Non-IgE mediated mechanisms of food allergy

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Disclosure

- PI in DBV SMILEE trial (protect time to conduct research)
- FARE Co-director of the FARE CHOP Center (protect time to conduct research)
- Sanofi consultants
- AAAAI-BCI secretary -volunteer
- EAACI-EoE IG-Board-volunteer
Adverse Reactions to Foods

Toxic reactions
- Food poisoning
- Heavy metal poisoning
- Sgombroid fish poisoning
- Caffeine
- Alcohol
- Histamine toxicity

Nontoxic reactions
- Lactase deficiency
- Galactosemia
- Pancreatic insufficiency
- Gallbladder / liver disease
- Hiatal hernia
- Gustatory rhinitis
- Anorexia nervosa
- Anxiety

Food intolerance
Immuno mediated
- Food allergy

Reproducible immune response to food allergen
Food Antigen Type 1 access to the mucosal immune system

0.75g/kg protein

Destruction of immunogenic epitopes by gastric acidity, pancreatic and luminal digestive enzymes

99%

IMMUNOLOGICAL IGNORANCE

1%

IMMUNOLOGICAL ACTIVE

Chehade M et al JACI 2005,
Heyman M et al Proc Nutr Soc 2001
Epithelial barrier

Epithelial cells are held together and communicate through junctions formed by transmembrane proteins
- **tight junction** (claudins and tight junction-associated MARVEL proteins (TAMPs));
- **adherens junction** (E-cadherin)
- **desmosome** (desmogelin and desmocollin)

They are connected to the actin cytoskeleton via cytosolic proteins (ZO1, catenins and desmoplakin).
Tight and adherens junctions interact with the actin cytoskeleton, and desmosomes connect to intermediate filaments.
Oral tolerance: role of T cells
Oral tolerance: role of T cells activation
Oral tolerance: Treg in the gut

Bacchetta R et al JACI 2007  Chehade M et al JACI 2005
Oral tolerance: role of T cells

b. High-dose Tolerance
- Anergy
- Peptide-MHC
- TCR
- CD95
- CD95L
- Deletion
- Effector T cell
- Ag-presenting cell

C. Low-dose Tolerance
- Suppression
- TGF-β
- TGF-βR
- IL-10R
- IL-10

a. Immunity
- Effector T cell
- Co-stimulatory molecules
- TCR
- Peptide-MHC
- CD28
- CD80/86
- Cytokine
- Ag-presenting cell
- B cell
- IgA

**CD4^+** cells
- **Th3** cells → suppression mainly through secreted TGF-β
- **Tr1** cells → suppression mainly through secreted IL-10
- **CD4^+CD25^+** cells → suppression possibly through surface-bound TGF-β
- **CD8^+** cells
- Natural killer T cells

Chehade M et al JACI 2005
Non-IgE mediated food allergy

- Celiac DELAYED REACTION-CHRONIC INFLAMMATION Th1 inflammation
- Eosinophilic Esophagitis (DELAYED REACTION-CHRONIC INFLAMMATION) Th2 inflammation
- FPIES (DELAYED REACTION-ACUTE INFLAMMATION)

Immediate

Late Phase

0 30 60 6 8 10 12

Minutes Hours

Chemokine cytokines

IgG

IgA

Masty

low affinity

B cell

T cell

Epithelial cell

EOS

APC
Celiac disease (CD) : Definition

• Celiac disease is a chronic, small-intestinal immune mediated enteropathy initiated by exposure to dietary gluten in genetically predisposed individuals and characterized by specific autoantibodies against tissue transglutaminase 2 (anti-tTG2), endomysium, and/or deamidated gliadin peptide

• The genotype HLA-DQ2 or HLA-DQ8, which is required for the development of celiac disease. Although up to 40% of the population carries, only 2% to 3% of HLA-DQ2 or HLA-DQ8 carriers subsequently develop celiac disease

• CD can develop at any age and can affect almost any race.

• Prevalence is 1% with regional differences (0-5.6%)

• Some patients such as patients with IgA deficiency, Autoimmune diseases of Thyroid and or Liver, Down Syndrome, Turner Syndrome, IgA nephropathy, Juvenile arthritis, William Syndrome are at higher risk (1.5-13.5%)

Di Sabatino A, 2009
Leonard MM et al, 2017
Celiac disease (CD) : Manifestation

Intestinal Manifestations (more common in children)
- Children < 3 years: diarrhea, loss of appetite, abdominal distention, and poor growth.
- Children 3 > years or adults: diarrhea, bloating, constipation, abdominal pain, or weight loss.

Extraintestinal Manifestations (due to inflammation, nutrient deficiencies)
- Poor growth, short stature, or delayed puberty (pre puberty)
- Dental enamel defects are (children < 7 years).
- Iron-deficiency anemia (in 32% of adults and 9% of children)
- An increased risk of miscarriage (woman)
- Skin manifestation: dermatitis herpetiformis, urticaria, psoriasis, and dry skin
- Neurological manifestation or psychiatric manifestations or both (up to 22% of patients with CD)
- Peripheral neuropathy is frequent, compared with healthy controls (nutritional deficit or inflammation)

Refractory celiac disease is defined as persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet for at least 6 - 12 months. Uncommon and severe complications such as ulcerative jejunitis and enteropathy-associated T-cell lymphoma

Silent coeliac disease
- Patients who do not complain of any symptoms and do not seek medical advice
- Most of these patients are relatives of patients with known coeliac disease or members of the general population found to be positive at the search for antiendomysial antibodies or hTTG antibodies

Minor coeliac disease
- Patients complaining of trivial, transient, or apparently unrelated symptoms (dyspepsia, abdominal discomfort and bloating, mild or occasional altered bowels habit without malabsorption mimicking irritable bowel syndrome, unexplained anaemia, isolated fatigue, cryptic hypertransaminasaemia, infertility, peripheral and central neurologic disorders, osteoporosis, short stature, dental enamel defects, dermatitis herpetiformis), or of isolated symptoms of autoimmune diseases often reported in association with coeliac disease
- Most of these patients are biopsied after positive search of antiendomysial antibodies or hTTG antibodies

Major coeliac disease
- Patients complaining of frank malabsorption symptoms (diarrhoea which is often nocturnal and with incontinence, steatorrhoea suggested by loose discoloured, greasy, and frothy stools that are difficult to flush away, weight loss and other features of malnutrition, cramps, tetany, and peripheral oedema due to electrolyte and albumin depletion); symptoms of other autoimmune diseases may be associated
- Most of these patients are biopsied only on the basis of symptoms

Di Sabatino A, 2009
Celiac disease (CD) : Diagnosis

Serology: anti-tissue transglutaminase (tTG-IgA), anti-endomysial (EMA-IgA), anti-Deamidated gliadin peptides (DGP-IgG)

<table>
<thead>
<tr>
<th>Serologic Study</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>Application in Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA tTG</td>
<td>73.9-100</td>
<td>77.8-100</td>
<td>First-line testing to screen for celiac disease(^b)</td>
</tr>
<tr>
<td>IgG DGP</td>
<td>80.1-96.9</td>
<td>86.0-96.9</td>
<td>First-line testing for celiac disease in patients with IgA deficiency</td>
</tr>
<tr>
<td>IgA EMA</td>
<td>82.6-100</td>
<td>94.7-100</td>
<td>Second-line confirmatory test to screen for celiac disease</td>
</tr>
<tr>
<td>IgG tTG</td>
<td>12.6-99.3</td>
<td>86.3-100</td>
<td>Not recommended for routine use because of poor sensitivity compared with IgG DGP</td>
</tr>
<tr>
<td>IgA DGP</td>
<td>80.7-95.1</td>
<td>86.3-93.1</td>
<td>Not recommended for routine use because of poor sensitivity and specificity compared with IgA tTG and IgA EMA</td>
</tr>
</tbody>
</table>

Biopsy (Duodenum)

- increased number of intraepithelial lymphocytes (>25 per 100 enterocytes)
- elongation of the crypts
- partial to total villous atrophy

Leonard MM et al, 2017
Celiac Disease: Th1 mediated autoimmune

Pathogenesis of celiac disease

- Genetic factors (HLA-DQ2/8)
- Autoantibodies (TTG, EMA)
- Intraepithelial lymphocytosis + Villous atrophy
- Gastrointestinal and systemic manifestations

Gluten

- Innate response
- Lamina propria Adaptive response
- Environmental factors
Celiac Disease: Gluten

Bread wheat (Triticum aestivum) is a globally important food crop. Accounts for 20% of the calories consumed by humans. It is an important source of protein, vitamins, and minerals. Storage proteins in wheat are collectively referred to as gluten, give viscosity to dough.

Gluten is actually an aggregate formed from two major types of protein:

**Gliadin** (soluble in 70-90% aqueous alcohol) – prolamin-flow of dough

**Glutenin** (insoluble in alcohol)-glutelins-elasticity

[Plant proteins are categorized in: albumins, globulins, prolamins, and glutelins]. Glutenin is composed of macropolymers, huge polymers of high- and low-molecular weight subunits crosslinked with disulfide bonds. These macropolymers intermingle randomly with individual particles of gliadins to form the aggregate, which is held together with non-covalent interactions.

