.76]
Marini 1996	4	42	8	40	4.3%	0.48 [0.16, 1.46]
Oldaeus 1997	14	45	11	46	5.6%	1.30 [0.66, 2.55]
Tsai 1991	8	15	11	18	5.2%	0.87 [0.48, 1.59]
von Berg 2003	53	483	60	483	31.1%	0.88 [0.62, 1.25]
Subtotal (95% CI)		**864**		**881**	**100.0%**	**0.99 [0.84, 1.17]**
Total events	188		195			
Heterogeneity: Chi² = 6.04, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
8.3.2 Childhood (prevalence)						
Hill 2000b	56	167	51	162	62.7%	1.07 [0.78, 1.45]
Kwinta 2002	1	33	3	29	3.9%	0.29 [0.03, 2.66]
von Berg 2003	20	221	27	211	33.4%	0.71 [0.41, 1.22]
Subtotal (95% CI)		**421**		**402**	**100.0%**	**0.92 [0.70, 1.20]**
Total events	77		81			
Heterogeneity: Chi² = 2.79, df = 2 (P = 0.25); I² = 28%						
Test for overall effect: Z = 0.64 (P = 0.52)						

RR 0.99, 95%CI 0.84, 1.17

RR 0.92, 95%CI 0.70, 1.20

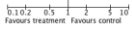
PHF vs CMF: Cow's milk allergy

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Infancy (incidence)						
Hill 2000b	1	147	3	191	15.4%	0.43 [0.05, 4.12]
Vandenplas 1992	5	32	15	35	84.6%	0.36 [0.15, 0.89]
Subtotal (95% CI)		**179**		**226**	**100.0%**	**0.38 [0.16, 0.86]**
Total events	6		18			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.31 (P = 0.02)						



PHF vs CMF infant **eczema** incidence

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 Infancy (incidence)						
Chirico 1997	0	21	2	14	1.6%	0.14 [0.01, 2.64]
de Seta 1994	3	23	5	39	1.9%	1.02 [0.27, 3.87]
Hill 2000b	64	147	93	191	42.4%	0.89 [0.71, 1.13]
Lam 1992	13	44	15	48	7.5%	0.95 [0.51, 1.76]
Marini 1996	4	42	8	40	4.3%	0.48 [0.16, 1.46]
Oldaeus 1997	14	45	11	46	5.7%	1.30 [0.66, 2.55]
Tsai 1991	8	15	11	18	5.2%	0.87 [0.48, 1.59]
von Berg 2003	53	483	60	483	31.4%	0.88 [0.62, 1.25]
Subtotal (95% CI)		**820**		**879**	**100.0%**	**0.89 [0.75, 1.06]**
Total events	159		205			
Heterogeneity: Chi² = 4.04, df = 7 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
8.3.2 Childhood (incidence)						
Marini 1996	4	40	9	38	15.8%	0.42 [0.14, 1.26]
von Berg 2003	47	221	48	211	84.2%	0.93 [0.66, 1.33]
Subtotal (95% CI)		**261**		**249**	**100.0%**	**0.85 [0.61, 1.19]**
Total events	51		57			
Heterogeneity: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%						
Test for overall effect: Z = 0.92 (P = 0.36)						
8.3.3 Childhood (prevalence)						
Hill 2000b	39	127	56	167	61.1%	0.92 [0.65, 1.28]
Kwinta 2002	1	33	3	29	4.0%	0.29 [0.03, 2.66]
von Berg 2003	20	221	27	211	34.9%	0.71 [0.41, 1.22]
Subtotal (95% CI)		**381**		**407**	**100.0%**	**0.82 [0.61, 1.09]**
Total events	60		86			
Heterogeneity: Chi² = 1.53, df = 2 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						

