Atopic Dermatitis and food allergy

Mysteries unravelled

UPDATE

MARCH 201

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Introduction

- Allergies have increased spectacularly over the past few decades
- Asthma 15% of children, eczema 10-20%, food allergies up to 10% in the first 1-2 years of life
- Many children are “co-allergic”

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Atopic Dermatitis in the Young Child

- Atopic Dermatitis (AD)= chronic pruritic skin rash of multifactorial origin
- Traditionally thought of as “an allergic response” BUT
- Better understanding of pathogenesis:
  - Disrupted epithelial barrier function
  - Immunodysregulation
  - IgE sensitisation to food and environment allergens

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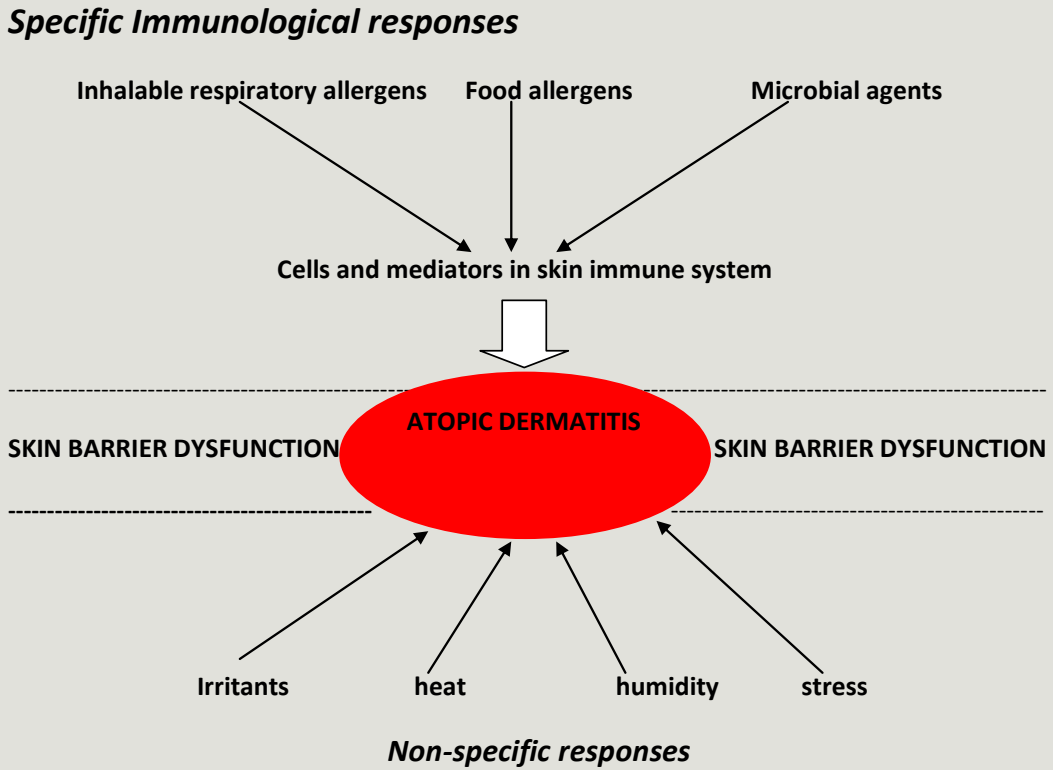
Atopic Dermatitis in the Young Child



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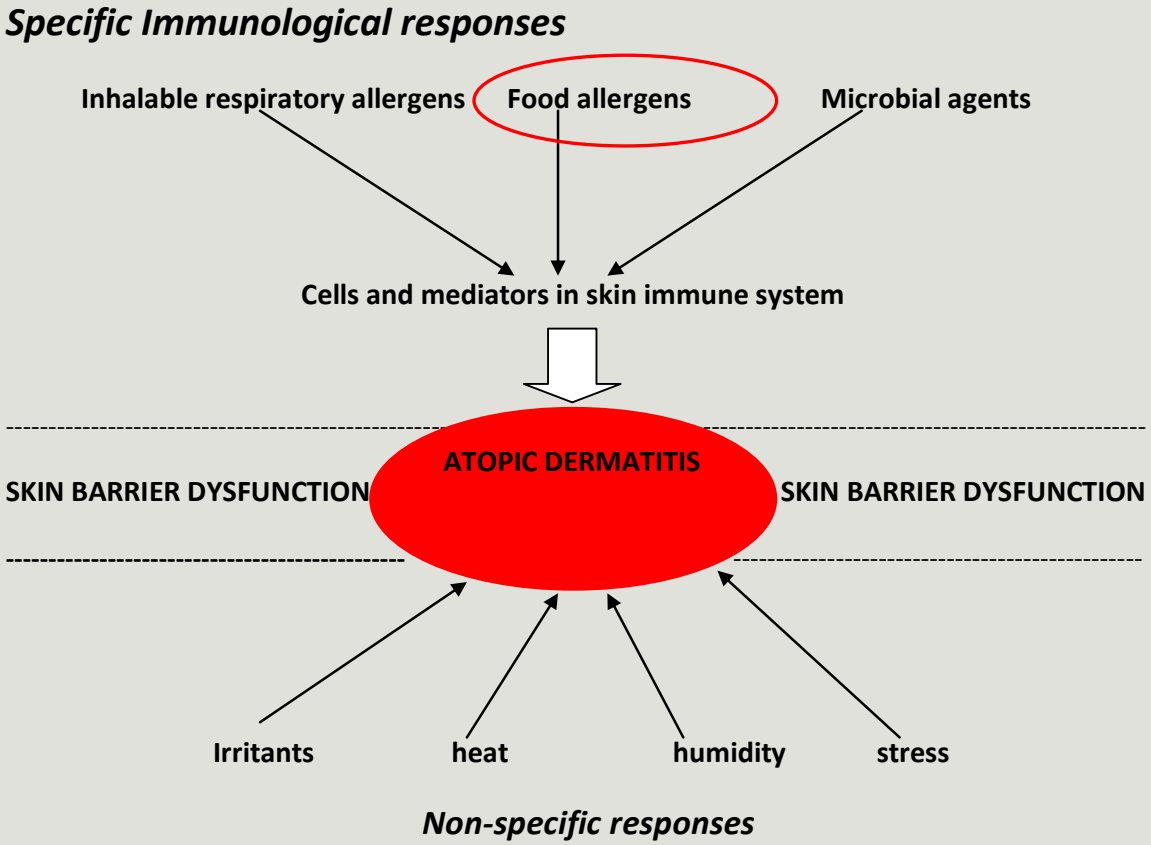
Atopic Dermatitis in the Young Child



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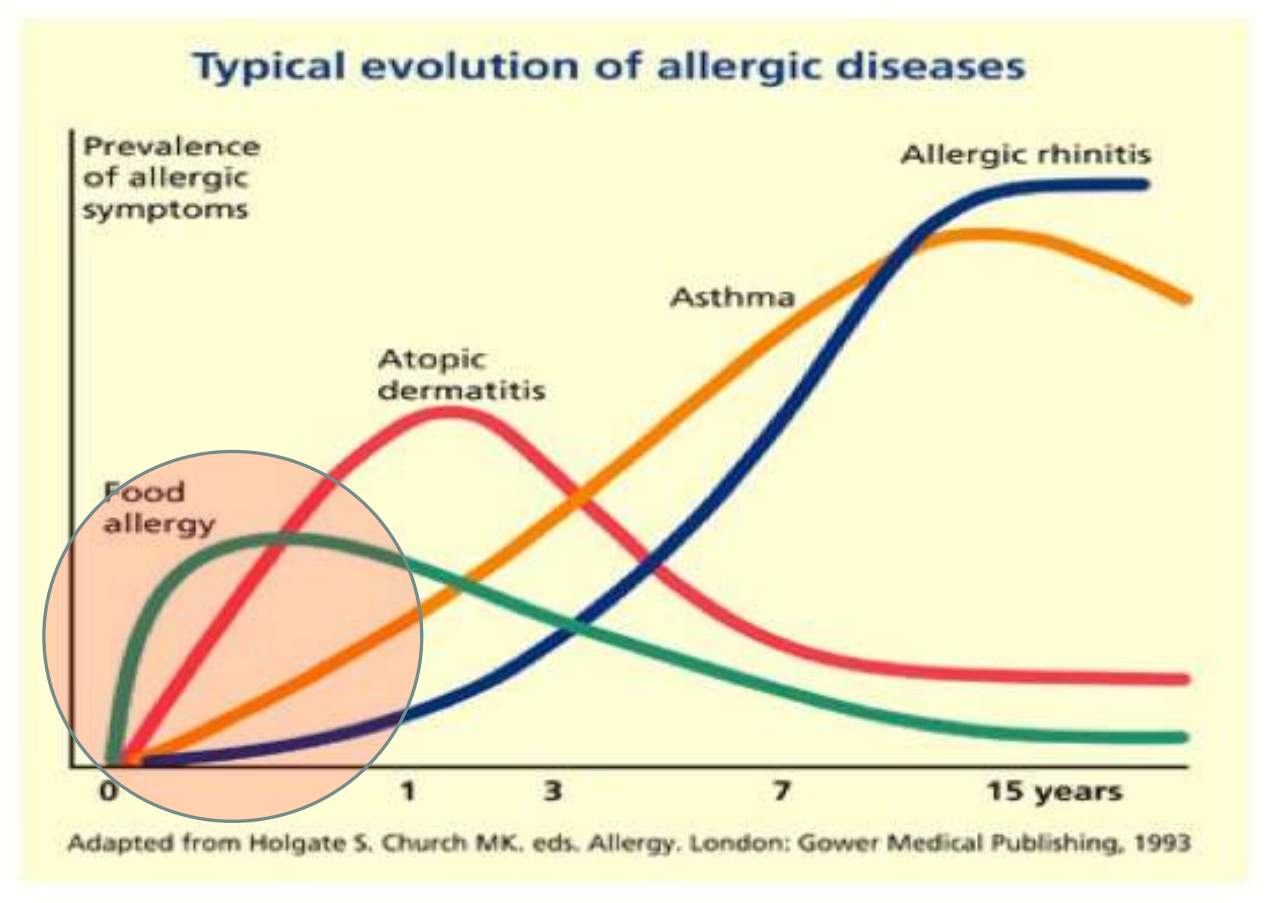
“Allergic March”



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Background: ? Role of food allergy?

- Diagnosis of food allergies important:
  - Food allergies can lead to dangerous reactions
  - Food allergies may be a trigger for persistent eczema
  - Unnecessary diets not based on proper diagnosis can lead to nutritional compromise

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Atopic Dermatitis and Food Allergy

Topics to be Discussed:

1. Association between food allergies and eczema
2. Diagnosis of food allergy in eczema
3. Elimination diets

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Eczema and Food Allergy: Myth or Reality?