![Diagram of wheat gluten proteins]

Urade R, 2018
Gluten proteins show extensive polymorphism. The number of genes encoding gluten proteins increased by duplication and translocation events. The amino acid sequences of these additional genes have altered due to substitution, deletion, and insertion events during their evolution, apparently in the absence of strong selection pressure. These changes have resulted in complex mixtures of homologous proteins that vary widely in molecular mass and charge. This variation has made the isolation and study of these proteins difficult.

Wheat cells have genomes A, B, and D. γ- and ω-gliadins = Gli-A1, Gli-B1, and Gli-D1, located on the short arms of the group 1 chromosomes. γ-gliadins 15–40 copies of genes and ω-gliadins 15–18 copies. The α- and β-gliadins = Gli-A2, Gli-B2, and Gli-D2 on the short arms of the group 2 chromosomes. 25 to 150 copies of the genes (similar so now only α-gliadin).
Gliadins are soluble in pure water when they are at concentrations of less than 10% by weight (wt%). At these concentrations, they yield a transparent solution. When they are in solutions of greater than approximately 15 wt%, gliadins form gel-like hydrated solids. These will not flow even if the container is inverted at 40 wt% or more.

- 0.025-0.5 wt% (a)
- 0.5–10 wt% (b)
- 15–20 wt% (c)
- 30–40 wt% (d)
- 50 wt%, (e)

Urade R, 2018
# Celiac Disease: Gluten proteins

<table>
<thead>
<tr>
<th></th>
<th>α-gliadin (30-34kD)</th>
<th>γ-gliadin (26-36kD)</th>
<th>ω-gliadin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIG (signal peptide)</td>
<td>20 AA</td>
<td>19 AA</td>
<td>19 AA</td>
</tr>
<tr>
<td>N (N-terminal region)</td>
<td>5 residues</td>
<td>12 residues</td>
<td>11 residues</td>
</tr>
<tr>
<td>R (repetitive domain)</td>
<td>110-130 residues</td>
<td>80-160 residues</td>
<td>238 residues</td>
</tr>
<tr>
<td></td>
<td>P(F/Y)PQ3–5.</td>
<td>PFPQQo–1(PQQ)1–2</td>
<td></td>
</tr>
<tr>
<td>C1 (cysteine rich)</td>
<td>4 cysteine</td>
<td>6 cysteine</td>
<td>No cysteines</td>
</tr>
<tr>
<td>CII (glutamine rich)</td>
<td>Glutamine residues</td>
<td>Glutamine res</td>
<td></td>
</tr>
<tr>
<td>CIII</td>
<td>35-39 residues+2</td>
<td>41-43 residues+2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cysteines</td>
<td>cysteines</td>
<td></td>
</tr>
<tr>
<td>Black boxes</td>
<td>2 polyglutamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>peptides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Urade R, 2018
Celiac Disease: Why you develop it?

Genetic factors

- basis of familial aggregation
- a concordance rate of about 85% between monozygotic twins
- COELIAC1 6p21-HLA-DQ (strong but mono-zygotes twins stronger than HLA identical)
  - DQ2 (alleles DQA1*05/DQB1*02)
  - DQ8 (alleles DQA1*03/DQB1*0302)
  - DQ2/-DQ8- (DQA1*05 or DQB1*02)
- COELIAC2 (5q31–33) Cytokines
- COELIAC3 (2q33) CTLA4
- COELIAC4 (19p13.1) myosin IXB (alters epithelial actin remodeling)
- GWAS- IL- 2 and IL- 21 (4q27)

Di Sabatino A, 2009
Celiac Disease: Pathogenesis

α2-gliadin-33mer

Di Sabatino A, 2009
Celiac Disease: Pathogenesis

Leonard MM et al, 2017
Celiac Disease: immunogenic Peptides

33-mer LQLQFPQPQPLYPQPQQLPYPQPQQLPYPQPQPF
(residues 57 to 89) it harbors six partly overlapping DQ2-restricted epitopes

<table>
<thead>
<tr>
<th>DQ2.5-restricted epitopes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ2.5-glia-α1a</td>
<td>PFPQPELPY</td>
</tr>
<tr>
<td>DQ2.5-glia-α1b</td>
<td>PYQPPELPY</td>
</tr>
<tr>
<td>DQ2.5-glia-α2</td>
<td>PQPELPYPQ</td>
</tr>
<tr>
<td>DQ2.5-glia-α3</td>
<td>FRPEQYPQP</td>
</tr>
<tr>
<td>DQ2.5-glia-γ1</td>
<td>PQQSFPFEQ</td>
</tr>
<tr>
<td>DQ2.5-glia-γ2</td>
<td>IQPEQPAQL</td>
</tr>
<tr>
<td>DQ2.5-glia-γ3</td>
<td>QQPEQYPQP</td>
</tr>
<tr>
<td>DQ2.5-glia-γ4a</td>
<td>SQPEQEPFP</td>
</tr>
<tr>
<td>DQ2.5-glia-γ4b</td>
<td>PQPEQEFPQ</td>
</tr>
<tr>
<td>DQ2.5-glia-γ4c</td>
<td>QQPEQFPFQ</td>
</tr>
<tr>
<td>DQ2.5-glia-γ4d</td>
<td>PQPEQFPCQ</td>
</tr>
<tr>
<td>DQ2.5-glia-γ5</td>
<td>QQPFQEPPQ</td>
</tr>
<tr>
<td>DQ2.5-glia-ω1</td>
<td>IFPQPQEPF</td>
</tr>
<tr>
<td>DQ2.5-glia-ω2</td>
<td>PQPEQFPFW</td>
</tr>
<tr>
<td>DQ2.5-glut-L1</td>
<td>PFSEQEQPV</td>
</tr>
<tr>
<td>DQ2.5-glut-L2</td>
<td>FSQQQESPQ</td>
</tr>
<tr>
<td>DQ2.5-hor-1</td>
<td>PFPQEPPFQ</td>
</tr>
<tr>
<td>DQ2.5-hor-2</td>
<td>PQPEQFPFP</td>
</tr>
<tr>
<td>DQ2.5-hor-3</td>
<td>PIPFQPQYP</td>
</tr>
<tr>
<td>DQ2.5-sec-1</td>
<td>PFQPQEPFP</td>
</tr>
<tr>
<td>DQ2.5-scc-2</td>
<td>PQPQFPFPQ</td>
</tr>
<tr>
<td>DQ2.5-ave-1</td>
<td>PYPEQEFPF</td>
</tr>
<tr>
<td>DQ2.5-ave-1b</td>
<td>PYPEQEPFP</td>
</tr>
<tr>
<td>DQ8-restricted epitopes</td>
<td></td>
</tr>
<tr>
<td>DQ8-glia-α1</td>
<td>EGFSQPSQE</td>
</tr>
<tr>
<td>DQ8-glia-γ1a</td>
<td>EQPQQFPFP</td>
</tr>
<tr>
<td>DQ8-glia-γ1b</td>
<td>EQPQQPYPE</td>
</tr>
<tr>
<td>DQ8-glut-H1</td>
<td>QGYPTSPQ</td>
</tr>
</tbody>
</table>

Risk phenotypes

- **High risk:** HLA-DQ2.5
  - Large peptide repertoire
  - Largely resistant to degradation
- **Low risk:** HLA-DQ8
  - Small peptide repertoire
  - Less resistant to degradation
- **Very low risk:** HLA-DQ2.2
  - Very small peptide repertoire
  - Low resistance to degradation

Non Celiac disease Gluten Sensitivity (NCGS)

The clinical symptoms of nonceliac gluten sensitivity begin after the ingestion of gluten-containing grains. Symptoms improve or disappear with withdrawal of these grains from the diet, and symptoms reappear after gluten challenge, usually within hours or days.

Gastrointestinal presentation of nonceliac gluten sensitivity is characterized by abdominal pain, bloating, bowel irregularity (diarrhea, constipation, or both), Extra-intestinal manifestations include patient report of a “foggy brain,” which is described as slowed thinking, memory disturbance, or reduced level of alertness, along with headache, joint and muscle pain, fatigue, depression, leg or arm numbness, dermatitis (eczema or skin rash), and anemia.
NCGS diagnosis

STEP 1
- Start GFD
- E E E E E E E

STEP 2
- GFD + A or B
  - GFD
  - GFD + B or A
  - Stop
  - E
  - E
  - E

Suspect NCGS

gluten-containing diet > 6 weeks

improved

1 week → 1 week → 1 week → NCGS confirmed or excluded

not improved

NCGS excluded
Effectiveness of gluten free diet in NCGS patients

<table>
<thead>
<tr>
<th>Author</th>
<th># of patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper et al 1980</td>
<td>6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Biesiekierski et al 2011</td>
<td>34</td>
<td>P=0.047</td>
</tr>
<tr>
<td>Carroccio et al 2012</td>
<td>276</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Di Sabatino et al 2015</td>
<td>61</td>
<td>P=0.047</td>
</tr>
</tbody>
</table>
Gluten sensitivity Non-celiac

- 34 patients (aged 29-59 years, 4 men) completed 6 weeks of double blind placebo controlled gluten exposure.
- Overall, 56% had human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8.
- 68% in the gluten group, reported that symptoms were not adequately controlled vs 40% on placebo (P=0.0001).
- On a visual analog scale, patients were significantly worse with gluten within 1 week for overall symptoms (P=0.047), pain (P=0.016), bloating (P=0.031), satisfaction with stool consistency (P=0.024), and tiredness (P=0.001).
- Anti-gliadin antibodies were not induced.
- There were no significant changes in fecal lactoferrin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability.
- There were no differences in any end point in individuals with or without DQ2/DQ8.

