



FORMULE PER IL TRATTAMENTO DELL'ALLERGIA ALLE PROTEINE DEL LATTE VACCINO

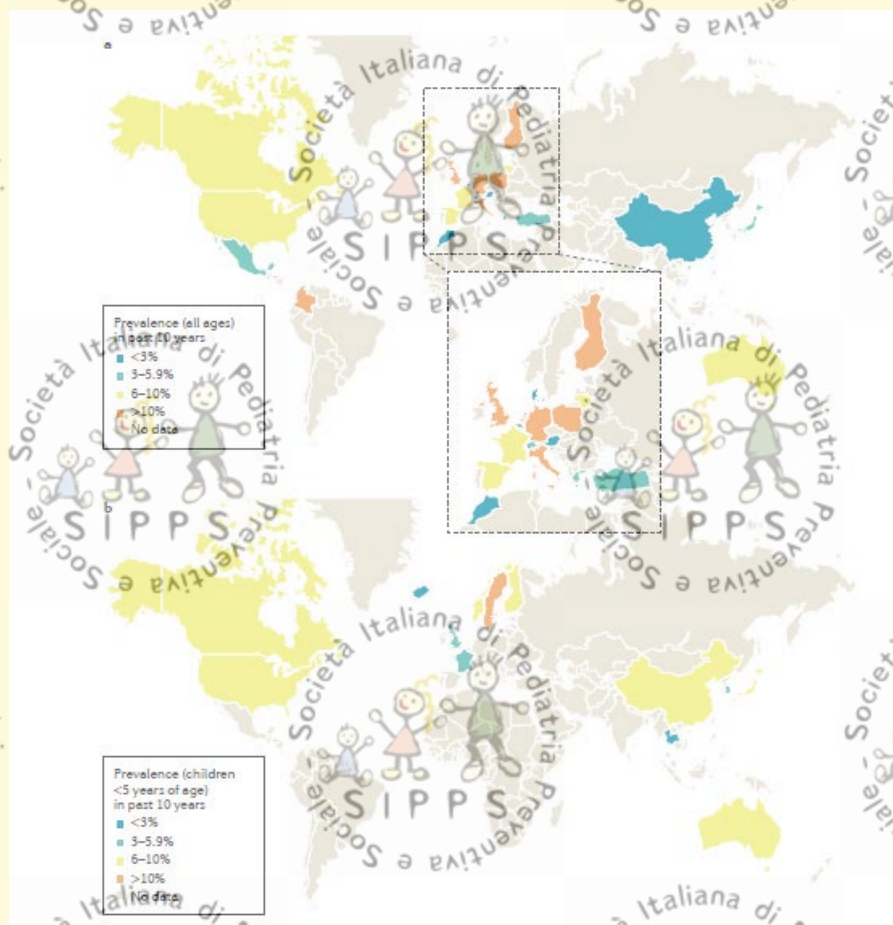
**Iride Dello Iacono
Benevento**

Food allergy

Harald Renz¹, Katrine J. Allen², Scott H. Sicherer³, Hugh A. Sampson³, Gideon Lack⁴,
Kirsten Beyer⁵ and Hans C. Oettgen^{6,7}

2 | ARTICLE NUMBER 17098 | VOLUME 4

2018

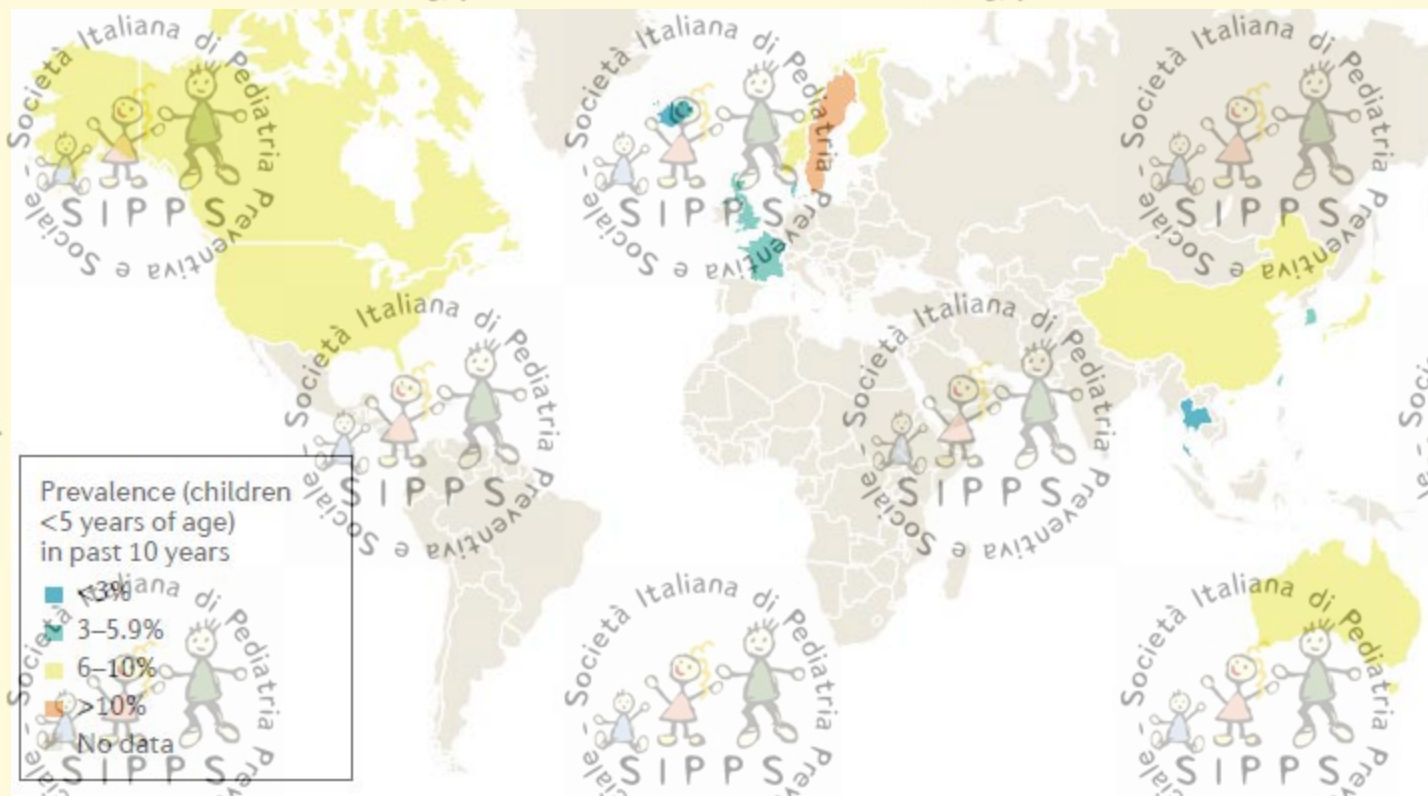


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BSACI guideline for the diagnosis and management of cow's milk allergy

D. Luyt¹, H. Ball¹, N. Makwana², M. R. Green¹, K. Bravin¹, S. M. Nasser³ and A. T. Clark³

¹University Hospitals of Leicester NHS Trust, Leicester, UK; ²Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK and ³Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

PREVALENCE

Table 1. Prevalence of cow's milk allergy in unselected populations diagnosed by oral challenge with fresh cow's milk

Authors, year	Prevalence
Halpern et al., 1973 [166]	20/1084 (1.8%)
Gerrard et al., 1973 [167]	59/787 (7.5%)
Jakobsson and Lindberg, 1979 [18]	20/1079 (1.9%)
Høst and Halken, 1990 [15]	39/1749 (2.2%)
Schrander et al., 1993 [168]	26/1158 (2.8%)
Saariinen et al., 1999 [19]	118/6209 (1.9%)
Venter et al., 2006 [16]	22/969 (2.3%)
Kvenshagen et al., 2008 [21]	27/555 (4.9%)

NATURAL HISTORY

Table 2. Natural history of cow's milk allergy expressed as percentage tolerant

Age (years)	Bishop (1990) [†] [7] (n = 97)			Host (2002) [†] [8] (n = 39)			Vanho (2004) [†] [23] (n = 162)			Saarinen (2005) * [†] [22] (n = 118)			Skrupak (2007) [†] [24] (n = 807)		Levy (2007) [†] [§] [28] (n = 105)		Santos (2010) [†] [§] [29]	
	All	IgE	nIgE	All	IgE	nIgE	All	IgE	nIgE	All	IgE	nIgE	IgE		IgE		All	IgE
1	—	56	24	100	—	—	—	—	—	45	38	66	—	—	—	—	9	—
1.5	—	69	—	—	—	—	—	—	—	—	—	—	—	—	—	—	23	—
2	28	77	—	—	44	30	59	51	—	—	—	—	9	—	—	—	34	—
3	87	—	—	—	69	—	—	—	—	—	—	—	—	—	19	—	40	5
4	56	—	—	—	77	59	—	—	—	—	—	—	26	—	—	—	36	16
5	—	92	—	—	—	—	—	—	—	81	74	100	—	—	31	—	56	22
6	78	—	—	—	—	—	—	—	—	—	—	—	44	—	—	—	63	37
8	—	—	—	—	—	—	—	—	—	89	85	100	—	—	—	—	—	—
8.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	38	—	—	—
10	—	92	—	—	—	—	—	—	—	—	—	—	64	—	—	—	66	4
11	—	—	—	—	—	—	—	—	—	—	—	—	—	—	41	—	—	—
12	—	—	—	—	—	—	—	—	—	—	—	—	77	—	—	—	—	—
14	—	—	—	—	—	—	—	—	—	—	—	—	83	—	—	—	—	—
15	—	97	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
16	—	—	—	—	—	—	—	—	—	—	—	—	88	—	—	—	—	—
18	—	—	—	—	—	—	—	—	—	—	—	—	93	—	—	—	—	—

Age – age when assessed, that is, underwent open food challenge with fresh milk; IgE, IgE mediated; nIgE, non-IgE mediated.