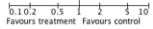


PHF vs CMF infant **asthma** incidence

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.2.1 Infancy (incidence)						
de Seta 1994	5	23	13	39	45.1%	0.65 [0.27, 1.59]
Marini 1996	1	42	3	40	14.4%	0.32 [0.03, 2.93]
Oldaeus 1997	2	45	6	46	27.8%	0.34 [0.07, 1.60]
Tsai 1991	2	15	3	18	12.8%	0.80 [0.15, 4.18]
Subtotal (95% CI)		**125**		**143**	**100.0%**	**0.54 [0.28, 1.04]**
Total events	10		25			
Heterogeneity: Chi² = 0.95, df = 3 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.84 (P = 0.07)						
8.2.2 Childhood (incidence)						
Marini 1996	2	40	5	38	100.0%	0.38 [0.08, 1.84]
Subtotal (95% CI)		**40**		**38**	**100.0%**	**0.38 [0.08, 1.84]**
Total events	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
8.2.3 Childhood (prevalence)						
Hill 2000b	40	127	47	168	57.6%	1.13 [0.79, 1.60]
Kwinta 2002	10	33	4	29	6.1%	2.20 [0.77, 6.26]
von Berg 2003	30	221	25	211	36.4%	1.15 [0.70, 1.88]
Subtotal (95% CI)		**381**		**408**	**100.0%**	**1.20 [0.91, 1.58]**
Total events	80		76			
Heterogeneity: Chi² = 1.44, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.27 (P = 0.20)						

EHF vs CMF: : Infant **eczema** incidence

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.3.1 Infancy (incidence)						
Mallet 1992	3	87	8	78	8.4%	0.34 [0.09, 1.22]
Oldaeus 1997	13	50	11	46	11.4%	1.09 [0.54, 2.18]
von Berg 2003	103	982	60	483	80.2%	0.84 [0.63, 1.14]
Subtotal (95% CI)		**1119**		**607**	**100.0%**	**0.83 [0.63, 1.08]**
Total events	119		79			
Heterogeneity: Chi² = 2.47, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 1.37 (P = 0.17)						
7.3.2 Childhood (incidence)						
von Berg 2003	86	440	48	211	100.0%	0.86 [0.63, 1.17]
Subtotal (95% CI)		**440**		**211**	**100.0%**	**0.86 [0.63, 1.17]**
Total events	86		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
7.3.3 Childhood (prevalence)						
Kwinta 2002	1	33	3	29	8.0%	0.29 [0.03, 2.66]
von Berg 2003	36	440	27	211	92.0%	0.64 [0.40, 1.02]
Subtotal (95% CI)		**473**		**240**	**100.0%**	**0.61 [0.39, 0.97]**
Total events	37		30			
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						



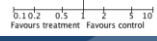
Subgroup analysis: **Eczema** - EHF vs PHF

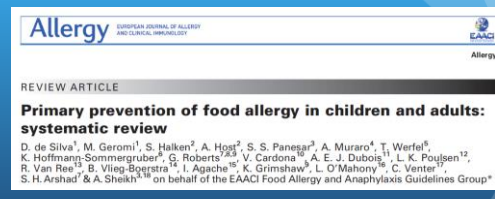
Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.3.1 Infancy (incidence)						
Halken 2000	36	161	24	85	22.3%	0.79 [0.51, 1.24]
Nentwich 2001	20	28	25	31	16.8%	0.89 [0.66, 1.18]
Oldaeus 1997	13	50	14	45	10.5%	0.84 [0.44, 1.58]
von Berg 2003	103	982	53	483	50.4%	0.96 [0.70, 1.31]
Subtotal (95% CI)		**1221**		**644**	**100.0%**	**0.89 [0.73, 1.10]**
Total events	172		116			
Heterogeneity: Chi² = 0.51, df = 3 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						

