Challenges in the management of anaphylaxis
Outline

- Gaps in the evidence

- Anaphylaxis in community settings

- Anaphylaxis and precision medicine
Epidemiology and clinical presentations

- Clinical definition and diagnostic criteria easy to use in practice by emergency room medical staff

- Universally accepted, epidemiological definition and associated coding criteria

- Clearer understanding of the risk factors for future occurrence of anaphylaxis

International Consensus

Large prospective cohort studies/registries
Emergency management

- Optimal dose and dosing intervals of IM adrenaline
- Role of other routes (e.g., inhaled, sublingual)
- Data comparing the pharmacokinetics of different auto-injectors
- Comparative efficacies of crystalloids and colloids in the treatment of CV instability
- Role of second-line drugs (oxygen and inhaled beta-2 agonists)
- Role of third-line interventions (H1-antihistamines and systemic steroids)

Pharmacokinetic and RCTs
Long term management

- Multiple different anaphylaxis management plans in use
- Evidence on the effectiveness and utility of anaphylaxis management plans

Consensus process
Large pragmatic trials

- Who should have an adrenaline auto-injector and how many?
- Will a stock supply of auto-injectors in locations such as schools/restaurants etc improve the management of anaphylaxis in the community?

Large prospective studies, well-phenotyped participants, clear criteria for anaphylaxis
Prophylactic interventions

- Effectiveness of prophylactic premedication
- The impact of other immunomodulatory interventions on reducing the risk of further episodes of anaphylaxis

Large RCT trials
Gaps in the evidence

Anaphylaxis in community settings

Anaphylaxis and precision medicine
Why special management

1. Community exposure

2. Variety of settings – school/early year settings/restaurant/take-away/sport field/camp/beach/friends home ….

3. Management (avoidance + treatment + social vulnerability)
The problem of bullying

The problem of bullying

The problem of bullying

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Child Outcomes Depending on Whether They Experience Bullying Due to Any Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes Bullying Average Score (SD), N = 74</td>
</tr>
<tr>
<td></td>
<td>No Bullying Average Score (SD), N = 177</td>
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<td></td>
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<tr>
<td>MASC-10 (anxiety)</td>
<td>10.29 (5.28)</td>
</tr>
<tr>
<td>PedsQL 4.0-Total</td>
<td>81.20 (11.64)</td>
</tr>
<tr>
<td>PedsQL 4.0-Social</td>
<td>82.26 (16.69)</td>
</tr>
</tbody>
</table>

The adolescent with food allergy

- Condition – specific association with persistent anxiety
  

- Downplay their allergy and frequently engage in risk-taking behavior in terms of their food choices to be similar to their friends
  

- Cyber bullying and the impact of previous adverse child experience
  
How to tackle FAA in adolescents

Tripartite management framework

1. better understanding of adolescence
2. incorporation of the constituents of adolescents' social networks
3. adolescent-tailored healthcare perspectives

Management of FAA in schools

Current recommendations focus on appropriate avoidance measures and prompt recognition and treatment of allergic reactions

School-wide approach, with comprehensive involvement of many stakeholders

Individual students require specific emergency action plan

Management of FAA in schools – key points

Patient/HCP side:

• Accurate diagnosis
• Anaphylaxis action plan developed with their HCP

School preparedness

• a copy of action plan be provided for each student
• epinephrine is readily available
• school personnel properly trained to recognize and treat allergic reactions
• ensure social engagement (bullying, etc)

Recommendations - comprehensive school policy (IV, D)

- Developed by the principal with a staff member coordinating allergy care and acting as liaison with the local allergy service

- Allergy aware management applicable in:
  - School
  - Trips, exchanges, excursions
  - Cooking and handling of food

- Children at risk are identified and proper PCPs are available and updated

- Emergency medication and trained staff readily available

Outline

- Gaps in the evidence
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- Anaphylaxis and precision medicine
Asthma and allergic diseases are ideally suited for precision medicine

Umbrella of different diseases that partially share biological mechanisms (endotypes) and present similar visible properties (phenotypes) requiring an individualized approach for:
- a better selection of treatment responders
- risk prediction
- design of disease-modifying strategies

