

Universiteit Antwerpen

Food allergy: pathogenesis & clinics

Didier EBO
Immunology - Allergology - Rheumatology

Content

1. Definitions
2. Pathogenesis (IgE-mediated)
3. Causes
4. Clinics & natural course
5. Diagnosis
6. Therapy

1. Definitions

- Babylonian speech confusion
- Classification (Ortolani C, Allergy 1995;50(S20)8-13)

Classification

Non-toxic adverse food reactions

Immunologic	Non-immunologic
Not IgE-mediated	Enzymatic
IgE-mediated	Pharmacologic
	Undefined



The good news is that you don't have mad cow's disease. The bad news is you're lactose intolerant.

Classification

Non-toxic adverse food reactions

Immunologic	Non-immunologic
Not IgE-mediated	Enzymatic
IgE-mediated	Pharmacologic
	Undefined

IgE-mediated food allergy

- Most prevalent, increasing
- Most severe (fatalities)
- Changing (geographical and age-related patterns > prognostic)

Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: a EuroPrevall analysis

P. Burney¹, C. Summers², S. Chinn¹, R. Hooper¹, R. van Ree³ & J. Lidholm⁴

¹Respiratory Epidemiology and Public Health, Imperial College, London, UK; ²Corporate Development and Performance, Greater Manchester Police Headquarters, Manchester, UK; ³Department of Experimental Immunology and Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands; ⁴Phadia AB, Uppsala, Sweden

To cite this article: Burney P, Summers C, Chinn S, Hooper R, van Ree R, Lidholm J. Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: a EuroPrevall analysis. *Allergy* 2010; **65**: 1182-1188.

- 24 foods
- 7,7% Iceland > 16,8% Belgium > 24,6% Portland (USA)

	Germany (%)	Italy (%)	France (%)	Belgium (%)	USA (%)	Australia (%)	Spain (%)	Norway (%)	Sweden (%)	Kingdom (%)	Iceland (%)	Switzerland (%)	Estonia (%)	Overall (%)
Hish	0.9	0.0	0.0	0.0	0.0	0.0	0.5	0.3	0.3	0.2	0.0	-	0.0	0.2
Egg	0.3	0.0	0.1	0.6	0.0	0.5	0.3	1.5	0.5	0.4	-	-	0.0	0.4
Cow's milk	1.3	2.1	0.1	0.6	2.3	1.1	0.1	1.3	1.3	0.6	0.0	-	0.0	0.8
Mustard	7.7	0.6	2.6	0.0	0.0	1.0	0.9	0.3	0.4	0.5	0.3	0.0	0.0	0.8
Melons	1.8	2.8	3.6	3.4	0.0	2.1	1.2	0.6	0.5	0.5	0.0	0.0	0.0	1.6
Peppery seed	3.2	3.6	4.1	0.8	2.0	1.9	1.1	0.7	0.6	0.5	0.0	0.0	0.0	1.8
Soy	3.3	3.8	3.2	1.7	4.7	1.8	1.9	0.8	0.6	1.0	0.0	-	1.2	2.1
Sunflower	3.7	2.1	4.8	2.0	2.0	1.9	1.9	1.2	1.2	1.9	0.0	0.0	0.0	2.1
Walnut	3.3	3.1	3.7	2.5	2.1	2.1	3.1	0.0	1.1	0.8	0.0	0.0	0.0	2.2
Banana	3.0	4.2	4.4	4.5	0.0	2.6	2.4	2.2	1.6	1.9	1.0	0.0	0.0	2.5
Peanut	4.2	3.8	3.0	2.0	9.3	3.0	1.9	0.8	1.0	1.5	1.2	-	-	2.6
Buckwheat	3.8	3.7	3.6	2.0	2.5	3.6	2.2	1.8	1.0	1.9	1.0	9.7	-	2.8
Rice	3.0	4.7	2.9	1.7	4.9	2.3	3.0	1.1	0.9	1.9	0.3	4.9	-	2.9
Tomato	5.6	4.5	3.8	3.7	4.2	4.1	3.5	1.8	1.8	2.7	0.8	0.0	-	3.3
Corn	5.7	5.2	3.9	2.9	4.9	3.4	3.2	1.4	1.7	2.9	0.7	3.2	-	3.3
Celery	6.0	6.5	4.8	4.0	4.2	2.1	1.0	2.9	4.0	1.4	0.0	0.0	-	3.5
Kiwifruit	7.0	6.3	6.0	6.2	6.2	4.1	1.8	3.2	3.4	1.5	0.7	0.0	0.0	3.6
Carrot	7.7	6.2	4.4	4.3	2.1	3.1	1.7	3.5	3.1	1.7	0.0	3.8	3.9	3.6
Sesame	5.6	4.1	4.2	3.2	4.9	5.1	3.1	2.2	2.1	2.1	1.0	9.7	-	3.7
Apple	10.3	5.7	4.7	7.0	1.7	2.6	2.2	5.4	5.1	1.8	0.0	4.0	0.0	4.2
Wheat	6.0	6.7	5.5	4.3	6.1	7.9	3.4	3.0	2.3	3.9	0.7	7.3	-	4.6
Strawberry	4.4	10.2	7.0	5.1	0.0	2.4	4.9	6.5	4.6	6.2	2.8	0.0	-	5.4
Cherry	11.7	7.5	5.5	8.2	3.5	3.1	3.8	2.7	6.5	2.9	0.3	9.0	0.0	5.4
Blackberry	14.7	7.7	6.0	8.0	14.9	4.1	2.6	5.9	11.8	4.9	0.4	12.6	3.9	7.2
Pineapple	21.8	21.9	14.1	16.8	24.6	15.4	11.1	21.7	17.2	14.5	7.7	-	-	16.2

*For each food, each country's prevalence is determined by averaging over centres within that country, and overall prevalence is determined by averaging over all countries.

Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: a EuroPrevall analysis

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- 24 foods
- 7,7% Iceland > 16,8% Belgium > 24,6% Portland (USA)
- Cave sensitization **DOES NOT** mean allergy !!!

Toxicology 278 (2010) 319-325

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Review

Food allergy – science and policy needs – The UK Food Standards Agency Research Programme

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ARTICLE INFO

Article history:
 Received 19 July 2010
 Received in revised form 13 August 2010
 Accepted 14 August 2010

Keywords:
 Food allergy
 Sensitization
 T lymphocytes
 Eosinophils
 Antibody
 Prevalence

ABSTRACT

Food allergy is a significant health issue in the UK, affecting between 1 and 2% of adults and 5 and 8% of children. The UK Food Standards Agency seeks to ensure the safety of food allergic consumers by providing them with information and guidance on food choices. Since 1995, with the aim of addressing important policy issues and improving the quality of the support and guidance available for food allergic consumers, the Agency (and before that the Ministry of Agriculture, Fisheries and Food), has had a programme of research dedicated to investigating the causes and mechanisms of food allergy and delivering benefits for UK consumers. In this paper, we outline some of the major scientific challenges that the programme has sought to address. We reflect on how the findings have been used as a basis for the development of sound, evidence-based policy and advice for UK consumers, and the current direction of research being supported by the programme.

