# Recent advances in clinical immunology & allergy

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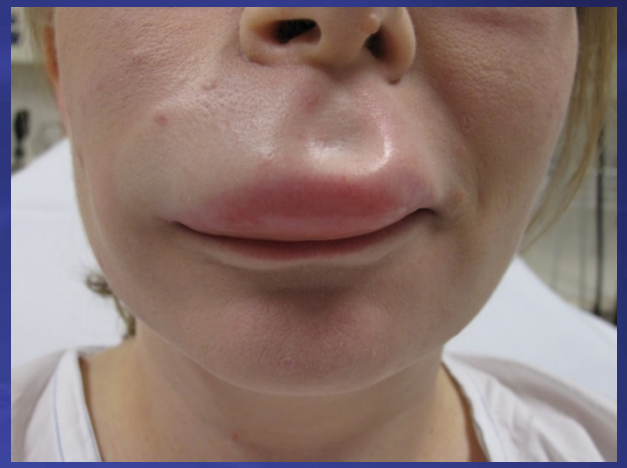
Clinical Immunology & Allergy
RAH/AllergySA

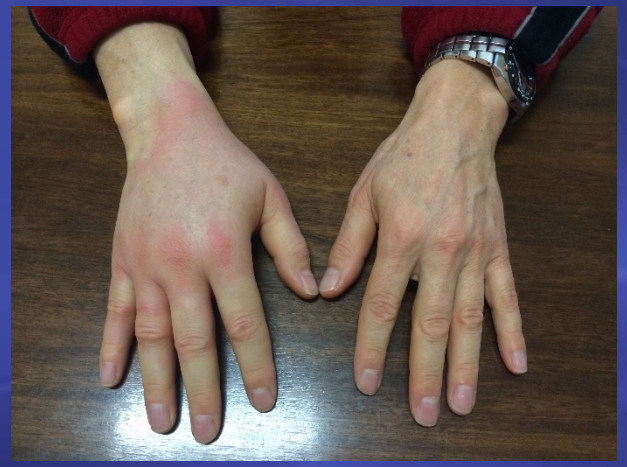
ascia
australasian society of clinical immunology and allergy

