Food Allergy and Atopic Dermatitis

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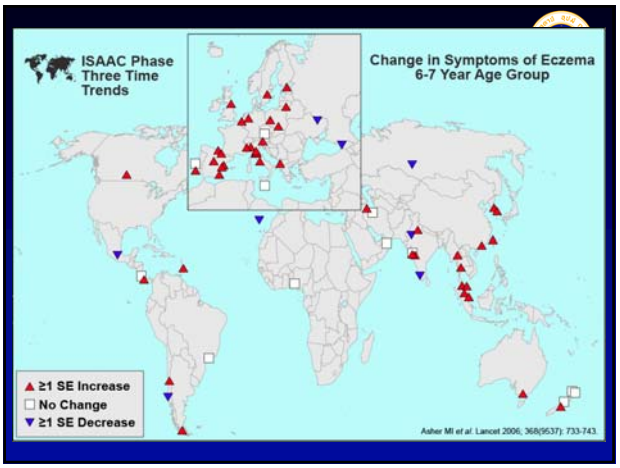
Outline of Talk - 1

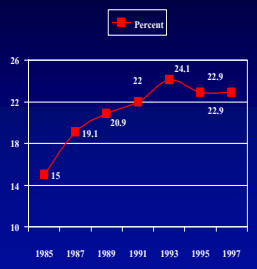
- Frequency of food sensitization among AD patients.
- Proof of causal relationship between food and AD
  - Results of food challenge, pros vs cons
  - Symptoms upon food ingestion
  - Results of food avoidance
- Common foods sensitized by AD patients
- Identify AD patients which food allergy may be involved

Outline of talk - 2

- Work up in AD patients in which food allergy is suspected
- What comes first AD or food allergy? Proposed pathogenesis
- Can we prevent AD by food avoidance?
- Can other means of treatment of food allergy affect AD?



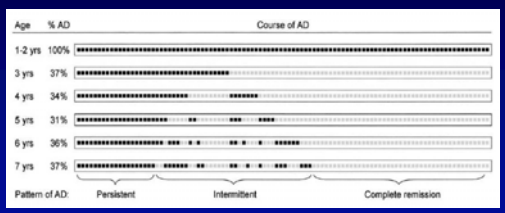
Prevalence of Atopic Dermatitis in the Asia-Pacific



- Prevalence of atopic dermatitis in Asia = 3-16% *(Williams et al, ISAAC-I, JACI 1999;103:125)*
- Prevalence in Japan and Singapore is very high (20%) and is increasing *(Yura 2001 and Tay 2002)*
- Prevalence of AD in Australian infants = 28%
  - 9.4% need topical steroids for 6 weeks in the first 12 mo of life
  - Risk of IgE-mediated food allergy = 5.9 fold of control subjects

Yura et al Brit J Dermatol 2001;145:966
Hill and Hosking. Ped Allergy Immunol 2004;15:241

Prognosis of Atopic Dermatitis The MAS study 2004



Illi et al J Allergy Clin Immunol 2004;113:925

Atopic dermatitis in the new centuries

Food Allergy And AD in Children - Historical Aspects

- 1918 Talbot described a series of eczema patients with positive SPT
- 1936, Engman challenged child with AD and wheat allergy.
  - 2 hrs itching and scratching.
  - Next morning typical eczematous lesion
- Wilson & Walzer– absorption of egg protein in infant – wheal at remote previously sensitized area

Talbot. Med Clin North Am 1918;1:985
Engman WF et al, Med Clin North Am 1936; 16:306-312
Wislon and Walzer. Am J Dis Child 1935;50:49

Food Allergy and AD Dermatologists'view

- AD is rarely associated with food allergy
- Food elimination has no role in AD Rx
- Food allergy in AD - controlled studies
  - Sampson & McCaskill 1985 – 33% (allergy clinic)
  - Burks 1988– 37% (allergy + derm)

Foods	No of Pts challenged	Positive Challenge
Eggs	15	0
Milk	17	1
Wheat	16	1
Soy	4	0

Total no = 17, No of positive SPT = 4, No of positive rast = 3
Rowland and Hanifin Dermatology Therapy 2006;19:97-103

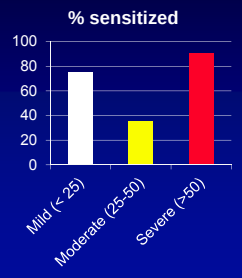
Food Allergy in AD patients referred to Ped Dermatologists at Johns Hopkins

