Anaphylaxis

Stephen R Durham
Head, Allergy and Clinical Immunology, Imperial College London and Royal Brompton and Harefield Hospitals NHS Foundation Trust

Isabel Skypala
Consultant Dietician, Royal Brompton and Harefield Hospitals NHS Foundation Trust

Paul Turner
MRC Clinician Scientist & Hon Consultant in Paediatric Allergy & Immunology, Imperial College London
Anaphylaxis

• Epidemiology
• Clinical features
• Pathophysiology
• Management
  ▪ Acute
  ▪ Long term (prevention)
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.”
Epidemiology

- Uncommon

- Incidence:
  - 8.4 - 21 per 100,000 patient years\(^1\)
  - 30-950 per 100,000 patient years\(^2\)
  - Lifetime prevalence of 1:1333 for UK population\(^3\)

\(^1\)Brown et al., MJA (2007); Sampson et al. JACI (2005)
\(^3\)Stewart AG, Ewan PW, Quarterly Journal of Medicine (1996)
Mortality

- About 1 per 1 - 3 million population p.a.
- In ED (Aus): 1 per 100-200 episodes
- Approx 20-30 deaths p.a. in UK, probably an underestimate.
  \[ \approx 1 \text{ per 100,000 patient years} \]
- Most due to medication or blood Tx, sometimes to insect stings; food less common.

Brown et al., MJA (2007)
Anaphylaxis is not uncommon, but death from anaphylaxis is very rare.
Adrenaline auto-injector devices

Thousands of prescriptions

150mcg
300+mcg
TOTAL

Hospital admissions for anaphylaxis

ICD Change

Admissions per 100,000 population

Year

Male
Female

Hospital admissions for anaphylaxis
Anaphylaxis: fatalities by age group

Addressing fatalities by age group, the data illustrates a notable pattern. The chart above delineates fatalities categorized by age group, with data points marked for food, drug, and insect sting. The lower chart provides a rate per 100,000 population, emphasizing the contrast and distribution across different age brackets.
Causes

- Foods
- Drugs
- Insect Stings
- Exercise
- Idiopathic
Foods commonly causing anaphylaxis

- Peanut
- Tree nuts
- Shellfish
- Milk
- Egg
- Fish
- Fruit
- Wheat
- Soy
- Sesame
Drugs causing anaphylaxis

Antibiotics
- Penicillins/other Beta-lactams
- Non-Beta-lactam antibiotics

General anaesthesia
- Neuromuscular blockers
- Anaesthetic agents
- Latex

Aspirin/NSAID’s
ACE-inhibitors
IV radiocontrast media

Others:
- Local anaesthetics
- Plasma expanders
- Insulin
- Heparin
- Chlorhexidine
- Opiates
- Vaccines
- Corticosteroids
# Stinging insects in UK

<table>
<thead>
<tr>
<th>Insect</th>
<th>Description</th>
<th>Image</th>
<th>Field stings-usual time of year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasp (Vespula vulgaris)</td>
<td>~19 mm long, yellow head with black stripes, black thorax with yellow sides, yellow abdomen with black bands, black antennae and yellow legs.</td>
<td><img src="image1.jpg" alt="Wasp Image" /></td>
<td>March–October</td>
</tr>
<tr>
<td>European Hornet (Vespa crabro)</td>
<td>35 mm long, reddish brown head, black and brown shaded thorax, yellow and black shaded abdomen.</td>
<td><img src="image2.jpg" alt="European Hornet Image" /></td>
<td>March–October</td>
</tr>
<tr>
<td>Honey bee (Apis mellifera)</td>
<td>12.7–25.3 mm, covered with short dense hair, usually golden brown and black, abdomen striped.</td>
<td><img src="image3.jpg" alt="Honey Bee Image" /></td>
<td>March–October, occasionally even in warm winter days</td>
</tr>
</tbody>
</table>
Key clinical features of anaphylaxis

1. Generalized allergic reaction with respiratory and/or cardiovascular involvement
   ➔ Respiratory much more prevalent in children

2. Involvement of many parts of the body

3. Rapid onset and progression.
Clinical Manifestations

Skin:
- Flushing
- Pruritus
- Urticaria
- Angioedema

CVS:
- Tachycardia (bradycardia)
- Hypotension/shock
- Arrhythmias
- Ischaemia, chest pain
Clinical Manifestations

Upper respiratory:
- Congestion
- Rhinorrhea
- Swelling

Lower respiratory:
- Throat/chest tightness
- Hoarseness
- Bronchospasm
- Wheeze, cough

GI tract:
- Oral pruritus
- Cramps, nausea, vomiting, diarrhoea
# Clinical Manifestations