Biesiekierski JR, 2011
Gluten sensitivity Non-celiac

-36 patients (aged 29-61 years, 6 men)
-completed 2 weeks of fermentable oligo-di-mono-saccharides and polyols (FODMAPs).

then

-1 group did gluten free diet
-1 group low gluten diet
-1 group high gluten diet

All had similar increase of symptoms

Biesiekierski JR, 2011
FODMAPs comprise:
- oligosaccharides, including fructans and galacto-oligosaccharides;
- disaccharides, including lactose;
- monosaccharides, including fructose;
- polyols, including sorbitol, xylitol, and mannitol.
Sources of fructans wheat (although some wheat strains such as spelt contain lower amounts), rye, barley, onion, garlic, Jerusalem and globe artichoke, asparagus, beetroot, chicory, dandelion leaves, leek, radicchio, the white part of spring onion, broccoli, brussels sprouts, cabbage, fennel and prebiotics such as fructooligosaccharides (FOS), oligofructose and inulin]

Sources of galactans Pulses and beans are the main dietary sources (though green beans, tofu and tempeh contain comparatively low amounts

Sources of polyols Polyols are found naturally in some fruit (particularly stone fruits), including apples, apricots, avocados, blackberries, cherries, lychees, nectarines, peaches, pears, plums, prunes, watermelon and some vegetables, including cauliflower, mushrooms and mange-tout peas. They are also used as bulk sweeteners and include isomalt, maltitol, mannitol, sorbitol and xylitol

Fructose and lactose People following a low-FODMAP diet may be able to tolerate moderate amounts of fructose and lactose, particularly if they have lactase persistence
### Eliminate foods containing FODMAPs

<table>
<thead>
<tr>
<th>excess fructose</th>
<th>lactose</th>
<th>fructans</th>
<th>galactans</th>
<th>polyols</th>
</tr>
</thead>
<tbody>
<tr>
<td>fruit</td>
<td>milk</td>
<td>vegetables</td>
<td>legumes</td>
<td>fruit</td>
</tr>
<tr>
<td>apple, mango, nashi, pear, tinned fruit in natural juice, watermelon</td>
<td>milk from cows, goats or sheep, custard, ice cream, yoghurt</td>
<td>artichoke, asparagus, beetroot, broccoli, brussels sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion (all), shallots, spring onion</td>
<td>baked beans, chickpeas, kidney beans, lentils, soy beans</td>
<td>apple, apricot, avocado, blackberry, cherry, longon, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon</td>
</tr>
<tr>
<td>sweeteners</td>
<td>cheeses</td>
<td>cereals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fructose, high fructose corn syrup</td>
<td>soft unripened cheeses eg. cottage, cream, mascarpone, ricotta</td>
<td>wheat and rye, in large amounts eg. bread, crackers, cookies, couscous, pasta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>large total fructose dose concentrated fruit sources, large serves of fruit, dried fruit, fruit juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>honey</td>
<td></td>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>corn syrup, fruisana</td>
<td></td>
<td>chicory, dandelion, inulin, pistachio</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FODMAPs are a group of short-chain carbohydrates that may cause symptoms in people with irritable bowel syndrome (IBS).*
### Foods suitable on a low-FODMAP diet

<table>
<thead>
<tr>
<th>Fruit</th>
<th>Vegetables</th>
<th>Grain Foods</th>
<th>Milk Products</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>banana, blueberry, boysenberry, cantaloupe, cranberry, durian, grape, grapefruit, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, pawpaw, raspberry, rhubarb, rockmelon, star anise, strawberry, tangelo&lt;br&gt;Note: if fruit is dried, eat in small quantities</td>
<td>alfalfa, bamboo shoots, bean shoots, bok choy, carrot, celery, choko, choy sum, endive, ginger, green beans, lettuce, olives, parsnip, potato, pumpkin, red capsicum (bell pepper), silver beet, spinach, squash, swede, sweet potato, taro, tomato, turnip, yam, zucchini</td>
<td>cereals, gluten-free bread or cereal products</td>
<td>milk, lactose-free milk*, oat milk*, rice milk*, soy milk*&lt;br&gt;*check for additives</td>
<td>tofu, sweeteners&lt;br&gt;sugar* (sucrose), glucose, artificial sweeteners not ending in ‘-ol’&lt;br&gt;honey substitutes&lt;br&gt;golden syrup*, maple syrup*, molasses, treacle&lt;br&gt;*small quantities</td>
</tr>
<tr>
<td>herbs&lt;br&gt;basil, chili, coriander, ginger, lemongrass, marjoram, mint, oregano, parsley, rosemary, thyme</td>
<td>polenta</td>
<td>bread&lt;br&gt;100% spelt bread</td>
<td>rice</td>
<td>oats</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>polenta&lt;br&gt;other&lt;br&gt;arrowroot, millet, psyllium, quinoa, sorgum, tapioca</td>
</tr>
</tbody>
</table>
Monash University "Low FODMAP Diet".

**Vegetables**: alfalfa, bean sprouts, green beans, bok choy, capsicum (bell pepper), carrot, chives, fresh herbs, *choy sum*, cucumber, lettuce, tomato, *zucchini*

**Fruits**: banana, orange, grapes, melon

**Protein**: meats, fish, chicken, *tofu*, *tempeh*

**Dairy**: lactose-free milk, lactose-free yoghurts, hard cheese

**Breads and cereals**: gluten-free bread and *sourdough* *spelt* bread, *crisped rice*, oats, gluten-free pasta, rice, *quinoa*

Biscuits (cookies) and snacks: gluten-free biscuits, rice cakes, corn thins

**Nuts and seeds**: *almonds* (no more than 10 nuts per serving), pumpkin seeds

**Beverage options**: water, *coffee*, *tea*
The Center for Pediatric Eosinophilic Disorders (CPED) is the largest clinical center in the world with over 1800 patients with EoE.

**CHOP Accomplishments**
- Identified the Genetic risk (TSLP, EMSY, CAPN14) factor for EoE
- Wrote the critical manuscript defining natural history
- Developed a new clinical test for food sensitivity in EoE
- Characterized efficacy of two treatment interventions
- Orchestrated the first multicenter consortium for EoE
- First clinical trial in Milk desensitization in the world (SMILEE)
EoE: Epidemiology

EoE prevalence 57/100,000

United States

Clinicopathologic diagnosis
-Presence of clinical symptoms related to esophageal dysfunction
  • Dysphagia, vomiting, abdominal pain, heartburn, feeding difficulty, etc.
-Isolated esophageal eosinophilia
  • 15 or more eosinophils per hpf in at least one esophageal biopsy
  • Histology of remainder of GI tract normal

EoE definition

DIAGNOSIS AND FOLLOW UP BASED ON REPETITIVE EGDs

Furuta, et al; Gastroenterology 2007; 133:1342.
Symptom Progression in EoE

Feeding Disorder/Failure to thrive
- 13%

GERD/vomiting
- 50%

Abdominal Pain
- 50%

Dysphagia
- 30% (Pediatric)
- 97% (Adults)

Food Impaction
- 13% (Pediatric)
- 51% (Adult)

Esophageal Stricture
- 10% (Pediatric)
- 37% (Adult)

Age
Quality of Life EoE is reduced and improved with treatment

1) subject age, EoE symptom burden, atopic comorbidities, and treatment type were associated with base line quality of life ratings of child and family impact.
2) EoE symptom severity scores decreased during the study, although number of symptoms did not.
3) symptom burden scores were consistently correlated with Quality of life scores at baseline and follow-up time points.
4) HRQoL improved during the course of evaluation and treatment, with positive changes being strongest for patients with lower symptom severity at BL.
Eosinophilic Esophagitis
Long term follow up @ CHOP

1995-2006 (512 patients with EoE)

- Follow up to 14.2 yrs
  - Average of 2.4 yrs with a total of 1782 biopsies
- No cases of EoE becoming Eosinophilic gastroenteritis
- 24 patients refused therapy or lost to F/U
  - Years since 1st visit – 6.2±3.6
  - # eosinphils 1st EGD – 35.4±24.8
  - # eosinophils recent EGD – 39.1±27.9
  - 20/24 initially presented with GERD symptoms
    - All returned with symptoms of dysphagia

Spergel et al. JPGN 2009
Is there a biomarker for EoE?