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Atopic Dermatitis and Food Allergy

Topics to be Discussed:

1. Association between food allergies and eczema
2. Diagnosis of food allergy in eczema
3. Elimination diets

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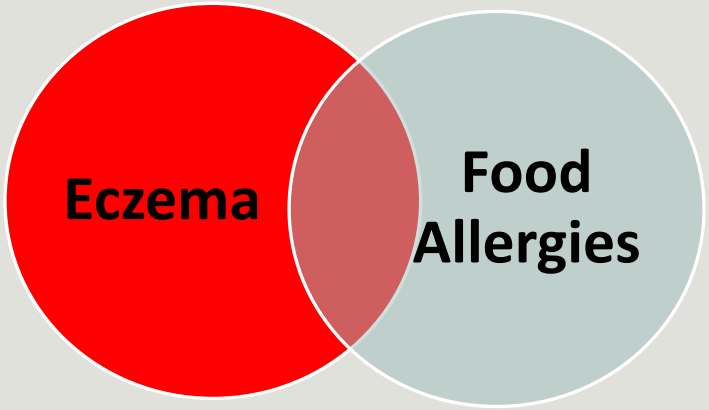
Association between food allergies and eczema:

1.The co-existence of food allergies in patients with eczema



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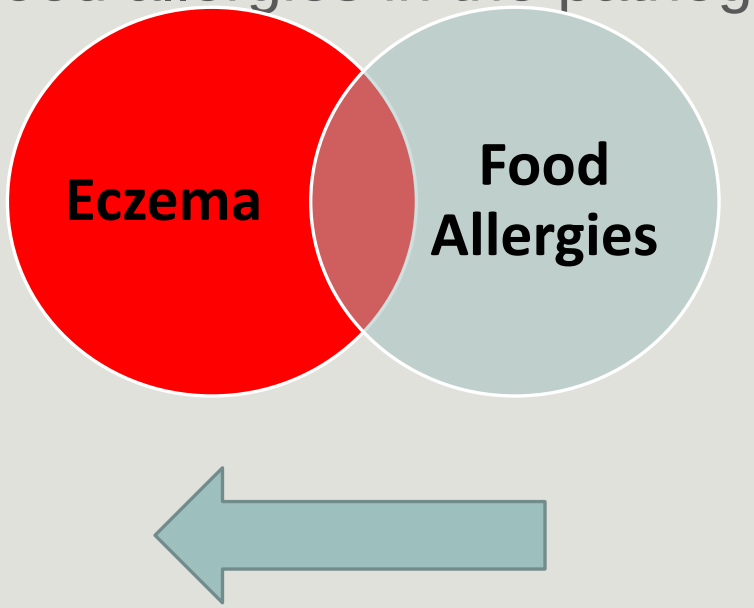
Association between food allergies and eczema:

2. The role of food allergies in the pathogenesis of eczema



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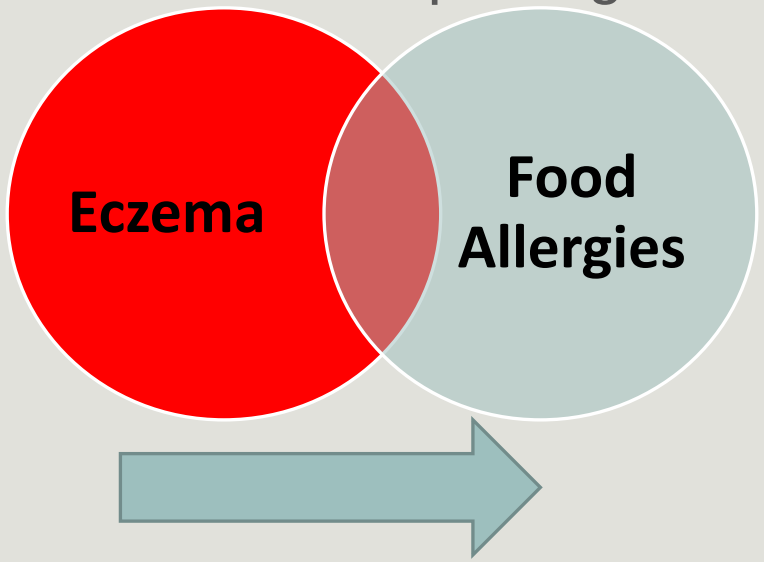
Association between food allergies and eczema:

3. The role of eczema in the pathogenesis of food allergies



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1. Association between food allergy and eczema

Debate 1: A positive allergy test is an accurate indicator that a child with eczema has a food allergy

Myth or Reality??

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Answer: Myth!

- Reality: Allergy tests are good screening tests but have a very high false positive rate
- At least half of eczema patients with positive allergy test are tolerant to that food and SHOULD continue to eat the food!

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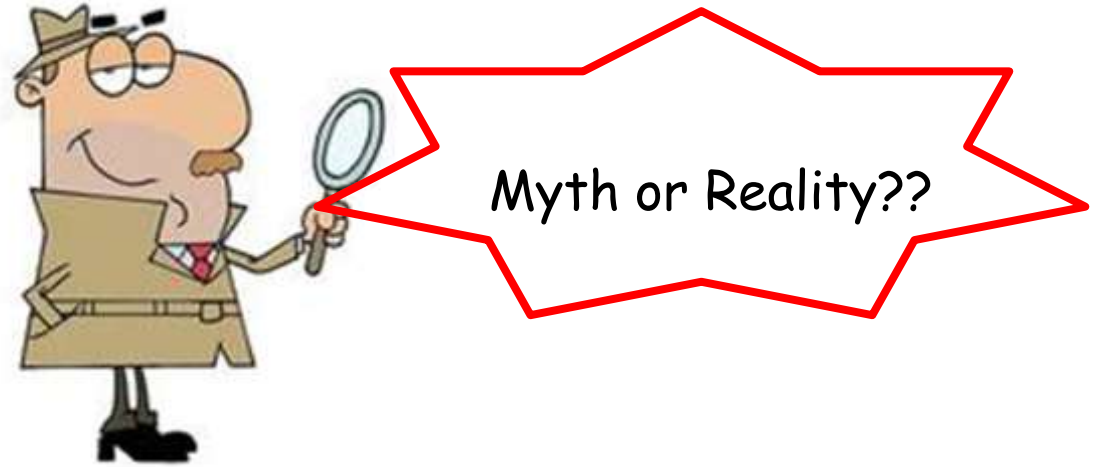
1. Association between food allergy and eczema

Debate 2: Most children with eczema have at least one food allergy



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Answer: Myth!

- Reality: Eczema patients do have a far higher allergy rate than the general population
- Allergy rate depends on the severity of the eczema
- Even in the most severe eczema 30-40% have associated food allergy

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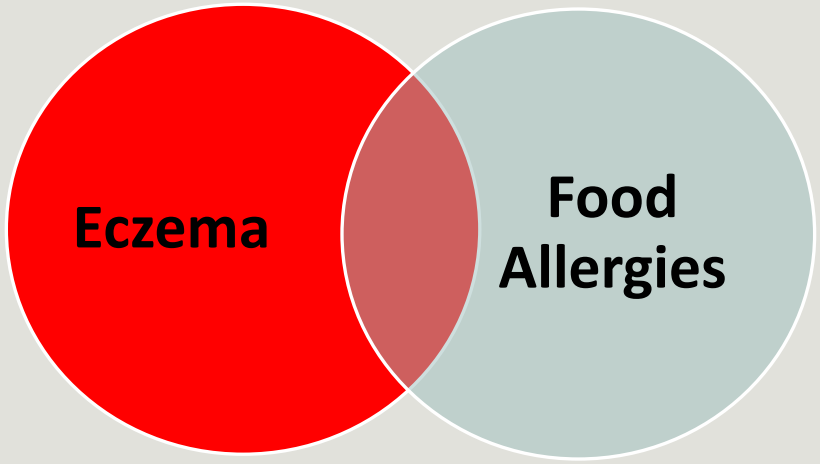
Association between food allergies and eczema:

1. The co-existence of food allergies in patients with eczema



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Eczema and food sensitisation

Sensitisation

(+ve SPT/ food specific IgE)

Vs

Allergy

(clinically significant reaction upon ingestion of the food)

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Eczema and food sensitisation

- Sensitisation to foods in children with atopic eczema = 50-60%
- A high % of children with eczema have high total IgE's
- The process of food sensitisation seems to be completed by the first birthday
- Higher values of SPT/sIgE more suggestive of allergy but do NOT predict severity of reaction

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Eczema and food sensitisation

EPAAC™ (Early Prevention of Asthma in Atopic Children): sensitisation patterns in 2200 infants with eczema globally:

Any food: 48.6%

Egg white 41.9% (SA 47.1%)

Cow's milk 27.4% (SA 28.4%)

Peanut 24.4% (SA 26.8%)

De Benedictis FM, Franceschini F, Hill D, Naspitz C et al. The allergic sensitization in infants with atopic eczema from different countries. *Allergy* 2009; 64: 295-303

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Eczema and food sensitisation

- South African data on 100 children with AD:

66% sensitised to any food

54% sensitised to hen's egg

27% sensitised to cow's milk

44 % sensitised to peanut

Gray et al Pediatric Allergy Immunology 2014

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Eczema and proven Food Allergies

- 30-40% of children with moderate to severe eczema have at least one food allergy
- 5 -8 X more prevalent than in the general population
- “food allergy”= positive food challenge or recent history of significant reaction in a sensitised patient

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Eczema and proven Food Allergies

Study (year)	Location	Number of Patients	Positive SPT or IgE (ie sensitised)	Positive Food Challenges
Burks et al (1998)	USA	165 (mean age 48 mths)	60% + SPT	38.7%
Eigenmann et al (1998)	USA	63 (mean age 2.8 yrs)	65% + IgE	37%
Eigenmann et al (2000)	Switzerland	74 (mean age 2.5 yrs)	59% + IgE	33.8%
Garcia et al (2007)	Spain	44 (mean age 7.5 months)	61% + SPT/IgE	27%
Gray et al (2014)	South Africa	100 (median age 42 months)	66% +SPT/IgE	40%

