Recent Advances in Food Allergy

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November 9, 2015
Outline

• Anaphylaxis
• FPIES
• LEAP study
• Chinese herbal formula
• Baked milk OIT
Time Trends in Australian hospital anaphylaxis admissions

Admission rates (per 100,000 per year)
1998-99 to 2004-05 vs. 2005-06 to 2011-12

• Total anaphylaxis
  – 6.3 to 10.6 (1.7x) vs. 12.2 to 17.7 (1.5x)

• Food-related anaphylaxis
  – 2.0 to 4.5 (2.2x) vs. 5.6 to 8.2 (1.5x)

Time Trends in Australian hospital anaphylaxis admissions

Admission rates (per 100,000 per year)

1998-99 to 2004-05 vs. 2005-06 to 2011-12

• Highest rates in children 0-4 y
  – 7.3 to 21.7 (2.3x) vs. 21.7 to 30.3 (1.4x)

• Greatest proportionate increase in 5-14y
  – 1.7 to 3.7 (2.1x) vs. 5.8 to 12.1 (2.1x)

Time trends for food anaphylaxis

% of total admissions per age group

Relative rates of admission for food-related anaphylaxis, 1999-2012

Conclusions

• Food-related anaphylaxis in Australia increased in all age groups since 2004-05
• Major burden on 0-4 year age group
• Recent acceleration in 5-14 years
• Older teens and young adults
  – Persistent FA has become chronic morbidity
  – Relative risk for fatal anaphylaxis at highest

UK anaphylaxis data 1992-2012

- Trends in anaphylaxis admissions and fatalities in England & Wales over 20yrs

- **615% increase** in hospital admissions from all-cause anaphylaxis
  - 1.0 to 7.0 per 100,000 pop per annum

- **Annual fatality rate stable** at 0.047 cases per 100,000 population

Turner PJ et al. J Allergy Clin Immunol 2015;135:956-63.e1
Highest rate of food-induced anaphylaxis in children and adults <24 years old

Turner PJ et al. J Allergy Clin Immunol 2015;135:956-63.e1
Age-standardized rate was 0.011 cases per 100,000 pop per annum.

Turner PJ et al. J Allergy Clin Immunol 2015;135:956-63.e1
**Fatal MVA in 2009 (US data)**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Fatalities per 100,000 resident population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 5 years old</td>
<td>2.02</td>
</tr>
<tr>
<td>5 to 9 years old</td>
<td>1.84</td>
</tr>
<tr>
<td>10 to 15 years old</td>
<td>3.02</td>
</tr>
<tr>
<td>16 to 20 years old</td>
<td>18.08</td>
</tr>
<tr>
<td>21 to 24 years old</td>
<td>19.11</td>
</tr>
<tr>
<td>25 to 34 years old</td>
<td>13.69</td>
</tr>
<tr>
<td>35 to 44 years old</td>
<td>11.62</td>
</tr>
<tr>
<td>45 to 54 years old</td>
<td>12.10</td>
</tr>
<tr>
<td>55 to 64 years old</td>
<td>10.87</td>
</tr>
<tr>
<td>65 to 74 years old</td>
<td>11.42</td>
</tr>
<tr>
<td>75 years old and over</td>
<td>15.52</td>
</tr>
</tbody>
</table>

US Census Bureau 2012
Suicide & Homicide Rates, 2009

![Graph showing suicide and homicide rates by age group from 0-9 to 65+ in 2009. The graph indicates higher rates in the 25-44 age group for both suicide and homicide, with notable differences between the two categories.]
Fatalities from food anaphylaxis

- 124 fatalities in UK assessed as “highly likely” to be caused by food ingestion
  - Mean age 25 years
  - Asthma in 97 (78%)
  - Prior anaphylaxis in 26 (21%)
  - Triggering food identified in 95 cases
    - Peanut or tree nuts in 69/95 (73%)
    - Cow’s milk in 8/39 (21%) children <16y

Turner PJ et al. J Allergy Clin Immunol 2015;135:956-63.e1
Cause of fatal food-induced anaphylaxis in UK

Turner PJ et al. J Allergy Clin Immunol 2015;135:956-63.e1
Food-induced anaphylaxis hospitalizations doubled in US

FPIES: 10 year experience

- 160 subjects (54% male)
  - median age of diagnosis 15 months
- 180 OFCs to 15 foods in 82 subjects
  - 41% reactive
  - 65% reacted to 1 food, 26% to 2, 9% to 3+
- Severity: hypotension in 14 OFCs
  - 12 milk or soy (86%)
  - 1 each: oat, wheat