- 63 AD patients referred to a pediatric dermatologist were studied (mean age 2.8 years)
- 41 were ImmunoCAP positive (65%)
- SCORAD of CAP pos pts = CAP neg pts
- 12 had convincing allergic history to food
- 19 underwent food challenge with 11 positive
- Overall relevant food allergy in this AD populations = 23/63 (37%, CI 25-50%)

Eigenmann et al Pediatrics 1998;101:1

Food sensitization and AD in Valencia - Spain

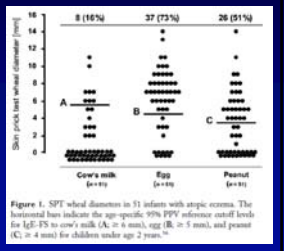
- Service of Dermatology and Unit of Allergy
- 44 infants (27M, 17F) mean age 7.5 mos
- SPT, positive in 27/44 (61%)
  - Eggs 100%, milk 30%
- Open challenge to egg
  - Positive 44% (12/27)



Garcia et al. Allergol et Immunopathol 2007;35:15-20

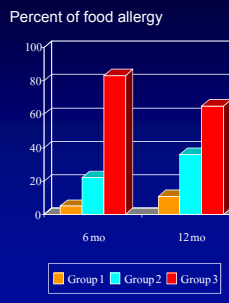
Food allergy in AD referred to Derm Clinic in Australia

- 55 consecutive AD infants referred to Derm clinic (median age = 34 weeks)
- SPT and CAP FEIA to milk, egg and peanut
- 86% positive by SPT, 83% by CAP exceeding cut-off
- A large majority developed reaction on
  - Breast feeding
  - Never ingested the food before



Hill et al J Pediatr 2007;151:359

Food Allergy in Patients Atopic Dermatitis

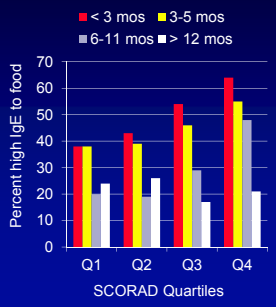


- Conflicting data on prevalence exist
  - Hanifin - 10%
  - Sampson - 74%
- Melbourne cohort study
  - 620 children with + family history of atopy
  - group 1 - no AD (402)
  - group 2 - mild AD (150)
  - group 3 - severe AD (41)
- Attributable risk from food allergy = 63-65%

Hill et al. J Pediatr 2000;137:475

EPAAC study AD and IgE to food

- 2048 AD patients from 94 centers from 12 countries
- Mean age 17.6 mos
- Mean age of AD 4.3 mos
- Mean SCORAD – 33
- IgE-FA to milk, egg, peanut
- 55.5% sensitized to food
- There were association between
  - AD severity
  - HR-IgE-FS level
  - Age of onset of eczema



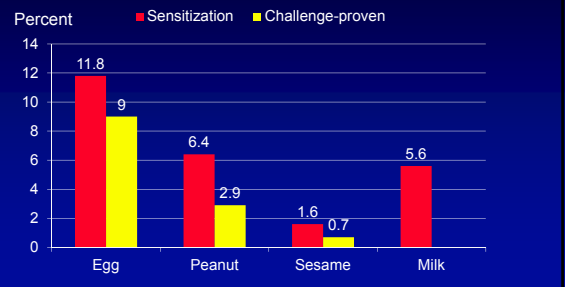
Hill et al. Clin Exp Allergy 2007;38:161

21 years of oral food challenges in 578 patients with AD

	Positive Challenge	Negative challenge	Total	%positive
All foods	1348	1559	2907	**46.4**
Major food allergens	777	766	1543	
Egg	351	160	511	**68.7**
Milk	202	185	387	**52.2**
Peanut	40	56	96	**41.7**
Wheat	79	164	243	**32.5**
Soy	105	201	306	**34.3**