RR 0.89, 95%CI 0.73, 1.10

EHF vs PHF: Food Allergy

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.5.1 Infancy (incidence)						
Halken 2000	3	161	4	85	33.2%	0.40 [0.09, 1.73]
Oldaeus 1997	5	50	10	45	66.8%	0.45 [0.17, 1.22]
Subtotal (95% CI)		**211**		**130**	**100.0%**	**0.43 [0.19, 0.99]**
Total events	8		14			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.00 (P = 0.05)						
9.5.2 Childhood (incidence)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.5.3 Childhood (prevalence)						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						





Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

REVIEW ARTICLE

Primary prevention of food allergy in children and adults: systematic review

D. de Silva[1], M. Geromi[1], S. Halken[2], A. Host[2], S. S. Panesar[3], A. Muraro[4], T. Werfel[5], K. Hoffmann-Sommergruber[6], G. Roberts[7,8,9], V. Cardona[10], A. E. J. Dubois[11], L. K. Poulsen[12], R. Van Ree[13], B. Vlieg-Boerstra[14], I. Agache[15], K. Grimshaw[7], L. O'Mahony[16], C. Venter[17], S. H. Arshad[7] & A. Sheikh[3,18] on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group*

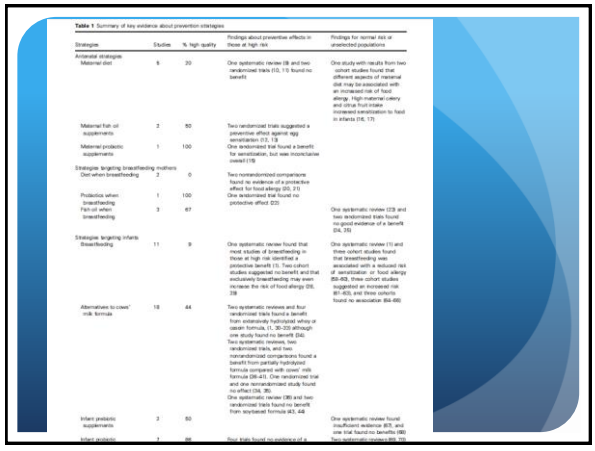
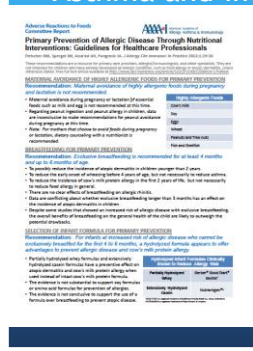


Table 1 Summary of key evidence about prevention strategies

Strategies	Studies	% high quality	Findings about preventive effects in those at high risk	Findings for normal risk or unselected populations
Antenatal strategies				
Maternal diet	9	20	One systematic review (8) and two randomized trials (10, 11) found no benefit	One study with results from two cohort studies found that different aspects of maternal diet may be associated with an increased risk of food allergy. High maternal celery and citrus fruit intake increased sensitization to food in infants (16, 17)
Maternal fish oil supplements	2	50	Two randomized trials suggested a preventive effect against egg sensitization (12, 13)	
Maternal probiotic supplements	1	100	One randomized trial found a benefit for sensitization, but was inconclusive overall (18)	
Strategies targeting breastfeeding mothers				
Diet when breastfeeding	2	0	Two nonrandomized comparisons found no evidence of a protective effect for food allergy (20, 21)	
Probiotics when breastfeeding	1	100	One randomized trial found no protective effect (22)	
Fish oil when breastfeeding	3	67		One systematic review (23) and two randomized trials found no good evidence of a benefit (24, 25)
Strategies targeting infants				
Breastfeeding	11	9	One systematic review found that most studies of breastfeeding in those at high risk identified a protective benefit (1). Two cohort studies suggested no benefit and that exclusively breastfeeding may even increase the risk of food allergy (26, 28)	One systematic review (1) and three cohort studies found that breastfeeding was associated with a reduced risk of sensitization or food allergy (55–62), three cohort studies suggested an increased risk (61–63), and three cohorts found no association (64–66)
Alternatives to cows' milk formula	18	44	Two systematic reviews and four randomized trials found a benefit from extensively hydrolyzed whey or casein formula, (1, 30–33) although one study found no benefit (34). Two systematic reviews, two randomized trials, and two nonrandomized comparisons found a benefit from partially hydrolyzed formula compared with cows' milk formula (35–41). One randomized trial and one nonrandomized study found no effect (34, 35). One systematic review (36) and two randomized trials found no benefit from soybased formula (42, 43)	
Infant probiotic supplements	3	50		One systematic review found insufficient evidence (67), and one trial found no benefits (68)
Infant prebiotic	2	66	Four trials found no evidence of a	Two systematic reviews (69, 70)