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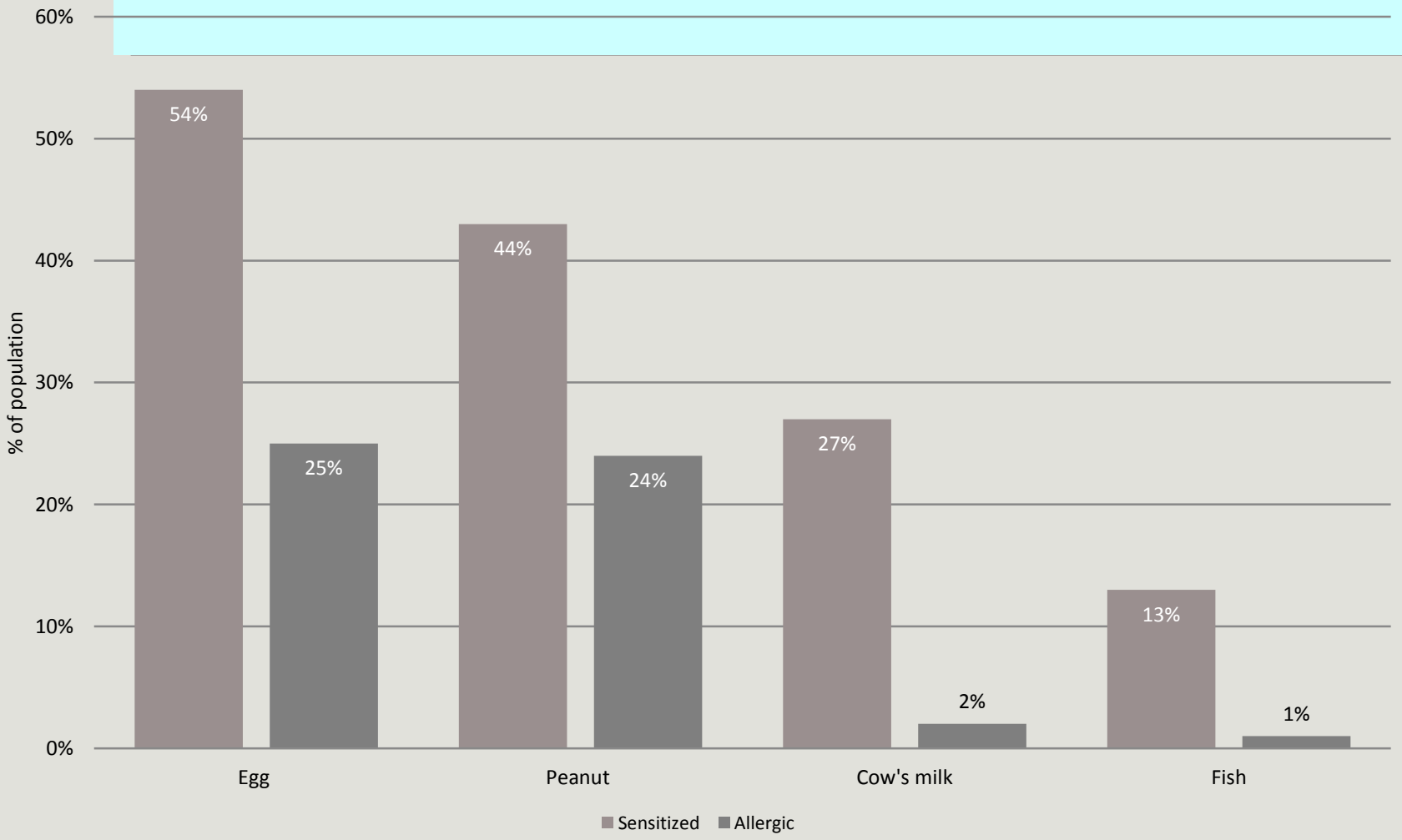
Figure 2 - Overall prevalence of sensitisation and allergy for egg, peanut, cow's milk and fish in South Africanfood allergy- eczema study [32]



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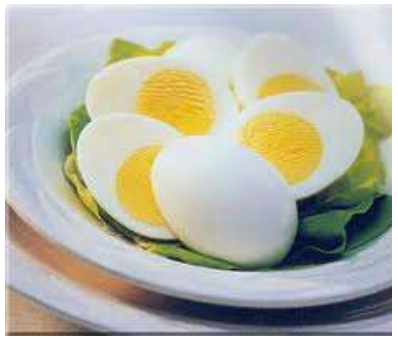
Types of Food Allergens

Milk, egg, peanut, wheat, soy account for 90% of allergenic foods in children with eczema


Typically outgrown (despite persistently+ SPT) apart from peanut

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Types of Food Allergens

- Adults: association between eczema and food allergies rare
- Most often associated with birch-pollen associated foods (Europe)

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Patterns of Clinical Reactivity to Foods in AD

1. ***Non- eczematous reactions (usually immediate)*** **:**

   cutaneous (pruritis, rashes, urticaria)/gastrointestinal (vomiting, diarrhoea) /respiratory symptoms/ anaphylaxis.

   50% of cases

   usually occur within 2 hours of food ingestion.

2. ***Isolated eczematous reactions*** **:**

   10% of reactions

   usually delayed > 6 hours after food ingestion

3. ***Combination of non- and eczematous reactions*** :

   occurs in 40% of cases

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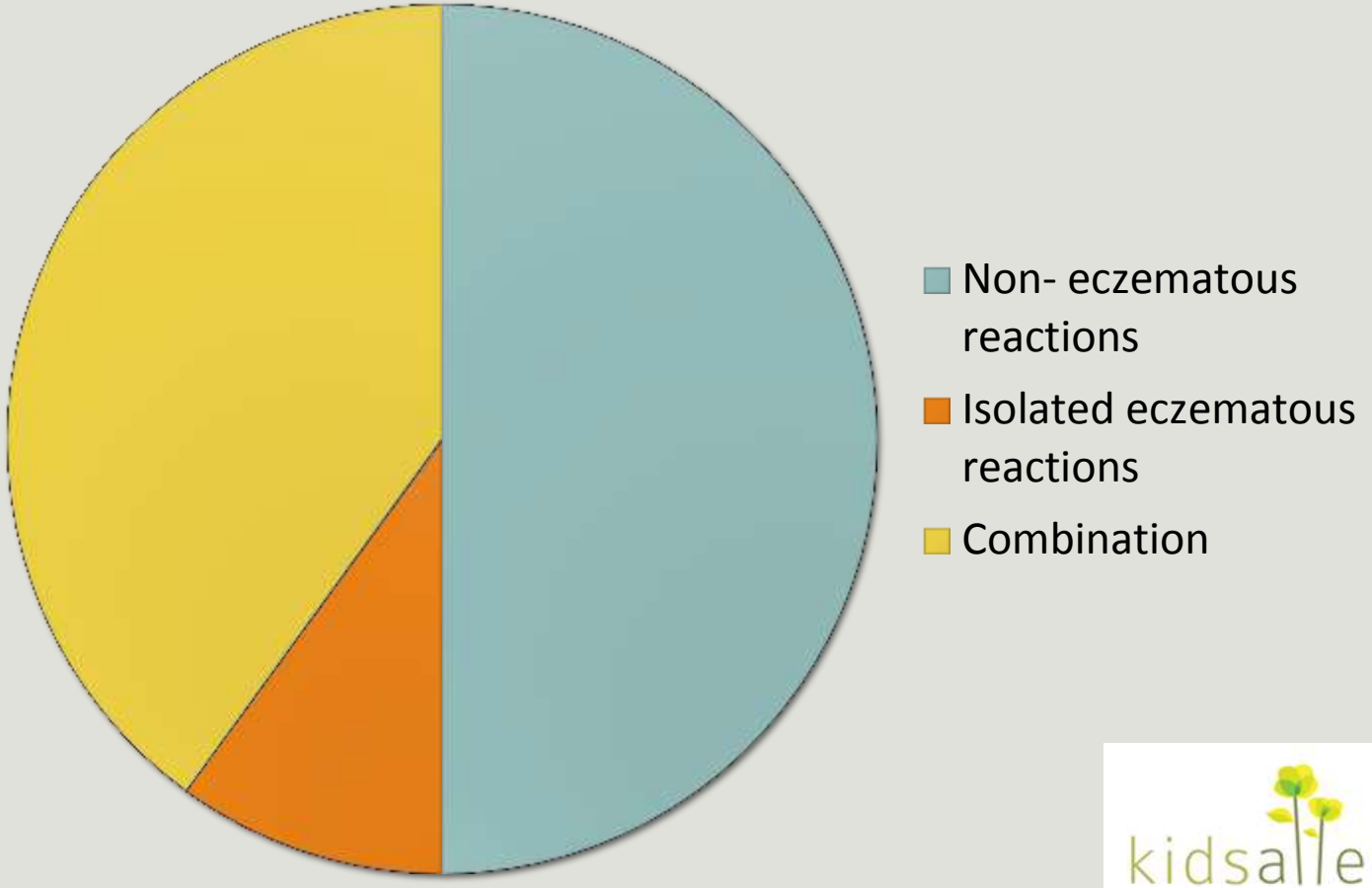
Patterns of Clinical Reactivity to Foods in AD



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Patterns of Clinical Reactivity to Foods in AD

Up to 95% of reactions involve cutaneous reactions:

- Morbilliform and macular rashes
- Pruritis
- Urticaria
- Eczematous reactions

Cutaneous reactions=eruptions at sites affected by/predisposed to eczema

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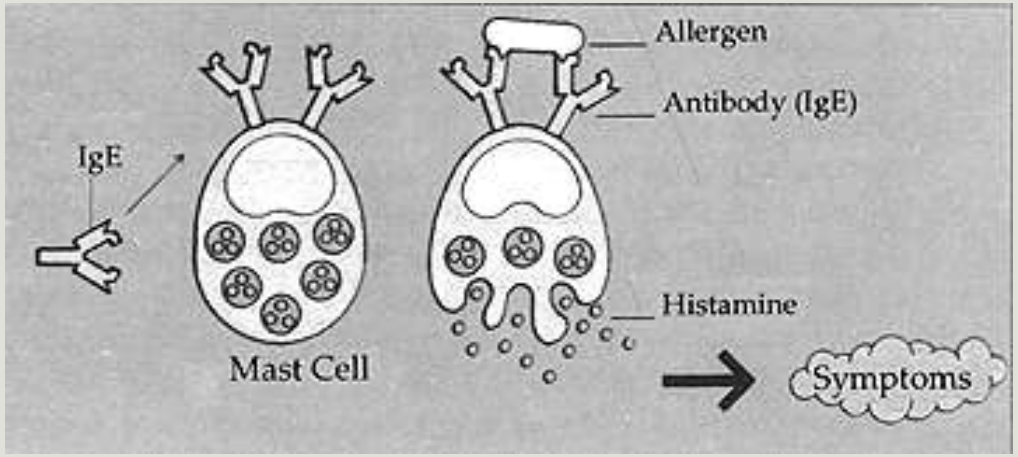
Patterns of Clinical Reactivity to Foods in AD

90% of cases of food allergy in eczema patients=IgE-mediated

- i.e. by far the majority of food allergies will be picked up during SPT/sIgE testing



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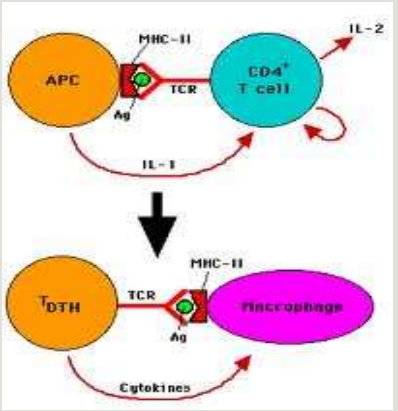
Patterns of Clinical Reactivity to Foods in AD