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Further fatalities caused by anaphylactic reactions to food, 2001-2006

To the Editor:

In 2001 we reported a group of 32 individuals who died because of food-induced anaphylaxis. The cases were accumulated in a registry kept by members of the American Academy of Allergy, Asthma & Immunology and The Food Allergy and Anaphylaxis Network.¹ The registry,

Bock A et al. *J All Clin Imm* 2007

TABLE 1: Food fatalities 2001-2006

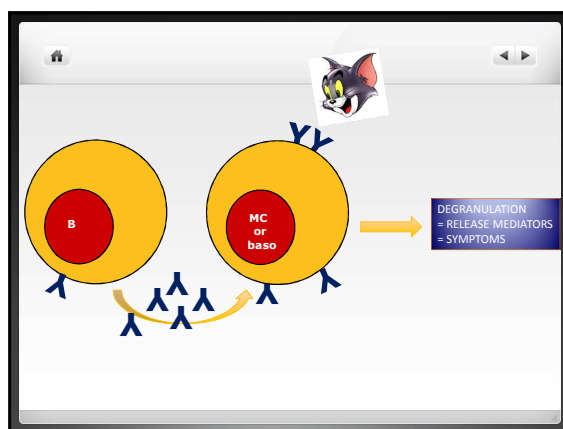
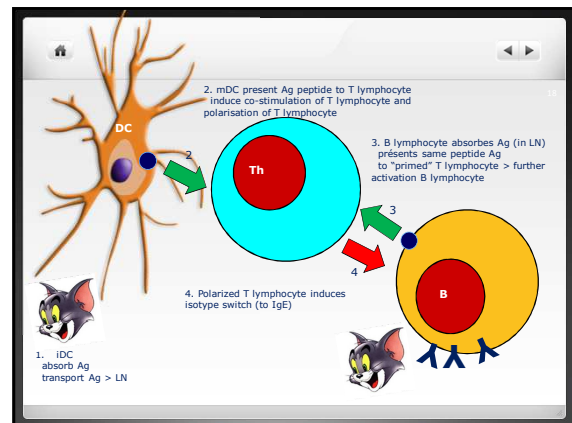
Patient no.	Age (y)	M/F	Date	Culprit	Asthma	Previous history	Food	Location	Timely epinephrine
1	32	M	3/1/2001	Nuts	Yes	Yes	Nut bowl	Restaurant	No
2	16	M	5/9/2001	Walnut	Yes	Yes	Chinese food	School, cooking class	Probably
3	9	M	5/18/2001	Peanut	Yes	Yes	Cookie	School outing	No
4	24	F	11/26/2001	Peanut	Yes	Yes	Chinese food	Home	No
5	25	F	10/30/2001	Nut meats	Yes	Yes	Candy	Home of friends	No
6	16	M	11/5/2002	Milk	Yes	Yes	Bread	Home	Unk
7	31	M	12/13/2002	Peanut	Yes	Yes	Catered food	Office party	No
8	50	M	12/24/2002	Nut	Yes	Yes	Cookie	Home	No
9	12	F	3/14/2003	Peanut	Unk	Unk	Egg roll	Unk	Unk
10	18	M	6/21/2003	Peanut	Unk	Unk	Wrap	Unk	Unk
11	32	M	3/15/2003	Shrimp	Yes	Yes	Meal	Restaurant	No
12	29	M	6/13/2003	Peanut	Yes	Yes	Meal	Restaurant	No
13	29	M	4/24/2000	Almond	Yes	Yes	Candy	Office	Yes
14	17	F	12/26/1996	Nuts	Yes	Yes	Cookie	Home of friends	No
15	21	F	10/9/2003	Peanut	Yes	Yes	Brownie	College	No
16	18	M	1/20/2004	Shrimp roll	Yes	Unk	Shrimp roll	Restaurant	No
17	27	M	2/1/2004	Peanut	Unk	Yes	Baked clam	Home	No
18	17	M	2/8/2004	Hazelnut	Yes	Yes	Candy	Home of friends	No
19	17	F	4/6/2004	Peanut	Yes	Yes	Peanut butter	Camp	No
20	34	F	5/29/2004	Peanut	Unk	Yes	Thai dish	Home	No
21	5	M	8/1/2004	Peanut	Unk	No	Peanuts	Home	No
22	9	M	7/22/2004	Milk	Unk	Unk	Milk	Camp	Yes
23	22	F	10/29/2004	Peanut	Yes	Yes	Dessert	Restaurant	No
24	14	F	1/22/2005	Peanut	Yes	Yes	Egg roll	Restaurant	No
25	36	M	3/21/2001	Peanut	Yes	Yes	Brownie	Work	No
26	17	M	3/5/2005	Milk/whey	Yes	Yes	Protein shake	Home	No
27	7	F	3/2/2005	Milk	Yes	Yes	Chocolate mix	Home	Unk
28	11	F	5/31/2005	Peanut	Unk	Yes	Candied apple	Carnival	Unk
29	40	M	2/8/2006	Tree nut	Unk	Yes	Cookie	Work	Yes
30	13	F	4/13/2006	Peanut	Yes	Yes	Wrap	Fast food in mall	No
31	16	M	8/1/2006	Peanut	Yes	Yes	Cookie	Home of friends	No