American Academy of Allergy Asthma and immunology (AAAAI)



Adverse Reactions to Foods Committee Report

AAAI American Academy of Allergy, Asthma & Immunology

Primary Prevention of Allergic Disease Through Nutritional Interventions: Guidelines for Healthcare Professionals

Pediatrics 106; Springer 346; Journal ed. Pediatrics 24; Allergy 24; Immunol. in Pediatr 24(1-2) 20-30

These recommendations are a resource for primary care providers, allergist/immunologists, and other specialists. They are based on a review of the literature and on the consensus of the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma, Immunology. Visit full text online at http://www.aaai.org/allergy/allergies/adverse_reactions_to_foods.asp

MATERNAL AVOIDANCE OF HIGHLY ALLERGENIC FOODS FOR PRIMARY PREVENTION

Recommendation: Maternal avoidance of highly allergenic foods during pregnancy and lactation is not recommended.

- Maternal avoidance during pregnancy or lactation [of essential foods such as milk and egg] is not recommended at this time.
- Data are insufficient to support or refute a benefit, and data are inconclusive to make recommendations for peanut avoidance during pregnancy at this time.
- *Note: For mothers that choose to avoid foods during pregnancy or lactation, dietary counseling with a nutritionist is recommended.*

Highly Allergenic Foods
Cow's Milk
Soy
Egg
Wheat
Peanuts and Tree nuts
Fish and Shellfish

BREASTFEEDING FOR PRIMARY PREVENTION

Recommendation: Exclusive breastfeeding is recommended for at least 4 months and up to 6 months of age.

- To possibly reduce the incidence of atopic dermatitis in children younger than 2 years.
- To reduce the early onset of wheezing before 4 years of age, but not necessarily to reduce asthma.
- To reduce the incidence of cow's milk protein allergy in the first 2 years of life, but not necessarily to reduce food allergy in general.
- There are no clear effects of breastfeeding on allergic rhinitis.
- Data are conflicting about whether exclusive breastfeeding longer than 3 months has an effect on the incidence of atopic dermatitis in children.
- Despite some studies that showed an increased risk of allergic disease with exclusive breastfeeding, the overall benefits of breastfeeding on the general health of the child are likely to outweigh the potential drawbacks.

SELECTION OF INFANT FORMULA FOR PRIMARY PREVENTION

Recommendation: For infants at increased risk of allergic disease who cannot be exclusively breastfed for the first 4 to 6 months, a hydrolyzed formula appears to offer advantages to prevent allergic disease and cow's milk protein allergy.