10% of food reactions in eczema patients are non-IgE mediated:

- No food-specific IgE
- Food specific T cells



- Generally more difficult to diagnose
- More commonly with wheat as compared with cow's milk/egg

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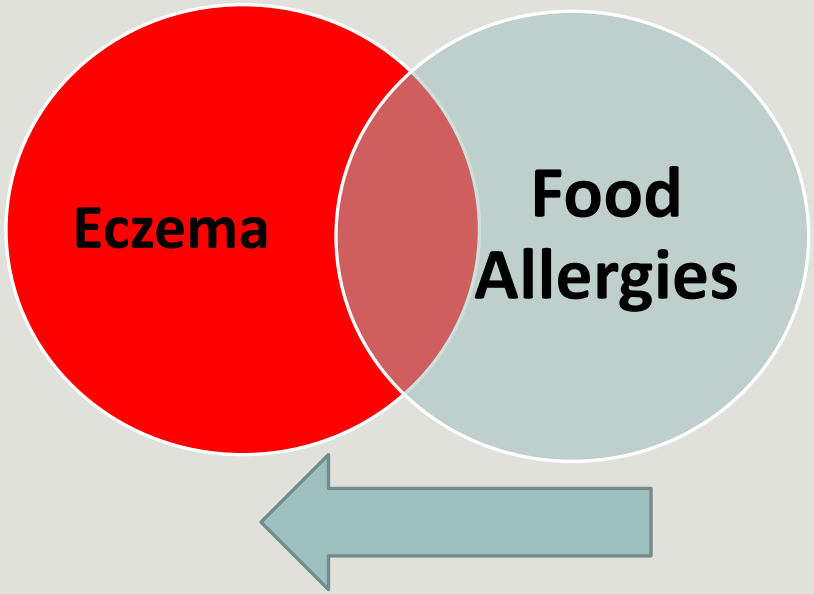
2. The role of food allergies in the pathogenesis of AD



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Manifestations of food allergies

FOOD ALLERGY

IgE mediated

- General
- Anaphylaxis
- Cross reactivity syndromes

Mixed IgE and non-IgE mediated

- Eosinophilic oesophagitis
- Eosinophilic gastroenteritis
- Dietary protein enteropathy
- Asthma
- Atopic eczema

Non-IgE mediated

- Allergic proctocolitis
- FPIES
- Coeliac disease
- Contact dermatitis
- Heiner's syndrome
- GI motility disorders

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1. Association between food allergy and eczema

Debate 3: Eczema is usually caused by an allergy to food(s)

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Answer: Myth

- Evidence of **role of food allergies in the pathogenesis of AD** in a subset of patients but not more than 20%
- More important in children
- Increasing evidence of the **role of eczema in food allergy pathogenesis**

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The role of food allergies in the pathogenesis of AD

- Relationship between AD and food allergy is complex and not always causal
- Evidence of a role of food allergy in eczema causation:
  - Clinical
  - Histological

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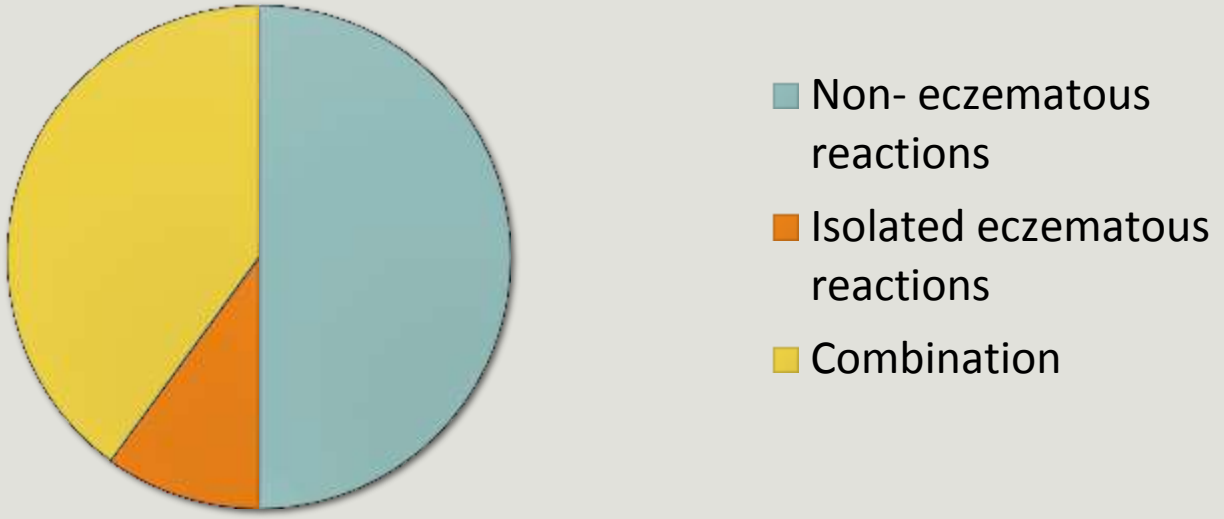
Clinical evidence of causality

1. At least 50% of the children with AD who react to certain foods will react with a worsening of AD.



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Clinical evidence of causality

2. Oral food challenges can reproduce skin

   symptoms in some cases.

3. Appropriate dietary elimination results in improvement of AD in selected patients

4. The presence of IgE to food and aeroallergens is associated with earlier onset and more severe AD

5. The greater the level of IgE and the earlier it is elevated, the more severe and persistent AD is likely to be

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Clinical evidence of causality

Wolkerstorfer A, Wahn U, Kjellman NI et al. Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETAC study group. *Clin Exp Allergy* 2002; 32:70-73

Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. *Pediatr Allergy Immunol* 2004;15: 421-427

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Histological evidence of causality

- The histology of lesions in *chronic* eczema suggests classical type 4 cell mediated immunity
- Patterns of cytokine expression found on lymphocytes infiltrating *acute* AD lesions are predominantly of the Th2 type →role of the IgE antibody+ TH2 cytokine milieu

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The role of food allergies in the pathogenesis of AD

- Eczema can be exacerbated in 2 ways:
  - either **directly** with development of new eczematous reactions which tend to occur as late reactions, or
  - **indirectly** with early morbilliform rash/pruritis leading to itch -scratch cycle and secondary exacerbation of AD.

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Itch-scratch cycle

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Summary: The role of food allergies in the pathogenesis of AD

- Food allergy plays a role in causation in 15-20% of cases of atopic dermatitis

- NICE and other guidelines for eczema: moderate to severe eczema < 6 months age : trial of extensively hydrolysed formula (or maternal elimination of CMP)

- In most of these cases eczema follows an acute reaction and can be screened for by tests for IgE-mediated food allergy

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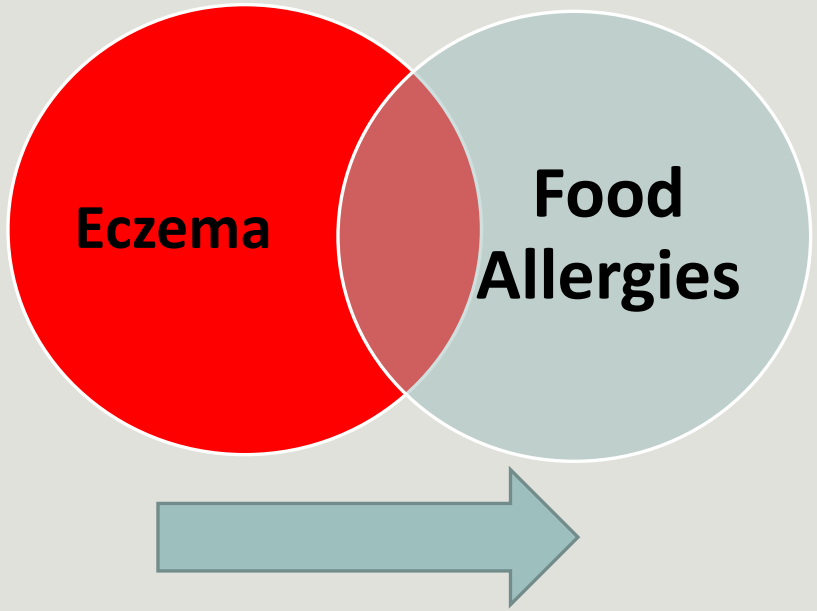
3. The Role of AD in the Pathogenesis of Food Allergy



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1. Association between food allergy and eczema

Debate 4: There is increasing evidence that the skin barrier defect in eczema leads to allergies

Myth or Reality??

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Answer: Reality!

- Role of modified epithelial barrier function increasingly recognised in early phase of allergic diseases

- Skin barrier defect →earlier sensitisation to food allergens by non-dietary (epicutaneous) route →evasion of oral tolerance →development of food allergies

- Atopic dermatitis is the main risk factor for food sensitisation in exclusively breastfed infants, and the risk increases as disease severity increases.

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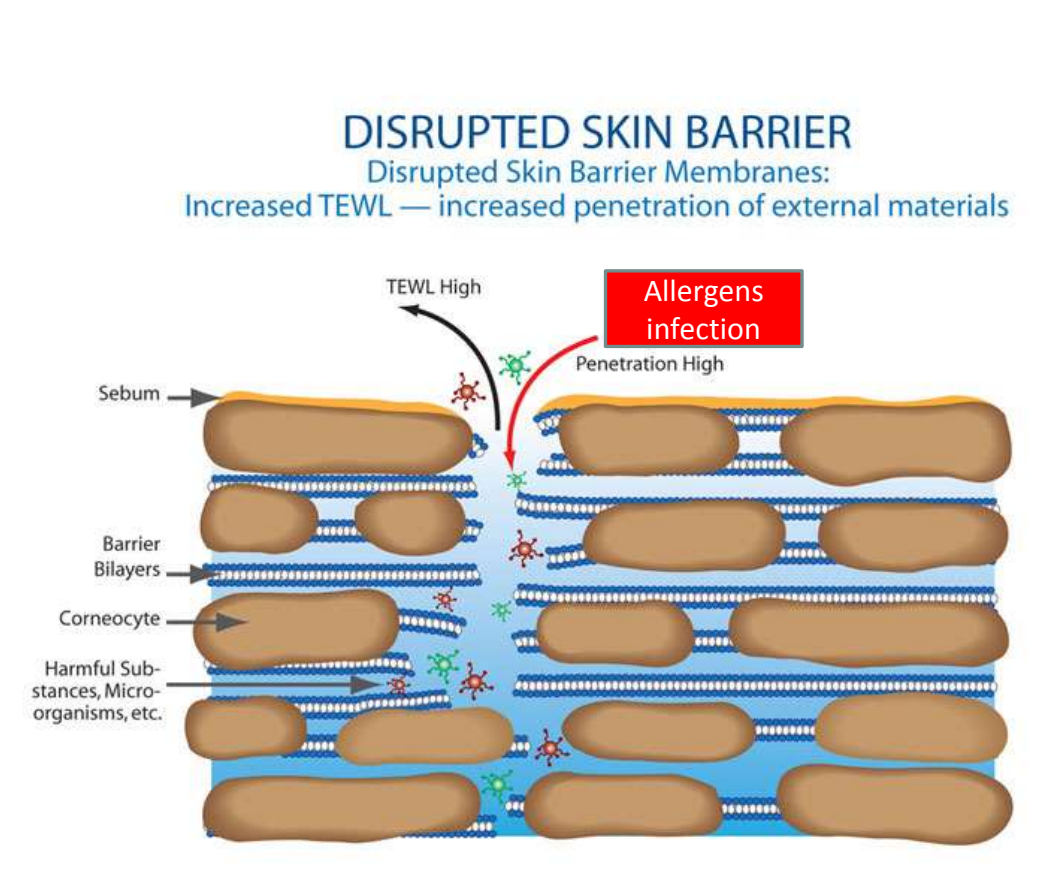
Disrupted skin barrier and penetration of allergens