Further fatal allergic reactions to food in the United Kingdom, 1999-2006

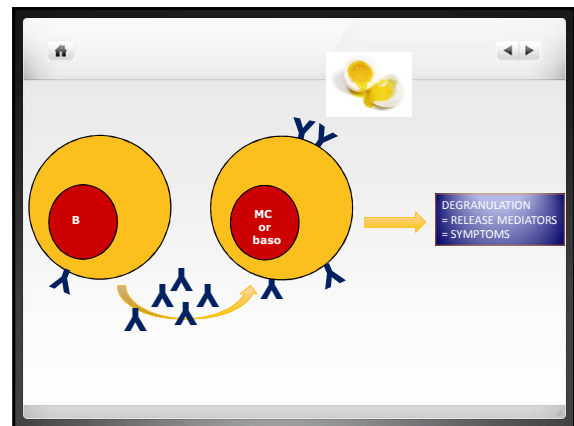
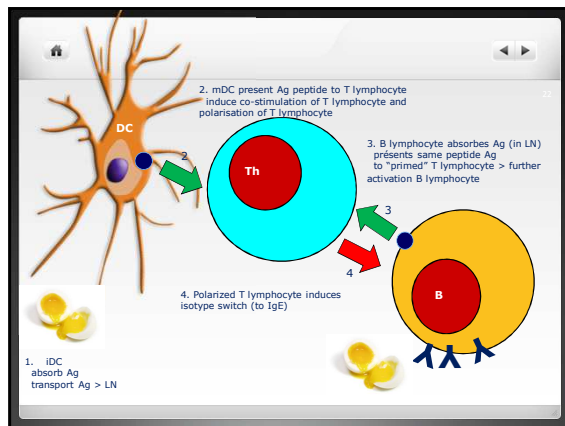
We report **48 additional deaths** meeting these criteria from 1999 to 2006. Ages ranged from 5 months to 85 years, with a median age of 21 years. The age distribution is similar to that in the previous report, with 7 aged 0-10 years, 26 aged 11-30 years, and 15 aged more than 30 years. There were 22 men (46%) reacting to milk (4), peanuts (3), nuts (2), fish (1) shellfish (1), snail (1), sesame (1), egg (1), and uncertain (8); and 26 women reacting to milk (2), peanuts (6), nuts (7), tomato (1), and uncertain (10). The circumstances comprised at home (14), the home of friends or relatives (10) at work (1), at school (2), at nursery (1), in a restaurant (11 of which 4 were abroad), out and about (6, of which 4 were from takeout food), in camp (2), and a wedding

Pumphrey RS et al. J All Clin Imm 2007

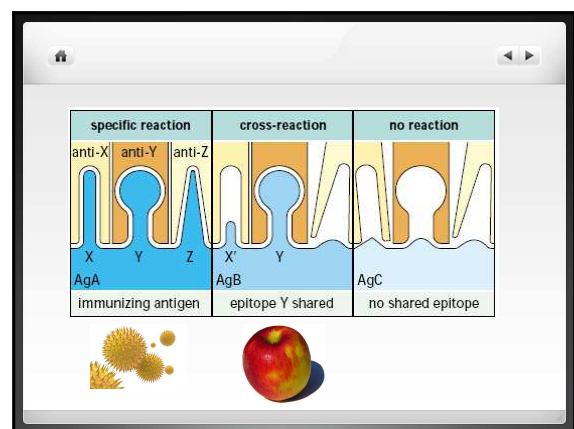
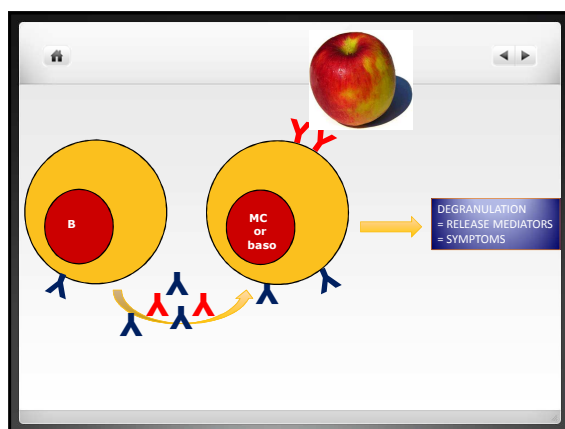
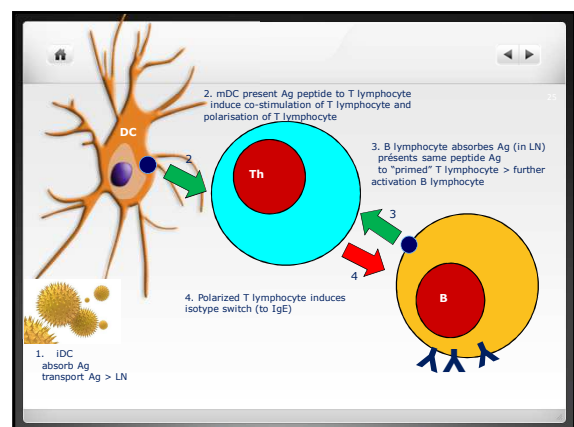
2. Pathogenesis of IgE-mediated allergy

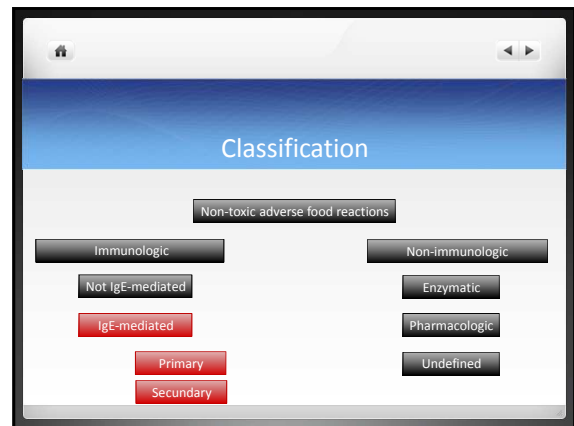
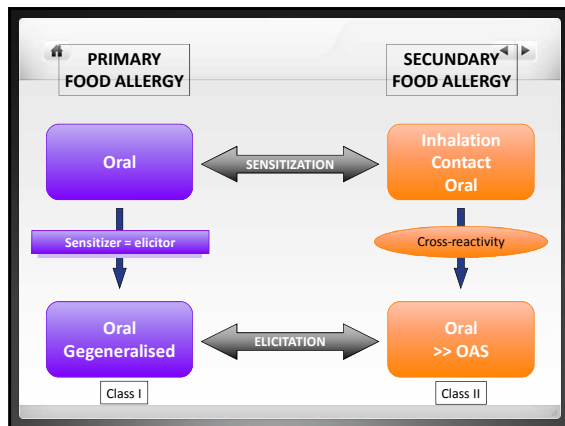