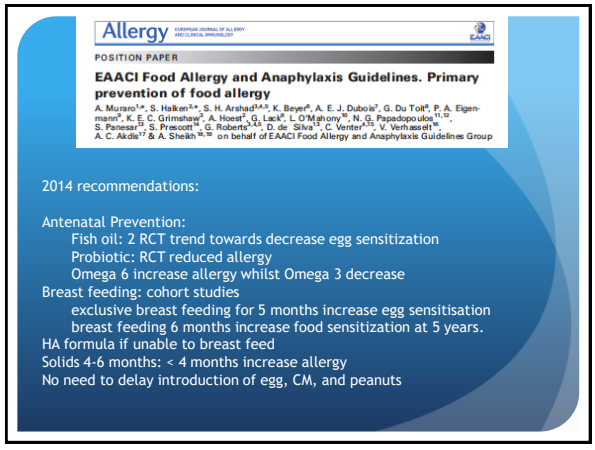
- Partially hydrolyzed whey formulas and extensively hydrolyzed casein formulas may be effective in reducing atopic dermatitis and cow's milk protein allergy when used instead of intact cow's milk protein formula.
- The evidence is not substantial to support any formulas or amino acid formulas for prevention of allergies.
- The evidence is not conclusive to support the use of a formula over breastfeeding to prevent atopic disease.

Hydrolyzed Infant Formulas Clinically Proven to Reduce Risk of Atopic Disease	
Partially Hydrolyzed Whey	Gerber® Good Start® Gentle
Extensively Hydrolyzed Casein	Nutramigen®

- No difference in CMA
- Another RCT suggest increase risk

- Fish allergen: fish in first year of life: protect against fish allergy

- Egg: protective if given 4-6 months



Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

POSITION PAPER

EAACI Food Allergy and Anaphylaxis Guidelines. Primary prevention of food allergy

A. Muraro[1,*], S. Halken[2,*], S. H. Arshad[3,4,5], K. Beyer[6], A. E. J. Dubois[7], G. Du Toit[8], P. A. Eigenmann[9], K. E. C. Grimshaw[3], A. Hoest[2], G. Lack[8], L. O'Mahony[10], N. G. Papadopoulos[11,12], S. Panesar[13], S. Prescott[14], G. Roberts[3,4,5], D. de Silva[13], C. Venter[4,15], V. Verhasselt[16], A. C. Akdis[17] & A. Sheikh[18,19] on behalf of EAACI Food Allergy and Anaphylaxis Guidelines Group

2014 recommendations:

Antenatal Prevention:
- Fish oil: 2 RCT trend towards decrease egg sensitization
- Probiotic: RCT reduced allergy
- Omega 6 increase allergy whilst Omega 3 decrease

Breast feeding: cohort studies
- exclusive breast feeding for 5 months increase egg sensitisation
- breast feeding 6 months increase food sensitization at 5 years.

HA formula if unable to breast feed
Solids 4-6 months: < 4 months increase allergy
No need to delay introduction of egg, CM, and peanuts

EAACI recommendations

- Cow milk in first few days of life: in 2 RCT
  - No difference in CMA
  - Another RCT suggest increase risk
- Fish allergen: fish in first year of life: protect against fish allergy
- Egg: protective if given 4-6 months

Changing Formula

- If constipation: more Whey, HA, Probiotics, Prebiotics
- If diarrhoea: Probiotics or prebiotics, electrolyte, fructose and glucose better absorbed, low lactose, sucrose free
- If Diarrhoea: ? Lactose Intolerance. > 2% required
  - LF formula or Soy
- If Colic: ? Reflux
  - HA for increase transit time
  - Probiotic or prebiotic formula
  - Thicken feeds
- Proton pump inhibitor or H2 receptor antagonist: add probioitc
- Reflux: corn starch, thickens in stomach not before: AR formula Casein dominant constipation
- Allergies: HA Whey dominant, less reflux
- Colic: reduce lactose, probiotics

Changing formula

HA: 100% Whey: not all HA preparation are the same in terms of size of molecules.