- Peripheral Biomarkers
  - FeNO, Eotaxin-3, Eosinophilic Proteins, Cytokines, Chemokines, siRNA, stool samples—none identified yet.

- Molecular Signature—Rothenberg Lab
  - Group of genes can distinguish EoE (But still need a biopsy)
    - 1607 significantly dysregulated transcripts (1096 upregulated, 511 downregulated) on RNA seq (Sherrill et al. Genes Immunity 2014)
    - 96 gene panel (EDP) –Wen et al. Gastro 2013
Do Symptoms match Histology?

<table>
<thead>
<tr>
<th>EEsAI PRO score cutoff</th>
<th>Cumulative remission, a n (%)</th>
<th>Cumulative frequency, b n (%)</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic remission: peak count of &lt;20 eosinophils/mm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>38/96 (39.6)</td>
<td>96/269 (35.7)</td>
<td>39.6</td>
<td>78.6</td>
<td>50.7</td>
<td>70.1</td>
<td>64.7</td>
</tr>
<tr>
<td>20</td>
<td>42/111 (37.8)</td>
<td>111/269 (41.3)</td>
<td>37.8</td>
<td>79.1</td>
<td>56.0</td>
<td>64.4</td>
<td>62.1</td>
</tr>
<tr>
<td>25</td>
<td>42/112 (37.5)</td>
<td>112/269 (41.6)</td>
<td>37.5</td>
<td>79.0</td>
<td>56.0</td>
<td>63.9</td>
<td>61.7</td>
</tr>
<tr>
<td>30</td>
<td>51/162 (31.5)</td>
<td>162/269 (60.2)</td>
<td>31.5</td>
<td>77.6</td>
<td>68.0</td>
<td>42.8</td>
<td>49.8</td>
</tr>
<tr>
<td>35</td>
<td>54/180 (30.0)</td>
<td>180/269 (66.9)</td>
<td>30.0</td>
<td>76.4</td>
<td>72.0</td>
<td>35.1</td>
<td>45.4</td>
</tr>
<tr>
<td>Histologic remission: peak count of &lt;60 eosinophils/mm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>49/96 (51.0)</td>
<td>96/269 (35.7)</td>
<td>51.0</td>
<td>70.5</td>
<td>49.0</td>
<td>72.2</td>
<td>63.6</td>
</tr>
<tr>
<td>20</td>
<td>54/111 (48.6)</td>
<td>111/269 (41.3)</td>
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<td>61.7</td>
</tr>
<tr>
<td>25</td>
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<td>112/269 (41.6)</td>
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<td>70.7</td>
<td>54.0</td>
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<td>61.3</td>
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<tr>
<td>30</td>
<td>68/162 (42.0)</td>
<td>162/269 (60.2)</td>
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<td>70.1</td>
<td>68.0</td>
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<td>35</td>
<td>71/180 (39.4)</td>
<td>180/269 (66.9)</td>
<td>39.4</td>
<td>67.4</td>
<td>71.0</td>
<td>35.5</td>
<td>48.7</td>
</tr>
</tbody>
</table>

NOTE. Data for 5 different cutoff values of EEsAI PRO score are shown. NPV, negative predictive value; PPV, positive predictive value.

aNumber of patients in histologic remission for a given EEsAI PRO score cutoff value.
bNumber of patients with a given EEsAI PRO score below the cutoff value.

Safroneeva et al. Gastro 2016
Atopy in EoE

- Large concomitant atopy up to 80% in Pediatrics and Adults

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Number of patients with EoE</th>
<th>Atopy</th>
<th>Asthma</th>
<th>Allergic Rhinitis</th>
<th>Atopic dermatitis</th>
<th>IgE specific for foods</th>
<th>Anaphylaxis to foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>NA</td>
<td>30%</td>
<td>8.5%</td>
<td>25%</td>
<td>10%</td>
<td>10%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Spergel et al., Philadelphia</td>
<td>620</td>
<td>NA</td>
<td>50%</td>
<td>61%</td>
<td>21%</td>
<td>50</td>
<td>10%</td>
</tr>
<tr>
<td>Assa’ad et al., Cincinnati</td>
<td>89</td>
<td>79%</td>
<td>39%</td>
<td>30%</td>
<td>19%</td>
<td>75%</td>
<td>NA</td>
</tr>
<tr>
<td>Sugnanam et al., Australia</td>
<td>45</td>
<td>NA</td>
<td>66%</td>
<td>93%</td>
<td>55%</td>
<td>NA</td>
<td>24%</td>
</tr>
<tr>
<td>Guajardo et al., World registry</td>
<td>39</td>
<td>80%</td>
<td>38%</td>
<td>64%</td>
<td>26%</td>
<td>62%</td>
<td>23%</td>
</tr>
</tbody>
</table>

The allergic march

- AD
- IgE-FA
- Asthma
- AR
- EoE

Hill DA 2018
Outgrowing FA and developing EoE

- Resolution of acute IgE-mediated allergy with development of eosinophilic esophagitis triggered by the same food

- Showed this mechanism in about 30 patients
Children with IgE-FA are at risk of developing EoE

- 35,528 Patients in EMR cohort
- 13,287 Patients with a food allergy
- 12,083 Patients with IgE diagnosis
- 836 Patients with EoE diagnosis
- 938 Patients with other diagnoses
  - A. 11,513 Patients IgE diagnosis only
  - B. 570 Patients with IgE and EoE
  - C. 266 Patients EoE diagnosis only

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs Female</td>
<td>2.27</td>
<td>1.89-2.78</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White vs Black</td>
<td>1.99</td>
<td>1.55-2.56</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic vs Non-Hispanic</td>
<td>0.99</td>
<td>0.67-1.47</td>
<td>ns</td>
</tr>
<tr>
<td>Specific food allergens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peanut</td>
<td>1.07</td>
<td>0.90-1.27</td>
<td>ns</td>
</tr>
<tr>
<td>Egg</td>
<td>2.27</td>
<td>1.91-2.64</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Tree nut</td>
<td>1.04</td>
<td>0.88-1.23</td>
<td>ns</td>
</tr>
<tr>
<td>Milk</td>
<td>4.19</td>
<td>3.52-4.97</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Shellfish</td>
<td>1.55</td>
<td>1.24-1.92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Number of food allergies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 foods</td>
<td>2.93</td>
<td>2.16-4.05</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>3+ foods</td>
<td>5.29</td>
<td>3.82-7.32</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

EMR, Electronic medical record; EoE, eosinophilic esophagitis; ns, nonsignificant.
Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis

Alfredo J. Lucendo, MD, PhD, FEBGH *; Ángel Arias, BSc, MSc †; and José M. Tenias, MD, PhD ‡

* Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Ciudad Real, Spain
† Research Unit, Complejo Hospitalario La Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain

Interventions | Incidence | n
--- | --- | ---
EoE after immunotherapy (overall) | 2.72% (1.7–4) | 9
Subgroups according to quality (type of publication)
- Medium to high (full-length article) | 3.51% (1.3–6.7) | 3
- Low (abstract) | 2.5% (1.3–4) | 6
# Outgrowing EoE

1995-2006 (512 patients with EoE)

<table>
<thead>
<tr>
<th></th>
<th>Total Resolution</th>
<th>Outgrown Some Food Allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td><strong>Age at Diagnosis (yr)</strong></td>
<td>5.6 yr</td>
<td>4.9 yr</td>
</tr>
<tr>
<td><strong>Follow-up (yr)</strong></td>
<td>5.2yr</td>
<td>6.8 yr</td>
</tr>
</tbody>
</table>

Spergel et al. JPGN 2009
Genetic Factors in EoE

Male 3:1

General population

0.06%

Siblings

2.4%

40 times

Twin

41%

683 times

Sibling Risk in Asthma == 2

Alexander et al. J Allergy Clin Immunol
Triggers

- Environmental Allergen
- Infections
- Foods
Diet Efficacy in EoE

Lucendo, Curr Gastroenterol Rep. 2015
Molina-Infante, JACI 2015, Molina Infante JACI 2017
Food Allergy and EoE: lesson learned from elemental diet

- Kelly and Sampson
  - 10 patients (5 yr, range: 8 mo-12.5 yr)
  - Endoscopy pre- & post-trial

Kelly et al. Gastroenterology 1995

Lucendo, 2015
How to predict the food implicated in food allergy driven EoE

• History not accurate
  - doesn’t predict level of inflammation
  - Reactions may be delayed and persist several days
  - More than one food can cause reaction

• Percutaneous Testing for most common foods
  - Strong NPVs (Negative predictive value) (NOT FOR MILK)
  - Low PPVs (Positive predictive values) 50-85% depending for which food

• IgE Microarray (CRD)-based dietary treatment was not effective in adult patients with EoE
  - missed sensitizations
  - limited relevance of IgE in the pathophysiology of EoE

  Kelly, et al, Gastroenterology 1995
  Liacouras et al Clin Gastroenterology and Hepatology 2005
  Spergel JACI 2007
  Van Rhijn BD JACI 2015
Percutaneous Testing

- Variable predictive
- Low NPV and PPVs 50-85%
- Low sensitivity
- Cross-reactivity between foods
  - Clinical significance?

