Recent advances in clinical immunology & allergy

William Smith
Clinical Immunology & Allergy
RAH/AllergySA
Topics

- Angioedema - the role of bradykinin, hereditary angioedema and ACE-inhibitors
- Chronic Urticaria - autoimmunity, mast cells, anti-IgE
- Exercise-induced anaphylaxis and wheat omega-5-gliadins
- Oral immunotherapy for severe food allergies
Angioedema

- Localised deep subcutaneous swelling, usually painless
- Idiopathic
- Allergic
  - food (IgE-mediated or food chemical intolerance)
  - drug (eg. penicillins or NSAID)
- Drug-induced (peptidase inhibitors)
- C1 inhibitor deficiency
  - Hereditary (type 1,2)
  - acquired
- Other hereditary angioedema (type 3)
  - Factor XII activating mutations
Bradykinin in angioedema

- **Histamine**
  - Allergic: All
  - Idiopathic: Most (80%) Some (20%)
  - ACE-inhibitor: All
  - Hereditary Angioedema: All
  - Acquired C1 Inhibitor deficiency: All

**Diagram**

- **Patient 1**
  - 77 fmol/ml
- **Patient 2**
  - 46 fmol/ml
  - 16 fmol/ml

**Normal Range** 0.2-7.1 fmol/ml
C1 inhibitor

Factor XII → Factor XIIa → Factor XIIf

Prekallikrein → Kallikrein

HMW Kininogen → Bradykinin → BDP

Bradykinin2 Receptor
Bradykinin

HMW Kininogen $\rightarrow$ Bradykinin $\rightarrow$ BDP $\rightarrow$ Bradykinin2 Receptor $\rightarrow$ Angioedema

Prekallikrein $\rightarrow$ Kallikrein

Factor XII $\rightarrow$ Factor XIIa $\rightarrow$ Factor XIIIf

C1 $\rightarrow$ C1i

C4 $\rightarrow$ C4b $\rightarrow$ C2 $\rightarrow$ C2b

Factor XIIa $\rightarrow$ surface

• Inherited deficiency of C1-inhibitor due to mutation SERPING1
  – Type 1- deficient protein
  – Type 2- dysfunctional protein
• Incidence 1:10,000-1:100,000
• Estimated cases in Australia ~500
• Autosomal Dominant (25% new mutations)
• Median age of onset 11, median age of diagnosis 26

• Spontaneous recurrent angioedema
• Episodes last 2-5 days
• Life-threatening, painful, debilitating
• 30% >1/month, 40% 6-11/year, 30% seldom
• Affect skin (100%), gut (97%), larynx (54%), uvula (22%), tongue (9%)
Hereditary Angioedema

- Intestinal angioedema - pain, distention, obstruction
- Duration 1-3 days
- Mimics other pathology - diagnosis often delayed, unnecessary surgery

- Laryngeal oedema
- Medical emergency
- 1/3 HAE deaths due to asphyxiation, 30 years premature
  - historical data
  - Most deaths in undiagnosed HAE

Diagnosis - C4 level
Hereditary Angioedema

- Bradykinin Antagonist - Icatibant (Firazyr®)

- C1-inhibitor for long-term prophylaxis

**Median time to first symptom improvement**

<table>
<thead>
<tr>
<th></th>
<th>FAST-1</th>
<th>FAST-2</th>
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<tbody>
<tr>
<td>Firazyr®</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Placebo</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>-</td>
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**Graph**

- Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema.
Safety, Pharmacokinetics, and Pharmacodynamics of Avoralstat, an Oral Plasma Kallikrein Inhibitor: Phase 1 Study

Allergy Online 12th May 2016
Hereditary Angioedema

Position Paper on Hereditary Angioedema (HAE)

August 2012 (to be revised in 2015)

Prof Conrie Katsarlis, Dr William Smith, Dr Raymond Mullins, Dr David Gillis

This is a revised version of the original ASCIA Position Paper on Hereditary Angioedema (HAE) developed by the ASCIA HAE Working Party in 2010.

Chair: Prof Conrie Katsarlis
Members: Dr Karl Baumgart, Dr David Gillis, A/Prof Alysson Kakakios, A/Prof Richard Loh, Dr Raymond Mullins, Dr Robert Fuy, Dr William Smith, A/Prof Min Tang, Dr Melanie Wong.

