Food allergic reactions: can we predict severity?

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Acknowledgements:

IMPERIAL COLLEGE LONDON
Robert Boyle
Adnan Custovic
Stephen Durham
Mohamed Shamji
John Warner

OTHER CENTRES:
Audrey DunnGalvin (Cork)
Geraldine Clough (Southampton)
Bernhard Gibbs (Medway)
Gideon Lack (KCL)
Clare Mills (Manchester)

CAMBRIDGE
Andrew Clark
Pam Ewan

AUSTRALIA
Dianne Campbell

MANCHESTER
Richard Pumphrey
Classification of Reactions

Adverse reaction to food

Non Toxic

Immune mediated (Food Allergy)

IgE mediated
  “Primary” food allergy
  PFAS

Non IgE mediated

Non-immune mediated (Food Intolerance)

Toxic

Coeliac Disease
Food Protein Enteropathies
Eosinophilic Gastroenteropathies
A (na) phylaxis

Originates from Greek, meaning against or without protection.

vs. prophylaxis, for protection

“A rapidly evolving, generalised multi-system reaction characterized by one or more symptoms or signs of respiratory, cardiovascular and other systems such as the skin and/or GI tract.”
Differing perceptions of severity...

- HCPs (Expert, Non-expert)
- Regulatory authorities
- Public
- Industry
- Patient + family
IS ANAPHYLAXIS ALWAYS SEVERE?
FIGURE 1. Annual incidence rate for different events in food-allergic people aged 0–19 years. Data are estimated risk of self-reported/medically coded/fatal food anaphylaxis and hospital admission for food anaphylaxis. Continuous bars represent means with 95% CI, dotted bars represent the range of point estimates from individual studies, in a systematic review undertaken by Umasonthar et al. [4*]. Wherein reference risks vary markedly between European and US populations, they are stated separately. Otherwise, reference risks are for the US population.
83% of (245) teenagers with anaphylaxis don’t use their AAI
Anaphylaxis is not uncommon, but death from anaphylaxis is very rare.

Brown et al., MJA (2007)
Perceptions...

• Food allergy common
• Allergen labelling widespread

Fatal anaphylaxis rare but unpredictable
CAN WE PREDICT SEVERITY?

Or…

what are the factors associated with severe, fatal reactions?
Can we predict severity of reaction / risk of anaphylaxis?

- Age: older child > younger child
- Dose of allergen
- Presence of asthma
- Nature of Allergen (nuts, shellfish, fish)
- Not the size of skin test / ssIgE
  - Predictor of probability of reaction but **not** severity
- ? Linear vs conformational epitopes
- ? Heat-stable vs labile epitopes
Age as a risk factor for fatal food anaphylaxis

Turner et al, JACI 2015
Fatal food anaphylaxis, UK 1992-2007

points 1992–1999 are plotted below the line
points 2000–2007 are plotted above the line
- Presentation e.g. food matrix, dose, route of exposure
- Allergen specific factors
- Host IgE levels and binding affinity/avidity
- Host cellular responses

- Intercurrent infection
- Asthma / BHR
- Cardiovascular disease
- Immune-activation
- Sex/gender, age
- GI absorption
- Other...

- Risk-taking:
  - Allergen exposure
  - (Avail)ability to use AAI
  - Access to EMS
  - Alcohol
  - Medication / drugs
  - Exercise

- Immunological
- Endocrine / hormonal
- Vascular
Allergen-related factors

- Food matrix / other food consumed
- Dose
- Route of exposure

Host immune response
- Host IgE levels
- IgE affinity / avidity
- Host cellular responses
- Risk taking
- Intoxication / situational awareness
- Caffeine
- Environment
- Exercise

Burden of allergic disease
- Asthma/BHR
- Rhinitis
- Eczema
- Mastocytosis
- Immune activation / viral infection

Medications
- ↑ risk:
  - NSAIDs
  - ACE inhibitors
  - β-blockers
  - Mast cell destabilisers
- ↓ risk:
  - Omalizumab
  - OIT

Other host factors
- Sex / gender
- Age
- Gut absorption
- ▲ cardiovascular disease

Ability to compensate
- Immune response
- Hormonal / endocrine
- Metabolism of inflammatory mediators
- Vascular

Inadequate or delayed treatment
- Symptom recognition
- Access to:
  - Rescue medication
  - EMS
- Delay in appropriate therapy

MILD REACTION

SEVERE REACTION

Modified from Smith et al, WAOJ 2015
How does the food matrix affect severity?

- High fat-content matrices may inhibit IgE-binding\textsuperscript{1,2}
  - Limited to allergens naturally high in protein e.g. peanut
  - Higher threshold reported with FC
  - Impacts upon mild “early warning” symptoms which may limit exposure?\textsuperscript{2}

- Heat processing: alters 3D structure (CM+egg proteins)\textsuperscript{3}
  - Dependent on wheat in matrix?\textsuperscript{4}
  - Baked CM/egg tolerated by up to 70% of allergic children\textsuperscript{3}
  - No tangible effect on thresholds?

What is the relationship between dose and severity?