NPV = negative predictive value; PPV = positive predictive value.
IgE Microarray (CRD) fail to identify trigger foods in EoE
Six Food Elimination Diet (SFED) Adults

- Food Reintroduction
  - most common food triggers were wheat (60%), Milk (50%), soy (10%), nuts (10%), egg (5%), seafood (0)
  - Three patients had more than one food trigger

- SPT accurately predicted only 13% of causal agents, and 67% of patients who had a food trigger identified by the reintroduction process had a negative SPT to all foods

Gonsalves et al. Gastroenterology 2012
SFED and EoE

Kagalwalla et al. 2006: 0.74 (0.57, 0.88)
Kagalwalla et al. 2007: 1.00 (0.03, 1.00)
Muir et al. 2010: 0.54 (0.25, 0.81)
Henderson et al. 2012: 0.81 (0.61, 0.93)
Gonsalves et al. 2012: 0.74 (0.60, 0.85)
Lucendo et al. 2013: 0.73 (0.61, 0.83)
Wolf et al. 2013: 0.40 (0.05, 0.85)

combined: 0.72 (0.66, 0.78)

Lucendo, Curr Gastroenterol Rep 2015
Four Food Elimination Diet (Milk, wheat, egg, legumes) Adults

FFGED

Responders (N=28)

(54%)

SFGED after failure of FFGED

Responders (N=6)

(21%)

TABLE II. Food triggers identified by sequential food challenge (n = 22) after response to the FFGED

<table>
<thead>
<tr>
<th>Food Triggers</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A single causative food group</td>
<td>10/22</td>
<td>45%</td>
</tr>
<tr>
<td>Milk</td>
<td>6/22</td>
<td>27%</td>
</tr>
<tr>
<td>Wheat</td>
<td>3/22</td>
<td>13%</td>
</tr>
<tr>
<td>Egg</td>
<td>1/22</td>
<td>4%</td>
</tr>
<tr>
<td>Two causative food groups</td>
<td>10/22</td>
<td>45%</td>
</tr>
<tr>
<td>Milk and egg</td>
<td>2/22</td>
<td>9%</td>
</tr>
<tr>
<td>Milk and legumes</td>
<td>2/22</td>
<td>9%</td>
</tr>
<tr>
<td>Milk and wheat</td>
<td>1/22</td>
<td>4%</td>
</tr>
<tr>
<td>Wheat and egg</td>
<td>3/22</td>
<td>13%</td>
</tr>
<tr>
<td>Egg and legumes</td>
<td>2/22</td>
<td>9%</td>
</tr>
<tr>
<td>Three or more causative food groups</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No causative food group</td>
<td>2/22</td>
<td>9%</td>
</tr>
</tbody>
</table>

Molina-Infante, JACI 2015
One Food Elimination Diet (Milk) children

Milk (64%)

Flovent (80%)

Kruszewski PG et al, Dis Esophagus 2015
GOAL = Find the least restrictive diet that can control EoE
**Most Common Foods in EoE**

*TABLE 3. The 10 most common foods confirmed by endoscopy after allergy testing*

<table>
<thead>
<tr>
<th>Food</th>
<th>Causative foods, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>17</td>
</tr>
<tr>
<td>Egg</td>
<td>11</td>
</tr>
<tr>
<td>Wheat</td>
<td>9.6</td>
</tr>
<tr>
<td>Soy</td>
<td>7.8</td>
</tr>
<tr>
<td>Corn</td>
<td>7.8</td>
</tr>
<tr>
<td>Beef</td>
<td>6.6</td>
</tr>
<tr>
<td>Chicken</td>
<td>6.1</td>
</tr>
<tr>
<td>Peanut</td>
<td>5.4</td>
</tr>
<tr>
<td>Potato</td>
<td>4.8</td>
</tr>
<tr>
<td>Rice</td>
<td>4.1</td>
</tr>
</tbody>
</table>
Most Common Foods in EoE

All pts had > 20 eos/hpf on GERD and AR medication and had
- Removal of a single food leading to normal esophageal biopsy (0 eosinophils/HPF).
- Addition of a single food leading to increased esophageal eosinophils on biopsy after a previously normal biopsy.

319 Children had definitive causative food (out of 941 patients examined)

<table>
<thead>
<tr>
<th>Food</th>
<th>No. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>78</td>
</tr>
<tr>
<td>Milk, meats*</td>
<td>24</td>
</tr>
<tr>
<td>Milk, egg, wheat, soy</td>
<td>20</td>
</tr>
<tr>
<td>Milk, soy</td>
<td>15</td>
</tr>
<tr>
<td>Grains*</td>
<td>13</td>
</tr>
<tr>
<td>Milk, egg, wheat, meats</td>
<td>11</td>
</tr>
<tr>
<td>Egg, wheat</td>
<td>10</td>
</tr>
<tr>
<td>Milk, egg</td>
<td>8</td>
</tr>
<tr>
<td>Milk, egg, wheat</td>
<td>8</td>
</tr>
<tr>
<td>Egg</td>
<td>8</td>
</tr>
<tr>
<td>Soy</td>
<td>7</td>
</tr>
<tr>
<td>Wheat</td>
<td>5</td>
</tr>
</tbody>
</table>

Younger children sensitive to more foods

Spergel et al JACI 2012
Some patients with milk-induced EoE are able to tolerate baked milk.
It is well known that cooking and/or processing can
- denature conformational epitopes, making them no longer recognizable by the epitope-specific IgE.
- strengthen certain protein bonds or create neoepitopes, such as when amino acids react with aldehyde or ketone groups on sugars (glycation) in enzymatic browning or roasting known as the Maillard reaction. (roasting peanuts or cooking shellfish) Peanut protein component Ara h2 forms aggregates during this reaction that are harder to digest and more easily recognized by epitope-specific IgE.
- The predominant protein in Egg White, ovalbumin (OVA), is a conformational epitope and heat labile, whereas the other major allergen, OM, is a sequential epitope and heat resistant, making OM potentially more allergenic.
- The whey proteins in CM, such as alpha-lactalbumin and beta-lactoglobulin, contain conformational epitopes that are heat labile (significantly reduced after 20 minutes of boiling), whereas casein contains mostly sequential and heat-resistant epitopes.
Baked Milk/Egg allergen: Matrix effect

- Heating is only one part of rendering baked milk and egg less allergenic. Interactions with proteins, fats, or sugar in a food matrix, such as wheat, are equally important.
- This is why the simple act of boiling cow’s milk may not be enough to decrease allergenicity to a degree comparable with a baked product.
- The food matrix may help to reduce exposure of the specific proteins to the immune system.
- For example, the beta-lactoglobulin fractions of whey form disulfide bonds with the other proteins in the food matrix, making them less recognizable by specific IgE.
- Ovomucoid polymerizes with proteins in the food matrix, such as gluten, to form large insoluble aggregates, making it less recognizable by epitope-specific IgE and potentially less allergenic.
There is clearly some uncertainty about the necessity of avoiding rye and barley in addition to wheat in elimination diets in adults and children with EoE. Published and unpublished data from our centers and others (including studies of patients with EoE and gluten-triggered celiac disease) are too limited to speculate whether total gluten elimination (wheat, barley, and rye) might be meaningfully more efficacious than elimination of only wheat in patients with EoE. Unless the theoretic risks of wheat, barley, and rye cross-reactivity/cross-contamination are confirmed with empiric evidence in patients with EoE, we advise against extending wheat elimination to include the exclusion of other gluten-containing grains.
How food can induce Eosinophilic-Th2 inflammation in EoE?

Food allergens, other trigger?

Eosinophilic-Th2 Inflammation
Pharmacologic Therapy

Systemic Steroids – effective at improving symptoms and histology of EoE in 95% of pts

- Upon discontinuation, 90% had recurrence of symptoms
- (Long term use) Side effects: bone abnormalities, poor growth, adrenal suppression
- May be needed short term for extreme cases

Topical/swallowed Steroids – less toxic to pt while still 50-85% effective

- After administration of topical steroids no food or drink is allowed for 30 minutes
- Accepted EoE treatment in adults and children.
- Upon discontinuation almost all patients have a recurrence of symptoms
- Often, large doses needed
- Side effects: esophageal candidiasis
- Potential: growth impairment and osteoporosis

- Aerosolized fluticasone propionate from a metered dose inhaler (no spacer) 110 mcg X 2 puffs twice daily for children year< 8 years of age; 220 mcg X 2 puffs twice daily for children year>8 years of age
- Budesonide is delivered as viscous budesonide, is made by mixing each 1 mg Pulmicort RespuleTM with 10 g (10 packets) of sucralose (SplendaTM) to create a volume of approximately 8mL. 0.5-2mg in 1 or 2 divided doses

Liacouras et al. Clin Gastroenterol Hepatol 2005
Furuta et al. Gastroenterology 2007
Cianferoni a et al 2015
## PPI-Responsive EOE PPI-REE Estimates

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Design</th>
<th># Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dranove</td>
<td>2009</td>
<td>Pediatric</td>
<td>Retro</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>Sayej</td>
<td>2009</td>
<td>Pediatric</td>
<td>Retro</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>Monte-Infante</td>
<td>2011</td>
<td>Adult</td>
<td>Prospective</td>
<td>35</td>
<td>74</td>
</tr>
<tr>
<td>Peterson</td>
<td>2010</td>
<td>Adult</td>
<td>RCT</td>
<td>12</td>
<td>33</td>
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<td>Moawad</td>
<td>2011</td>
<td>Adult</td>
<td>RCT</td>
<td>20</td>
<td>35</td>
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<td>Dellon</td>
<td>2013</td>
<td>Adult</td>
<td>Prospective</td>
<td>65</td>
<td>37</td>
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<tr>
<td>Schroeder</td>
<td>2013</td>
<td>Adult</td>
<td>Retro</td>
<td>7</td>
<td>71</td>
</tr>
</tbody>
</table>
PPI-REE vs EoE

Dranove et al J Ped 2009
Which are the cells that produce Th2 cytokines in EoE?