ABBREVIATIONS USED IN DOCUMENT

ACE angiotensin converting enzyme
ASCIA Australasian Society of Clinical Immunology and Allergy
C1 INH C 1 inhibitor
ED emergency department
HAE hereditary angioedema
HRT hormone replacement therapy
IRT individual replacement therapy
OCP oral contraceptive pil
PBS Pharmaceutical Benefits Scheme
PID primary immunodeficiency
TA tranexamic acid
TGA Therapeutic Goods Administration
SAS Special Access Scheme

ACTION PLAN FOR Hereditary Angioedema (HAE)

MILD HAE SYMPTOMS
- Periorbital swelling, mild facial swelling
- Mild abdominal pain

ACTION
- Pain relief
- Observe for progression

MODERATE TO SEVERE HAE SYMPTOMS - PERIPHERAL SWELLING
- Severe facial, genital or peripheral swelling, causing significant discomfort or disability

ACTION
- In adults administer icatibant (Firazyr) subcutaneously or C1 INH (Berinert) 20 U/kg iv or Cinryze 1,000 U MXP²
- In children administer C1 INH (Berinert) 20 U/kg iv or Cinryze 3,000 U MXP³

MODERATE TO SEVERE HAE SYMPTOMS - ABDOMINAL SYMPTOMS
- Moderate to severe abdominal pain
- Vomiting, diarrhea
- Dehydration (e.g. dry mouth, thirst, confusion)

ACTION
- In adults administer icatibant (Firazyr) subcutaneously or C1 INH (Berinert) 20 U/kg iv or Cinryze 1,000 U MXP²
- In children administer C1 INH (Berinert) 20 U/kg iv or Cinryze 3,000 U MXP³
- Seek urgent hospital treatment if symptoms worsen or last longer than 2 hours

ADDITIONAL HOSPITAL TREATMENT:
- Ondansetron
- IV fluid rehydration
- Give 2nd dose of specific treatment

MODERATE TO SEVERE HAE SYMPTOMS - AIRWAY SWELLING
- Tongue swelling
- Throat swelling
- Difficulty with breathing, swallowing, talking (hoarse voice)

ACTION
- In adults administer icatibant (Firazyr) subcutaneously or C1 INH (Berinert) 20 U/kg iv or Cinryze 1,000 U MXP²
- In children administer C1 INH (Berinert) 20 U/kg iv or Cinryze 3,000 U MXP³
- Phone ambulance - 000 (ALL) or 112 (mobile)
- Seek urgent hospital treatment

ADDITIONAL HOSPITAL TREATMENT:
- Prepare for emergency intubation or tracheostomy
- Give 2nd dose of specific treatment if inadequate response after 1 hr

NOTE: 1. Baseline FDP is determined using regular clotting assay
2. Patients can self-inject at home or at hospital
3. C1-INH (C1 esterase inhibitor concentrate) is approved for use in children and adults with HAE
4. Protocols used in this Action Plan may vary regulated hence this information is specific for HAE treatment in Australia
5. Additional medications and treatments are ineffective for HAE attacks.
C1 inhibitor for:

- treatment of acute HAE attacks
- pre-procedural prophylaxis (for high risk procedures)
- routine prophylaxis (for patients who experience eight or more acute attacks per month).
ACE-inhibitor induced angioedema

- 0.5-5%
- first days—many years of treatment
- usually no trigger
- tends to be head/neck
- prolonged intubation/fatalities reported
- not responsive to antihistamines, corticosteroids, adrenaline
- also ARB, DPP4-inhibitors, rtPA

- supportive management
- if available, can use icatibant (unregistered- SAS-A)

Therapeutic Efficacy of Icatibant in Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors: A Case Series

Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema

J. S. Fok, C. H. Katelaris, A. F. Brown, and W. B. Smith
Chronic Urticaria

- Chronic Idiopathic Urticaria
- Chronic Spontaneous Urticaria
Chronic (idiopathic) (spontaneous) urticaria

Classical activation by allergen

Activation by autoantibodies

Histamine, other mediators

Anti-FcεR1

Anti-(cell bound) IgE
Chronic (idiopathic) (spontaneous) urticaria
Chronic (idiopathic) (spontaneous) urticaria

Classical activation by allergen

Activation by autoantibodies

Histamine, other mediators
Chronic (idiopathic) (spontaneous) urticaria
Chronic (idiopathic) (spontaneous) urticaria