Study types (potentially influencing outcome)

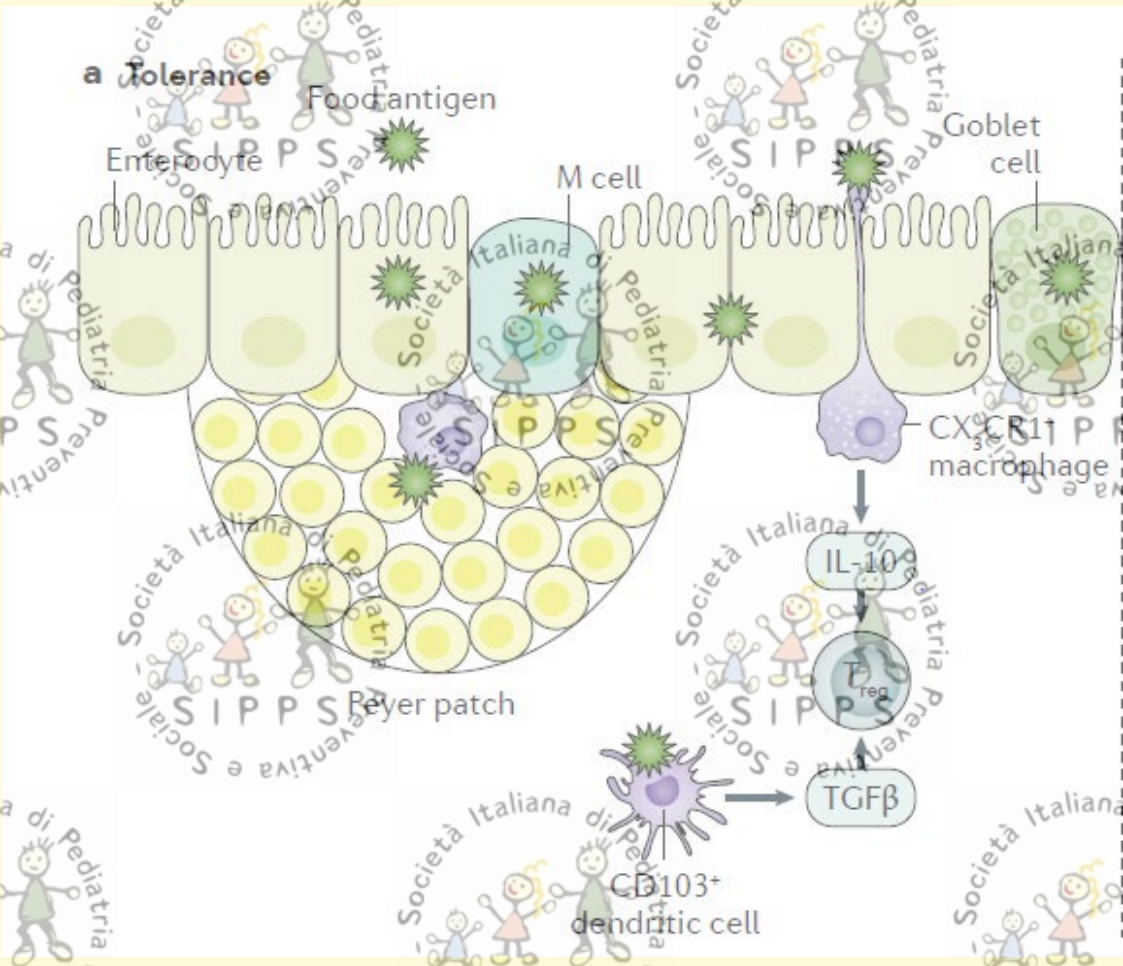
*Birth cohort.

[†]Tertiary centre.

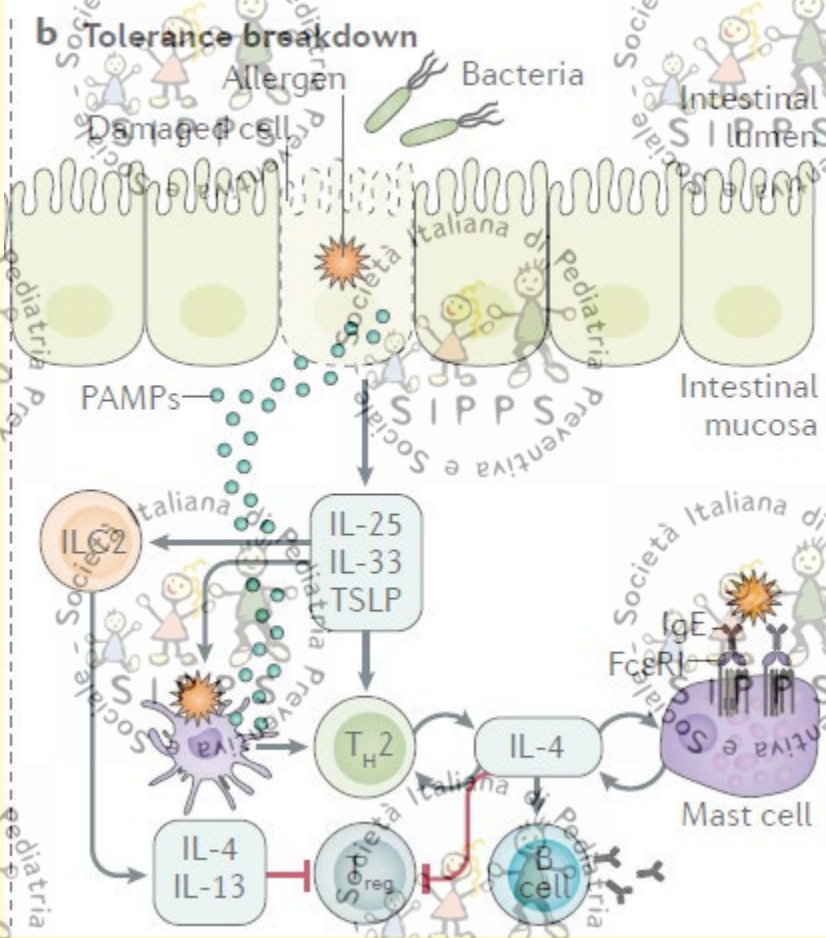
[‡]Regular challenges performed.

[§]Challenges performed only when sIgE levels have fallen.

TOLERANCE



TOLERANCE BREAKDOWN



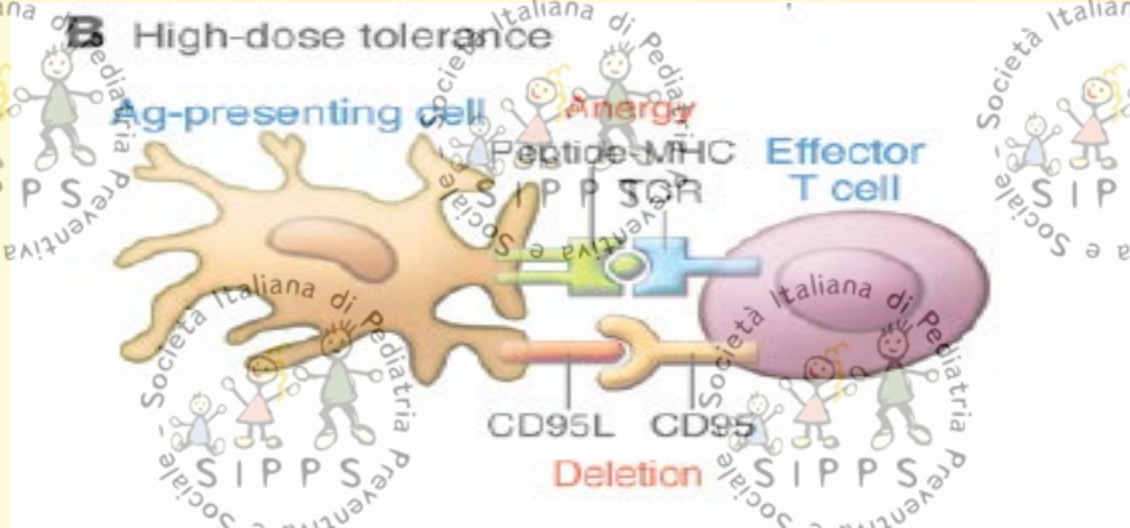
Food allergy

Julie Wang and Hugh A. Sampson

Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai Hospital, New York, New York, USA.