- Eosinophils
- NKT cell
- Th2
- GATA 3
- Stat6
- Mast cells
- Basophils

(Eosinophils, T-cells, Mast cells, IgE+ cells)

(Strauman AJ Allergy Clin Immunol 2001;108:954-61.)
<table>
<thead>
<tr>
<th>Publication</th>
<th>Human Cytokine Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straumann et al. JACI 2002</td>
<td>Increased expression of IL-5</td>
</tr>
<tr>
<td>Straumann et al. Inflamm Bowel Dis, 2004</td>
<td>Increased expression of IL-5 and TNF-a in epithelial cells</td>
</tr>
<tr>
<td>Gupta et al. Am J Gastro 2006</td>
<td>Eosinophils express “activation” markers: 60% express IL-13 and IL-4</td>
</tr>
<tr>
<td>Blanchard et al. J Clin Invest 2006</td>
<td>41% of intestinal eosinophils express IL-13 at baseline, circulating eosinophils do not express IL-4 or IL-13</td>
</tr>
<tr>
<td>Aceves et al. JACI 2007</td>
<td>No increase in cysLT</td>
</tr>
<tr>
<td>Blanchard et al. JACI 2011</td>
<td>50-fold increase in Eotaxin-3 in biopsy</td>
</tr>
<tr>
<td>Aceves et al. JACI 2007</td>
<td>Esophageal remodeling with increased TGFb, phospho-Smad2/3, VCAM</td>
</tr>
<tr>
<td>Battacharya et al, Hum Pathol 2007</td>
<td>Increased Eotaxin-3 in archived biopsies</td>
</tr>
<tr>
<td>Blanchard C et al JACI 2011</td>
<td>Increased IL-13, IL-4, IL-5, IL-15 in esophageal bx of patients with active EoE</td>
</tr>
<tr>
<td>Zhou H et al Gastroenterology 2010</td>
<td>Eosinophilia in Esophageal bx correlates with IL-15 levels</td>
</tr>
<tr>
<td>Rothenberg ME, Spergel JM, Nat Genet. 2010</td>
<td>Increased TSLP in esophageal bx of patients with active EoE</td>
</tr>
</tbody>
</table>
Anti-IL-5 EoE

- Anti-IL-5 (mepolizumab/reslizumab) reduces Eosinophilic infiltration in humans but has no significant effects on dysphagia.

Spergel et al. 2011 abstract
Strauman A. Gut 2010
1) The detection of specific IgEs for food allergens, either by SPT or by specific sera IgE (sIgE), has not proven successful for the identification of causative foods in EoE.
2) Clinical trials and case series have shown that therapy with omalizumab is not effective in inducing remission of EoE.
3) Oral immunotherapy, which has been used successfully in IgE-mediated food allergy, is associated with an increased risk of developing EoE (e.g. in 2 to 10% of treated patients).
4) Children who outgrow IgE-mediated food allergy and therefore are able to reintroduce these foods in their diet can later develop EoE to the same food.
5) In experimental models in which food allergens are able to induce an EoE-like disease, mice with depleted IgE and devoid of mast cells still could develop esophageal inflammation and consequent food impaction similar to the wild-type mice.
In animal model EoE is Non IgE mediated food allergy

Not IgE dependent

Noti et al, Nat. Medicine 2013
EoE ≠ IgE Mediated Disease

In a double blind placebo control trial Omalizumab Has No Effect on Eosinophil Content or, Relative to Placebo Controls, Symptoms

Table 2. Esophageal Mucosal Tissue IgG4 Is Strikingly and Specifically Increased

<table>
<thead>
<tr>
<th></th>
<th>Normal controls</th>
<th>Eosinophilic esophagitis</th>
<th>Eosinophilic esophagitis/control ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM, mg/g protein</td>
<td>0.16 ± 0.07</td>
<td>0.38 ± 0.21</td>
<td>2.4 (0.91–5.5)</td>
</tr>
<tr>
<td>IgA, mg/g protein</td>
<td>0.32 ± 0.15</td>
<td>0.51 ± 0.18</td>
<td>1.6 (0.84–3.5)</td>
</tr>
<tr>
<td>IgG1, mg/g protein</td>
<td>2.2 ± 0.73</td>
<td>3.1 ± 1.1</td>
<td>1.4 (0.78–2.4)</td>
</tr>
<tr>
<td>IgG2, mg/g protein</td>
<td>0.76 ± 0.14</td>
<td>1.4 ± 0.64</td>
<td>1.8 (0.88–2.9)</td>
</tr>
<tr>
<td>IgG3, mg/g protein</td>
<td>0.10 ± 0.05</td>
<td>0.15 ± 0.092</td>
<td>1.5 (0.48–3.7)</td>
</tr>
<tr>
<td>IgG4, mg/g protein</td>
<td>0.029 ± 0.013</td>
<td>1.3 ± 0.99</td>
<td>45 (7.5–109)</td>
</tr>
<tr>
<td>IgG4, % total IgG</td>
<td>0.92 ± 0.43</td>
<td>17 ± 7.7</td>
<td>18 (8.4–40)</td>
</tr>
</tbody>
</table>
EoE ≠ IgE Mediated Disease

<table>
<thead>
<tr>
<th>Immunoglobulin, median (IQR)</th>
<th>Control subjects</th>
<th>Subjects with EoE</th>
<th>EoE/control ratio</th>
<th>P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>19.5 (18.8-20.4)</td>
<td>18.7 (18.2-19.1)</td>
<td>1.0</td>
<td>.0620</td>
</tr>
<tr>
<td>IgA</td>
<td>0.9 (0.5-1.4)</td>
<td>2.0 (1.8-4.6)</td>
<td>2.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IgM</td>
<td>0.9 (0.6-1.5)</td>
<td>2.3 (0.9-3.9)</td>
<td>2.6</td>
<td>.0102</td>
</tr>
<tr>
<td>IgG1</td>
<td>9.0 (6.6-10.2)</td>
<td>13.4 (9.5-18.4)</td>
<td>1.5</td>
<td>.0132</td>
</tr>
<tr>
<td>IgG2</td>
<td>8.1 (2.7-11.2)</td>
<td>16.2 (9.7-32.6)</td>
<td>2.0</td>
<td>.0122</td>
</tr>
<tr>
<td>IgG3</td>
<td>0.6 (0.5-1.0)</td>
<td>2.2 (1.3-5.1)</td>
<td>3.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IgG4</td>
<td>0.2 (0.1-0.9)</td>
<td>4.2 (1.0-13.1)</td>
<td>21.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IgG4, % total IgG</td>
<td>4.5% (1.8-9.3)</td>
<td>18.0% (6.5-23.5)</td>
<td>4.0</td>
<td>.0122</td>
</tr>
</tbody>
</table>

Rosenberg CE, Allergy 2018
IgG4 specific for some foods maybe important, but their clinical value is to be determined.
Esophageal IgG4 levels are increased in patients with EoE compared with control individuals and strongly correlate with esophageal eosinophil numbers and multiple features of histological grade and stage scores. Esophageal IgG4 protein levels correlate with multiple components of the disease as assessed by transcriptome profiling, including IL4, IL13 and IL10 mRNA expression levels. IgG4 heavy chain mRNA expression is proportional to IgG4 protein levels and IL10 mRNA expression levels in the esophagus of patients with EoE.

Rosenberg CE, Allergy 2018
IgG4 to cow’s milk protein in EoE

Schuyler AJ et al JACI 2018
IgG4 to cow’s milk protein in EoE

FIG 2. sIgG₄ levels (geometric mean [95% CI]) to Bos d 4, Bos d 5, and Bos d 8 in 71 patients with EoE and 210 control subjects with or without CM sensitization. Values below the dotted line indicate the number not detectable (#ND) and were excluded from calculation of the geometric mean. Statistical analysis was performed with the Mann-Whitney test.