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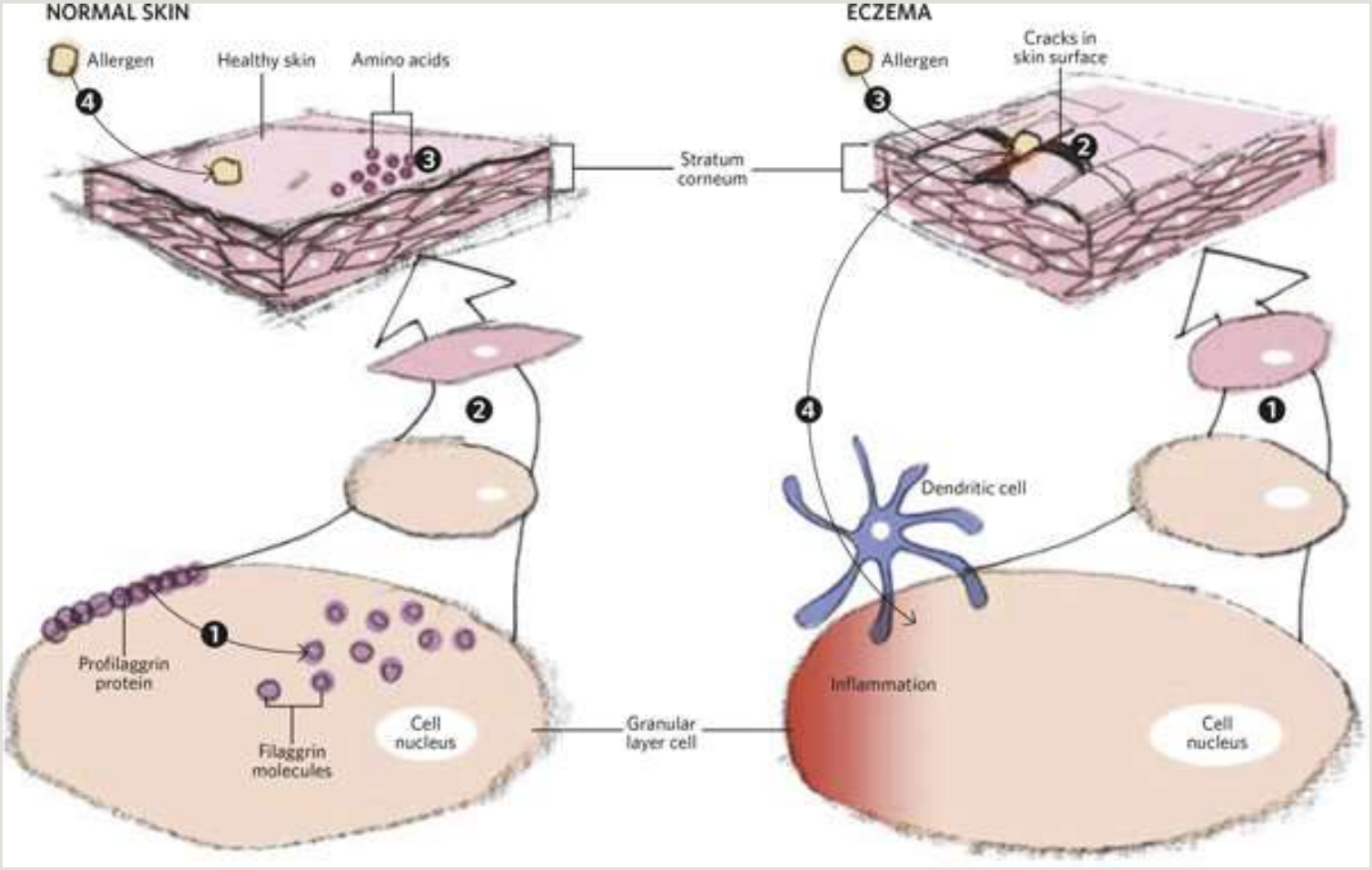
The Role of AD in the Pathogenesis of Food Allergy

- Filaggrin gene defects or inhibited filaggrin expression → risk of severe eczema + food sensitisation

Filaggrin and skin barrier



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The Role of AD in the Pathogenesis of Food Allergy

Venkataraman D, Soto-Ramirez N, Kurukulaaratchy RJ et al. Filaggrin loss of function mutations are associated with food allergy in childhood and adolescence. J Allergy Clin Immunol **2014**; 28: epublished ahead of print

Flohr C, Perkin M, Logan K et al. Atopic dermatitis and disease severity are the main risk factors for food sensitisation in exclusively breastfed infants. J Invest Dermatol **2014**;134:345-50

Noti M, Kim BS, Siracusa MC et al. Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin – basophil axis. J Allergy Clin Immunol **2014**; 133 1390-9

Thawer-Esmail et al. South African amaXhosa patients with AD have decreased levels of filaggrin breakdown products but no loss-of-function mutations. **JACI 2014**; 133: 280-2

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The Role of AD in the Pathogenesis of Food Allergy

- **Early onset eczema** and **more severe** eczema→ significantly greater risk of acquiring food allergies

The Role of AD in the Pathogenesis of Food Allergy

South African Eczema study:

Onset < 6 months: 66% had one/more food allergy

Onset 6-12 months: 28%

Onset > 12 months: 17%

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Figure 3 - Influence of Age of Onset of Eczema on Sensitisation and Allergy Rates in South African food allergy-eczema study [32]