# 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

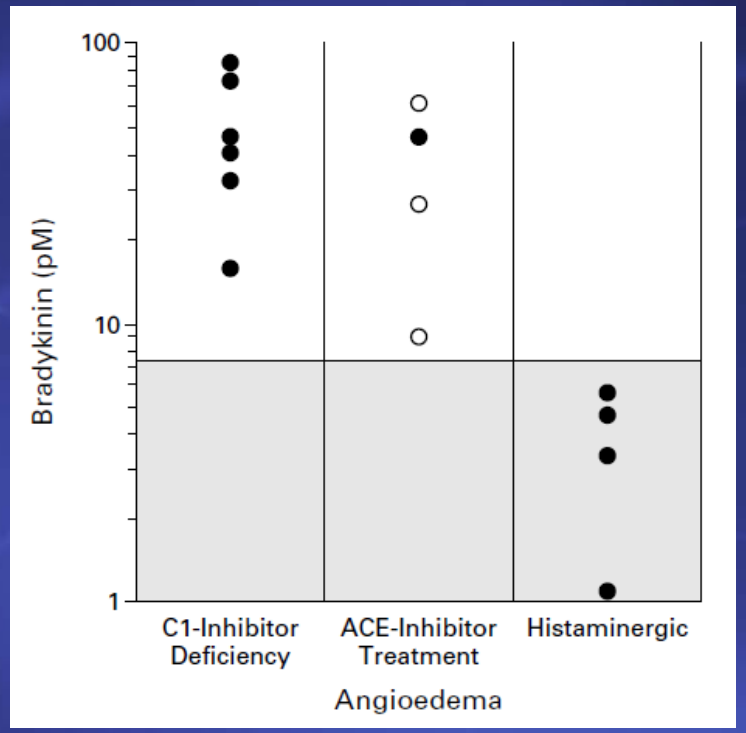


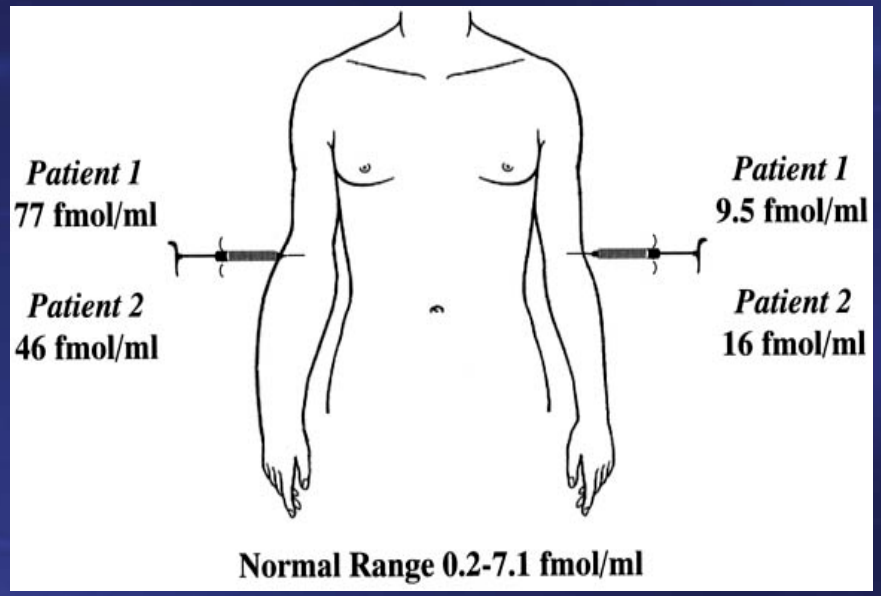


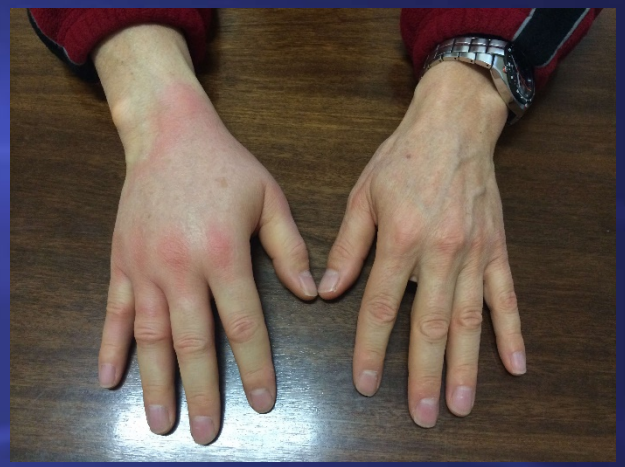
- Localised deep subcutaneous swelling, usually painless