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td>90%</td>
</tr>
<tr>
<td>Urticaria and Angioedema</td>
<td>85-90%</td>
</tr>
<tr>
<td>Flushing</td>
<td>45-55%</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>40-60%</td>
</tr>
<tr>
<td>Dyspnea and Wheeze</td>
<td>45-50%</td>
</tr>
<tr>
<td>Laryngeal Angioedema</td>
<td>50-60%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>25-20%</td>
</tr>
<tr>
<td><strong>CVS</strong></td>
<td>30-35%</td>
</tr>
<tr>
<td>Dizziness, syncope, hypotension</td>
<td></td>
</tr>
<tr>
<td><strong>Gut</strong></td>
<td>25-30%</td>
</tr>
<tr>
<td>n+v, cramp, diarrhoea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Food</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Respiratory</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma/atopy</td>
<td>Common</td>
</tr>
<tr>
<td>Onset</td>
<td>Less rapid</td>
</tr>
<tr>
<td>Site of Ag presentation</td>
<td>Orogastric mucosa</td>
</tr>
<tr>
<td>Triggering threshold</td>
<td>++ interperson variability</td>
</tr>
<tr>
<td></td>
<td>(up to 4 log)</td>
</tr>
<tr>
<td>Mechanism</td>
<td>No change in MCT seen,</td>
</tr>
<tr>
<td></td>
<td>frequently</td>
</tr>
</tbody>
</table>
Risk factors for death from food-induced anaphylaxis

- Trigger: Peanut / tree nut / fish most common
- Asthma (even well controlled), cardiac disease
- Mastocytosis
- Previous allergic reaction to same food
- Biphasic course
- Not at home when reaction occurs
- Non-timely delivery of adrenaline but mortality not prevented by early adrenaline alone

Sampson et al, NEJM (1992)
Pathophysiology

Trigger

IgE-mediated Pathway

Mast cells

Symptoms of anaphylaxis

IgE-independent mechanism

?
PRODUCTS OF MAST CELL ACTIVATION

- **Histamine**
- **Proteoglycans**
  - heparin
  - chondroitin sulphate
- **Proteases**
  - tryptase, carboxypeptidase, chymase, cathepsin G, elastase, plasminogen activator, renin, matrix metalloprotease 9
- **Cytokines**
  - IL-4, IL-5, IL-6, IL-8, IL-13, GM-CSF, TNF-α, fibroblast growth factor, stem cell factor
- **Other Enzymes**
  - β-hexosaminidase
  - β-glucuronidase
  - arylsulphatase
- **Lipid mediators**
  - prostaglandin D₂
  - leukotriene C₄
  - platelet activating factor
MANAGEMENT
Anaphylactic reaction?

Airway, Breathing, Circulation, Disability, Exposure

Diagnosis - look for:
• Acute onset of illness
• Life-threatening Airway and/or Breathing and/or Circulation problems
• And usually skin changes

• Call for help
• Lie patient flat
• Raise patient’s legs

Adrenaline

When skills and equipment available:
• Establish airway
• High flow oxygen
• IV fluid challenge
• Chlorphenamine
• Hydrocortisone

Monitor:
• Pulse oximetry
• ECG
• Blood pressure
**Management**

Check ABC
Call for help
Lie person flat, raise legs
Give IM adrenaline
Establish Airway, high flow O2
Establish IV line, fluid challenge
Chlorpheniramine IV
Hydrocortisone IV
Repeat IM Adrenaline
(if no response after 5 min )

**Monitor**

Pulse
Blood pressure
Pulse Oximetry
Peak flow rate
Blood sample for tryptase at 60 min
First Line Treatment of Anaphylaxis: Adrenaline IM:

0.5 ml of 1:1000 Adrenaline

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>500 micrograms IM (0.5 mL)</td>
<td></td>
</tr>
<tr>
<td>Child more than 12 years</td>
<td>500 micrograms IM (0.5 mL)</td>
<td></td>
</tr>
<tr>
<td>Child 6-12 years</td>
<td>300 micrograms IM (0.3 mL)</td>
<td></td>
</tr>
<tr>
<td>Child less than 6 years</td>
<td>150 micrograms IM (0.15 mL)</td>
<td></td>
</tr>
</tbody>
</table>
Adrenaline Auto-injectors

- Recommended for patients with previous anaphylaxis
- Training essential
- Anaphylaxis action plan essential
- Seek advice if needed.
Who needs an AAI - EAACI Guidance

Absolute indications:
- Previous cardiovascular or respiratory reaction to a food, insect sting or latex.
- Exercise induced anaphylaxis.
- Idiopathic anaphylaxis.
- Child with food allergy and co-existent persistent asthma*.