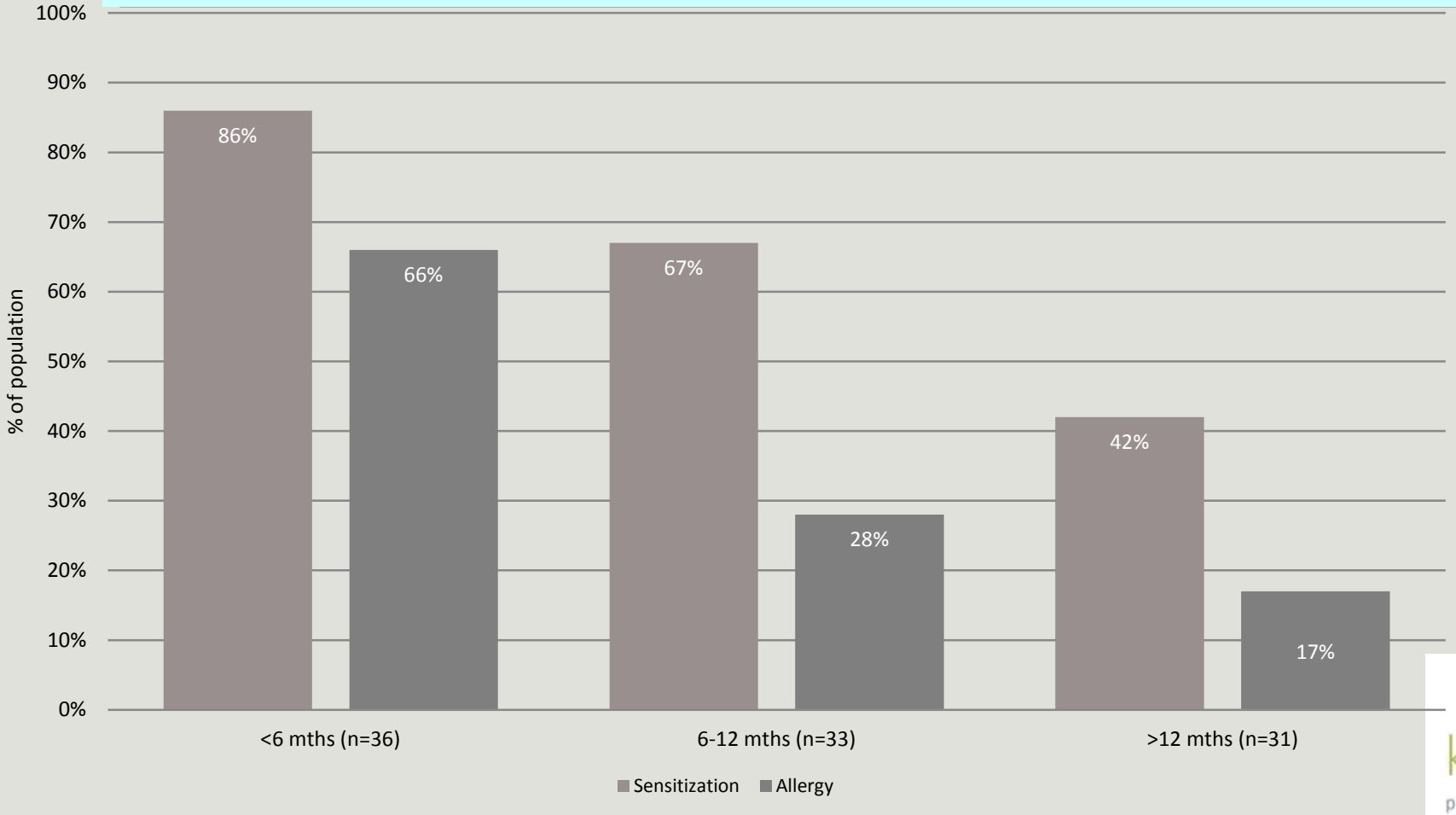

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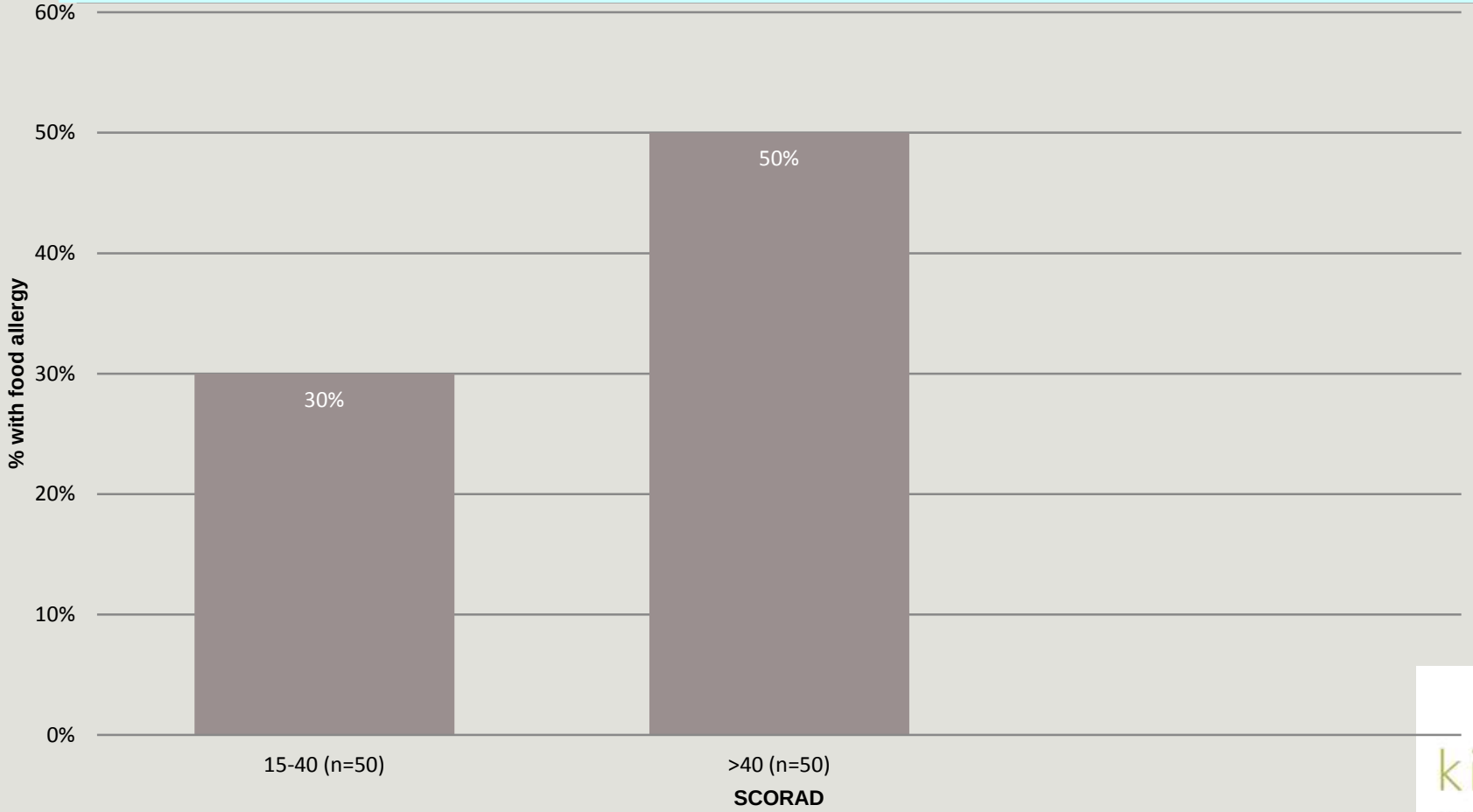
Figure 4: Influence of eczema severity on food allergy prevalence in South African food allergy-eczema study



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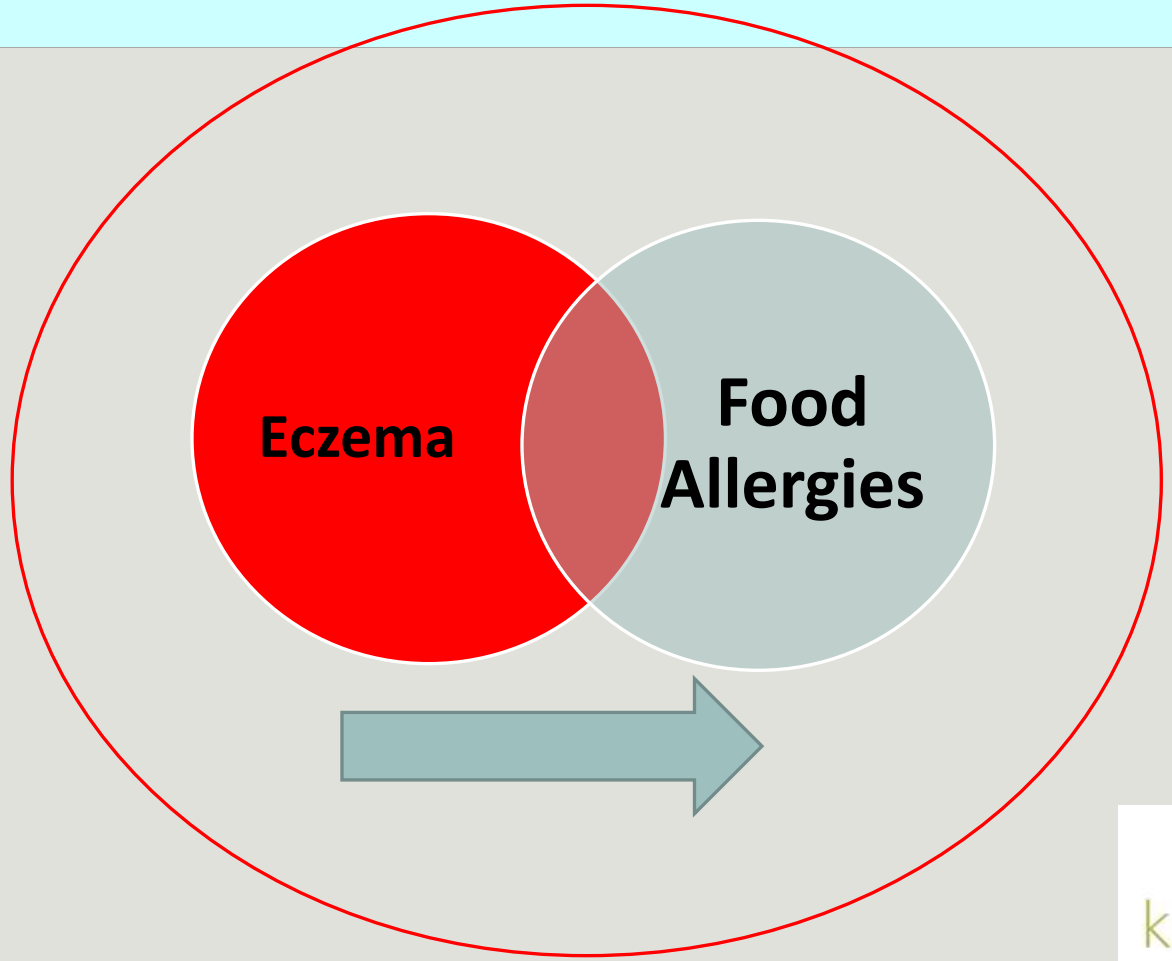
“It all begins with the skin”



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The Role of AD in the Pathogenesis of Food Allergy

Excellent skin care and maintaining a good skin barrier is probably the most effective allergy prevention strategy

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The Role of AD in the Pathogenesis of Food Allergy

PROTECTIVE

2 studies of early emollient use vs no emollients (n=124, n=116):
40-50% reduction in AD at 6 months

Simpson EL, et al. J Allergy Clin Immunol 2014; 134: 818-23

Horimukai K, et al. J Allergy Clin Immunol 2014; 134: 824-30

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Atopic Dermatitis and Food Allergy

Topics to be Discussed:

1.Association between food allergies and AD ("3–way process")

2.Diagnosis of food allergy in AD

3.Elimination diets

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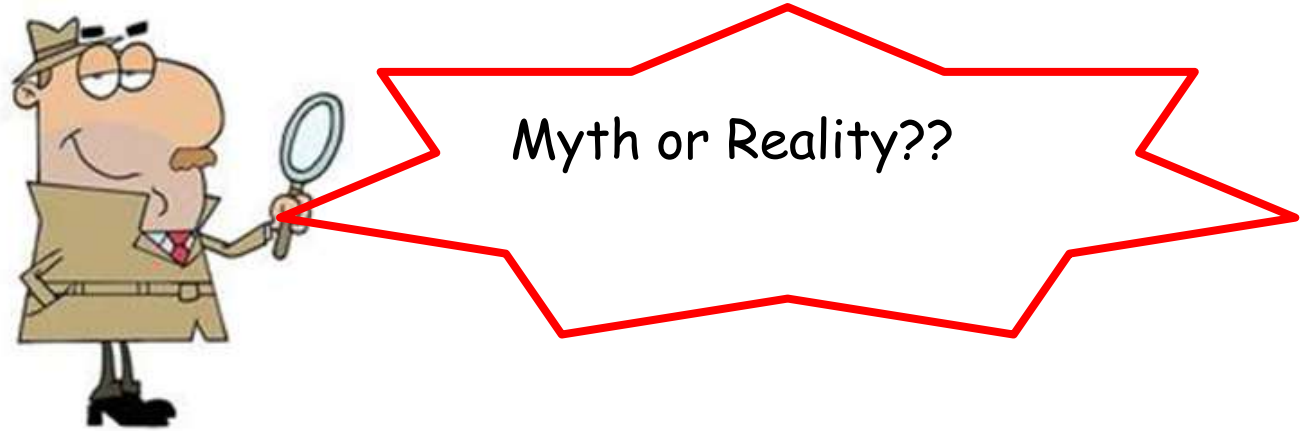
1. Association between food allergy and eczema

Debate 5: All patients with eczema need food allergy screening



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Answer: Myth

- Basically if a child has tolerated food without any obvious reactions, keep that food in the diet
- There are specific indications for food allergy screening:

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Diagnosis of Food Allergy in Eczema Patients

Consider Evaluation for Food Allergy:

1. Cases of moderate to severe AD in an infant/child, especially if not responding to standard treatment
2. Early onset eczema < 6 months
3. History of acute reactions to food
4. Convincing history of AD exacerbated by foods
5. In severe AD in teens/adults

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Diagnosis of Food Allergy in Eczema Patients

Aims of food allergy evaluation in AD:

1. Proving that food allergies result in IgE-mediated reactions (non-eczematous type reactions) which may be of immediate danger to the patient

versus

2 Proving that food allergies result in delayed eczematous reaction that directly exacerbates AD.

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Diagnosis of Food Allergy in Eczema Patients

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Proving that food allergies result in non-eczematous type reaction

IgE-mediated reactions in > 90%

- History
- SPT
- Specific IgE
- (Atopy Patch Test)
- Food Challenge

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Proving that food allergies result in non-eczematous type reaction