FPIES: Foods involved

- Milk only 22%
- Soy only 22%
- Solid only 31%

Rates of concomitant FPIES to multiple foods

<table>
<thead>
<tr>
<th>If FPIES to:</th>
<th>Milk</th>
<th>Soy</th>
<th>Solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>NA</td>
<td>38%</td>
<td>20%</td>
</tr>
<tr>
<td>Soy</td>
<td>37%</td>
<td>NA</td>
<td>14%</td>
</tr>
<tr>
<td>Solid</td>
<td>20%</td>
<td>13%</td>
<td>44%</td>
</tr>
</tbody>
</table>

- More than 50% of the subjects with solid FPIES reacted to 2 or more foods.
- 44% of subjects with FPIES to rice reacted to oat.

### Characteristics of OFCs

<table>
<thead>
<tr>
<th>+OFCs/total # OFCs (%)</th>
<th>74/180 (41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82 subjects</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Symptoms, # (%)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>• Repetitive vomiting</td>
<td>70 (96)</td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td>59 (80)</td>
</tr>
<tr>
<td>• Hypotension</td>
<td>14 (19)</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>5 (7)</td>
</tr>
<tr>
<td>• Lethargy</td>
<td>5 (7)</td>
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<table>
<thead>
<tr>
<th>Timing of reaction, median (range)</th>
<th></th>
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<tbody>
<tr>
<td>• From 1st dose</td>
<td>150 (35-370)</td>
</tr>
<tr>
<td>• From last dose</td>
<td>120 (5-320)</td>
</tr>
<tr>
<td>• To complete recovery</td>
<td>50 (0-460)</td>
</tr>
</tbody>
</table>

OFC reactions

• No statistically significant differences between characteristics of OFCs to milk, soy, grains, or other foods

• Severity of reaction during OFC did not correlate with reported severity of initial reaction to incriminated food

Kaplan-Meier curves for tolerance development

**MILK**
Median 5.1 years if sIgE undetectable

**SOY**
Median 6.7 years

**RICE**
Median 4.7 years

**OAT**
Median 4 years

FPIES: 10 year experience

• FPIES typically resolves by age 5 years

• Milk FPIES, especially with +sIgE, can have protracted course and evolve into acute reactions/anaphylaxis
  – No subject with +milk IgE became tolerant to milk during study
  – Median cow’s milk IgE level 5.14 kU Al/L
    • range, 0.39 to >100; IQR, 0.7 - 37.1

LEAP study

- Infants 4-11 months of age with severe eczema and/or egg allergy
- All infants skin tested to peanut
  - Those with >4 mm wheal excluded
- Randomized into 2 groups
  - Consumption vs. Avoidance
- Primary outcome: % PA at 60 months

Consumption Group

• Baseline open-label food challenge
  – Reaction → avoid
  – No reaction → 6g peanut protein per week until 60 months of age

• Preferred peanut source was Bamba: peanut butter & puffed maize (17g)
  – provides 2g peanut protein

Results

- 640 infants, median age 7.8 months
  - 98.4% retention rate
- Consumption group: median of 7.7g of peanut protein per week during the 1st 2 years of the trial
- Avoidance group: median of 0g
  - Adherence was 92%

Group with (-) peanut SPT

- 530 infants
- Peanut allergy at 60 months of age
  - 13.7% in avoidance group
  - 1.9% in consumption group
- 86.1% relative reduction in PA prevalence

Group with (+) peanut SPT

- 98 infants
  - SPT 1-4 mm

- Peanut allergy at 60 months of age
  - 35.3% in avoidance group
  - 10.6% in consumption group

- 70.0% relative reduction in PA prevalence

Conclusions

• Very early sensitization observed in infants with no history of peanut consumption

• Early oral introduction of peanut can prevent allergy in high risk infants – both sensitized and non-sensitized

Unknowns

• Alternative dosing regimens
• Minimal time needed for “treatment”
• Risks of discontinued or sporadic feeding
  – Will a period of abstinence cause some to react upon re-exposure? LEAP-On study
• Does this apply to other foods?
• Does this apply to low risk infants?
• Unintended consequences
  – Requiring evaluation before peanut consumption may result in more delays in introduction
AAP recommendations