2. Pathogenesis: primary food allergy



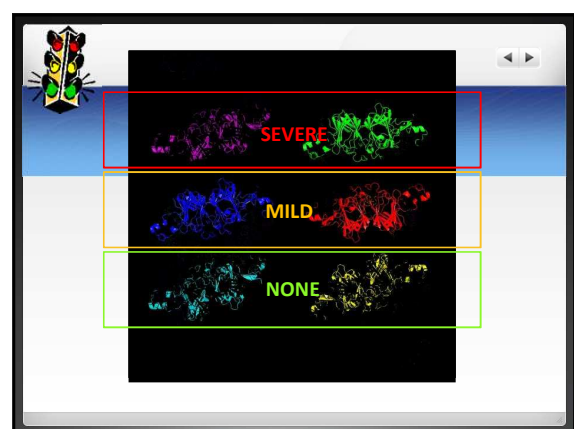
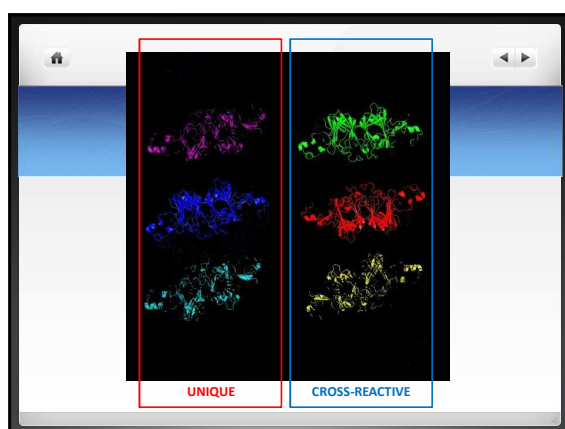
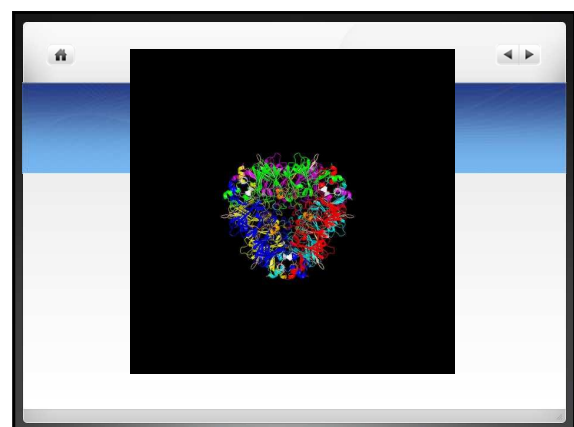
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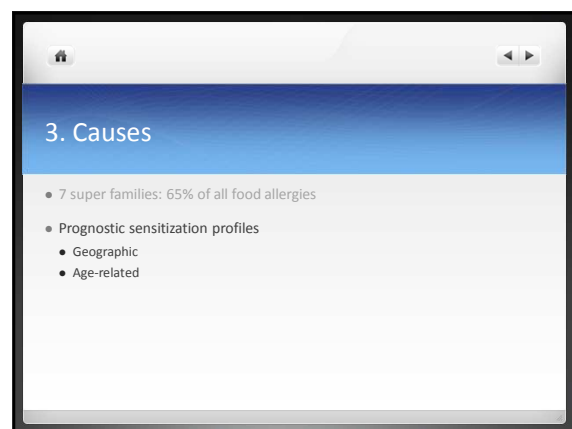
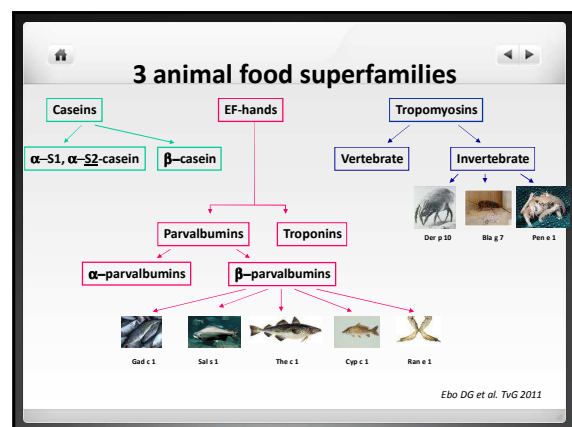
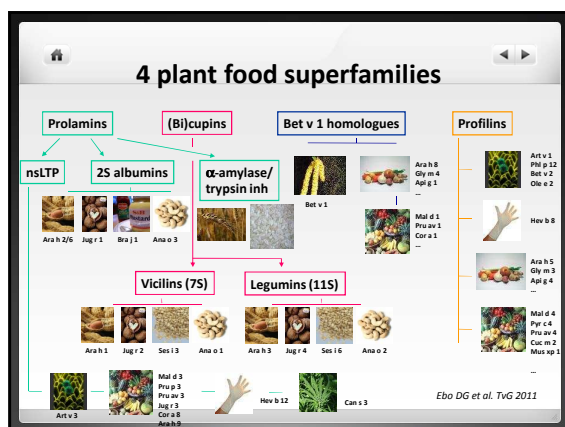
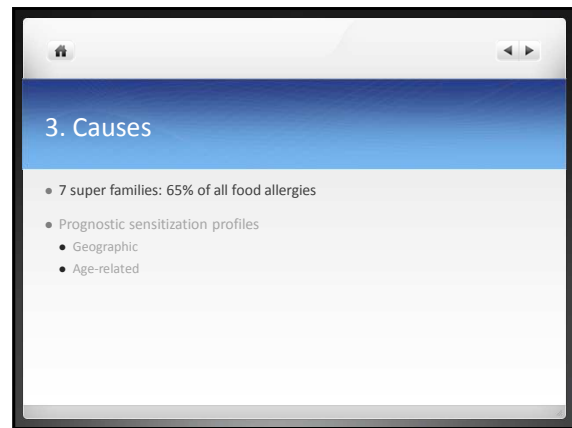
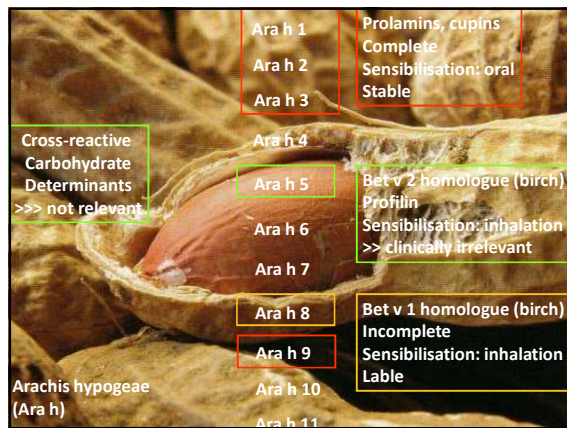