The Journal of Clinical Investigation <http://www.jci.org> Volume 121 Number 3 March 2011

Mechanisms of oral tolerance



With high doses of oral antigen leading to anergy or deletion

Food allergy

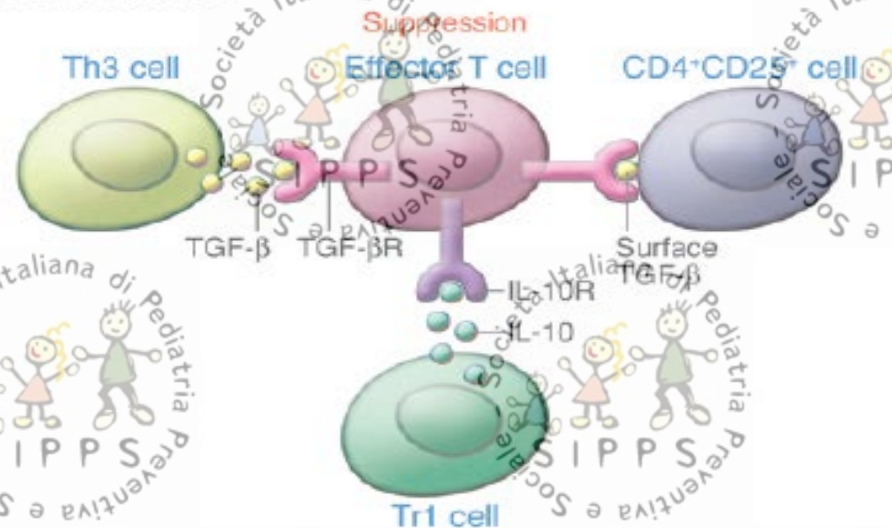
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Mechanisms of oral tolerance

C Low-dose tolerance



Low doses of oral antigen lead to the activation of regulatory T cells, which suppress immune responses through soluble or cell surface-associated suppressive cytokines (IL-10 and TGF-β).

Management of Food Allergy: le LG

2010

J ALLERGY CLIN IMMUNOL
VOLUME 126, NUMBER 6

BOYCE ET AL 85

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

JAMA

Diagnosing and Managing Common Food Allergies: A Systematic Review

REVIEW ARTICLE

World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines

2011

Issue date: February 2011

Food allergy in children and young people

Diagnosis and assessment of food allergy in children and young people in primary care and community settings

POSITION PAPER

EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy

doi: 10.1111/j.1365-2230.12302

BSACI GUIDELINES

Clinical & Experimental Allergy 44, 642-673

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BSACI guideline for the diagnosis and management of cow's milk allergy

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2014

Food Allergy

Institute of Allergy and Infectious Disease

and, treat, and prevent infectious, immunologic, and allergic diseases.

Food Intolerances

GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF FOOD ALLERGY

2010

Adverse Food Reaction

Intolleranza alimentare

Immune Mediated
(Food Allergy and Celiac Disease)

Non-Immune Mediated
(Primarily Food Intolerances)

IgE Mediated
(e.g. acute urticaria, oral allergy syndrome)

Non-IgE Mediated
(e.g. food protein-induced enteropathy, Celiac disease)

Mixed IgE and Non-IgE Mediated
(e.g. eosinophilic gastroenteritis)

Cell Mediated
(e.g. Allergic Contact Dermatitis)

Metabolic
(e.g. lactose intolerance)

Pharmacologic
(e.g. caffeine)

Toxic (e.g. scombroid fish toxin)

Other/Idiopathic/Undefined
(e.g. sulfites)

Presenza
delle IgE

FOOD ALLERGY

OTIPI IMMUNOLOGICI

IgE-mediated reactions

IgE mediated
(acute onset)

Acute urticaria/angioedema

Food commonly causes acute (20%) but rarely chronic urticaria.

Primarily "major allergens" (see text)

Contact urticaria

Direct skin contact results in lesions.

Multiple

Anaphylaxis

Rarely this is due to direct histamine release (nonimmunologic).

Any but more commonly peanut, tree nuts, shellfish, fish, milk, and egg

Food-associated, exercise-induced anaphylaxis

Rapidly progressive, multiple organ system reaction can include cardiovascular collapse.

Wheat, shellfish, and celery most often described

Oral allergy syndrome
(pollen-associated food allergy syndrome)

Food triggers anaphylaxis only if ingestion is followed temporally by exercise.

Raw fruit/vegetables; cooked forms tolerated; examples of relationships: birch (apple, peach, pear, carrot), ragweed (melons)

Immediate gastrointestinal hypersensitivity

Pruritus and mild edema are confined to oral cavity and uncommonly progress beyond the mouth (~7%) and rarely to anaphylaxis (1% to 2%). Might increase after pollen season.

Major allergens

Immediate vomiting, pain

Non-IgE

FOOD ALLERGY

TIPI IMMUNOLOGICI

Cell-mediated reactions

Cell mediated
(delayed onset/chronic)

Food protein-induced enterocolitis
syndrome

Primarily affects infants; chronic
exposure: emesis, diarrhea; poor
growth, lethargy; re-exposure after
restriction, emesis, diarrhea,
hypotension (15%) 2 hours after
ingestion

Cow's milk, soy, rice, oat, meat

Food protein-induced allergic
proctocolitis

Allergic contact dermatitis

Mucus-laden, bloody stools in infants

Milk (through breast-feeding)

Often occupational because of chemical
moieties, oleoresins. Systemic contact
dermatitis is a rare variant because of
ingestion

Spices, fruits, vegetables

Heiner syndrome

Pulmonary infiltrates, failure to thrive,
iron deficiency anemia

Cow's milk

IgE/non-IgE

FOOD ALLERGY

TIPI IMMUNOLOGICI

Combined IgE and cell-mediated reactions

Combined IgE and cell-mediated (delayed onset/chronic)

Atopic dermatitis

Associated with food allergy in ~35% of children with moderate-to-severe rash

Major allergens, particularly egg, milk

Eosinophilic esophagitis

Symptoms might include feeding disorders, reflux symptoms, vomiting, dysphagia, and food impaction

Multiple

Eosinophilic gastroenteritis

Vary on site(s)/degree of eosinophilic inflammation; might include ascites, weight loss, edema, obstruction

Multiple

ICON: Food allergy

A. Wesley Burks, MD,^a Mimi Tang, MBBS, PhD,^b Scott Sicherer, MD,^c Antonella Muraro, MD, PhD,^d Philippe A. Eigenmann, MD,^e Motohiro Ebisawa, MD, PhD,^f Alessandro Fiocchi, MD,^g Wen Chiang, MBBS, MRCPCH,^h Kirsten Beyer, MD,ⁱ Robert Wood, MD,^j Jonathan Hourihane, MB, DM, MRCPI, FRCPHC,^k Stacie M. Jones, MD,^l Gideon Lack, FRCPCH,^m and Hugh A. Sampson, MD^c Chapel Hill, NC, Parkville, Australia, New York, NY, Padua, Italy, Geneva, Switzerland, Kanagawa, Japan, Milan, Italy, Singapore, Berlin, Germany, Baltimore, Md, Cork, Ireland, Little Rock, Ark, and London, United Kingdom

J Allergy Clin Immunol 2012

*The primary therapy for food allergy is strict avoidance of the causal food or foods.

*This is true for IgE-mediated, non-IgE-mediated, and mixed IgE- and non-IgE-mediated food allergy syndromes.

GRADE

World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines

Treating cow's milk allergy (CMA) entails a nutritional risk, as milk is a staple food in particular for children less than 2 years of age. When a replacement formula is needed, the allergist can avail themselves with different types of formula:

1. Amino acid formula (AAF)
2. Extensively hydrolyzed formula of cow's milk proteins (EHF)
3. Soy formula (SF)
4. Rice extensively hydrolyzed formula (RHF)
5. Soy hydrolyzed formula (SHE)
6. Other mammal's milks

2010

APLV IgE-mediata: fenotipi clinici

WAO (WAO) Diagnosis and Rationale for Treatment of Food Allergy (DRACMA) Guidelines

Andrea von Berg, K. Maria Antonietti, Alberto Martelli, Fa...
Jan Brozek, Holger Schünemann, (Chair), Sami L. Bahna,
ver, Martin Bozzola, Julia Bradsher, Enrico Compalati, Motohiro Ebisawa,
n, Haiqi Li, Ralf G. Heine, Paul Keith, Gideon Lack, Massimo Landi,
Rancé, Hugh Sampson, Airtion Stein, Luigi Terracciano, and Stefan Vieths

WAO Journal - April 2010

Clinical Recommendations

In children with IgE-mediated CMA at high risk of anaphylactic reactions (prior history of anaphylaxis and currently not using extensively hydrolyzed milk formula), we suggest amino acid formula rather than extensively hydrolyzed milk formula (conditional recommendation/very low quality evidence).

In children with IgE-mediated CMA at low risk of anaphylactic reactions (no prior history of anaphylaxis or currently on extensively hydrolyzed milk formula), we suggest extensively hydrolyzed milk formula over amino acid formula (conditional recommendation/very low quality evidence).

**APLV non-IgE
mediata:
fenotipi clinici
eHF**

**APLV IgE/non-IgE:
fenotipi clinici
AAF/eHF**

Eosinophilic
oesophagitis
Cow's milk protein
allergy-induced
reflux-associated
oesophagitis

Eosinophilic
gastroenteritis

Cow's milk
protein induced
enteropathy
Eosinophilic
gastroenterocolitis

FPIS

Cow's milk protein
induced proctocolitis

2010

DRACMA one year after: Which changes have occurred in diagnosis and treatment of CMA in Italy?