- Introduce soft peanut-containing foods into diets of “high-risk” infants 4-11 months of age in countries with prevalent peanut allergy

- For infants with early atopic disease, consider evaluation by allergist
  - May include skin testing & oral challenge
Serum sIgE more sensitive than SPT as indicator of peanut sensitization in this cohort (4-11 mo)

DuToit G et al. JACI 2013; 131:135-43
EXAMPLES OF PEANUT FOODS used in LEAP trial

- Smooth peanut butter (1 tsp) mixed with milk or with mashed/pureed fruit
- Bamba snack (Osem)
  - 21 sticks or 2/3 oz
  - For infants <7 mos, soften with 20-30 mL water or milk and mixed with milk or with mashed/pureed fruit/vegetables
- Peanut soup
- Finely ground peanuts
  - mixed into other foods such as yogurt

**Whole peanut not recommended due to choking hazard in children <4 years of age**
Peanut avoidance is associated with allergy in high-risk children

Do not delay allergen introduction in the general to low-risk population

Begin changing culture of early feeding practices with regard to allergy
Food Allergy Herbal Formula-2

• FAHF-2 = 9-herb formula
• Multicenter, randomized, DBPC phase II clinical trial (NY, AR, IL)
• 68 subjects, ages 12-45 years
  – 46 received FAHF-2
  – 22 on placebo (corn starch)
• 10 tablets 3 times a day for 6 months

FAHF-2

- FA to PN, TN, fish, SF, sesame confirmed by DBPCFC (2g protein)
- 6 months of FAHF-2 or placebo followed by DBPCFC (5g protein)
- If improved, then another DBPCFC performed 3 months after stopping therapy
- Primary endpoint: % subjects who could consume 2g protein or >4x increased dose compared to baseline


Active vs. Placebo
17.4% vs. 45.5%
success rate
$P = .01$
Was placebo really better?

- Post-hoc analyses performed using NIH-funded CoFAR study protocols
  - Must tolerate at least 500 mg protein if baseline tolerance 0-25 mg
  - Must tolerate at least 10x increase if baseline tolerance 75-250 mg
  - Must tolerate 5g protein or more if baseline tolerance >500 mg
- No statistical difference between 2 groups
### Adherence to study medication

<table>
<thead>
<tr>
<th>Assessments made at each study visit</th>
<th>No. of subjects with adherence &lt;80%</th>
<th>Percentage with adherence &lt;80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 2</td>
<td>8</td>
<td>13%</td>
</tr>
<tr>
<td>Month 4</td>
<td>11</td>
<td>19%</td>
</tr>
<tr>
<td>Month 6</td>
<td>19</td>
<td>32%</td>
</tr>
</tbody>
</table>

FAHF-2 limitations

• Unequal rates of withdrawal
  – 21% in active vs. 5% in placebo

• High tablet load
  – Dropouts
  – Low adherence
    • Nearly ½ had <80% adherence for at least 2 out of 6 months

• Treatment duration suboptimal
  – 2-3 years in humans = 7 weeks in mouse

Baked milk OIT

• 15 patients (>4 years) who previously withdrew from milk OIT in Israel due to reactions

• Baseline OFCs to BM performed
  – Muffin cooked at 350F for 30 min

• Starting dose individualized
  – Less than eliciting dose
  – Increased 50% monthly until 1.3g/d BM

Clinical background and reaction history to milk of BM-reactive

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>14/15</td>
</tr>
<tr>
<td>House dust mite +</td>
<td>7/15</td>
</tr>
<tr>
<td>History of Anaphylaxis</td>
<td>14/15</td>
</tr>
<tr>
<td>Past Epinephrine use</td>
<td>14/15</td>
</tr>
<tr>
<td>Emergency room visit</td>
<td>14/15</td>
</tr>
<tr>
<td>Admissions</td>
<td>7/15</td>
</tr>
<tr>
<td>Epinephrine during Milk-OIT</td>
<td>12/15</td>
</tr>
</tbody>
</table>

Baked milk OIT

• Only 3 (21%) patient tolerated 1.3g/d dose
• Some initially progressed in BM OIT
  – 8/11 developed IgE reactions
    • 2 patients with anaphylaxis requiring IM epi during home maintenance
  – 3/11 developed non-IgE reactions

Baked milk OIT

Baked milk dose (mg) progression for patients >3 months in treatment

Desensitization to unheated milk

OFCs pre-tx, 6 mos, 12 mos


*P < .003
Questions?