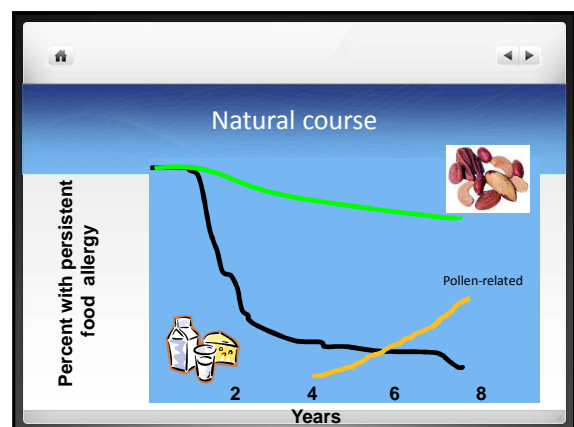
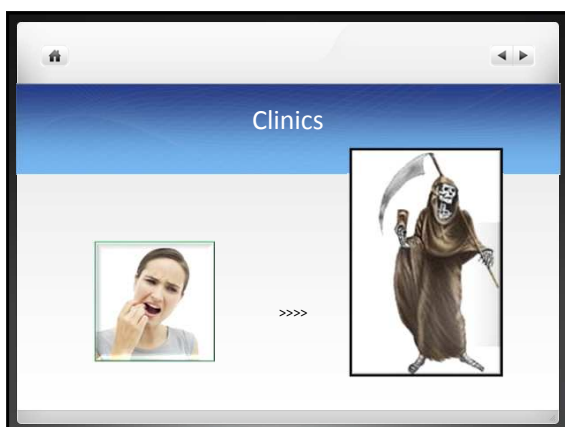
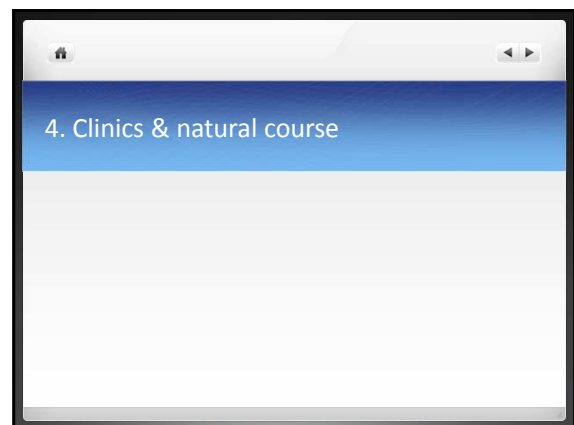
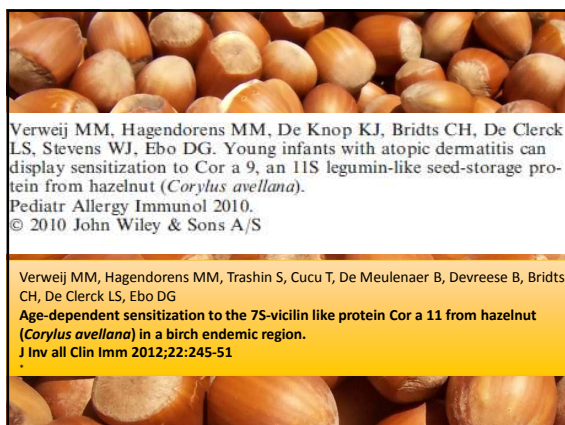
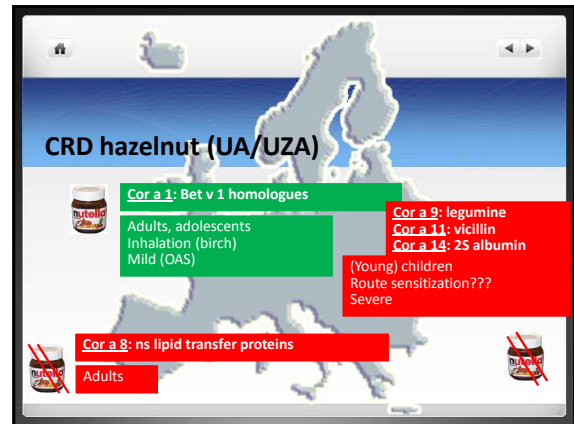


2. Pathogenesis: components

An allergen = collection of allergen components that can all trigger production of sIgE antibodies

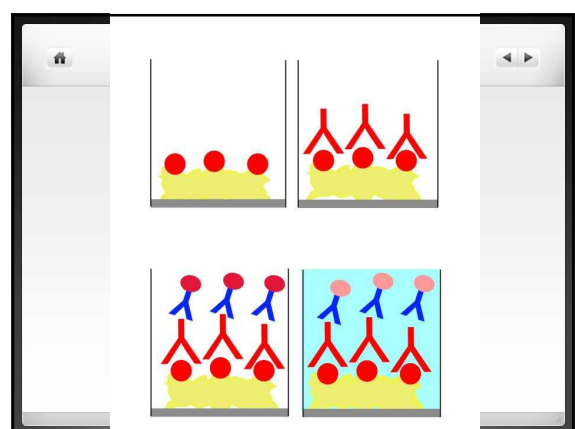
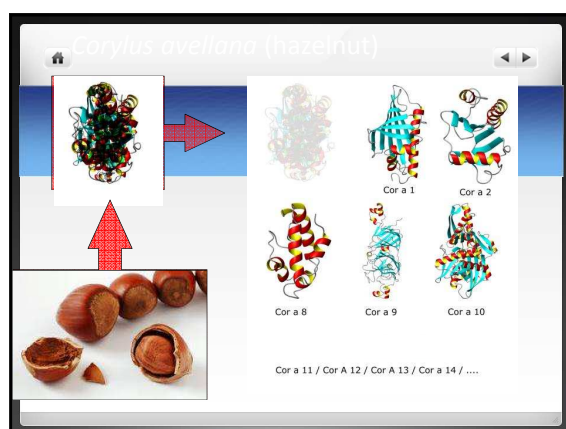
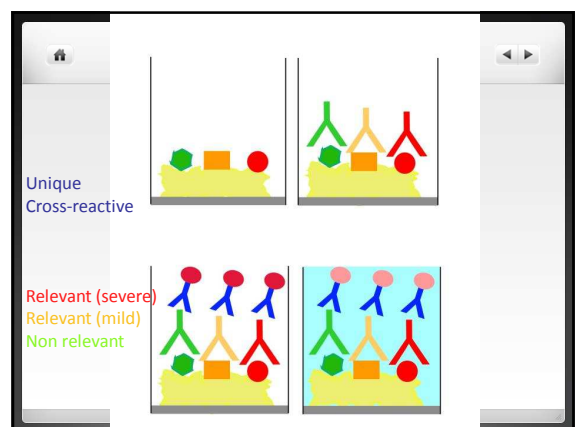
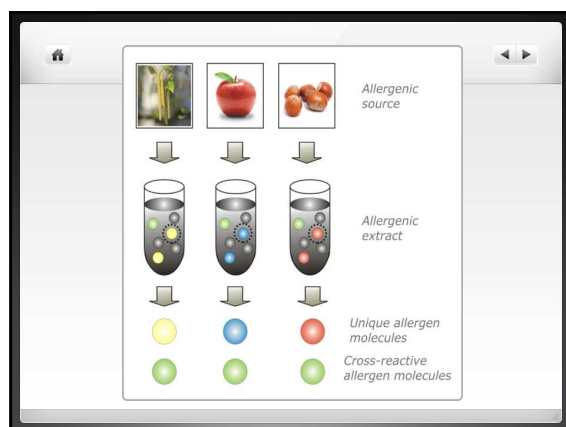