2011

CLINICAL RECOMMENDATIONS

Clinical presentation

Anaphylaxis

Acute urticaria or angioedema

Atopic dermatitis

Immediate gastrointestinal allergy

Allergic eosinophilic oesophagitis

Gastroesophageal reflux disease (GERD)

Cow's milk protein-induced enteropathy

Food protein-induced enterocolitis syndrome (FPIES)

Cow's milk protein-induced gastroenteritis and proctocolitis

Severe irritability (colic)

Constipation

Milk-induced chronic pulmonary disease (Heiner's syndrome)

1st choice

AAF⁺

eHF^{5b}

eHF^{5b}

eHF^{5b}

AAF^b

eHF^{5b}

eHF⁺

eHF^b

eHF^b

eHF^b

AAF^Δ

2nd choice

eHF^{5b}

AAF^Δ/SF

AAF^Δ/SF

AAF^Δ/SF

AAF

AAF

AAF

AAF

AAF

AAF

eHF

3rd choice

SF

Donkey milk^{*}

SF

EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy

(B1) Elimination diet

A sufficient elimination diet should be based on a formal allergy diagnosis identifying the food allergen(s) responsible of the patient's symptoms/reactions. The indications should be re-evaluated at appropriate intervals.

Appropriate dietary avoidance is the key treatment in the management of food allergy. Patients with food allergy who are on long-term elimination diets should have access to appropriate dietetic counseling, ideally by a dietitian with competencies in food allergy and regular monitoring of growth (in children).

Extensively hydrolyzed cow's milk formulas with documented hypoallergenicity can be recommended as first choice for the treatment of cow's milk allergy, especially in infants and young children. Amino acid formulas can also be recommended especially for the subgroup of patients with more severe symptoms.

Soy formulas should not be recommended before 6 months of age and at any age in the presence of gastrointestinal symptoms. From 6 to 12 months, it can be considered on a case-by-case basis.

formula (67) or meat-based formula (68). In summary, it is recommended that the choice of an appropriate cow's milk substitute should be assessed carefully balancing the following factors: age, type of food allergy (IgE/non-IgE), coexistence of gastrointestinal symptoms, history of life-threatening reactions, and nutritional requirements as well as cost-effectiveness.

Fenotipi
immunologici
e clinici

2014

AMERICAN ACADEMY OF PEDIATRICS

Committee on Nutrition

Hypoallergenic Infant Formulas

2000

HYPOALLERGENIC INFANT FORMULA

To establish the risk of hypersensitivity in infants, carefully conducted preclinical studies must be performed that demonstrate a formula may be hypoallergenic.

The formula needs to be tested in infants with hypersensitivity to cow's milk or cow's milk based formula and the findings verified by properly conducted elimination-challenge tests.

These tests should, at a minimum, ensure with 95% confidence that 90% of infants with documented cow's milk allergy will not react with defined symptoms to the formula under double-blind, placebo-controlled conditions.

BSACI GUIDELINES**BSACI guideline for the diagnosis and management of cow's milk allergy**D. Luyt¹, H. Ball¹, N. Makwana², M. R. Green¹, K. Bravin¹, S. M. Nasser³ and A. T. Clark³¹University Hospitals of Leicester NHS Trust, Leicester, UK, ²Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK and ³Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

- **A hypoallergenic formula is one that meets the defined criterion of 90% clinical tolerance (with 95% confidence limits) in infants with proven cow's milk allergy.**
- **Only amino acid and extensively hydrolysed formulas meet this criterion and are the formulas of choice for the treatment of cow's milk allergy.**
- **Some individuals highly sensitized to cow's milk may react to residual cow's milk proteins in extensively hydrolysed formulas (EHFs) and will thus require an amino acid formula (AAF)**

FORMULE IDROLISATE

Secondo il grado di idrolisi :

- Idrolisi parziale (pHF o HA) (“lowdegree”)
- Idrolisi estensiva (eHF) (“extensive” or “high degree”)

Secondo le proteine utilizzate:

- Idrolisati di caseina (eHF-C)
- Idrolisati di sieroproteine (eHF-W)

Formule a base di AA:

costruite dal “basso” con l’aggiunta di AA

BSACI GUIDELINES

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Extensively hydrolysed formulas

As different EHF's are derived from different protein sources and are designed to meet the needs of whole protein intolerance (cow's milk allergy) and malabsorption conditions, there are differences between brands.

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Extensively hydrolysed formulas

Although many infants will tolerate all protein hydrolysates, the following should be considered when choosing an EHF for an individual:

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1) The protein source.

The hydrolysate may be based on whey or casein proteins from cow's milk or be derived from soya and pork. The latter may not be suitable in some religions.

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2) The size of peptides.

The presence of larger peptides is associated with higher allergenicity. It may therefore be preferable to use a hydrolysate with the greatest percentage of peptides under 1000 Daltons.

BSACI guideline for the diagnosis and management of cow's milk allergy

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3) Palatability.

Hydrolysed protein is bitter in taste. Differences in taste are related to protein source (i.e. casein, whey, bovine), degree of hydrolysis, and the presence or absence of lactose. Palatability may influence formula choice, especially in older infants or where a less hydrolysed formula can be tolerated.

Cow's milk allergy: evidence-based diagnosis and management for the practitioner

Carlos Lifschitz • Hania Szajewska

Which formula and to whom

Extensively hydrolyzed formulas

The American Academy of Pediatrics defines as “extensively hydrolyzed formula” those containing only oligopeptides that have a molecular weight <3,000 Da to which at least 90 % of infants do not manifest any clinical symptoms in controlled double-blind studies .

IDROLISATI SPINTI (eHF)

Tipologia della formula	Nome commerciale	<1000 Da	Lattosio	MCT	Ca mg%	Ditta
IDROLISATI SPINTI (eHF)	caseina (eHF-C)					
	Pregestimil	95%	No	SI	94	M&J
	Blemil idrolizzato	95%	No	SI	59	Ordesa
	Nutramigen (1 & 2 LGG)	95%	No	No	77	M&J
	Nutriben idrolizzato		No	No	67	Nutriben
	Althéra	95%	SI	No	41	Nestlé
	Aptamil Pepti (1 & 2)	73%	SI	No	52	Milupa
	siero (eHF-W)					
	Polilat	62%	SI	No	47	Mellin
	Aptamil Pregomin SP (ex Pepti Junior)	57%	No	SI	50	Milupa
	Alfaré	95%	No	SI	50	Nestlé
	Hypolac		No	No	50	Noos

Novalac Allernova AR ----> Idrolisato di caseina 95% peptidi < 1000 Da Menarini

Humana AT1 -> Idrolisato di sieroproteine e di caseina 95% peptidi < 1000 Da Humana

Safety and tolerance of a new extensively hydrolyzed rice protein-based formula in the management of infants with cow's milk protein allergy

Vandenplas 2014

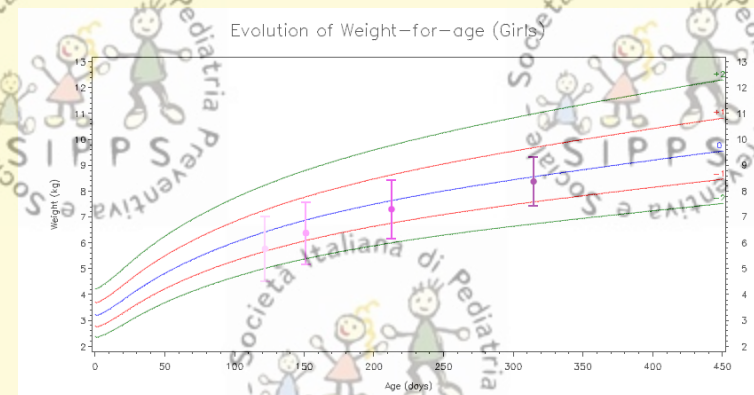
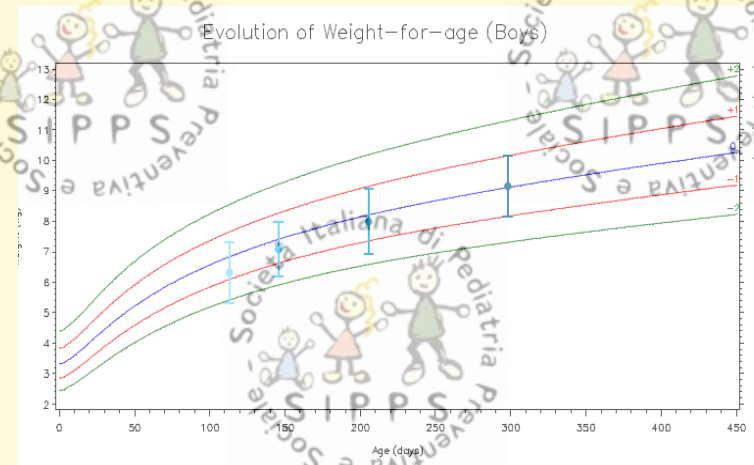
A prospective trial was performed to evaluate the hypo-allergenicity and safety of a new eRHF in infants with a confirmed CMPA. Patients were fed the study formula for **6 months**.

Clinical tolerance of the eRHF was evaluated with a symptom-based score (SBS) and growth (weight and length) was monitored.

Forty infants (mean age, 3.4 months; range, 1–6 months) with CMPA confirmed by a food challenge were enrolled.