Schuyler AJ et al JACI 2018
IgG4 to cow’s milk protein in EoE

Schuyler AJ et al JACI 2018

**FIG 4.** slgG4 levels to Bos d 4, Bos d 5, and Bos d 8 in patients with EoE before and after a 6- to 8-week CM elimination diet (n = 13) compared with baseline levels in control subjects (n = 210). Statistical analysis was performed with the Wilcoxon matched pair test and the Mann-Whitney test.
Can sIgG₄ levels to CM be useful as a biomarker for the diagnosis or monitoring of EoE?

- Need prospective investigation,
- Large overlapping between normal and EoE
- The difference in ORs between girls and boys reported here suggests that this question should be addressed with consideration to sex.

Schuyler AJ et al JACI 2018
IgG4 and EoE Food allergy in adults

Wright et al. 2016
IgG4 Are they pathogenetic?

- SIgG4 is not sufficient as to cause EoE is supported by the fact that 10% of control subjects also had high-titer SIgG4 to CM proteins.
- CM SIgG4 is an epiphenomenon in patients with EoE, perhaps related to an aberrant T_{H2} or regulatory T-cell response.
- A pathogenic role for IgG4 cannot be dismissed.
- IgG4 could be pathogenic by forming extracellular immune complexes, due to SIgG4 antibody levels largely restricted to a single allergen (group) in presence of high concentrations of allergen in the tissue before Fab arm exchange occurred. Indeed SIgG4 levels to CM proteins contributed more than 10% of total IgG4 in 35% of our patients with EoE.
- Taken together, the question of whether high-titer SIgG4 is an epiphenomenon or is mechanistically involved in the inflammation seen in patients with EoE is an important area for future inquiry.
- B-cell class-switch recombination (CSR) to IgG4 like the IgE one is induced by IL-4 and IL-13. IgG4 has also been associated with high levels of IL-10 secreted from regulatory B and T cells.
- Patients with EoE have increased levels of TGF-b1 localized to eosinophils and mast cells in the esophagus. TGF-b1 can suppress IgE CSR and also promote mast cell accumulation and eosinophil survival.
- T cell play a central role in thus upstream defects in T-cell activation or development could contribute to both the pathology and IgG4 production in patients with EoE.
The IgE: IgG4 conundrum

In Eosinophilic Esophagitis:

1. IgG4 to food proteins is increased – but role in pathophysiology of disease is unclear
Genetic Studies EoE

- Candidate Gene
- Genomic Wide Association Studies

<table>
<thead>
<tr>
<th>TSLP SNP</th>
<th>5q.22.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSLP-R SNP</td>
<td>Xp22.3; Yp11.3</td>
</tr>
<tr>
<td>Eotaxin 3</td>
<td>7q11.23</td>
</tr>
<tr>
<td>CAPN14</td>
<td>2q.23</td>
</tr>
<tr>
<td>EMSY</td>
<td>11q13.5</td>
</tr>
</tbody>
</table>
Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease

Leah C Kottyan1,3,3, Benjamin P Davis3,1,1, Joseph D Sherrill3,1, Kan Liu3, Mark Rockman1, Kenneth Kaufman1,2, Matthew T Weiratsche4, Samuel Vaughn4, Sara Lazar4, Andrew M Raput4, Mojtaba Kohram4, Emily M Stuck4, Katherine A Kemen2, Albert Magnusen4, Hua Hu5, Phillip Drexheimer6, Mirna Chehade6, Robert A Wood7, Robbie D Pesc4, Brian P Vecky7, David M Heischer8, Robert Lindblad8, Hugh A Sampson8, Vincent A Nukada9, Michael E Putnam5, I Pablo Abonia3, Lisa J Martin1, John B Harley1,8,11 & Marc E Rothenberg3,11

GWAS identifies four novel eosinophilic esophagitis loci

Patrick M.A. Sleiman1,2, Mei-Lun Wang2,3, Antonella Cianferoni2,4, Seema Acesev5, Nirmala Gonsalves6, Kari Nadeau7, Albert J Bredenoord8, Glenn T. Furuta9, Jonathan M. Spergel2,4 & Hakon Hakonarson1,2

Thymic stromal lymphopoietin–elicited basophil responses promote eosinophilic esophagitis

Mario Not1,3,4, Ella D Tait Wng1,3, Brian S Kim1,3, Mark C Stracasa2,3, Paul R Giacomin1,4, Maera G Irai1,3, Alain J Benitez2, Kathryn R Bayman2, Amanda B Muir3, David A Hill2,3, Kudakwashe R Chiwara3, Amin M Doghaidah3, Quentin J Sattert4, Amna A Alex10,4, Chau Zhou10,4, Jennifer H Yenley7, Paul Menard-Katcher6, Masato Kubo1,3, Kazuhiko Odaka Ninomiya1,3, Hajime Kasaesagi1,3, Michael R Corneau7, Terri Brown-Whitehorn3, Rene de Waal Malefyt9, Patrick M Sleiman1-25, Hakon Hakonarson1-25, Antonella Cianferoni2, Gary W Falk2,3,25, Mei-Lun Wang2,3,25, Jonathan M Spergel2,3,25 & David Artis1,3,25

DOI: 10.1038/ncomms6593

Common variants at 5q22 associate with pediatric eosinophilic esophagitis

Marc E. Rothenberg1,11, Jonathan M. Spergel2,3,11, Joseph D Sherrill1,11, Kiran Annaiah4,11, Lisa J Martin5,11, Antonella Cianferoni2,3, Laura Gober2, Cecilia Kim4, Joseph Glessner4, Edward Frackelton4, Kelly Thomas4, Carine Blanchard1, Chris Liacouras3,6, Ritu Verma3,6, Seema Acesev7, Margaret H Collins8, Terri Brown-Whitehorn2,3, Phil E Putnam9, James P Franciosi9, Rosetta M Chiavacci4, Struan F A Grant3,4,10, J Pablo Abonia3, Patrick M.A. Sleiman1, Hakon Hakonarson3,4,10

ARTICLE

Received 18 July 2014 | Accepted 16 October 2014 | Published 19 November 2014

Thymic stromal lymphopoietin–elicited basophil responses promote eosinophilic esophagitis

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DOI: 10.1038/ncomms6593
TSLP: Thymic stromal lymphopoietic

- IL-7-like cytokine
  - Expressed in thymus and epithelial cells
  - Potent inducer maturation of dendritic cells
  - Primes TH cells into TH2 cells
  - Induced by virus, bacterial, allergen

- TSLP is ↑ in lesional skin in AD and asthma.
Thymic stromal lymphopoietsin–elicited basophil responses promote eosinophilic esophagitis

Basophil and TSLP dependent
TSLP-thymic stromal lymphopoietin

- IL-13
- B-1 cells
- Basophils
- Mast-cells
- Eosinophils
- CD4+ T cells
- CD8+ T cells
- iNKT
- TSLP
- Progenitors

Responses:
- Chemokines
- OX40L
- Survival
- Th2
- Recruitment
- Cytotoxicity
- IL-4, Th2
- IL-12, IL-23p40
- CD4+ T cells
RS3806932  TSLP SNP is associated with multiple food allergy in EoE
381 biopsy confirmed pediatric EoE patients.

<table>
<thead>
<tr>
<th>TSLP Risk Allele (homozygous/heterozygous)</th>
<th>Odds Ratio</th>
<th>Standard Error</th>
<th>P value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 EoE food allergen triggers</td>
<td>4.616825</td>
<td>1.626283</td>
<td>&lt;0.0001</td>
<td>2.314763-9.208321</td>
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<tr>
<td>Asthma</td>
<td>0.8805519</td>
<td>0.3394478</td>
<td>0.741</td>
<td>0.4136391-1.874513</td>
</tr>
<tr>
<td>AR</td>
<td>1.1322</td>
<td>0.496835</td>
<td>0.777</td>
<td>0.4790672-2.675775</td>
</tr>
<tr>
<td>AD</td>
<td>0.6805757</td>
<td>0.2524066</td>
<td>0.299</td>
<td>0.3289952-1.407873</td>
</tr>
<tr>
<td>IgE-FA</td>
<td>0.6867766</td>
<td>0.2398334</td>
<td>0.282</td>
<td>0.3463875-1.36166</td>
</tr>
<tr>
<td>Any Atopic Disease</td>
<td>1.653602</td>
<td>1.126703</td>
<td>0.460</td>
<td>0.4349646-6.286487</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.037716</td>
<td>0.2626875</td>
<td>0.884</td>
<td>0.6318373-1.704322</td>
</tr>
</tbody>
</table>

Fahey et at Clinical and Translational Gastroenterology 2018
2 independent GWAS identified SNP at 2p23 as risk factor for EoE
CAPN14 is a functional protease
CAPN14 is increased in the biopsies of patients with active EoE
Th2 Cytokines induce CAPN14 expression
CAPN14 induces loss of epithelial cell architecture and barrier function
CAPN14 reduces Desmoglein 1 (DSG1) expression
Calpain 14 a proteasis and Th2 Inflammation
Epithelial damage

Kottyan 2014 Nature Genetics
EoE pathogenesis

- Genetics:
  - TSLP SNP (5q22.1)
  - TSLP-R SNP (Xp22.3; Yp11.3)
  - Eotaxin 3 (7q11.23)
  - CAPN14 (2q.23)
  - EMSY (11q13.5)

- Esophageal epithelium

- TH2 Cytokines

- Mast cells
- Basophils
- DC
- Eosinophils
- TH2 Cytokines
- iNKT
- Cell. T CD4+
Th2 antigen response

Th0

Th2

Treg

Th1

Th17

Allergen - Protein

TSLP

Dendritic cells

iNK T cell

Th2-Cytokine
In 20 patients with milk induced EoE T cell were activated to produce Th2 cytokines

Cianferoni et al JACI submitted
In patients with milk induced EoE, T cell were activated to produce IL-5 cytokines by milk antigens.