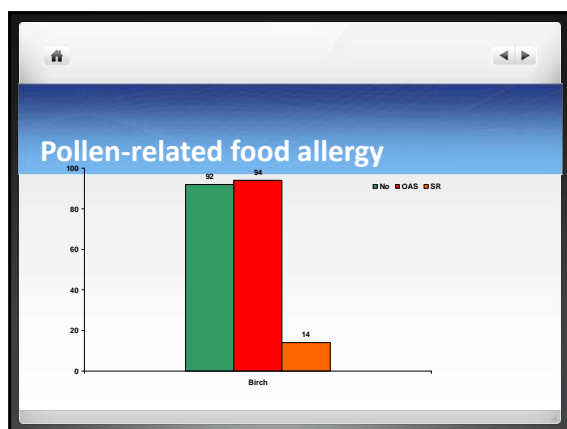
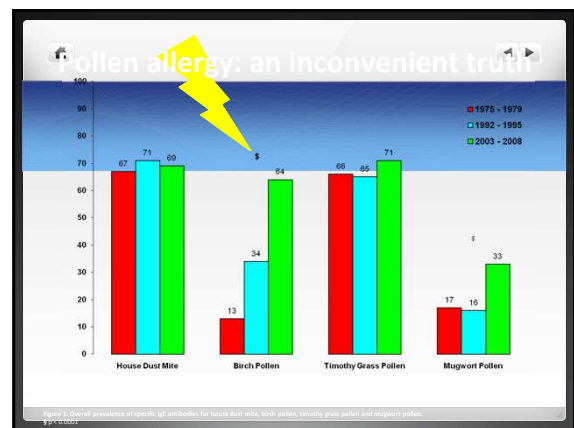
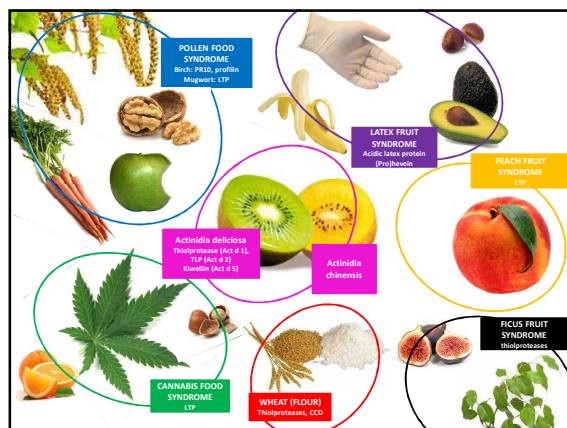
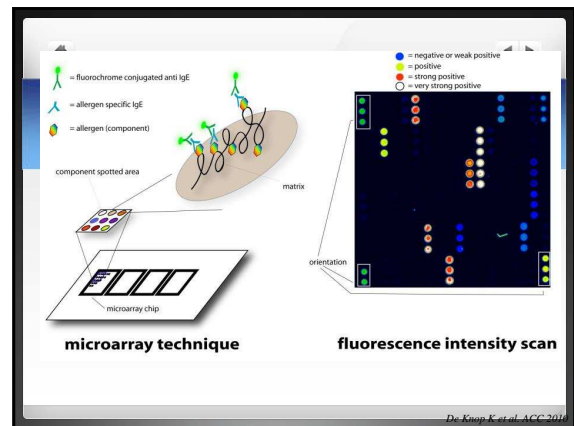
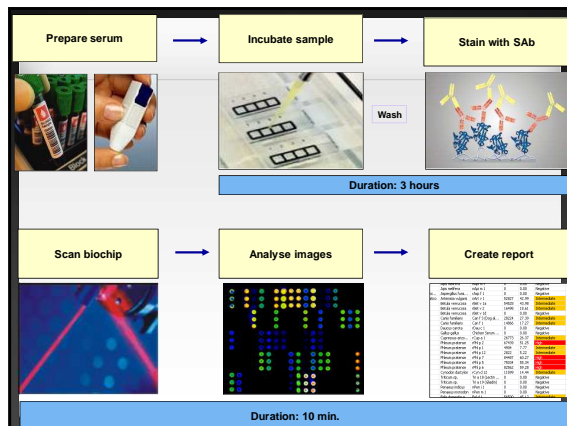


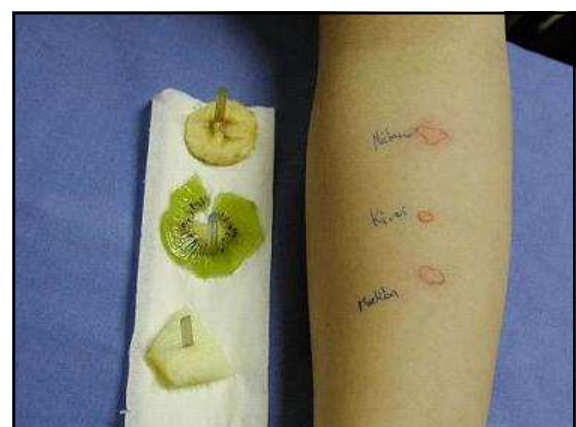
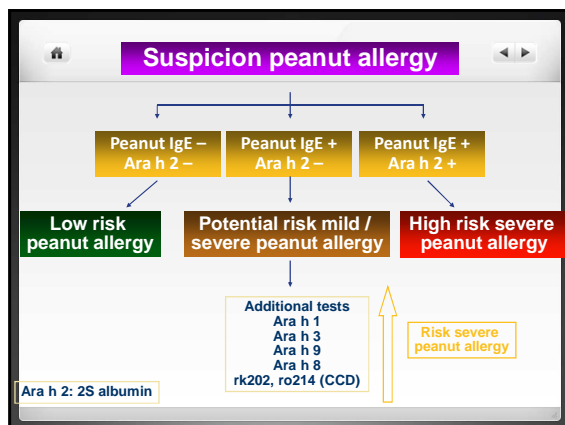
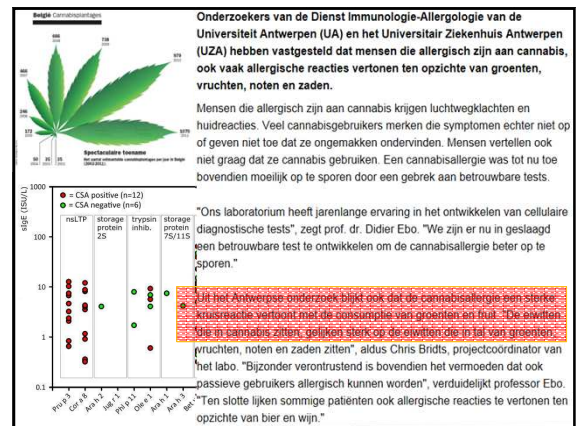
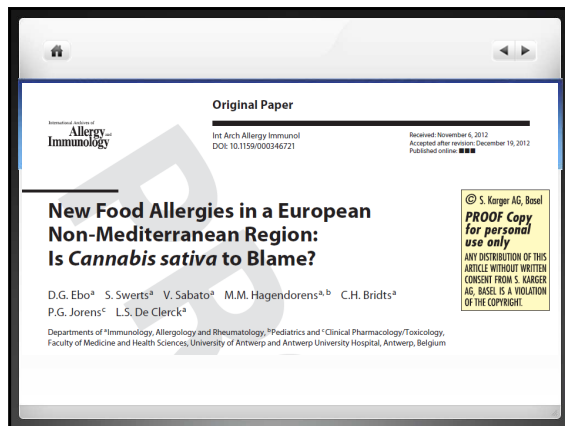