- 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

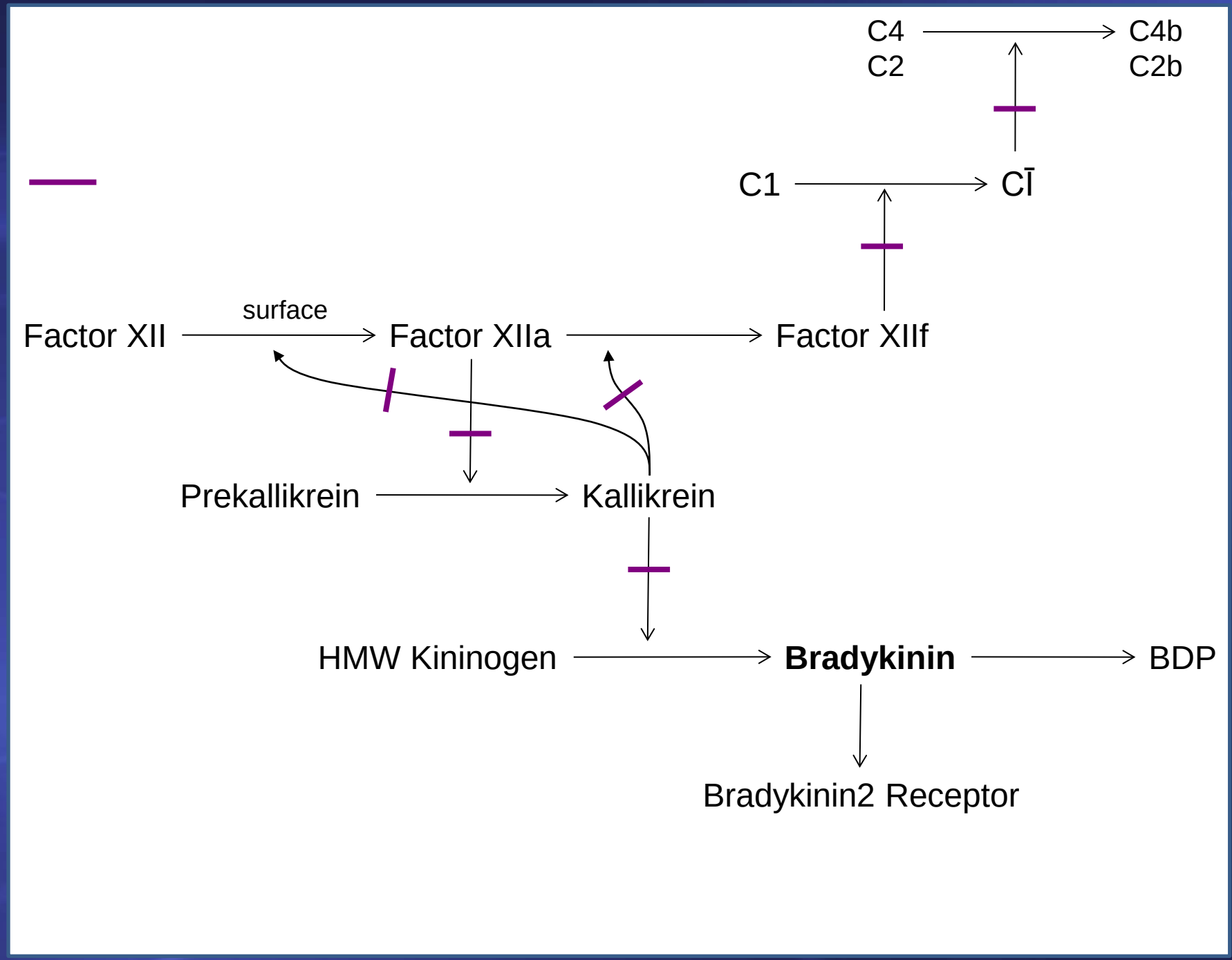


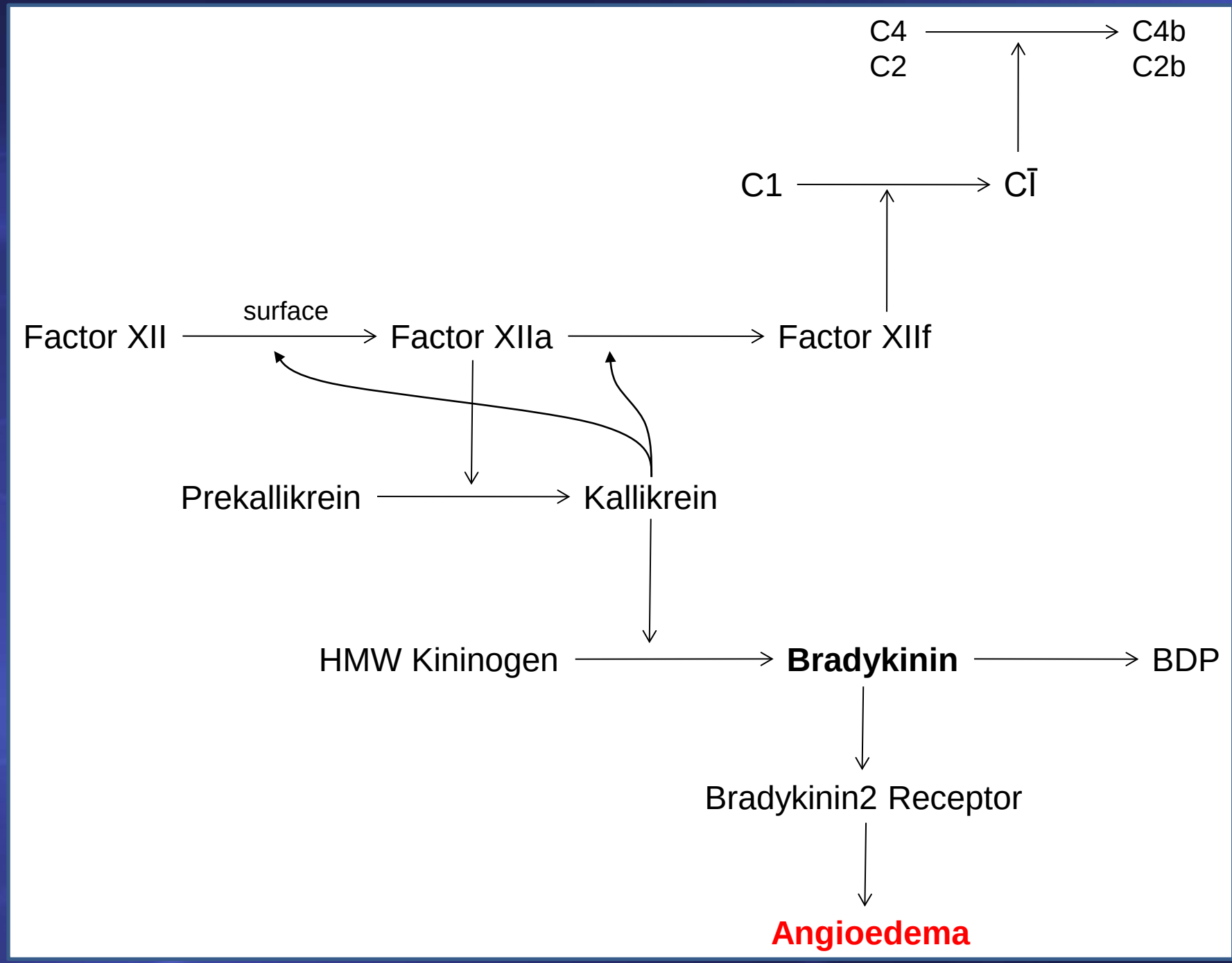



| | HISTAMINE | BRADYKININ |
|---|---|---|
| Allergic | All | |
| Idiopathic | Most (80%) | Some (20%) |
| ACE-inhibitor | | All |
| Hereditary Angioedema | | All |
| Acquired C1 Inhibitor deficiency | | All |