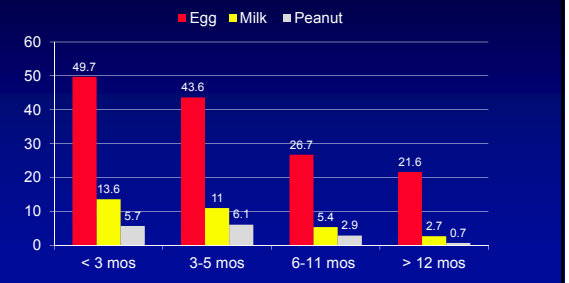
Lisa Ellman-Grunther and Hugh A. Sampson, Atopic dermatitis and Foods. Atopic dermatitis, Bieber T and Leung

Prevalence of sensitization and challenge-proven FA among Australian children – the Healthnut Study



Osborne J Allergy Clin Allergy 2011;127:668

EPAAC study
High-risk Food IgE in AD



Hill et al. Clin Exp Allergy 2007;38:161

Food allergy in Chinese infants

497 infants were screened, 80 were challenged. 18 were positive
Prevalence = 3.8 (CI 2.5-5.9%)

Table 2 Symptoms (reported and during OFC) and results of SPT in18 subjects confirmed food allergy

No.	Age (months)	Reported symptoms	SPT (mm)	Food	Symptoms in OFC	No.	Age (months)	Reported symptoms	SPT (mm)	Food	Symptoms in OFC
1	4.6	Edema of eyelids	4	Cow's milk	Vomiting + milk refusal	10	7	–	3	Egg	Edema of eyelids
2	9.8	Eczema	8	Egg	Eczema flare up*	11	11	Eczema	10	Egg	Eczema flare up
3	8.6	Eczema	3	Egg	Eczema flare up	12	9.1	Eczema	12	Egg	Eczema + itching
4	7.8	Vomiting	6	Egg	Vomiting	13	5.8	–	5	Egg	Eczema flare up
5	2.7	Edema of eyelids	<3	Cow's milk	Vomiting	14	6.8	–	16	Cow's milk	Wheal
6	8.9	–	5	Egg	Eczema flare up	15	4.5	Eczema	<3	Cow's milk	Eczema*
7	11.8	Eczema	12	Cow's milk	Eczema flare up	16	8	Eczema	3	Egg	Eczema*
8	4.1	–	14	Egg	Eczema flare up	17	6.5	Milk refusal	3	Cow's milk	Milk refusal
9	4.1	–	3	Egg	Eczema flare up	18	6	–	4	Egg	Eczema*

SPT, skin prick test; OFC, oral food challenge.
*The symptoms occurred 24 h after ingestion.

Chen J, Hu Y, Allen KJ, et al. The prevalence of food allergy in infants in Chongqing, China. Pediatr Allergy Immunol, 2011, 22(4): 356-360

Egg allergy and AD

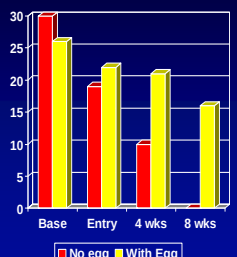
Food Allergy And AD Clinical Studies in Children

- **Elimination**
  - *Businco et al*[1] dietary exclusion of milk and/or egg from 59 children with severe AD resulted in clinical improvement in 80% of cases
  - *Lever et al*[2]: RCT placebo VS egg elimination significantly greater mean reduction in BSA affected by eczema (19.6 to 10.9%) in dietary gr comparison to control gr (21.9 to 18.9%). At the end dietary phase, egg hypersensitivity was confirmed by positive DBPCFC

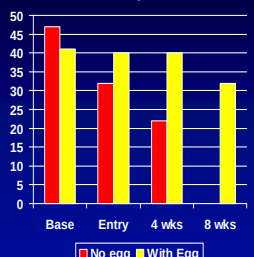
1Businco et al, Allergo Immnunopathol 1982; 10:238-288
2Lever R et al, Pediatr Allergy Immunol 1998; 9:13-19

Egg Elimination in Egg-sensitive Atopic Dermatitis

Percent skin area involved

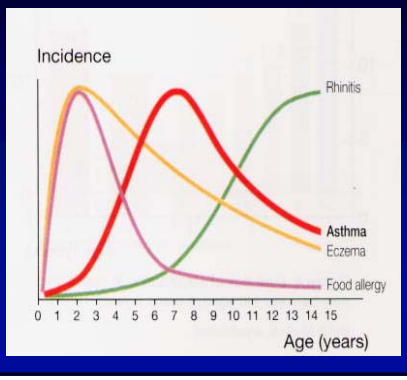


Severity scores



Lever et al. Pediatr Allergy Immunol 1998;9:13
Sicherer & Sampson. J Allergy Clin Immunol 1999;104:S114