Relative indications:
- Any reaction to small amounts of a food (e.g. airborne food allergen or contact only via skin).
- History of only a previous mild reaction to peanut or a tree nut.
- Remoteness of home from medical facilities.
- Food allergic reaction in a teenager.
NOT Recommended:

- Asthma without anaphylaxis or systemic allergy
- Positive skin or sIgE test only
- Family history of anaphylaxis
- Local reactions to insect stings
- Resolved food allergy
Food-induced Allergic Disorders

IgE-mediated

- Pollen Food Allergy Syndrome
  - Urticaria
  - Angioedema
  - Rhinoconjunctivitis
  - Asthma
- Gastrointestinal
  - Anaphylaxis
  - Food-dependent Anaphylaxis

Mixed IgE and Non IgE-mediated

- Atopic eczema Dermatitis
- Eosinophilic Gastrointestinal Disorders

Cell-mediated

- Dietary protein-induced Proctitis & Proctocolitis
- Food Protein-Induced Enterocolitis Syndrome (FPIES)

Dietary protein-induced Proctitis & Proctocolitis

Allergy: European Journal of Allergy and Clinical Immunology

EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy

Food Allergy Standard diagnostic tests

- Clinical history is cornerstone of diagnosis
- Skin tests/sIgE provide objective confirmation of IgE sensitisation
- Skin tests/IgE have a good negative predictive value
- Skin tests/ IgE have low positive predictive value
- If history suggestive, interpret negative SPT/sIgE with caution (Muraro 2014)

- IgE sensitization to foods is common and often related to IgE sensitization to pollen allergens (Burney et al 2014)
- High total IgE may skew results (Gupta et al 2014)
Aeroallergen sensitisation

Establishing symptoms to pollens, mites and animal dander is vital when interpreting the history.

Positive tests to pollen or house dust mite can be linked to reported cross-reactive reactions to fruits, vegetables, nuts or shellfish.
SPT to common inhalant allergens
Prick-to-prick testing for foods
Component resolved diagnosis

- Molecular allergy testing
- Immunocap or microarray tests (eg ISAC chip)
- If tests inconclusive, CRD provides additional diagnostic information (Muraro et al 2014)
Foods (component resolved diagnosis)

The following have been associated with severe allergy and *high risk* of anaphylaxis:

Peanut (Ara h 1, Ara h 2, Ara h3 and Ara h 9)

Hazelnut (Cor a 9, Cor a 14)

Soya bean (Gly m 5, Gly m 6)
The following have been associated with cross reactive sensitisation birch pollen Bet v 1 (pollen food syndrome) and *low risk* of anaphylaxis:

Peanut *(Ara h 8)*

Hazelnut *(Cor a 1)*

Soya bean *(Gly m 4)*
Risk assessment in food allergy (role of CRD?)

Higher risk

nsLTPs
(Pru p 3, Cor a 8, Jug r 3, Ara h 9, Tri a 14)

Storage proteins
Ara h 1, Ara h 2, Ara h 3, Cor a 9, Cor a 14, Jug r 1, Jug r 2, Gly m 5, Gly m 6)

PR10 (Gly m 4)

Wheat \(\omega_5\)-gliadin (Tri a 19)

Profilins (Cor a 2, Pru p 4, Mal d 4, Cuc m 2, Dau c 4)

PR-10 (Ara h 8, Cor a 1, Mal d 1, Cuc m 1, Dau c 1)

CCD

Lower risk

Luengo and Cardona Clinical and Translational Allergy 2014, 4:28
http://www.ctajournal.com/content/4/1/28
Insect stings
(component resolved diagnosis)

Wasp venom
- rVes v 1
- rVesp v 5

Bee venom
- Api m 1

Polistes (paper wasp) venom
- Pol d 5
Recommendations for Diagnosis

Standardised tests and procedures should be used

IgE sensitisation does not always predict clinically relevant food allergy – specific allergy testing should be directed by case history

Either SPT or sIgE can be used depending on local availability and contraindications for SPT

Evidence of IgE sensitisation can support a diagnosis of food allergy in conjunction with clinical history and/or food challenge

In the presence of a suggestive history, a negative SPT/sIgE needs to be interpreted with caution

If tests inconclusive, CRD may provide additional diagnostic information
If clinical history plus SPT/sIgE results not highly predictive then oral food challenge is required

Total IgE useful in patients with severe eczema; high total IgE suggests +ve sIgE tests should be interpreted with care
Education & Risk Assessment

Education:
Diagnosis communicated to patients, parents/caregivers care givers
Management plan - allergen avoidance, symptom recognition, indication for treatment and administration of specific medication
Encourage contact with patient organisations

Medication:
Adrenaline - previous anaphylaxis, asthma, FDEIA
- persistent FA, peanut/tree nut FA, low threshold, high risk
When – cardiovascular/respiratory altered voice, stridor, bronchospasm
Short-acting beta agonists required for all with co-existing asthma
Patient-held glucocorticosteroids to prevent late phase reactions
Review in emergency department for all who have received adrenaline
Acknowledgements

Isabel Skypala
Consultant Dietician, Royal Brompton and Harefield Hospitals NHS Foundation Trust

Paul Turner
MRC Clinician Scientist & Hon Consultant in Paediatric Allergy & Immunology,
Imperial College London