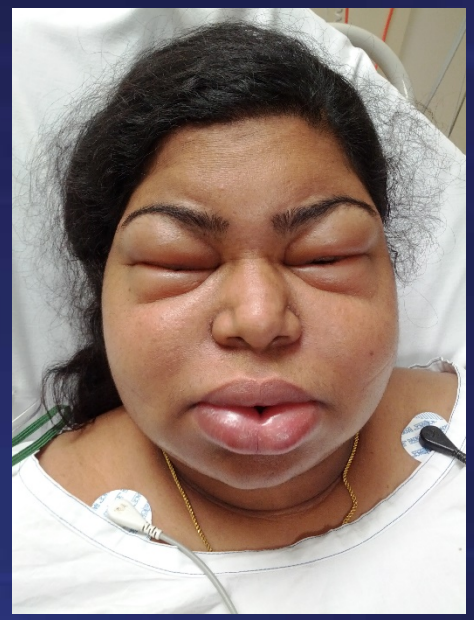
# C1 inhibitor




C4
C2
C4b
C2b
C1
C1̄
surface
Factor XII
Factor XIIa
Factor XIIf
Prekallikrein
Kallikrein
HMW Kininogen
Bradykinin
BDP
Bradykinin2 Receptor
Angioedema

# Hereditary Angioedema

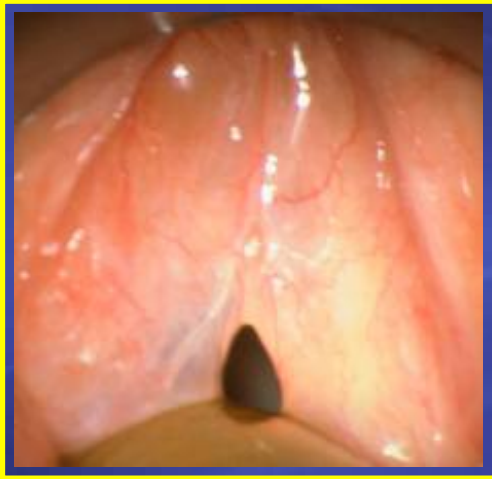
- Inherited deficiency of C1-inhibitor due to mutation SERPING1
  - Type 1- deficient protein
  - Type 2- dysfunctional protein
- Incidence 1:10,000-1:100,000
- Estimated cases in Australia ~500
- Autosomal Dominant (25% new mutations)
- Median age of onset 11, median age of diagnosis 26



- 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

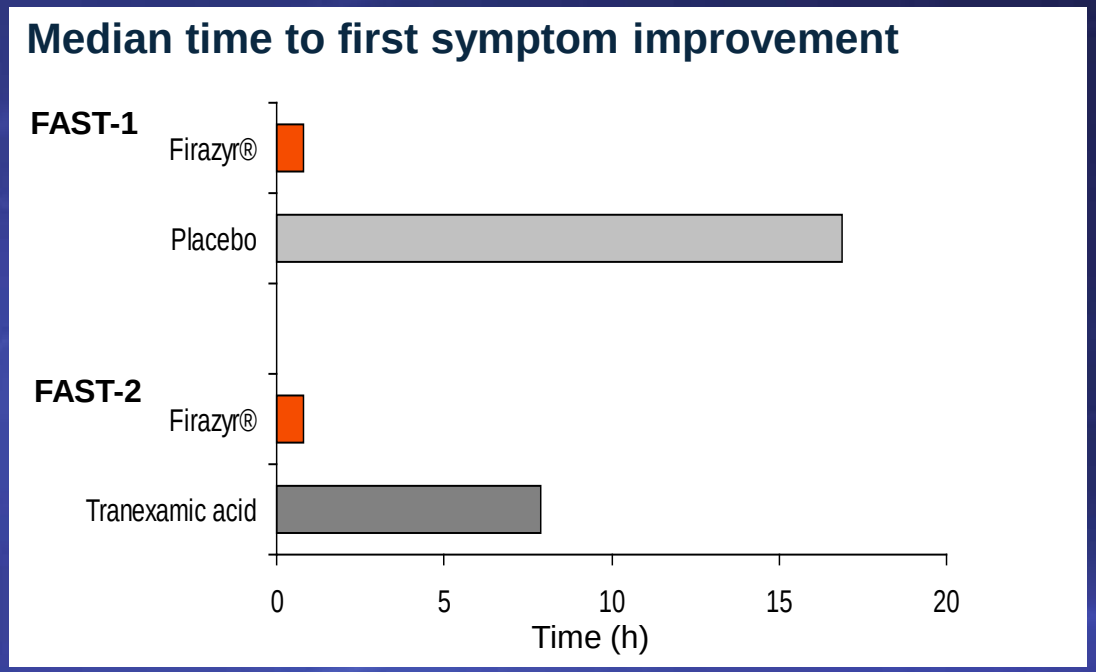


- Laryngeal oedema
- Medical emergency
- 1/3 HAE deaths due to asphyxiation, 30 years premature
  - historical data
  - Most deaths in undiagnosed HAE