- 60% autoimmune
- 40% remain idiopathic
SEVERE CHRONIC URTICARIA\(^{(A,B)}\)

Check for reversible causes\(^{(C)}\):
- Clinical diagnosis
  - UAS > 16\(^{th}\) Lasting for more than 6 weeks
  - With or without angioedema
- Urticaria may be spontaneous or may have physical triggers (not the same disease but management pathway similar)
- Drug allergy, food intolerance, Helicobacter or other infection, GLE
- May have an autoimmune basis but this cannot be confirmed by currently available tests
- Non-sedating 2X or 4X standard dose of H1 blocker (cetirizine) add doxepin add montelukast

SEVERE CHRONIC IDIOPATHIC URTICARIA\(^{(D)}\)

Responds to antihistamines\(^{(E)}\):
- Yes
  - Continue antihistamines
- No
  - Trial immunomodulatory medication\(^{(F,G)}\)
    - Hydroxychloroquine 500-400mg/day (2 months)
    - Dapsone 100mg/day (1 month)
    - Cyclosporin 2.5-5mg/kg/day (1 month)

Response
- Proceed through in order depending on response, tolerance, contraindications (time to assess response)
- Can also trial colchicine, methotrexate, azathioprine, sulfasalazine, mycophenolate mofetil

CONTINUE 6-12 months then trial cessation
Omalizumab - anti-IgE

- Binds free IgE in circulation
- Anti-allergy
- Efficacy in asthma
- Other disorders-
  - Food allergy
  - Allergic rhinitis
  - Anaphylaxis
  - Adjunct to immunotherapy
Omalizumab for CU

- Case reports
  - (antihistamine-resistant cases)
- Now large RCT (4 trials, >1,000)
- Mechanism? (mast cell FcεR1)
High-affinity anti-IgE

ligelizumab
omalizumab

ligelizumab
omalizumab

ligelizumab
omalizumab
Nov 2015
PBAC recommends listing of omalizumab for chronic idiopathic urticaria (S100 Highly Specialised Drugs Program)
WHEAT-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

Adriana Le, Mahmood Al Kindi, Anthony Smith, JuAnn Tan, Pravin Hissaria, Bob Heddle, Frank Kette, William Smith
Coeliac disease
Classic food allergy (urticaria, anaphylaxis- pediatric)
Baker’s asthma
Wheat-dependent exercise-induced urticaria/anaphylaxis (WDEIA)
Non-coeliac gluten sensitivity (??)
Fructose/Fructan/FODMAP intolerance
Hydrolysed wheat protein (HWP) contact allergy
Asymptomatic wheat sensitisation
Wheat flour contamination with mites, mould
Factors may modify/potentiate/trigger anaphylaxis:

- Exercise
- NSAID
- Alcohol
- Stress
- Pyrexia
- Menses

- Food-dependent exercise-induced anaphylaxis (FDEIA)
  - Wheat, Shellfish, any allergenic food

- Food usually tolerated, unless followed by exercise
Wheat seed = 10-15% protein

Proteins divided into fractions:
- Water soluble (Albumins)
- Salt soluble (Globulins)
- ETOH soluble (Gliadins)
- Insoluble (Glutenins)

Gliadins + Glutenins = Gluten

Gliadins (wheat), secalins (rye), hordein (barley) -> ‘Glutens’

Gliadins -> α/β, γ, ω -> ω1-ω5

Critical Component ω5-Omega-5-gliadin (O5G)
Serum gliadin levels

Wheat alone

Exercise alone

Wheat + exercise

Wheat + aspirin
WDEIA

- Wheat-Dependent Exercise-Induced Anaphylaxis
- Specific IgE to O5G (Immunocap assay)
- 2007-2013- 67 individuals with positive tests (SA Pathology)
  - Age 22-84 (median 44)
  - Male 60%
  - Symptom onset to diagnosis 0.5-14 years (median 2.6)
- Survey of presenting clinical features & cofactors- clinical spectrum
O5G allergy

Initial presentation pattern

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of pts (N = 67)</th>
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<tbody>
<tr>
<td>Wheat-dependent exercise-induced urticaria or anaphylaxis (WDEIU/A)</td>
<td>13</td>
</tr>
<tr>
<td>Food-dependent exercise-induced allergy (FDEIA)</td>
<td>13</td>
</tr>
<tr>
<td>Exercise-induced urticaria or anaphylaxis (EIUI/A)</td>
<td>16</td>
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<tr>
<td>Idiopathic anaphylaxis (IA)</td>
<td>10</td>
</tr>
<tr>
<td>Food-induced allergy (FIA)</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent acute urticaria (RAU)</td>
<td>5</td>
</tr>
</tbody>
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Brown severity grade of reported episodes