The Allergic March



Development of IgE-mediated CMA in unselected infants - Israel

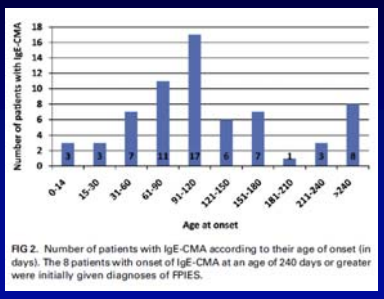
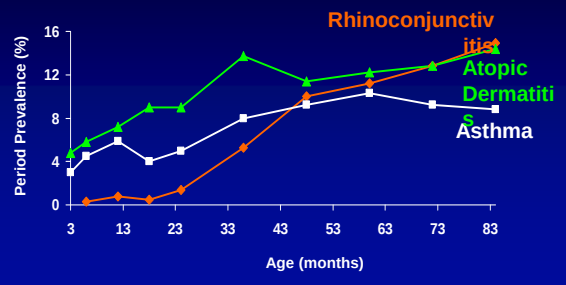


FIG 2. Number of patients with IgE-CMA according to their age of onset (in days). The 8 patients with onset of IgE-CMA at an age of 240 days or greater were initially given diagnoses of FPIES.

Katz. J Allergy Clin Immunol 2010;126:77-82

THE GERMAN MULTICENTER ALLERGIC STUDY (MAS)



Wahn, Allergy 2000

Dual-allergen Exposure Hypothesis in Food Allergy

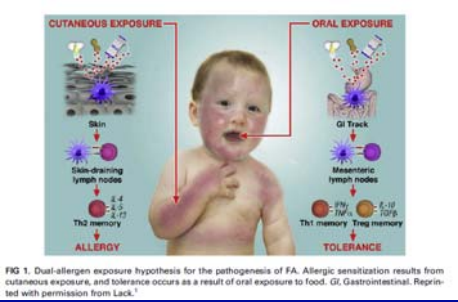


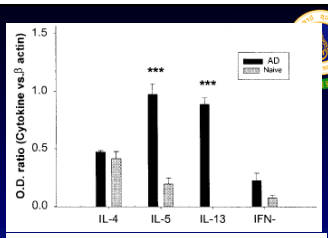
FIG 1. Dual-allergen exposure hypothesis for the pathogenesis of FA. Allergic sensitization results from cutaneous exposure, and tolerance occurs as a result of oral exposure to food. *GI*, Gastrointestinal. Reprinted with permission from Lack.[1]

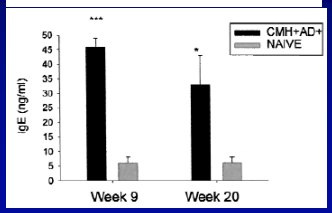
Lack. J Allergy Clin Immunol 2012;129:1187

Murine Model Of AD Induced By Oral sensitization

- Development of an eczematous rash that occurs in a subset of mice orally sensitized to food proteins
- Approximately 1/3 of mice sensitized with milk or peanut proteins developing a dry, erythematous, scaly, pruritic rash within 9-14 weeks of initiating the sensitization protocol

Li XM et al, J Allergy Clin Immunol 2001;107:693-702.)





Li XM et al, J Allergy Clin Immunol 2001;107:693-702.)

Dual-allergen exposure hypothesis

- Allergen absorption and allergen priming – increased in Filaggrin-mutated mice
- Low-dose skin exposure to arachis oil in infants led to increase peanut allergy at 5 years of age
- High household exposure of peanut – ↑ in peanut allergy patient
- High maternal peanut consumption in pregnancy – high infant specific IgE to peanut and PA
- Single oral high-dose peanut flour led to oral tolerance and IgE sensitization
- PA in the UK:Israel = 10:1 whereas consumption of peanut UK:Israel = 0:7

Diagnosis of FA in AD

- **History** – association of foods and AD flare
- Moderate to severe disease
- Requirement for median to high potency topical corticosteroids for symptom control
- Known history of food hypersensitivity
- Special tests
  - Skin prick test
  - Specific IgE
  - Atopy patch test