5. Diagnosis

- History
- Total IgE
- sIgE + components (prognostic patterns)
- Skin tests
- Basophil activation tests
- Food challenges
 - Double blind placebo controlled (adults)
 - Open (children)







Skin prick test (SPT)

- Difficult to standardize
 - Inoculums 0.04 – 80 nanoliter
- Practical issues
 - E.g. stop anti H1
- Risk (refusal)



Table 1. Recent protocols used in low-dose challenge studies with peanuts

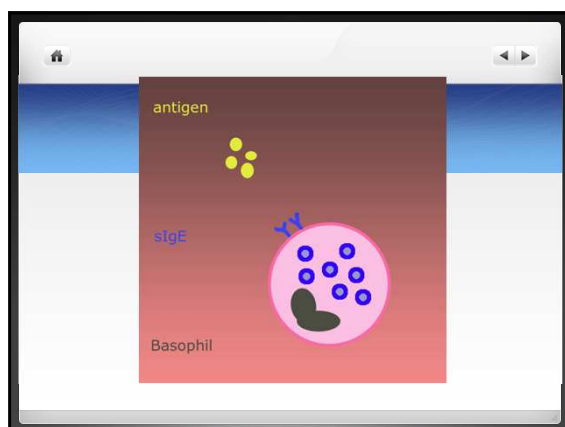
Authors	Starting dose	Last dose	Peanut material and matrix	Interval between doses (min)	Stop criteria	Duration of challenge
Peeters et al. (2007) (45)	10 µg	3 g	Partially defatted peanut flour in whole wheat instant cereals	15–30	3 times subjective symptoms or 45 min duration otherwise objective symptoms	1 day
Flisemann 2006 (42)	5 µg	1.5 g	Partially defatted peanut flour in whole wheat instant cereals	15–30	3 times subjective symptoms otherwise objective symptoms	1 day
Houbrave 2005 (42)	1 mg first dose reactors	4 g	Roasted and part. Defatted peanut flour chocolate	15–30	Not defined	1 day
Ernstshew 2002 (46)	30 µg	1 g	Roasted peanut meal (Runner)	30	Subjective symptoms lasting >1 h otherwise objective symptoms	1 day 2nd day for higher doses
Wiering 2002 (13)			Mashed potato cereal			
Moneret-Vautrin 1998 (48)	5 mg	20 g	Peanut seeds in mashed potato or apple puree	Not defined	Abdominal pain otherwise objective symptoms	1 day 2nd day for higher doses
Houbrave 1997 (41)	10 µg	50 mg	Peanut flour in wholegrain wheat flour	10–15	Objective symptoms	1 day

From: Crevel RWR et al. *Allergy* 2008;63:597-609

Challenge tests

- Different types
 - Open: children
 - DBPCFC: adults
- Practical issues
 - E.g. stop anti H1
- Risk !!!

- Identification of safe food (equivocal IgE/ST)



6. Therapy

- Omalizumab (anti-IgE)
- Immunotherapy
 - Pollen (SCIT, SLIT): pollen-related food allergy
 - Food (oral)

A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy

nut protein. While no firm conclusions can be drawn from these limited data, the results are consistent with findings of a similar anti-IgE preparation, HU-901⁵—that is, although the study was stopped early and most subjects on omalizumab did not reach the predefined study endpoints, omalizumab may increase the tolerability to peanut in a subset of patients with peanut allergy and may deserve further investigation.

Sampson H et al. J All Clin Imm 2011 (May)

~ 300 mg/2 wk (€ 400 / 150 mg)
€ 8000 / year (life-long)
Not reimbursed

doi: 10.1111/j.1365-2222.2011.03794.x Clinical & Experimental Allergy 41, 1177–1200
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BSACI GUIDELINES

Immunotherapy for allergic rhinitis


Although some studies have shown limited improvement of oral allergy symptoms following immunotherapy with birch pollen extracts [74–79] others have disagreed. Improvements appear more likely to occur in patients over 20 years who are monosensitized to birch pollen and with more intense oral symptoms. Resolution is less likely in patients treated with combined grass and tree pollen immunotherapy [75]. Symptoms may become worse [75, 80] and new sensitizations may develop while on treatment [81]. Symptoms may also recur once treatment has been discontinued. On the basis of current evidence, the presence of oral allergy syndrome is neither an indication nor a contra-indication to birch pollen SCIT or SLIT.

Immunotherapy in food allergy

- SCIT / oral
- Option in controlled trials
- Desensitization (temporary) vs. induction of tolerance (definitive)
 - Partial or total
- Frequent (controllable side effects)
- Need additional studies before entrance in mainstream clinical practice

6. Therapy

- Omalizumab (anti-IgE)
- Immunotherapy
 - Pollen (SCIT, SLIT): pollen-related food allergy
 - Food (oral, SLIT, SCIT)
- >>> **NO CURE (avoidance)**




TERRIFYING

poor labels
hidden allergens
unawareness
new allergies

TERRIFYING

poor labels
hidden allergens
unawareness
new allergies

% positive test

	Peanut	Hazelnut
"May contain"	25	36
"Present in environment"	25	23
No warning	11	25

	Peanut	Hazelnut
"May contain"	43	79
"Present in environment"	7	60
No warning	25	50

Pele M et al. Food Addit Contam. 2007
Dec;24(12):1334-44

TERRIFYING

poor labels
hidden allergens
unawareness
new allergies



Anaphylaxis from Passive Transfer of Peanut Allergen in a Blood Product

TO THE EDITOR: Anaphylactic reactions to blood transfusions are rare and their causes often remain elusive.¹ The inducement of clinically relevant allergic reactions by means of the passive transfer of IgE in blood products has been well documented.² In an editorial comment written in 2003, Erick speculated on the possibility that allergic transfusion reactions could be induced by the passive transfer of food allergens.³ We present such a case.