Conclusion: In accordance with current guidelines, this eRHF was tolerated by more than 90 % of children with proven CMPA with a 95 % confidence interval.

This eRHF is an adequate and safe alternative to cow milk-based eHF.



Cow's milk allergy: From allergens to new forms of diagnosis, therapy and prevention



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^bDepartment of Medical and Chemical Laboratory Diagnostics, Medical University of Vienna, Austria

The casein fraction (Bos d 8, Bos domesticus) consists of four proteins which account for different percentages of the whole fraction; aS1-casein (Bos d 9, 32%), aS2-casein (Bos d 10, 10%), b-casein (Bos d 11, 28%) and j-casein (Bos d 12, 10%) with aS1-casein being the most important allergen of the casein fraction.

Table 1
Main characteristics of cow's milk allergens, adapted from Jost [62]

nomenclature (<http://www.allergen.org>) [21,59,61,68]

	Allergen name	Protein	Cow's milk content (%)	Mr of aa/molecule	pI	Prevalence (% of patients)	Microarray results (% of patients) [21]	Allergenic activity (% of patients) [21]
Whey (20%) (≤5 g/L)	Bos d 4	α-Lactalbumin	14.2	123	4.8	0-67	63	12
	Bos d 5	β-Lactoglobulin	18.3	162	5.3	13-62	50	19
	Bos d 6	Bovine serum albumin	66.3	582	4.9-5.1	0-76	4	1
	Bos d 7	Immunoglobulins	0.4	160	5.1	12-36		
Whole casein (80%) (~30 g/L)		Lactoferrin	0.6	703	8.7	0-35	5	3
	Bos d 9	αS1-casein	12-15	23.6	199	4.9-5.2	65-100	49
	Bos d 10	αS2-casein	3-4	25.2	207	5.2-5.4		26
	Bos d 11	β-Casein	9-11	24	209	5.1-5.4	35-44	44
	Bos d 12	κ-Casein	3-4	19	169	5.4-5.6	35-41	35
							30	26

FENOTIPI MOLECOLARI

**Bos d4,
Bos d5**

**Bos d d4,
Bos d5,
Bos d8**

Bos d8

Bos d5

**Bos d4,
Bos d8**

Bos d4

**Bos d5,
Bod d8**



Dietary baked milk accelerates the resolution of cow's milk allergy in children

Jennifer S. Kim, MD,* Anna Nowak-Węgrzyn, MD,* Scott H. Sicherer, MD, Sally Noone, RN, Erin L. Moshier, MS, and Hugh A. Sampson, MD New York, NY

J Allergy Clin Immunol 2011;128:125-31

FENOTIPI
MOLECOLARI E
CLINICI INSIEME

milk allergy produce IgE antibodies informational epitopes (dependent on the structure), whereas those with persistent allergy produce antibodies against sequential epitopes, which

are heat stable.

Greater IgE epitope diversity and higher IgE affinity are associated with more severe milk allergy.

IgEs

IgEs caseina

Forme più severe e persistenti

FENOTIPI MOLECOLARI

Bos d4,
Bos d5

Bod d4,
Bos d5

Bos d8

CHALLENGE CON LE SINGOLE MOLECOLE??? (Meglio P.)

Bos d5

Bos d4,
Bos d8

Bos d4

Bos d5,
Bod d8



FENOTIPI MOLECOLARI

eHF-C ?

eHF-W ?

Bos d4,
Bos d5

Bod d4,
Bos d5,
Bos d8

Bos d8

Bos d5

Bos d4,
Bos d8

Bos d4

Bos d5,
Bos d8



Food protein–induced enterocolitis syndrome: an update on natural history and management

Stephanie A. Leonard, MD* and Anna Nowak-Węgrzyn,

Ann Allergy Asthma Immunol

Specific
eHF-C

MANAGEMENT

For infants, exclusively breastfeeding can be protective.
If this is not possible or the infant is exclusively formula-fed,
casein hydrolysate– based formula is recommended

Non-IgE-mediated gastrointestinal food allergy

Anna Nowak-Węgrzyn, MD,^a Yitzhak Katz, MD,^b Sam Soheil Mehr, MBBS, BMedSci, FRCPA, FRACP,^c and Sibylle Koletzko, MD^d
New York, NY, Tel Aviv, Israel, Westmead, Australia, and Munich

J Allergy Clin Immunol 2015;135

eHF ma
non
specific

TABLE IV. Empiric recommendations for dietary management of FPIES (adapted from Jarvinen and Nowak-Węgrzyn⁹)

Age	Milk/soy-induced FPIES	Solid food-induced FPIES	Milk/soy- and solid food-induced FPIES
0-6 mo	<p>Avoid CM/soy*</p> <p>Preferably exclusive breast-feeding† or extensively hydrolyzed formula‡; soy introduction in case of milk FPIES can be considered, although soy formula is not preferred^{5,94}; OFC or home introduction at the discretion of the treating physician</p>		

If not tolerated, an amino acid-based formula should be initiated.

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

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

NUTRITIONAL MANAGEMENT FOR FPIES

Summary Statement 26: Use hypoallergenic formula in formula-fed infants or infants who can no longer breast-feed and are given a diagnosis of FPIES caused by CM. [Strength of recommendation: Strong; Evidence strength: IIa/IIb; Evidence grade: B]

Most children tolerated extensively hydrolyzed formula, although there are selected children who exclusively tolerate AAFs

AAFs are the only completely nonallergenic formulas and can be effective in patients not responding to extensively hydrolyzed formulas and those with FTT (Failure to thrive)

Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines



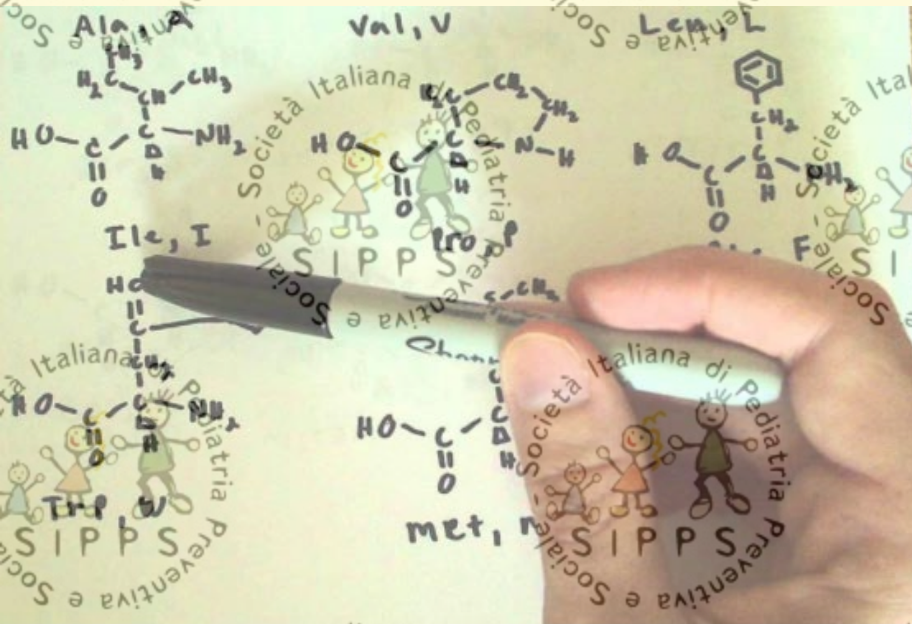
The factors that determine the choice of formula used in an individual infant include residual allergenic potential, formula composition, costs availability, infant's acceptance, and presence of clinical data showing the efficacy of the formula

Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines



eHF based on CMP: The majority of infants and children with CMPA tolerate an extensively hydrolyzed formula with whey or casein as a nitrogen source.

Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines



AAF: Formulae containing free amino acids as the only nitrogen source are the best option in infants reacting to eHF. This risk is estimated to be $<10\%$ of all infants with CMPA, but it may be higher in the presence of severe enteropathy or with multiple food allergies. For that reason, AAF may be considered a first-line treatment despite limited evidence in infants with severe anaphylactic reactions and infants with severe enteropathy indicated by hypoproteinemia and faltering growth

Palatability of Hydrolysates and Other Substitution Formulas for Cow's Milk-Allergic Children: A Comparative Study of Taste, Smell, and Texture Evaluated by Healthy Volunteers

Table 2. Slope of the First Segment of the Peptide Molecular Weight Distribution Line and Palatability Scores for Formulas*