SPT:

- Negative predictive value > 95%
- Positive predictive Value 30-50%
- Results do not correlate with loss of clinical reactivity

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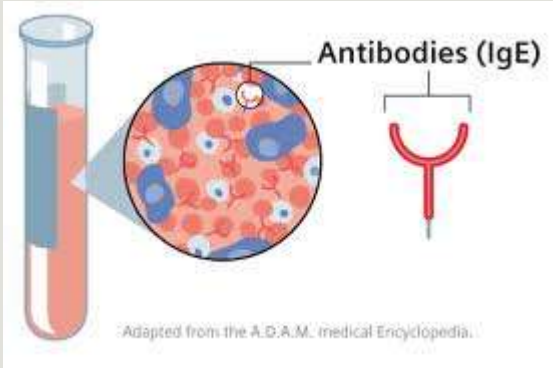
Proving that food allergies result in non-eczematous type reaction

Specific IgE:

- Negative predictive value 75%
- Positive predictive value 20-60%



APT:

- May reflect delayed phase clinical reactions
- Thus far limited additional value

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Proving that food allergies result in non-eczematous type reaction

Food Challenge:

- Gold standard-other tests have poor PPV
- If any discrepency between history and SPT/sIgE
- E.g. sensitised but “not sure if reacts”, “doesn’t like”, “told not to eat”, “never eaten it”, “used to react”
- DBPCFC vs open
- Ideally observe 6 hours after max dose
- Follow up 24 hours later for worsening of eczema

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Proving that Food allergy results in delayed eczematous reaction

Scenarios:

- Sensitised (especially high values/monosensitised) but clear tolerance for immediate non-eczematous reactions
- No sensitisation but high suspicion eczema exacerbation

Elimination-reintroduction diet

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Proving that Food allergy results in delayed eczematous reaction

Principles of elimination-reintroduction:

- Eliminate food (s)from diet for 4-6 weeks under dietetic advice
- Perform standard OFC with a single food in incremental doses. If there is no immediate reaction, then give the food for 3 days in a row and monitor eczema scores daily.
- Challenge with new foods every 4-7 days (or longer of skin needs to recover from previous challenge.)

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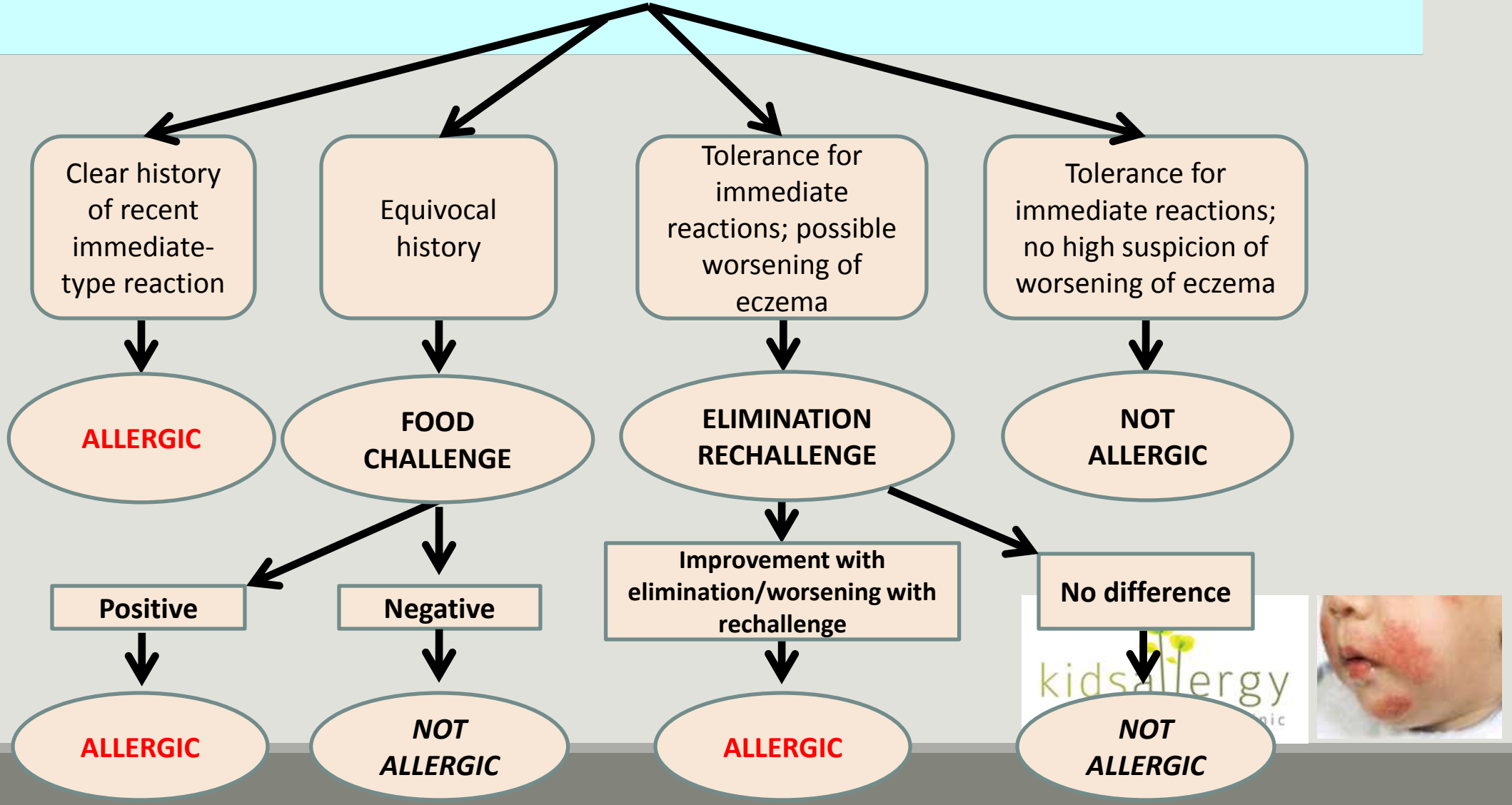
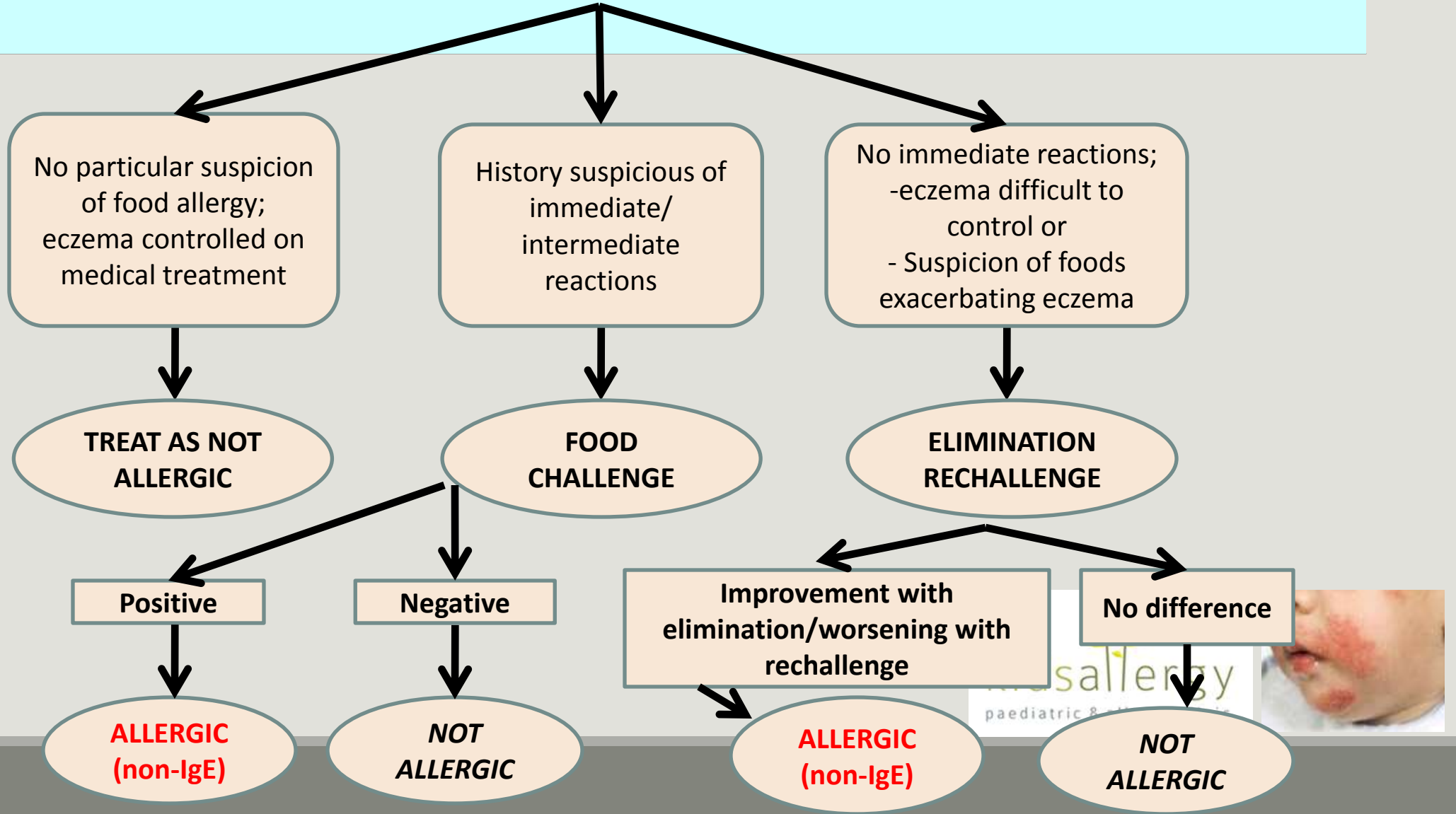
Atopic Dermatitis and Positive SPT/sIgE to Food(s)



Atopic Dermatitis and Not Sensitised to Food(s)



Diagnosis of food allergies in eczema patients

Werfel T, Ballmer-Weber B, Eigenmann P et al. Eczematous reactions to food in atopic dermatitis: position paper of the EAACI and GA2LEN. *Allergy* 2007; 62: 723-728

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Atopic Dermatitis and Food Allergy

Topics to be Discussed:

