GI Allergy and Tolerance

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Disclosure

• Medical Advisor- Mead Johnson Nutrition
Food Allergy
Types

• IgE mediated
  - immediate
  - dramatic

• Non-IgE mediated
  - less acute
  - more common
Food Allergy
IgE- Mediated Disease

- Older Children, Adults
- Cutaneous, Systemic Manifestations
- Often Foods Other Than Milk (Peanuts, Shellfish)
- Abrupt Onset, Resolution
- Normal Biopsies
Most Common Non-IgE Disorder

Allergic Enterocolitis/Proctocolitis in Infants
Most Common Non-IgE Disorder
Allergic Enterocolitis

• Earlier onset: Age 1-8 weeks
• GI symptoms predominate
• Abnormal biopsies
• Insidious onset and resolution
• Predominantly non-IgE disease but may develop IgE antibodies later
Diagnostic Value Of IgE Testing In G.I. Allergy

- Limited To IgE mediated Disease
  - + Suggests Possibility Of Allergy
  - - Eliminates Possibility Of IgE Allergy
- Patch testing may be more useful in non-IgE disease but is not reliable enough for routine clinical use
- Challenge only reliable means of diagnosis
Endoscopic Diagnosis Of Non IgE Cows’ Milk Protein Allergy

- Rectum -- patchy erythema, loss of ramifying vasculature
- Eosinophilic and plasmacytic infiltrate in the lamina propria (>6 eos/hpf) on biopsy
- Patchy
Allergic Proctocolitis

Lymphonodular Hyperplasia

Ulceration
Allergic Proctocolitis

Eosinophilic Infiltrate
Duodenal Bulb Nodularity: an endoscopic sign of cow's milk protein allergy in infants

Fussy Babies
Differential Diagnosis

• Allergic colitis, enteritis
• Gastroesophageal reflux
• Infantile colic
Gastroesophageal Reflux

- Recurrent emesis
  - Small amounts
  - Soon after feeding
- Irritability
- No response to formula change
- Dramatic Response to acid suppression
<table>
<thead>
<tr>
<th>% of patients</th>
<th>Lanzoprazole (n=81)</th>
<th>Placebo (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom within 1 hour after feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crying, Fussing or irritable</td>
<td>-19.9% (21.1)</td>
<td>-19.9% (22.8)</td>
</tr>
<tr>
<td>Spitting up/vomiting</td>
<td>-14.1% (24.4)</td>
<td>-11.4% (17.3)</td>
</tr>
<tr>
<td>Stopping Feeding after starting</td>
<td>-6.8% (19.8)</td>
<td>-7.5% (14.8)</td>
</tr>
</tbody>
</table>

Infantile Colic

- Episodic crying
- Distracted by stimuli
- Normal periods
- Normal growth and development
- Absence of other symptoms
  - No diarrhea
  - No vomiting
Cow Milk Allergy

- Continuous crying
- Not distracted by stimuli
- Poor feeding
- May have impaired growth
- Vomiting, loose stools
Treatment in Infants
Change Formula

- Soy?
- Extensive Hydrolysate
  - With probiotics?
- Amino acid
- Elimination diet for breast feeding mothers
Infant Formulas That Are Not Hypoallergenic

- Lactose-free
- Soy, and probably rice
- Alternative mammalian milk (goat)
- Partially hydrolyzed formulas
Could a Hydrolysed Rice Protein Formula Induce Sensitization to Rice Protein?

De Boissieu D, Rouziere J. Hospital Necker, Paris, France

<table>
<thead>
<tr>
<th>Atopy Patch Test</th>
<th>With Cow’s Milk</th>
<th>With HRPF</th>
<th>With Native Rice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Case 2</td>
<td>Positive</td>
<td>ND</td>
<td>Positive</td>
</tr>
<tr>
<td>Case 3</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Cost and Hypoallergenicity

• The more hypoallergenic, the more it costs
• Exception-Human Milk
Allergy and IBD Are Becoming More Common

Lehtinen P, et al. Inflamm Bowel Dis 2010
Recently Described Presentations of Food Allergy

- Allergic constipation
- Multiple food protein intolerance
- Allergic colitis in children and adults
Why Do Infants Become Allergic?

- Hyperpermeability of the newborn GI tract
- Immunological immaturity
- Immature gut barrier
- Poor acquisition of tolerance
Paradigm Shift in Food Allergy Management

• Old paradigm: Allergen avoidance
• New paradigm: Tolerance induction
Tolerance induction through breast-feeding?