OR

• Does controlling the level of exposure ("dose") limit the resulting symptoms?
Symptoms during FC appear dose-dependent

n=71 peanut allergic children

(Data courtesy Dr A Clark)
21/27 children with +ve OFC developed anaphylaxis:
- 3 as initial symptom
- 13 with subsequent peanut exposure.
Severe reactions can occur at all levels of exposure:

Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE

C. Rolinck-Werninghaus, B. Niggemann, L. Grabenhenrich, U. Wahn & K. Beyer

To cite this article: Rolinck-Werninghaus C, Niggemann B, Grabenhenrich L, Wahn U, Beyer K. Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE. Allergy 2012; 67: 951–957.
But perhaps not:

- University Medical Center Groningen, The Netherlands
- Analysis of 232 DBPCFCs with positive outcome
- Multiple regression analysis using a prediction model
- ED was a significant predictor for severity (along with age, allergen, sslgE).
- But: only 2.1% of the variance in severity was predicted by the level of exposure.
Peanut-allergic individuals with a history of anaphylaxis are not more sensitive to low doses than those without.

Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals

Steve L. Taylor\textsuperscript{a,*}, D.A. Moneret-Vautrin\textsuperscript{b}, Rene W.R. Crevel\textsuperscript{c}, David Sheffield\textsuperscript{d}, Martine Morisset\textsuperscript{b}, P. Dumont\textsuperscript{b}, Benjamin C. Remington\textsuperscript{a}, Joseph L. Baumert\textsuperscript{a}

Food and Chemical Toxicology 48 (2010) 814–819

\textbf{ED}_{10} \text{ doses}\textsuperscript{*} for whole peanut as assessed by the log-normal probability distribution model for Severity Grade.

<table>
<thead>
<tr>
<th>Severity grade</th>
<th>Total no. of peanut-allergic individuals</th>
<th>\text{ED}_{10}</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe\textsuperscript{a}</td>
<td>40</td>
<td>10.4</td>
<td>4.8, 22.6</td>
</tr>
<tr>
<td>Non-severe\textsuperscript{b}</td>
<td>123</td>
<td>10.2</td>
<td>6.4, 16.1</td>
</tr>
<tr>
<td>No prior history\textsuperscript{c}</td>
<td>123</td>
<td>27.0</td>
<td>17.4, 42.0</td>
</tr>
</tbody>
</table>

All values reported in mg whole peanut.
Statistically valid \text{ED}_{05} estimates could not be provided due to the limited number of subjects in all of the severity grade classes.
\textsuperscript{a} Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.

NB: Subjects with prior severe reactions were not excluded.
Dose may be important in determining the occurrence of anaphylaxis in many (but not all) individuals...

Reaction progression

- Dose triggering subjective symptoms
- Dose triggering mild objective symptoms
- Dose causing anaphylaxis

Remember that fatal reactions do not occur to these:

- May contain ........
- Produced on shared equipment which also processes ........
- Made in a production area that also uses ........
- Produced in a factory which handles ........
- Made in a factory that also produces ........

Due to the methods used in the manufacture of this product, it may occasionally contain........

Not suitable for...........allergy sufferers

Packed in an environment where...........may be present

May contain traces of ........
<table>
<thead>
<tr>
<th></th>
<th>Cow’s milk</th>
<th>Egg</th>
<th>Wheat</th>
<th>Soya</th>
<th>Peanut</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ED_{05}</strong></td>
<td>![Cow’s milk sample]</td>
<td>![Egg sample]</td>
<td>![Wheat sample]</td>
<td>![Soya sample]</td>
<td>![Peanut sample]</td>
</tr>
<tr>
<td><strong>ED_{01}</strong></td>
<td>![Smaller Cow’s milk sample]</td>
<td>![Smaller Egg sample]</td>
<td>![Smaller Wheat sample]</td>
<td>![Smaller Soya sample]</td>
<td>![Smaller Peanut sample]</td>
</tr>
</tbody>
</table>

But to these... Not a trace!
Allergen Sanitation in the Food Industry: A Systematic Industrial Scale Approach To Reduce Hazelnut Cross-Contamination of Cookies

MARTIN RÖDER, IRIS BALTRUWEIT, HELWIG GRUYTERS, ANJA IBACH, INGO MÜCKE, REINHARD MATISSEK, STEFAN VIETHS, AND THOMAS HOLZHAUSER

<table>
<thead>
<tr>
<th>Device</th>
<th>Range of product contamination by HNP (mg/kg) after cleaning protocol:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiral kneader</td>
<td>I: 1.5–9.2, II: 0.4–0.5, III: &lt;LOD–0.3</td>
</tr>
<tr>
<td>z-Kneader</td>
<td>I: 16.6–17.3, II: 0.2–0.7, III: 0.3</td>
</tr>
<tr>
<td>Rotary moulder</td>
<td>I: 3.9–140, II: ND, III: &lt;LOD–1.0</td>
</tr>
<tr>
<td>Wire cutting machine</td>
<td>I: 1.7–&gt;1,000, II: ND, III: &lt;LOD–0.9</td>
</tr>
</tbody>
</table>

“With standard cleaning, 50% of individuals allergic to hazelnut could suffer an allergic reaction to just 2 cookies”
SUMMARY

• Severity means different things, to different people
• Life-threatening reactions cannot be predicted
• Severity and sensitivity are separate concepts
  • with a poorly defined relationship between them
• How does dose impact upon severity?
  • Can data from FC inform that relationship?
• Is dose-limitation important in allergen risk management?