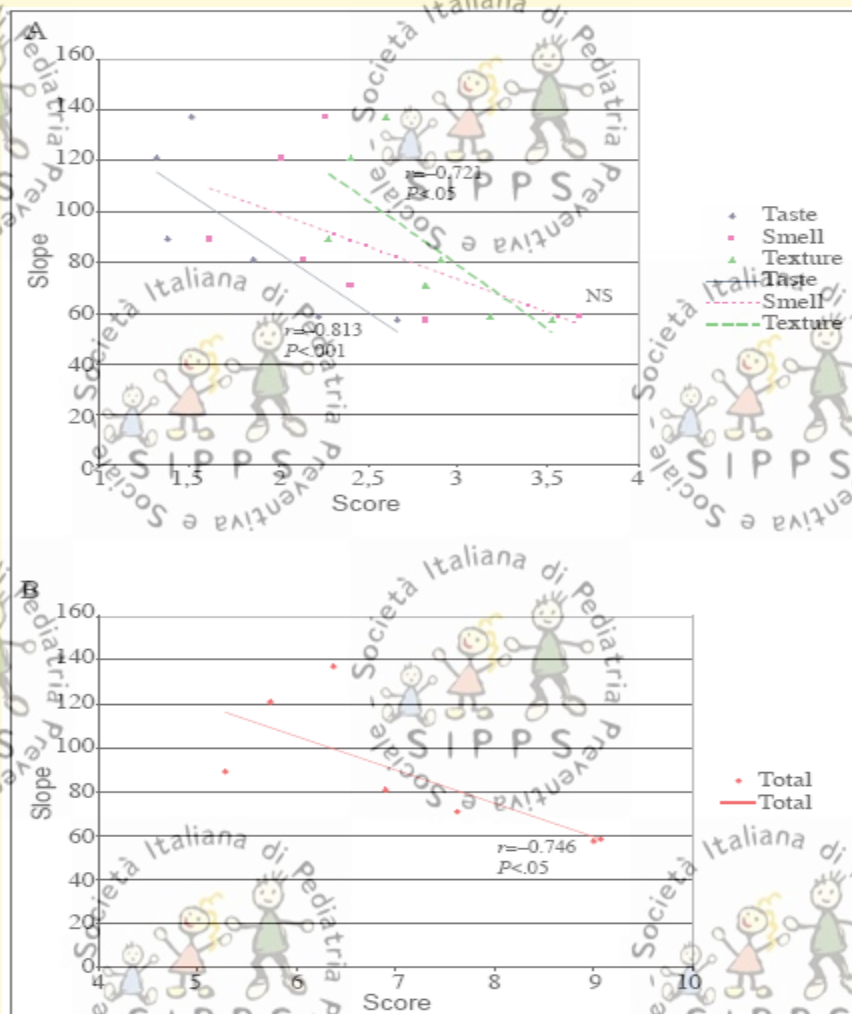
	Slope	Taste	Smell	Texture	Total	P Comparison	
						With CM	With IF
Cow's milk		4.10	3.74	4.06	11.9		
Initiation formula		3.44	3.22	3.22	9.88		
Partial hydrolysate		2.78	3.22	3.54	9.54	<.001	NS
Mixed hydrolysate 1	58.57	2.22	3.68	3.18	9.08	<.001	NS
Whey hydrolysate 2	57.30	2.66	2.82	3.52	9.00	<.001	NS
Casein hydrolysate 2	81	1.86	2.14	2.90	6.90	<.001	<.001
Whey hydrolysate 1	137	1.52	2.26	2.60	6.38	<.001	<.001
Casein hydrolysate 1	120.80	1.32	2.02	2.40	5.74	<.001	<.001
Mixed hydrolysate 2	89	1.38	1.62	2.28	5.28	<.001	<.001
Soy formula		2.80	2.70	2.94	8.44	<.001	NS
Rice hydrolysate		2.36	2.64	2.74	7.94	<.001	<.05
Soy hydrolysate	71	2.40	2.40	2.82	7.62	<.001	<.001

*CM indicates cow's milk; IF, initiation formula; NS: not statistically significant.

Gli idrolisati di caseina hanno in generale una palatabilità inferiore a quella dei latt di soia o di riso

Pedrosa M et al, J Invest Allergol Clin Immunol 2006; 16: 351-6

Palatability of Hydrolysates and Other Substitution Formulas for Cow's Milk-Allergic Children: A Comparative Study of Taste, Smell, and Texture Evaluated by Healthy Volunteers



In generale sembra esistere una correlazione inversa tra grado di idrolisi e palatabilità (più è idrolizzato, meno è palatabile)



**FENOTIPI
IMMUNOLOGICI**

**FENOTIPI
CLINICI**

SOSTITUTO DEL LV E TOLLERANZA

**FENOTIPI
MOLECOLARI**

**FENOTIPI E
STORIA
NATURALE
DELLA APLV**

Food allergy

Julie Wang and Hugh

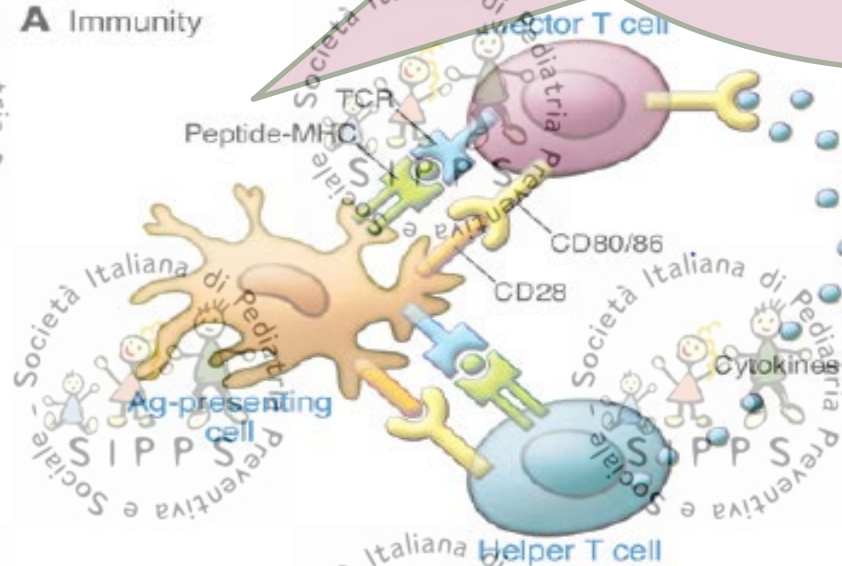
Division of Allergy and Immunology, Department of Pediatrics

The Journal of Clinical Investigation <http://www.jci.org>

Mechanisms of

**PEPTIDI NON
RICONOSCIUTI COME
REATTOGENI MA
INDUTTORI DELLA
RISPOSTA
TOLLEROGENICA**

A Immunity



Generation of an immune response requires ligation of the T cell receptor with peptide-MHC complexes in the presence of appropriate costimulatory molecules (CD80 and CD86) and cytokines.

Impact of dietary regimen on the duration of cow's milk allergy: a random allocation study

L. Terracciano, G. B. Bouygue, T. Sarratud, F. Veglia, A. Martelli and A. Bocchi

Department of Child and Maternal Medicine, Paediatric Division, University of Milan Medical School at the Melloni Hospital, Milan, Italy