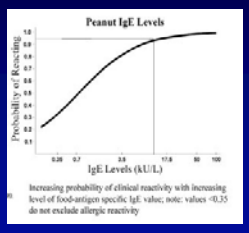
Specific IgE and Food Challenge

95% Predictive Level

Allergen	[kU$_A$/L]	PPV
Egg	7	98
- Infants ≤ 2 yrs[+]	2	95
Milk	15	95
- Infants ≤ 2 yrs[++]	5	95
Peanut	14	100
Fish	20	100
Tree nuts[+++]	~15	~95
Soybean	30	73
Wheat	26	74

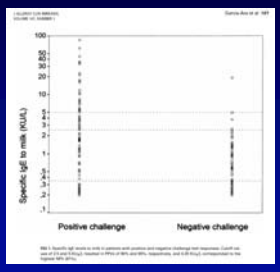
\+ Boyano MT, et al. Clin Exp Allergy 2001; 31(9):1464-9
++ Garcia-Ara C, et al. J Allergy Clin Immunol 2001; 107(1):185-90
+++ Clark AT, Ewan P. Clin Exp Allergy. 2003; 33(8):1041-5

PPV = Positive predictive value



Sampson J Allergy Clin Immunol 2001;107:891

Cut-off of 2.5 KIU/L in cow milk allergy patient < 1 year of age



Garcia-Arac et al. J Allergy Clin Immunol 2001;107:185

Cut-off of Specific IgE to Egg at 0.35 KIU/Lin 2 year old infants

Table 3. Performance characteristics of CAP System FEIA at 0.35KU$_A$/L

Parameter evaluated	Allergen			
	Egg white	Yolk	OVA	OVM
Sensitivity (%)	91(84–98)	63(51–75)	72(61–83)	73(62–84)
Specificity (%)	77(57–97)	93(80–100)	83(62–100)	82(59–100)
PPV (%)	94(88–100)	98(94–100)	96(90–100)	96(90–100)
NPV (%)	68(47–89)	37(22–52)	36(19–53)	35(16–54)
PLR	3.9	9	4.3	4
NLR	8.2	2.5	3	3
Efficacy (%)	88	68	74	74

The data that appear between parenthesis correspond to the confidence interval at 95%. OVA = ovoalbumin; OVM = ovomucoid; PPV = positive predictive value; NPV = negative predictive value; PLR = positive likelihood ratio; NLR = negative likelihood ratio.

Boyano-Martinez et al. Clin Exp Allergy 2001;31:1464

Diagnosis: APT

Evaluation of predictive capacity of spIgE, SPT, and APT for early and/or late-phase clinical reactions to allergen challenges (n=133)

High False pos

	Sensitivity	Specificity	PPV	NPV
Specific IgE in serum	86%	29%	62%	59%
Skin prick test	83%	70%	79%	75%
	55%	95%	93%	60%

gh false neg

Niggemann et al. Allergy 2000: 55: 281-285

Diagnosis: APT

Evaluation of predictive capacity of specific IgE in serum, SPT, and APT for late-phase reactions (n=21)

	Sensitivity	Specificity	PPV	NPV
Specific IgE in serum	71%	29%	37%	72%
Skin prick test	58%	70%	41%	81%
Atopy patch test	76%	95%	81%	93%

Niggemann et al. Allergy 2000: 55: 281-285

APT, SPT and SpIgE in 437 children

TABLE I. Performance of single tests: sIgE measurement, the SPT, and the APT

	CM (n = 428)			HE (n = 424)			Wheat (n = 423)			Soy (n = 425)		
	sIgE	SPT	APT	sIgE	SPT	APT	sIgE	SPT	APT	sIgE	SPT	APT
Sensitivity (%)	87	85	31	96	93	41	82	75	27	65	29	23
Specificity (%)	49	70	95	48	54	87	34	64	89	50	85	86
PPV (%)	62	73	86	79	79	86	41	49	58	22	33	30
NPV (%)	79	83	60	85	81	43	77	85	69	86	82	82
Efficiency (%)	68	78	63	80	79	56	51	68	67	52	73	74

PPV, Positive predictive value; *NPV*, negative predictive value.