- 1 only: 30%
- 1 and 2: 35%
- 1, 2 and 3: 30%
- 3 only: 5%

Symptoms:
- Erythema/warmth: 90%
- Pruritis: 80%
- Urticaria: 70%
- Angioedema: 60%
- SOB/wheeze: 50%
- Chest/throat: 40%
- Nausea/vomiting: 30%
- Diarrhoea/incontinence: 20%
- Cyanosis/desaturation: 10%
- Hypotension: 5%

Brown severity grade:
- Grade 1: 10%
- Grade 2: 20%
- Grade 3: 70%

Cofactors:
- No co-factor: 80%
- Exercise: 70%
- Alcohol: 60%
- Aspirin: 50%
- Non-aspirin NSAIDs: 40%
- Ambient heat: 30%
- Psychological stress: 20%
- More than one co-factor: 10%
sIgE to O5G + wheat ingestion + cofactor = allergic reaction

Nature and severity of allergic reaction variable- urticaria → anaphylaxis

Characterised by inconsistent reactions- unpredictable

Management- eliminate wheat, or avoid wheat + cofactors?
  - Eliminate wheat- 3/13 had repeat reactions (accidental ingestion)
  - Avoid combination- 7/14 had repeat reactions

Epipen
Oral immunotherapy for food allergy

Collaborators:
FMC- Billy Tao, Tim Chataway
UniSA- Preethi Eldi, John Hayball
Food allergy increasing
Oral immunotherapy for peanut allergy

• Introduction of peanut at sub-threshold dose, periodic updosing under observation
• Clinical trials
  • initial challenge to prove peanut allergy (not just sensitisation)
  • Outcome
    – achievement of target dose
    – adverse reaction rate
    – tolerance of peanut challenge
      • whilst still taking regular peanut dose
      • after a period of cessation of regular peanut dose
    – immunological parameters
High rate of allergic reactions during updosing and maintenance phases - limits dose, some withdrawals

Some patients develop eosinophilic oesophagitis

Is this curative -

- **Desensitisation** - can tolerate peanut as long as peanut dosing continued
- **Tolerance/Sustained unresponsiveness** - no reaction to peanut even after prolonged cessation of regular peanut dosing
  - May be achieved despite persistence of IgE - likely to require alteration of T-cell phenotypes
Peanut-specific-
- IgE often does not change
- SPT may remain positive despite desensitisation
- IgG (IgG4) rises- protective (blocking) antibodies
- BAT (basophil activation test) reduced
- Post-desensitisation sera reduces BAT

- Th2 cells/Th2 cytokines decrease (IL-4, IL-5, IL-13)
- T-regulatory cells increase (FOX-p3)
- Anergic T cells increase

Critical parameters for sustained unresponsiveness (cure) remain unknown
Approaches to improve safety/efficacy

Safety-
• Add Omalizumab (block IgE)
• Modify peanut
  • peptides
  • enzyme-digested
  • recombinant modified
• Injected peptides
• Sublingual immunotherapy
• Transcutaneous immunotherapy (patches)

Efficacy-
• Add probiotics
• Add adjuvants
• bacterial/viral vector for delivery of recombinant antigens
Boiled peanut immunotherapy

Dr Billy Tao-
Chinese have low incidence of peanut allergy
Infants and mothers consume boiled peanuts in soup

Boiled peanuts are hypoallergenic
Boiled peanut immunotherapy

Boiled peanut extracts contain T-cell reactive peptides

Boiled peanut extracts stimulate CD4 T-cell proliferation
Boiled peanuts- potential low cost immunotherapy

In-vitro studies suggest potential improved safety, efficacy

Pilot study- reduced reaction rate, IgG4 increased after boiled peanut phase

Randomised controlled trials planned

Collaboration- RAH/FMC/Adelaide University/UniSA
Conclusion & Future

• Potential for specific immunotherapy to treat food allergies
• Future approaches-
  • peptide vaccination immunotherapy
  • viral vectors to deliver allergen genes
• Immunotherapy for allergy to other foods
• Generic approach to allergy- high-affinity anti-IgE
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