CEA 2010

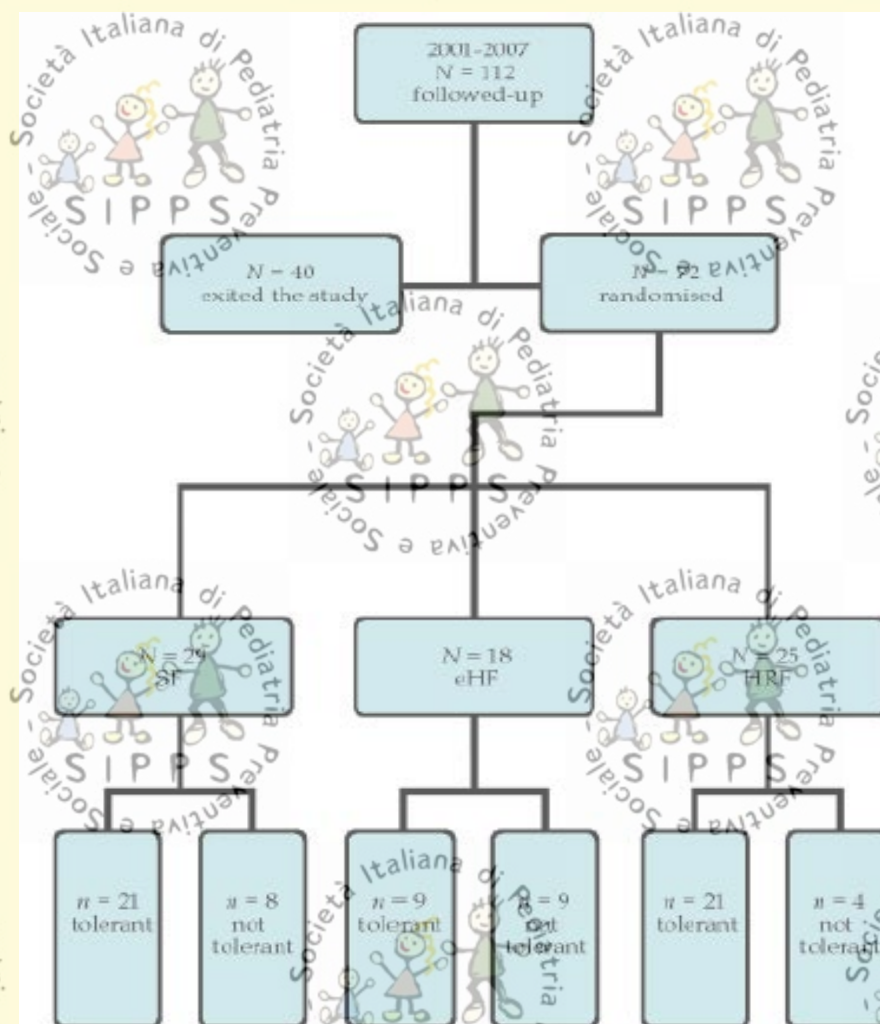


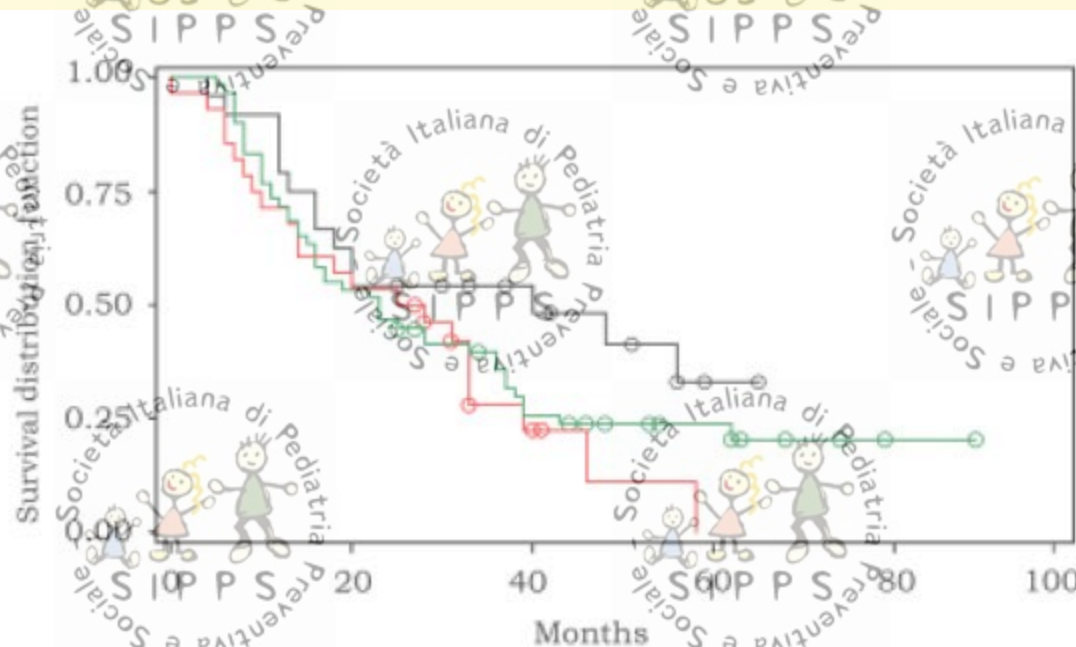
Fig. 1. The Milan Cow's Milk Allergy Cohort study patient flowchart.

Impact of dietary regimen on the duration of cow's milk allergy: a random allocation study

L. Terracciano, G. B. Bouygue, T. Sarratud, F. Veglia, A. Martelli and A. Flocchi

Department of Child and Maternal Medicine, Paediatric Division, University of Milan Medical School at the Melloni Hospital, Milan, Italy

CEA 2010



The background of the slide is a repeating pattern of the SIPPSS logo. The logo is circular, featuring three stylized figures (a blue one on the left, a yellow one in the middle, and a green one on the right) holding hands. Below the figures, the letters 'SIPPSS' are written in a bold, sans-serif font. The text 'Società Italiana di Pediatria Preventiva e Sociale' is written around the perimeter of the circle.

Le formule con Probiotici
aiutano ad acquisire
la tolleranza?

Effect of Lactobacillus GG on tolerance acquisition in infants with milk allergy: A randomized trial

Infants (age, 1-12 months) consecutively referred for strongly suspected CMA but still receiving CMP were invited to participate in the study.

JACI 2012; 129: 580-2

Meno della metà dei bambini aveva una APLV IgE mediata

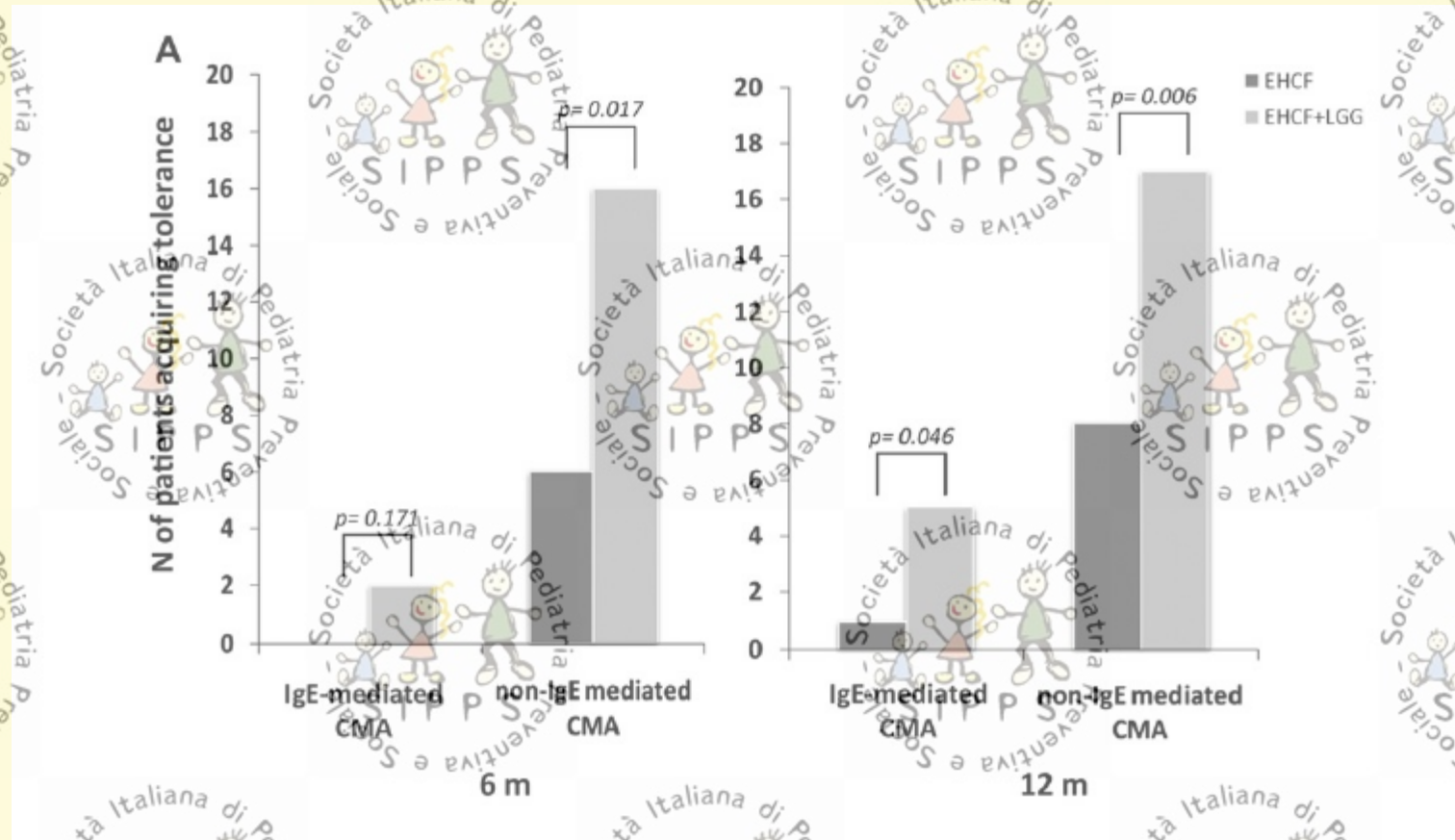
Table 1. Baseline main demographic and clinical characteristics of study population

	Group 1	Group 2	P value
n	28	27	
Age, mo	21 (75.0)	16 (59.3)	.214
Age, mo	3.2 (2.1-4.3)	3.9 (2.5-5.2)	.421
Body weight, kg	5.7 (5.1-6.4)	5.8 (4.9-6.7)	.899
IgE-mediated CMA, no. (%)	12 (42.9)	9 (33.3)	.467
Breast-feeding, no. (%)	2 (8.2)	22 (81.5)	1.0
<2 mo	26 (91.4)	21 (77.7)	.698
Gastrointestinal symptoms, no. (%)	17 (60.7)	19 (70.4)	.452
Vomiting, no. (%)	12 (42.9)	7 (25.9)	.187
Diarrhea, no. (%)	5 (17.9)	11 (40.7)	.062
Cutaneous symptoms, no. (%)	12 (42.9)	12 (44.4)	.906
Atopic dermatitis, no. (%)	12 (42.9)	8 (29.6)	.308
Urticaria, no. (%)	1 (3.6)	4 (14.8)	.193
Respiratory symptoms, no. (%)	6 (21.4)	4 (14.8)	.729

*IgE-mediated CMA was defined by the presence of a clinical history suggestive of IgE-mediated mechanisms (acute onset of symptoms after the ingestion of CMPs), DBPCFC results (occurrence of typical symptoms within 2 hours after the administration of the last dose), occurrence of typical symptoms of IgE-mediated food allergy (vomiting, urticaria, asthma, and rhinitis) during the challenge, and positivity of SPT responses.

Effect of Lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: A randomized trial

Berni Canani R et al, JACI 2012; 129: 580-2



Which disease is cured by Lactobacillus?

Goldberg M, Katz Y.

J Allergy Clin Immunol. 2012 Mar;129(3):872

Population with IgE-mediated CMA

- How can these infants still consume CMP at diagnosis?
- Only 1/21 IgE-mediated CMA patients presented with urticaria
- How 21/55 patients were classified as having IgE-mediated CMA?