1. Association between food allergies and AD ("3–way process")
2. Diagnosis of food allergy in AD
3. Elimination diets

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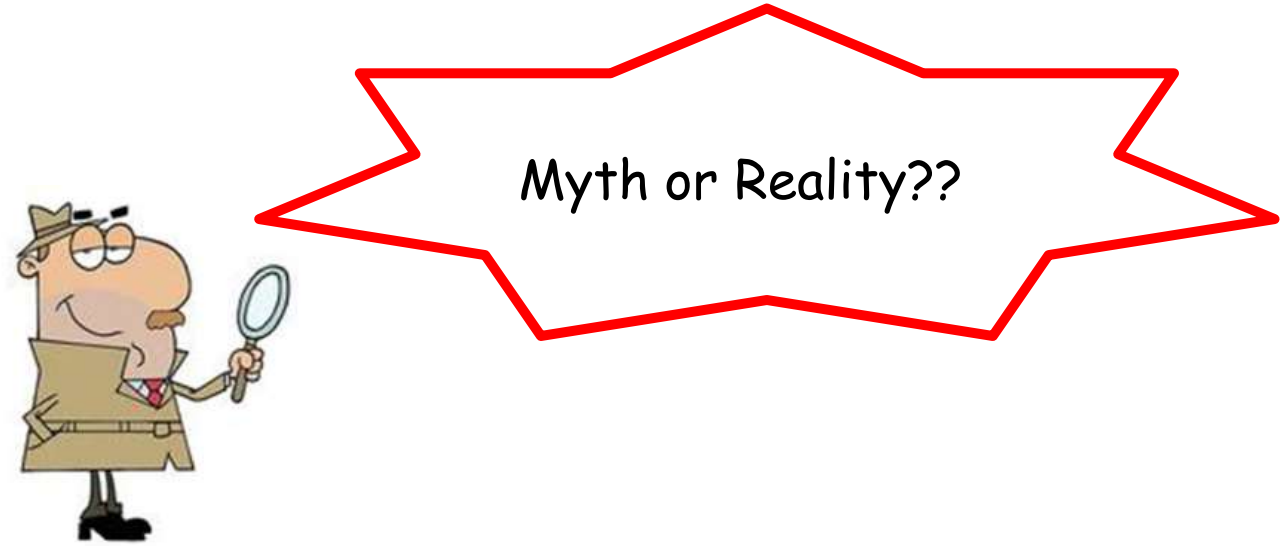
Elimination Diets

Debate 6: Patients with severe eczema need a trial of an empiric exclusion diet



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Answer: Myth

- Notion of multiple “empiric” food exclusions in the management of eczema is out-dated and carries many disadvantages

- As a rule of thumb we try to keep those foods in the diet which are not obviously causing an immediate flare

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Elimination Diets

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Elimination Diets

- No good quality evidence to support use of blanket exclusion diets

  (Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for improving established atopic eczema in adults and children: systemic review. *Allergy* 2009; 64: 258-264)

- Evidence for targeted food avoidance resulting in improvement of skin symptoms

- ie Advise elimination of those foods which have been proven to cause symptoms (eczematous or non-eczematous)

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Elimination Diets

- Should always be supervised by a dietician to ensure proper elimination and nutritional adequacy

- Should always be combined with atopic skin care and pharmacological therapy when needed

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Elimination diets

- 1/3 of children outgrow reactivity after 1-2 years of allergen avoidance (Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115: 23-27)

- Elimination should be continued for 12-24 months in early childhood and then clinical relevance reviewed

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Elimination Diets: Practice Points

- No role for “blanket” elimination of foods in eczema
- Many children with eczema have positive allergy tests but will tolerate the food
- Food allergy needs to be proven before recommending specific elimination diets!
- We can actually “create” allergies by eliminating foods unnecessarily

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Elimination Diets

- What about the introduction of solids in young children with eczema?
- What is the best time to minimise food allergies?

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Elimination Diets/solids introduction

Debate 7: Patients with eczema should delay their introduction of allergenic solids eg egg and nuts

Myth or Reality??

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Answer: Myth

- Delayed introduction of solids > 6 months does not seem to be beneficial
- Window for optimal introduction of solids seems to be 4-6 months
- Studies on highly allergenic foods in healthy and “at risk” patients are ongoing and results point to earlier introduction!

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study	population	intervention	outcome
EAT (UK)	General population	Exclusive breastfeeding till 3 months then sequential intro of allergenic foods v exclusive BF 6 months	IgE mediated food allergy 1-3 years
LEAP (UK)	High risk infant (eczema/egg allergy)	Peanut consumption from 4-10 months v peanut avoidance	Peanut allergy at 5 years REDUCED with EARLY INTRO
HEAP (Germany)	General population	Hen's egg powder introduction between 4-6 months v avoidance	Egg allergy
PEAAD (Germany)	High risk	Peanut snack 3x per week from 5-30 months v avoidance	Peanut allergy after 1 year
STAR (Australia)	High risk infants (eczema)	Daily intro of egg powder between 4-8 months v avoidance	IgE-egg allergy at 12 months
STEP (Australia)	Intermediate risk (maternal but not infant allergy)	Daily egg powder between 4-8 months v avoidance	Egg allergy at 1 year
BEAT (Australia)	Intermediate risk	Egg protein from 4-6 months v avoidance	Egg sensitisation

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Summary: Eczema and Food Allergy: Pearls and Pitfalls

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Summary points

- 30-40% of children with AD have co-existing food allergy, mostly IgE-mediated
- In approx half of those who react to food, there will be a flare-up of eczema, usually in combination with other symptoms, sometimes in isolation
- i.e in 15-20% of children with AD, food allergies play a role in eczema pathogenesis

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Summary points

- Food allergies should be actively excluded in moderate to severe eczema/ where there is high suspicion
- History, SPT, sIgE are sensitive but not specific:
- Crucial role for food challenges to confirm/refute allergies
- High suspicion of food allergies exacerbating eczema but no immediate symptoms/not sensitised: elimination-rechallenge diets

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Summary Points

- Early diagnosis of food allergies- better management
- Blanket elimination diets ineffective and potentially dangerous
- Targeted elimination diets+ atopic skin care=best management
- We like to keep as many foods in the diet as possible!

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Summary Points

- Eczema and food allergies closely associated with development of respiratory allergies

- “Integrated management” of atopic patient as treatment of one atopic condition can lead to improvement in another

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THANK YOU!

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Cases

Case 1:

4 month old girl referred with severe eczema

Breastfed for a month, mild colic

At 1 month: Nan HA ⟹ ++crampy, dry skin

Novolac AC, Nan Pellargon ⟹ skin worse

Isomil ⟹ severe flare of skin

Novolac Allernova ⟹ much better but diarrhoea and battled to feed

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Case 1 ctd

Then: goat's milk ⟹ extreme flare of eczema

Advised to go on Neocate ⟹ gut better, eczema settling but still active

On examination, thriving, diffuse moderate eczema especially flexures and face

SPT: negative to cow's milk, egg, soya, wheat, fish, peanut, maize

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Case 1:

Conclusion?

Food allergy causing (at least partly) AD

Lucky not to have obvious related IgE mediated allergies

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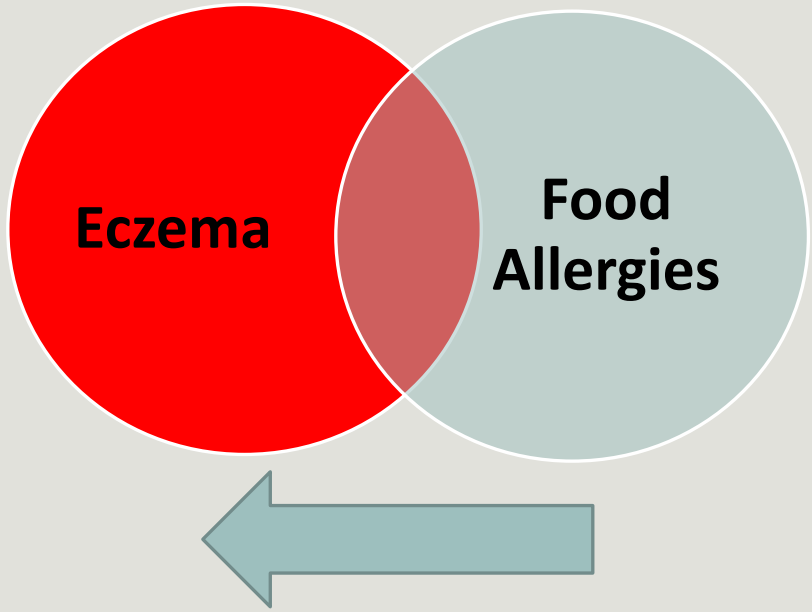
Association between food allergies and eczema:

2. The role of food allergies in the pathogenesis of eczema



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Case 2:

7 month old boy with eczema from 4 months whilst still breastfeeding

History of yoghurt ingestion at 6 months: peri-oral hives and swelling of eye

On examination moderate diffuse AD

Treated with emollients and topical steroids for a week and cleared well, with no changes in maternal diet

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Case 2

SPT:

Cow’s milk extract 4 mm

Fresh cow’s milk 7.5 mm

Egg white extract 6 mm

Egg fresh 8 mm

Soya 2 mm

Peanut 3.5 mm

Wheat 0

Fish 0

Case 2

Confirmed cow's milk protein allergy

Highly likely egg allergy

Possible peanut allergy

Unlikely wheat, fish, soya (challenge passed)

Baked egg and milk challenges fine

Continue to monitor SPT to milk, egg and peanut

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Case 2

Conclusion?

AD as cause of multiple food allergies because of broken skin barrier and likely transepidermal sensitisation

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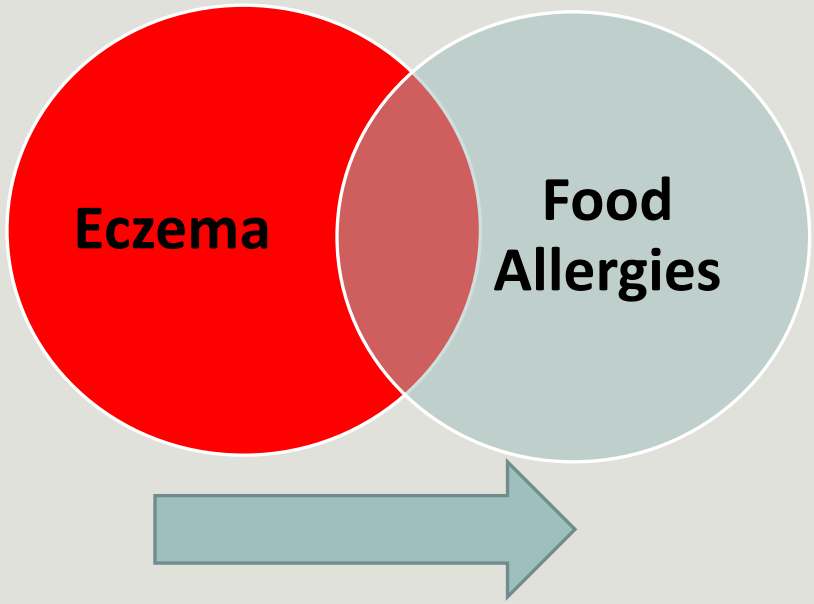
Association between food allergies and eczema:

3. The role of eczema in the pathogenesis of food allergies



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THANK YOU!

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