Precision medicine and anaphylaxis

Risk prediction

Response to immune modulation
Biomarkers in anaphylaxis

- Tryptase levels
- Molecular sensitisation profiles
- BAT test
- DNA methylation biomarkers
Tryptase levels and FA anaphylaxis

Sahiner UM, et al Allergy. 2014;69(2):265-8
Tryptase levels – word of caution

1. Impact of age and sex

1. Interference of heterophylic antibodies (autoantibodies or anti-animal antibodies are able to interfere with sandwich immunoassays)

1. Thresholds
Tryptase levels increase with age and are significantly higher in males.

CMA

A. Reaction level
11.4 μg/L (OR = 4 for anaphylaxis, 7.4 for severe reaction)

B. Postreaction
> 2 ng/mL + 1.2 × (baseline tryptase level)

Role of component resolved diagnosis (CRD)

CRD have been introduced in order to increase the **probability** of:

1. Differentiate between sensitisation and disease
2. Identify patients at high risk of severe reactions
3. Identify patients more prone to persistent disease

1. Predict response to AIT

CRD - the EAACI U-shape approach

### Biomarkers in anaphylaxis (besides tryptase)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venom anaphylaxis</td>
<td>Api m1, Ves v 1, Ves v 5, and Pol d 5</td>
</tr>
<tr>
<td></td>
<td>Basal platelet-activating factor acetylhydrolase</td>
</tr>
<tr>
<td></td>
<td>Expression and function of C5a receptor in endothelial cells</td>
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<td></td>
<td>The angiotensinogen AGT p.M235T gene polymorphism</td>
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<tr>
<td></td>
<td>9α,11β-PGF2 (mast cell activation)</td>
</tr>
<tr>
<td>VIT anaphylaxis</td>
<td>High basophil allergen CD63 sensitivity phenotype</td>
</tr>
<tr>
<td>Latex anaphylaxis</td>
<td>Hev b 1, Hev b 3, Hev b 5, and Hev b 6</td>
</tr>
<tr>
<td>Shrimp anaphylaxis</td>
<td>Tropomyosin, sarcoplasmic-calcium-binding-protein, myosin light chain</td>
</tr>
<tr>
<td>Peanut anaphylaxis</td>
<td>Ara h2, Ara h6</td>
</tr>
<tr>
<td>Wheat induced anaphylaxis</td>
<td>ω-5-gliadine, HMW and LMW glutenin, gliadin</td>
</tr>
<tr>
<td>Co-factor induced anaphylaxis</td>
<td>ω-5-gliadine, lipid transfer proteins (LTP)</td>
</tr>
<tr>
<td>Red meat delayed anaphylaxis</td>
<td>α-gal</td>
</tr>
<tr>
<td>Anisakis allergy</td>
<td>Ani s1, Ani s4, Ani s7, and Ani s13</td>
</tr>
<tr>
<td>Mild reactions</td>
<td>Carbohydrate determinants and profilins</td>
</tr>
</tbody>
</table>
BAT predicting risk - venom

BAT predicting risk - peanut and nut

BAT - monitoring treatment

Blood DNA methylation biomarkers

A DNAm signature of 96 CpG sites outperformed allergen-specific IgE and skin prick tests for predicting OFC outcomes.

FA status was correctly predicted in the replication cohort with an accuracy of 79.2%.

Summary

Key points for moving the field forward:

• Profiling anaphylaxis subendotypes (specific biomarkers)

• Use relevant targets:
  • Risk assessment
  • Prognostic value
  • Health economics
  • Quality of life

• Build consensus amongst stakeholders
Guidelines

Grounded in evidence based on;
- Comprehensive **systematic reviews**
- **Meta-analyses** of literature, where appropriate

- Will support health care professionals' use of AIT
- Will highlight benefits at public and policy maker levels
- Will promote **health economics** of AIT

Available on [www.eaaci.org](http://www.eaaci.org)
The EAACI Molecular Allergology User’s Guide is a straightforward guide on molecular allergology describing what are components, the clinical benefits of testing for components as well as how to interpret results including understanding cross-reactions. It is divided into four parts with 41 chapters written by 65 authors.

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Impact Factor 6.335

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