Population with non IgE-mediated CMA

- Confounding factors may be difficult to rule out

Formula Selection for Management of Children with Cow's Milk Allergy Influences the Rate of Acquisition of Tolerance: A Prospective Multicenter Study

Roberto Berni Canani, MD, PhD^{1,2}, Rita Nocerino, CPN³, Gianluca Terrin, MD, PhD³, Tullio Frediani, MD¹, Sandra Lucarelli, MD⁴, Linda Cosenza, MD¹, Annalisa Passariello, MD, PhD⁵, Ludovica Leone, LDN¹, Viviana Granata, MD³, Margherita Di Costanzo, MD¹, Vincenza Pezzella, MS¹, and Riccardo Troncone, MD^{1,2}

[JPediatr.](#) 2013 Sep;163(3):771-7

Table. Baseline main demographic and clinical characteristics of the study population

	Group 1 EHCF	Group 2 EHCF + LGG	Group 3 RHF	Group 4 SF	Group 5 AAF
N	55	71	46	55	33
Male, n (%)	41 (74.5)	38 (53.5)	28 (60.9)	37 (67.3)	23 (69.7)
Age, m (95% CI)	5.03 (4.20-5.86)	5.73 (4.83-6.62)	6.65 (5.53-7.76)	6.45 (5.45-7.45)	5.93 (4.57-7.30)
Weight, kg (95% CI)	6.47 (6.00-6.95)	6.66 (6.14-7.18)	6.97 (6.36-7.58)	6.96 (6.41-7.51)	6.04 (5.31-6.78)
Breastfeeding ≥ 2 months, n (%)	41 (74.5)	54 (76.1)	38 (82.6)	38 (69.1)	24 (72.7)
IgE-mediated CMA, n (%)	24 (43.6)	27 (38)	23 (50)	23 (41.8)	14 (42.4)
Gastrointestinal symptoms, n (%)	35 (63.6)	51 (71.8)	30 (65.2)	31 (56.4)	25 (75.8)
Vomiting, n (%)	23 (41.8)	27 (38)	17 (37)	18 (32.7)	10 (30.3)
Diarrhea, n (%)	18 (32.7)	24 (33.8)	13 (28.3)	13 (23.6)	19 (57.6)
Cutaneous symptoms, n (%)	25 (45.5)	29 (40.8)	17 (37)	27 (49.1)	11 (33.3)
Atopic dermatitis, n (%)	21 (38.2)	26 (36.6)	15 (32.6)	21 (38.2)	9 (27.3)
Urticaria, n (%)	6 (10.9)	6 (8.5)	5 (10.9)	8 (14.5)	5 (15.2)
Respiratory symptoms, n (%)	6 (10.9)	7 (9.9)	6 (13)	7 (12.7)	3 (9.1)

Disegno: Studio prospettico **non-randomizzato** multicentrico. I bambini inviati per sospetta APLV di età <12 mesi venivano sottoposti a TPO in DBPC e se questo confermava la APLV continuavano la dieta con il latte che era stato prescritto in precedenza dal curante. Dopo 12 mesi veniva ripetuto il TPO per saggiare lo sviluppo della tolleranza. Di 329 bambini inizialmente valutati, 260 sono risultati positivi al TPO e sono stati arruolati. In questo modo si sono formati 5 gruppi di bambini. 7 bambini sono stati persi al follow-up

“The main limitations of our study are related to the lack of randomization and the lack of patient groups treated with other potentially available dietary strategies for the management of CMA (ie, extensively hydrolyzed whey formula, or extensively hydrolyzed SF)”

Management of Children with Cow's Milk Allergy: The Rate of Acquisition of Tolerance: A Retrospective Multicenter Study

	OR	95% CI	p
EHCF vs EHCF + LGG	4.822	2.210-10.521	<.001
EHCF vs SF	0.400	0.176-0.907	.026
EHCF vs RHF	0.626	0.222-1.719	.357
EHCF vs AAF	0.267	0.100-0.700	.015
EHCF + LGG vs SF	0.089	0.039-0.193	<.001
EHCF + LGG vs RHF	0.130	0.056-0.300	<.001
EHCF + LGG vs AAF	0.050	0.021-0.120	<.001
SF vs RHF	1.563	0.651-3.759	.316
SF vs AAF	0.716	0.349-1.117	.547
RHF vs AAF	0.459	0.156-1.350	.152

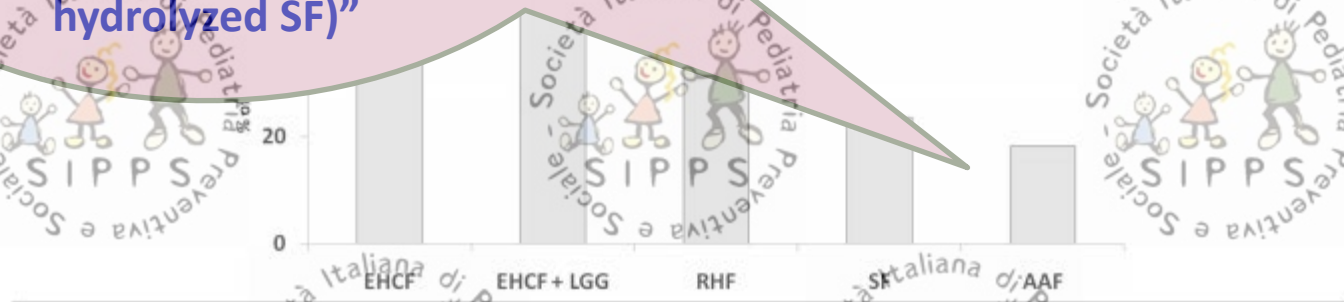


Figure 3. Rate of patients acquiring tolerance to oral food challenge after 12 months of exclusion diet with different formulas.

Dopo 12 mesi di dieta i bambini alimentati con idrolizzato estensivo di caseina + LGG raggiungevano la tolleranza più frequentemente degli altri gruppi. Quelli alimentati con idrolisato di caseina la raggiungevano più frequentemente solo rispetto alla formula a base di aminoacidi. A distanza di 12 mesi la tolleranza si è sviluppata più frequentemente nelle forme non-IgE (OR 0.12; CI 0.06-0.26). In entrambi i casi la formula di caseina +LGG ha ottenuto prima la tolleranza

FENOTIPI CLINICI

TIPO DI
FORMULA
IDROLISATA

FENOTIPI
IMMUNOLOGICI

SOSTITUTO
DEL LATTE
VACCINO

COSTO

FENOTIPI
MOLECOLARI

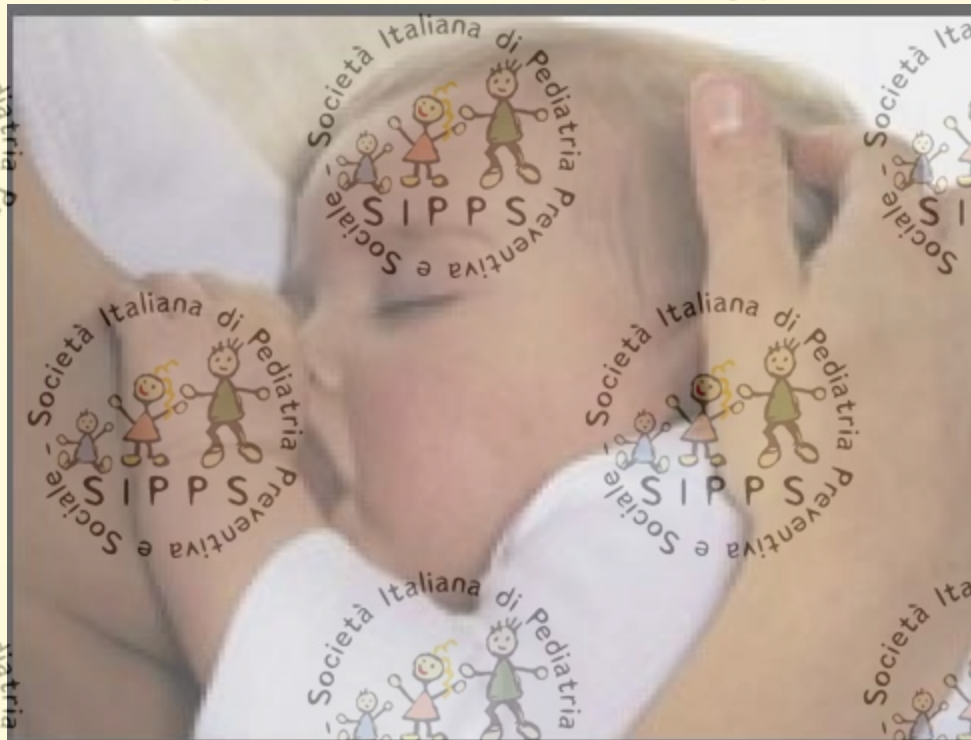
PUBBLICITA'

BSACI GUIDELINES

BSACI guideline for the diagnosis and management of cow's milk allergy

D. Luyt¹, H. Ball¹, N. Makwana², M. R. Green¹, K. Bravin¹, S. M. Nasser³ and A. T. Clark³

¹University Hospitals of Leicester NHS Trust, Leicester, UK, ²Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK and ³Cambridge University Hospital NHS Foundation Trust, Cambridge, UK





GRAZIE