Cianferoni et al, JACI submitted.
Dupilumab (Anti-IL4R) in EoE

Primary Endpoint
Dupilumab significantly reduced SDI PRO score at Week 10

Secondary Endpoint
Dupilumab significantly reduced overall peak esophageal intraepithelial eosinophil count at Week 12
Th2 cytokines and epithelial dysfunction
Th2 Inflammation and Epithelial damage

CALPAIN 14

Kottyan 2014 Nature Genetics
Calpain 14 and Barrier dysfunction
Multilayered stratified nonkeratinized quamous epithelium composed of the:
- stratum granulosum,
- stratum spinosum,
- stratum germinativum (i.e. basal layer; fig. 2).

- Tight junctions (occludins and claudins 1-4)
- Adherent junctions (E-cadherin).
- Desmosomes (desmogelin and desmocollin)
EoE pathogenesis

Cianferoni A, 2015

1. Genetics
2. Esophageal epithelium
3. TH2 inflammation

- Eotaxin 3
- TSLP SNP
- TSLP-R SNP
- Eotaxin 3
- CAPN14
- EMSY

Demage

- Mastcells
- Basophils
- DC
- iNKT
- Eosinophils
- Cell. T CD4+
- TH2 Cytokines
Conclusions

- Eosinophils are part of the inflammatory cells typical of Th2 inflammation, but are not essential for pathogenesis
- A dysfunctional epithelium in atopic genetically susceptible individuals induce local atopic inflammation by
  - Secreting mediators that promote Th2 cytokines
  - Increase access to antigens
  - Inducing local sensitization to allergen such as foods
  - Promote chronic inflammation
FPIES: Food protein enterocolitis

FPIES is a non-IgE-mediated food allergy hallmarked by delayed onset of profuse, repetitive emesis, and lethargy that may be accompanied or followed by watery/bloody diarrhea

International Consensus Guidelines AAAAI.
A Nowak- Węgrzyn, et al (Submitted)
Clinical features of FPIES

- Vomiting (typically around 2 hours post ingestion)
- Diarrhea (typically 5 hours post ingestion)
- Lethargy
- Dehydration that may progress to:
  - Acidemia
  - Hypotension
  - Methemoglobinemia
- May also find elevated PMN/PLTs count
- Occasional hypoalbuminemia and FTT
Treatment of acute reaction

- Intravenous fluid boluses
- Ondasetron
- Steroids
- Supportive care
- Epinephrine traditionally does NOT help
Allergy testing for food specific IgE by either prick skin testing or serologic assessment is typically of little or no value in the diagnosis of FPIES, as FPIES is not an IgE-mediated process.

Atopy patch testing (APT) has also been evaluated as a possible means of identifying specific food sensitivities in patients with FPIES.

However, only two studies performed to date have evaluated APT, with conflicting results as to its diagnostic value in predicting challenge outcome. 

On 462 children (1031 episodes) Most common foods were

- Grain = rice, oat, WHEAT (very rare)
- Meat = chicken, turkey
- Vegetables = sweet potato, peas, squash
- Fruit = Banana, apple

Ruffner et al. JACI in practice 2014
Foods That Trigger FPIES (Mount Sinai Data)

FIG 1. FPIES food triggers.

Caubet, et al. JACI 2014; 134:382-9
**FPIES: Foods**

- On 462 children (1031 episodes) Most children were allergic to only 1-2 foods

![Graph showing percentage of patients based on the number of foods they were allergic to.]

Ruffner et al JACI in practice 2014
T cell response to specific antigens in FPIES

Goswami et al JACI 2017
T cell response to specific antigens in FPIES

Goswami et al JACI 2017
T cells
-milk, soy, or rice-responsive T cells, and TNF-α–producing CD1541 T cells, were significantly lower in those with outgrown FPIES compared with those with active FPIES. However, levels were within the normal range and were inconsistent with a role in the pathophysiology of FPIES.

-pan–T-cell activation and redistribution from the circulation after a positive food challenge but not in those who had outgrown their FPIES

Innate immune system
-monocytes, neutrophils, natural killer cells, and eosinophils activated after food challenge only in children with active FPIES

Goswami et al JACI 2017
What are the mechanism that cause FPIES

Berin C, JACI 2016.
160 children retrospectively studied
• 39% had IgE sensitization to another food.
• 24% subjects had positive specific IgE levels to the food inducing FPIES.
• Among children with specific IgE to cow’s milk, 41% changed from a milk FPIES to an IgE-mediated phenotype over time.
• none of the subjects with milk specific IgE became tolerant to milk during the study

Can FPIES become IgE mediated allergy?

Caubet et al JACI 2014
Modified from
http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/A/AntigenPresentation.html
Conclusions

- Non-IgE mediated allergies continue to provide unique challenges
- Lack of clear in vitro specific diagnostic test
- Difficulties in the diagnosis of Food allergy that rely heavily on Oral food challenges and EGD make these emerging diseases
- Ongoing studies maybe able to answer some of the questions
Thanks

- ILSI Health & Environmental Sciences Institute (HESI)
- Protein Allergenicity Technical Committee (PATC) for invitation
- All the families and patients that participate to the study
- APFED/AAAAAI
- FARE
Wheat is a cereal grain composed of 4 fractions of proteins (i.e., albumins, globulins, and “gluten” [gliadins and glutenins]), any of which might elicit an IgE-mediated allergic response. 16% of IgE-mediated allergic patients to wheat react to Rye, up to 16-55% to barley, they usually tolerate oat...
Humoral and cellular responses to casein in patients with food protein–induced enterocolitis to cow’s milk

Jean Christoph Caubet, MD, Ramon Bencharitiwong, PhD, Andrew Ross, BA, Hugh A. Sampson, MD, M. Cecilia Berin, PhD, and Anna Nowak-Węgrzyn, MD

Geneva, Switzerland, and New York, NY
Humoral and cellular responses to casein in patients with food protein–induced enterocolitis to cow’s milk

| TABLE I. Summary of pathologic findings in patients with FPIES compared with control subjects |
|---|---|
| **Positive findings** | **Negative findings** |
| **Humoral responses** |  |
| Lower levels of milk-specific IgG and IgG₄ in patients with CM-FPIES compared with those in patients tolerating CM (active vs resolved) | No difference in levels of specific and total IgM |
| Trend toward lower ratios of casein-specific IgG/total IgG in patients with active CM-FPIES and patients with resolved CM-FPIES compared with those in patients with CM-tolerant FPIES | No difference in levels of specific IgD to casein, α-lactalbumin, and β-lactoglobulin |
| Lower casein-specific IgM/total IgM ratio in patients with active CM-FPIES compared with that in patients tolerating CM | No difference in amounts of total κ Ig-fLC, λ Ig-fLC, CM-specific fLC, or λ Ig-fLC/κ Ig-fLC ratio |
| Significantly lower milk-specific λ Ig-fLC/κ Ig-fLC ratio in patients with active CM-FPIES compared with that in patients tolerating CM |  |
| **T-cell and cytokine responses** |  |
| Significantly lower secretion of IL-10 in patients with CM-FPIES compared with that in patients with IgE-CMA | Proliferating casein-specific CD4⁺ T-cell frequency in patients with CM-FPIES similar to patients with IgE-CMA and control subjects |
|  | No difference found in TNF-α cytokine secretion, as well as IFN-γ and TNF-α secretion |
| **Serum cytokines** |  |
| At baseline: |  |
| 1. Higher median concentration of IL-10 in patients with a negative OFC result compared with those with a positive OFC result | No change in the secretion of MCP-1, MIP-1α, and MIP-1β after a positive OFC result |
| 2. Higher median IP-10 concentration in patients with a positive OFC result |  |
| Significant increase in IL-10 and IL-8 secretion after a positive OFC result |  |
| **Tryptase level before and after an OFC** |  |
| Baseline serum tryptase levels significantly higher in patients with FPIES with a positive OFC result compared with levels in those with a negative OFC result | Serum tryptase levels not significantly different after a positive OFC result in patients with FPIES |

MCP-1, Monocyte chemoattractant protein 1; MIP, macrophage inflammatory protein.
Model of Milk induced inflammation in EoE

- Demaged
- TSLP-SNP
- Esophageal Epithelial Cells
- Basophils
- TSLP
- iNKT cell
- Th0-Th2-Th1-Th17
- Dendritic cells
- Milk-Protein
- Reduced bacteria
- Genetic predisposition (EoE-SNP risk – TSLP-CANP14-EMSY)
- Virus
- Allergen

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