# Diagnosis- C4 level

# Hereditary Angioedema

- Bradykinin Antagonist- Icatibant (Firazyr®)



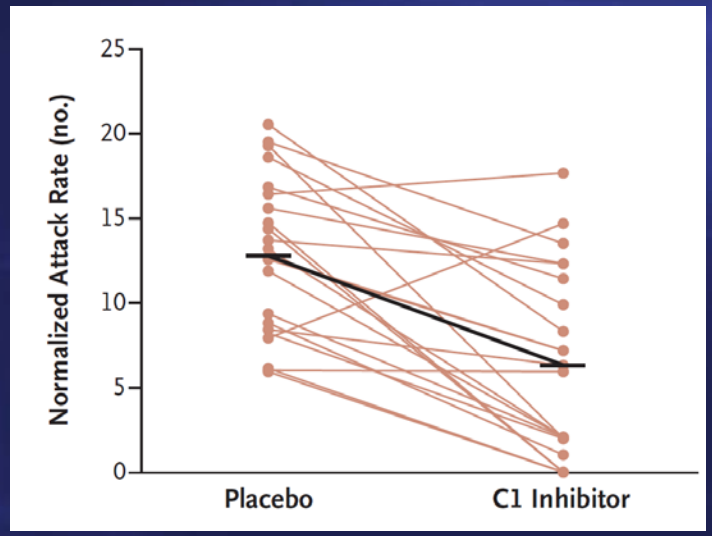


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

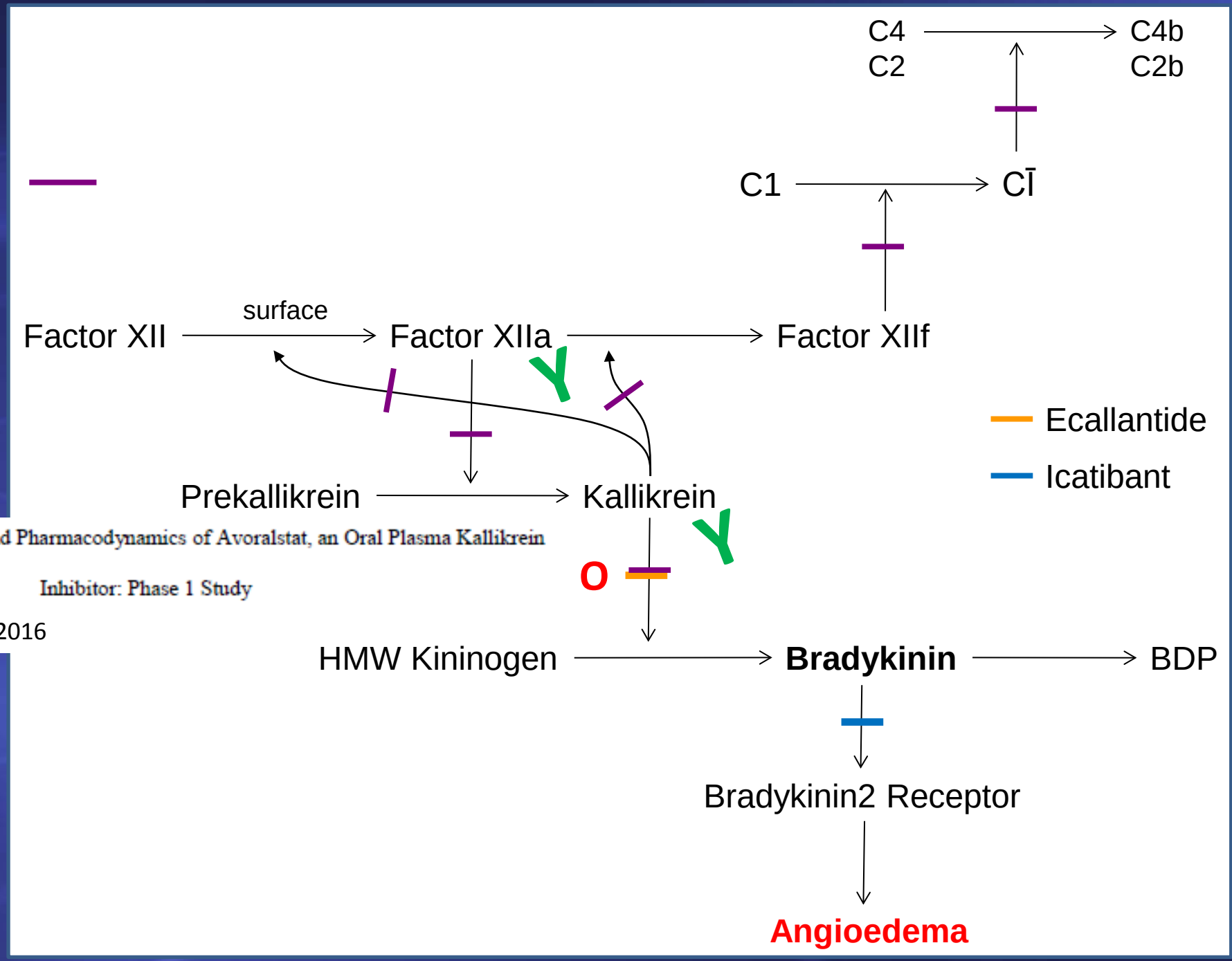
Icatibant, a New Bradykinin-Receptor Antagonist, in Hereditary Angioedema

- C1-inhibitor for long-term prophylaxis




Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. Zuraw BL et.al. N Engl J Med. 2010 Aug 5;363(6):513