AR: ratio of Casein: varies 100% casein to 100% whey

Probiotics: added: if prepared at >60C will kill probiotics and vitamins

Different probiotics: L reuteri for colic

Constipation: probiotics

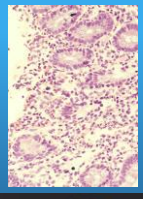
2 Formula feeding in syndromes associated with cows milk protein allergy*

Syndrome	Onset of reaction	Maternal elimination of CMP if breastfeeding?	Choice of formula: First†	Second (if first not tolerated)	Third (if second not tolerated)	NHMRC level of evidence‡	Consensus panel agreement§
Immediate reaction							
Immediate food allergy	< 1 h	Yes	eHF (< 6 months)	AAF	—	II	11/11
			Soy (> 6 months)	eHF	AAF		
Anaphylaxis	< 1 h	Yes	AAF (followed by urgent consultation with paediatric allergist)	—	—	IV	11/11
Food protein-induced enterocolitis syndrome	1–3 h	No	eHF	AAF	—	IV	10/11
Delayed reaction							
Atopic eczema	Hours to days	Yes¶	eHF (< 6 months or > 6 months with FTT)	AAF	—	IV	11/11
			Soy (> 6 months, no FTT)	eHF	AAF		
Gastrointestinal syndromes, GORD, allergic eosinophilic gastroenteritis, food protein-induced enteropathy, constipation, severe irritability (colic)	Hours to days	Yes¶	eHF (< 6 months or > 6 months with FTT)	AAF	—	I (severe irritability), III (GORD), IV (others)	11/11
			Soy (> 6 months, no FTT)	eHF	AAF		
Food protein-induced proctocolitis							11/11
Formula-fed	> 24 h	—	eHF	AAF	—	IV	
Breastfed	> 24 h	Yes¶	—	—	—		
Eosinophilic oesophagitis in infants	Days to weeks	Yes	AAF	—	—	IV	11/11

CM protein induced enteropathy

- Non IgE
- 80% respond to EHF
- Often allergic to soy, chicken, rice and fish
- Mx: mother avoid CMP. Egg, Nuts

Allergic eosinophilic gastroenteritis

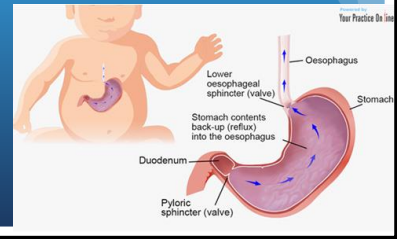


- ♦Use EHF to AAF
- ♦IgE and Non IgE
- ♦Blood loss, Iron deficiency
- ♦Eosinophils in mucosa
- ♦swallowed aerosolized fluticasone Anti-IL-5 therapy

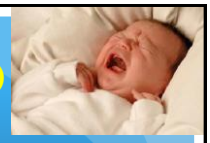
Chehade M et al JPGN 2006;42;516-521

Gastro-oesophageal reflux disease (GORD)

- Non IgE
- 40% who reach specialist have CMPA
- EHF to AAF



Severe irritability (colic)



- Non IgE
- Persistent crying
- Systematic review
  - Hypoallergic formula reduce colic: EHF
  - No role of soy in the prevention or management of infantile colic or regurgitation

Constipation

- Non IgE
- At tertiary referral level
  - 70% of chronic constipation can be due to CMA

Resolution of CMA

- 1yr 56%, 2yr 77% 3yr 87% 5yr 92% 15yr 97%
- Desensitization: Gradual increase dose if SPT negative.
- Cow milk intolerance.
- AAF:
- EHF
- HA
- CMP
- Gradual increasing mixture
- Probiotics
- Vit D

Why not use Cow milk in first year of life

- Low content and bioavailability of iron
- High calcium, high phosphorous, low vitamin C decreases bioavailability of iron
- may contribute to the high incidence of cow's milk protein allergy (7- 16%)

The Paediatric Centre St Leonards

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- Paediatric Allergy: Allergy testing and Immunotherapy
- Neonatology
- Nephrology
- Allied Health
  - Clinical Psychologist, Occupational therapist; Physiotherapist, Speech therapist, Dietician,

Any practical advice on your patient care please email or telephone:

- info@thepaediatriccentre.com.au Tel: 94052386 Fax 94052387
- www.thepaediatriccentre.com.au