Mother ingests Food Antigens

Antigen processed by maternal digestive system

Antigens transfer across gut barrier

Infant Exposed to Maternal Diet Antigens & Microbiome

Secreted in Breast Milk

Antigen Hones to Breast

Perez PF et al. *Pediatrics* 2007;119;e724
Immunopathogenesis of Allergy

Cow’s Milk Proteins

Healthy Infant

Immune System

Recognized as “harmless”

Oral tolerance

Non-responsiveness

Atopic Infant

Recognized as “dangerous”

Allergic inflammation

Hyper-responsiveness
Importance of Oral Tolerance

- Oral tolerance: no adverse reactions to cow milk protein
- Oral tolerance: the absence of a clinical and immunological reactions to cow milk protein
- Oral tolerance: the immune system recognizes cow milk proteins as “harmless”
- Oral tolerance is an active regulated immune response
- Oral tolerance is specific to an antigen, in this case cow milk proteins
Allergy vs. Tolerance is Dynamic

Cow’s milk protein

Healthy infant

Recognized as “harmless”
Oral tolerance
No adverse reactions

Atopic Infant

Recognized as “dangerous”
Allergic inflammation

Immune system

Break of tolerance
Acquisition of tolerance

Allergic reactions
Traditional farming environment as a prototypic model situation for an allergyprotective environment

- Mother exposed
- Contact to dung
- Raw and unskimmed milk
- Early Exposure

Contact to dust
Contact to animals
Contact to hay

Holger Garn
Courtesy: Erika von Mutius
ESPGHAN Meeting 28/04/2012
Important Probiotic Concept

• Benefits of probiotics are strain-specific
• These must be proven for each strain in randomized clinical studies
• Not all proven strains are appropriate for all indications
• Think of probiotics like antibiotics, pick the strain proven for the specific disorder you want to prevent or treat
Canis familiaris
Lactobacillus GG

- Single circular chromosome 3.01 Mbp
- 2944 genes
- 0 plasmids
- 331 strain specific proteins (7% secreted or cell surface exposed)
Extent of Rash in Infants with Milk Allergy

LGG in Infants with Cow’s Milk Allergy
Fecal Calprotectin

- 26 infants with cow’s milk allergic colitis
- Randomized to receive EHCF + or - LGG
- Calprotectin was significantly reduced with LGG, compared to control

Baldassarre ME et al. J Pediatr 2010;156:397-401
Occult blood stool after 4 wk. of dietary treatment

<table>
<thead>
<tr>
<th></th>
<th>EHF LGG</th>
<th>EHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Positive</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>14</td>
</tr>
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\[X^2 = 11.798 \quad p = 0.001\]

Baldassarre ME et al. J Pediatr 2010;156:397-401
55 infants (1-12 months of age) with proven CMPA, randomly assigned to two treatment groups: EHCF (28) and EHCF + LGG (27).

After 6 and 12 months (visit 3 and 4) of exclusion diet with one of the two formulas, a DBPC challenge was performed.
• 80 infants with suspected CMA

• Randomized to receive EHCF + LGG or control

• After remission of symptoms, CMA confirmed by oral challenge in 55 patients (study population)

• Rechallenged at 6 and 12 months

• At both timepoints, significantly more infants acquired tolerance in the LGG group vs control

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

Roberto Berni Canani, MD, PhD¹,², Rita Nocerino, CPN¹, Gianluca Terrin, MD, PhD³, Tullio Frediani, MD⁴, Sandra Lucarelli, MD⁴, Linda Cosenza, MD¹, Annalisa Passariello, MD, PhD⁵, Ludovica Leone, LDN¹, Viviana Granata, MD¹, Margherita Di Costanzo, MD¹, Vincenza Pezzella, MS¹, and Riccardo Troncone, MD¹,²

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<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>EHCF vs EHCF + LGG</td>
<td>4.522</td>
<td>2.210-10.521</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>EHCF vs SF</td>
<td>0.400</td>
<td>0.176-0.907</td>
<td>.026</td>
</tr>
<tr>
<td>EHCF vs RHF</td>
<td>0.625</td>
<td>0.377-1.042</td>
<td>.257</td>
</tr>
<tr>
<td>EHCF vs AAF</td>
<td>0.287</td>
<td>0.102-0.806</td>
<td>.015</td>
</tr>
<tr>
<td>EHCF + LGG vs SF</td>
<td>0.083</td>
<td>0.016-0.323</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>EHCF + LGG vs RHF</td>
<td>0.130</td>
<td>0.056-0.300</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>EHCF + LGG vs AAF</td>
<td>0.060</td>
<td>0.027-0.170</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>SF vs RHF</td>
<td>3.063</td>
<td>1.601-5.873</td>
<td>.001</td>
</tr>
<tr>
<td>SF vs AAF</td>
<td>0.718</td>
<td>0.248-2.117</td>
<td>.547</td>
</tr>
<tr>
<td>RHF vs AAF</td>
<td>0.059</td>
<td>0.136-1.350</td>
<td>.152</td>
</tr>
</tbody>
</table>

Figure 3. Rate of patients acquiring tolerance to oral food challenge after 12 months of exclusion diet with different formulas.
The immunomodulatory activity of the 60-69 domain has been widely demonstrated.

The 193-209 domain is encrypted in β-CN 193-209 that has a well established immunomodulatory activity \textit{in vitro}. 
Cow Milk Protein Intolerance/Allergy
Prognosis

• Resolution at varying times
  - many by 1 year
  - some earlier
  - some may persist

• IgE type lasts longer, may be lifelong
Conclusions

• Gastrointestinal allergy is underappreciated
• Effective treatment involves symptom relief and tolerance induction
• Diagnosis imprecise, careful clinical assessment required
• New therapeutic options are becoming available for treatment and promotion of tolerance