A 6-year-old boy with acute lymphoblastic leukemia had an anaphylactic reaction while receiving a leukoreduced pooled buffy-coat product with ABO-identical platelets. During transfusion, rash, angioedema, hypotension, and difficult breathing occurred. The patient recovered within 30 minutes after resuscitation with adrenaline. His serum level of mast-cell tryptase, measured directly after the reaction, was 24 μg per liter (normal level, <5), which confirmed the clinical pic-

Jacobs JFM et al. NEJM 2011

CASE REPORT

Dangerous Liaison: Transmitted Allergic Reaction to Nuts

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Abstract

Brazil nuts are the second most frequent cause of documented Brazil nut allergy who developed allergic reaction after intercourse with her boyfriend who had earlier consumed Brazil nuts. Skin prick testing with a sample before nut consumption was negative.

Key words: Brazil nut allergy; Semen; Sexual intercourse

We report the case of a 20-year-old woman with no history of allergy who developed allergic reaction after intercourse with her boyfriend who had earlier consumed Brazil nuts. Skin prick testing with a sample before nut consumption was negative.

Bansal AS et al. JIACI 2007

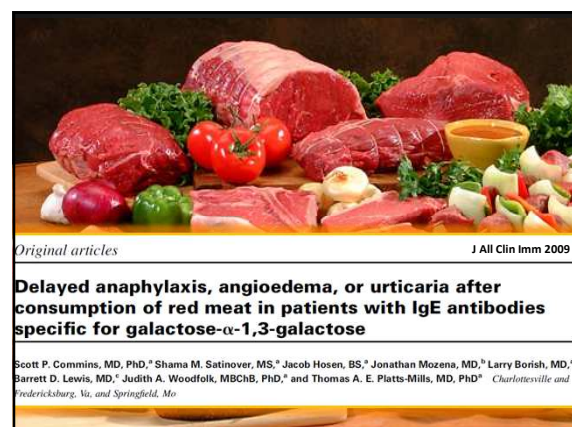
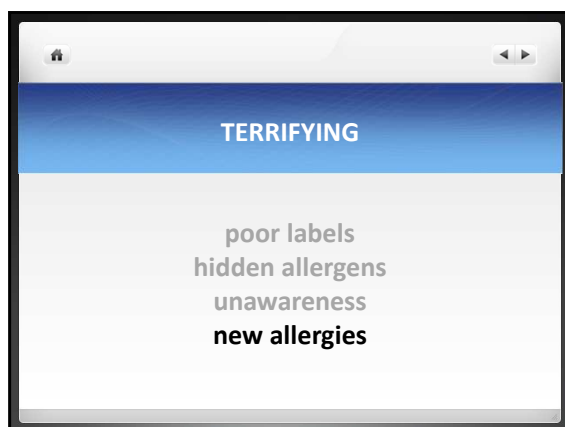
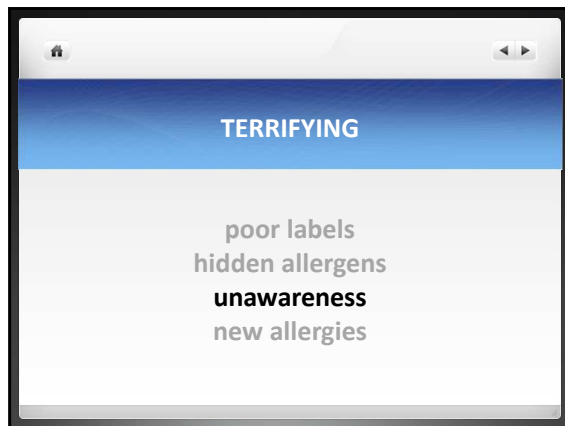


Table: Characteristics of patients allergic to red meat, dairy or gelatin.

Parameter	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8	PT9	PT10
Subtype	M/S	F/S	M/S	F/S	F/S	M/S	F/S	M/S	F/S	F/S
Clinics	Ur	Ur	Ur	Ur	Ur	Ur	Ur	Ur	Ur	Ur
Causes	Pork, Beef, Lamb, Gel	Pork, Beef, Lamb, Gel	Pork, Beef, Lamb, Gel	Pork, Beef, Lamb, Gel	Various meats	Pork	Gel	Pork	Beef	Beef products
Interval (hours)	4-6	2-4	<4	3	3	4-6	1-15	4-6	4	10 min
Tick bites	Yes	U	Yes	U	U	Yes	U	Yes	U	U
Total IgE	1922	664	554	237	201	183	814	170	49	494
Specific IgE (IgE, normal <0.35 UAS)										
stlg e-gal	>100	27.1	>100	19.60	3.44	1.32	1.13	45.5	3.19	<0.35
stlg gelatin	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	<0.35	3.70
stlg pork	21.00	6.30	20.90	22.30	5.24	3.10	1.11	5.12	1.65	<0.35
stlg beef	21.90	5.96	45.70	25.90	6.38	0.57	1.14	8.65	2.24	<0.35
stlg rabbit	5.29	3.40	11.80	N.A.	2.54	<0.35	0.56	2.24	N.A.	<0.35
stlg milk	9.33	7.14	6.97	4.15	3.02	0.59	0.42	2.01	<0.35	<0.35
stlg BSA	1.25	0.36	1.93	<0.35	<0.35	<0.35	<0.35	0.40	N.A.	<0.35
stlg epitaxy	1.59	1.64	3.77	0.40	<0.35	<0.35	<0.35	0.69	<0.35	<0.35
Skin prick tests (SPT, wheals and flares expressed in mm)										
Pork	3/5	0/2	N.A.	3/8	2/5	0/0	3/6	8/17	2/4	0/0
Beef	2/10	N.A.	N.A.	5/10	N.A.	0/0	0/0	2/3	1/5	0/0
Cetuximab	6/13	3/5	3/23	4/6	9/14	8/15	0/0	5/27	2/6	0/0
Gelofusin*	5/6	5/15	0/0	4/5	8/15	0/0	4/12	0/0	0/0	5/13

Ur: urticaria; B: bronchospasm; A: angioedema. Gel: gelatin-based colloid plasma (PT2), gelatin-containing marshmallow (PT7, PT10). Ur: unknown, N.A.: not available.

* denotes an atopic status

* patient 2 had generalized urticaria and significant bronchospasm starting immediately after infusion of a bovine gelatin-based colloid plasma substitute (Gelofusin*, 40 mg/ml, gelatin, B. Braun Melsungen AG, Germany) during general anesthesia for knee arthroscopy

* large amount of marshmallows containing bovine gelatin (patient is vegetarian)

* history taking revealed these reactions to occur after topical application of several hair care products and conditioners applied on the scalp. Careful revision of the product leaflets disclosed some of these products to contain collagen and gelatin.

* nausea, vomiting, facial erythema, angioedema of the throat and wheezing about 10 minutes after eating some marshmallows containing bovine gelatin. History revealed an IgE-mediated latex allergy with a sensitization to Hev b 5 and Hev b 6. A diagnosis of a genuine IgE-mediated gelatin allergy unrelated to e-gal was made.