TABLE II. Performance of combination of sIgE measurement, the SPT, and the APT

	CM			HE			Wheat			Soy		
	A (n = 148)	B (n = 138)	C (n = 103)	A (n = 68)	B (n = 82)	C (n = 53)	A (n = 71)	B (n = 57)	C (n = 37)	A (n = 111)	B (n = 86)	C (n = 67)
Sensitivity (%)	69	74	82	85	91	92	43	62	60	14	31	20
Specificity (%)	97	94	95	89	83	82	90	81	85	96	85	93
PPV (%)	92	90	91	92	91	92	50	65	60	43	27	33
NPV (%)	86	83	90	80	83	82	86	78	85	82	87	87
Efficiency (%)	87	86	90	87	88	89	80	74	78	79	77	82

A, APT + SPT; B, APT + sIgE; C, APT + SPT + sIgE; *PPV*, positive predictive value; *NPV*, negative predictive value.

Mehl A. et al, J Allergy Clin Immunol 2006;118:923-9

APT, SPT and Sp IgE in 437 children

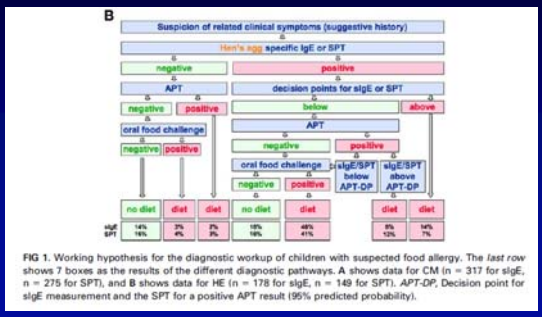


FIG 1. Working hypothesis for the diagnostic workup of children with suspected food allergy. The *last row* shows 7 boxes as the results of the different diagnostic pathways. **A** shows data for CM (n = 317 for sIgE, n = 275 for SPT), and **B** shows data for HE (n = 178 for sIgE, n = 149 for SPT). *APT-DP*, Decision point for sIgE measurement and the SPT for a positive APT result (95% predicted probability).

Mehl A. et al, J Allergy Clin Immunol 2006;118:923-9

Atopic Patch Tests

- Variability in the test as the reagents have not been standardized
- Compared to the SPT, the APT is more specific, but less sensitive
- Combining APT with SPT or Sp IgE, only 0.5-14% of food challenge could be avoided.

Management: Allergen avoidance diets

- Allergen avoidance diets are recommended when positive food challenges
- Proper food avoidance, patients typically experience significant improvement in their symptom
- If no significant clinical improve within 2-3 week, food challenges with less common food allergens may be provoking the symptom

- GINI: 3-year follow-up study showed protective effect in the per protocol analysis of AD in high-risk infants
  - an extensive casein hydrolysate (odds ratio, 0.53; 95% CI, 0.32-0.88) or
  - partial whey hydrolysate (odds ratio, 0.60; 95% CI, 0.37-0.97)

Preventive effect of hydrolyzed infant formulas persists until age 6 years: Long-term results from GINI

	No. of followed children (N = 988)			
	CMF (N = 270)	pHF-W (N = 256)	eHF-W (N = 242)	eHF-C (N = 220
Cumulative incidence, birth to 1 y				
Cases (%)	65 (14.1)	53 (11.9)	71 (15.0)	52 (11.3)
RR (95% CI)	1	0.84 (0.60-1.18)	1.07 (0.78-1.46)	0.80 (0.57-1.13
Cumulative incidence, birth to 3 y				
Cases (%)	139 (30.8)	99 (22.6)	124 (26.6)	91 (20.1)
RR (95% CI)	1	0.77 (0.61-0.98)	0.93 (0.75-1.16)	0.69 (0.54-0.88
Cumulative incidence, birth to 6 y				
Cases (%)	169 (37.9)	135 (31.1)	151 (33.1)	120 (27.1)
RR (95% CI)	1	0.79 (0.64-0.97)	0.92 (0.76-1.11)	0.71 (0.58-0.88

ITT analyses: study formula in comparison with cow's milk feeding

Andrea von Berg et al, J Allergy Clin Immunol 2008;121:1442-7

Prevention of AD in Children with Food Allergy

	Group/publication			
Definitions/interventions	AAP 2008 Clinical Report	AAP 2000 recommendations	ESPACI/ESPGHAN 1999, ESPGHAN 2008 recommendations	SP-EAACI, 2004, 2009 recommendations
Risk category: "high risk"	Parent or sibling with documented allergic disease	Biparental or parent plus sibling history of allergy	Parent or sibling affected (1999)	Parent or sibling with documented allergic disease
Pregnancy avoidance	Lack of evidence	Possibly peanut		No special diet*
Breast-feed "exclusively" until	Evidence for 3-4 mo (waiting 4-6 mo tied to introducing solids*)	6 mo	4-6 mo*	At least 4 mo, prefer 6 mo
Maternal lactation avoidance of allergens	Some evidence for reduced atopic dermatitis	Peanuts, tree nuts and "consider" egg, milk, fish, and "perhaps other foods"		No special diet*
Prevention formulas	Compared with whole cow's milk protein, evidence for certain extensive hydrolysates, partial hydrolysates, but not soy (see text)	"Hypoallergenic formula" (extensive hydrolysate, possibly partial hydrolysate); not soy.	Confirmed reduced allergenicity (1999)	Extensively hydrolyzed until 4 mo of age (2004 documented reduced allergenicity (2008)
Types of "solids" and complementary foods	Evidence to wait 4 (to 6) mo; lack of convincing evidence for avoiding specific allergenic foods	Solids held to 6 mo Dairy products, age 1 y Egg, age 2 y Peanuts, nuts, fish, age 3 y	Not before 17 wk and no later than 26 wk; no convincing evidence for delaying potentially allergenic foods such as fish, egg (2008)*	No evidence of diet effec after 4-6 mo

Sicherer S et al, J Allergy Clin Immunol 2008;122:29-33.

Natural History of Food Allergy in Children with AD

- 3 factors: the greatest importance in determining the probability of patients losing their clinical reactivity
  - The food to which patient was allergic (soy, wheat, milk, egg more likely to develop tolerance)
  - The level of specific IgE to particular food
  - The degree to which patient adhered to elimination diet (ingest small amount of allergen were less likely to develop tolerance)

Natural Course of Cow's Milk Allergy in Children with AD

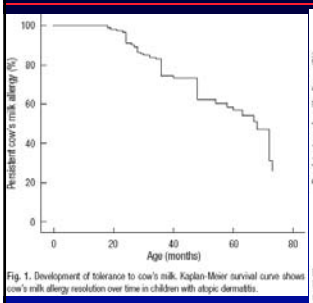


Fig. 1. Development of tolerance to cow's milk. Kaplan-Meier survival curve shows cow's milk allergy resolution over time in children with atopic dermatitis.

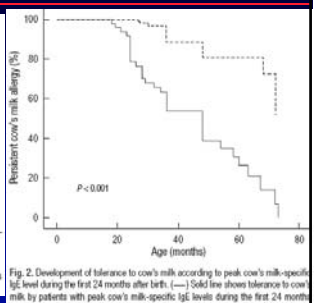


Fig. 2. Development of tolerance to cow's milk according to peak cow's milk-specific IgE level during the first 24 months after birth. (——) Solid line shows tolerance to cow's milk by patients with peak cow's milk-specific IgE levels during the first 24 months after birth of less than 15 kU/L. (- - -) Dotted line shows tolerance to cow's milk by patients with peak cow's milk-specific IgE levels during the first 24 months after birth of 15 kU/L or more.

Suh J et al, J Korean Med Sci 2011; 26: 1152-1158

Egg Oral Immunotherapy

Table 2. Success Rates on Oral Food Challenge.

Challenge	Participants Tested*		Response Rate		
	Placebo (N=15)	Oral Immunotherapy (N=40)	Placebo (N=15)	Oral Immunotherapy (N=40)	P Value
	number		*number (percent)*		
Desensitization, 5 g at 10 mo	13	35	0	22 (55)	<0.001
Desensitization, 10 g at 22 mo	1†	34	0	30 (75)	<0.001
Sustained unresponsiveness at 24 mo‡	0	29§	0	11 (28)	0.03

Burks et al. N Engl J Med 2012;367:233

Conclusion

- Food is a significant factor for exacerbations in a significant numbers of AD patients
- Egg seems to be the most important food item in this group of patients followed by cow milk and peanut
- Diagnosis of FA in AD is a must, particularly in young infants with severe disease
- Atopy patch test seems to have minor role in the diagnosis
- Avoidance is a major treatment modality although oral tolerance induction may be an option