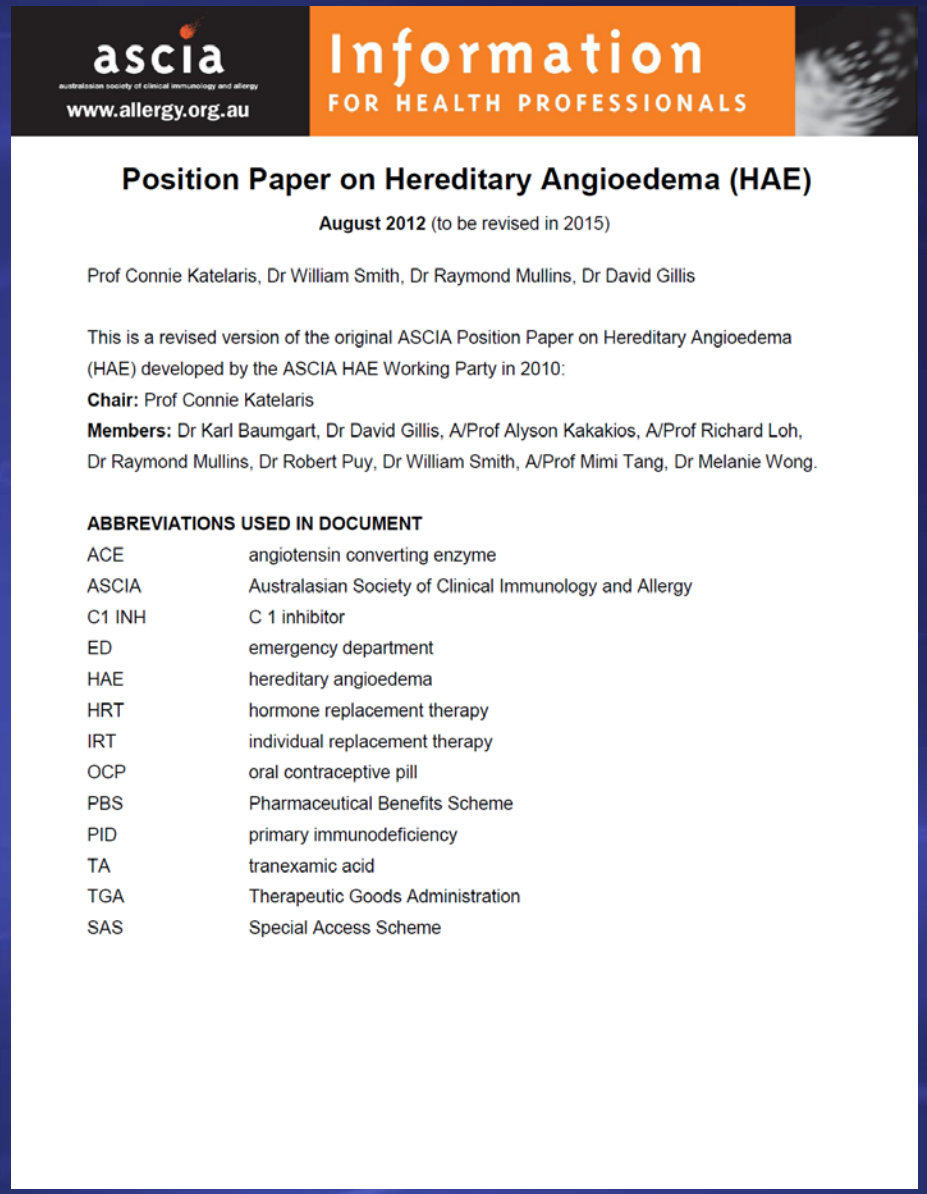
# C1 inhibitor




Safety, Pharmacokinetics, and Pharmacodynamics of Avoralstat, an Oral Plasma Kallikrein Inhibitor: Phase 1 Study

Allergy Online 12th May 2016

# Hereditary Angioedema



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Information
FOR HEALTH PROFESSIONALS

## Position Paper on Hereditary Angioedema (HAE)

**August 2012** (to be revised in 2015)

Prof Connie Katelaris, 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 Connie Katelaris

**Members:** Dr Karl Baumgart, Dr David Gillis, A/Prof Alyson Kakakios, A/Prof Richard Loh, Dr Raymond Mullins, Dr Robert Puy, Dr William Smith, A/Prof Mimi 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 pill |
| PBS | Pharmaceutical Benefits Scheme |
| PID | primary immunodeficiency |
| TA | tranexamic acid |
| TGA | Therapeutic Goods Administration |
| SAS | Special Access Scheme |

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ACTION PLAN FOR
Hereditary Angioedema (HAE)

**Patient details**

Name:

Date of birth:

Photo

Family/emergency contact name:

Work Ph:

Home Ph:

Mobile Ph:

**Plan prepared by:**

Dr

Signed

Date

Additional information:



**MILD HAE SYMPTOMS**

- Peripheral 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®)**[1,2] subcutaneously or **C1 INH (Berinert®** 20 U/Kg IVI or **Cinryze®** 1,000 U IVI)[2,3]
- In children administer **C1 INH (Berinert®** 20 U/Kg IVI or **Cinryze®** 1,000 U IVI)[2,3]

**MODERATE TO SEVERE HAE SYMPTOMS - ABDOMINAL SYMPTOMS**

- Moderate to severe abdominal pain
- Vomiting, distention
- Dehydration (e.g. dry mouth, thirst, confusion)

**ACTION**

- In adults administer **Icatibant (Firazyr®)**[1,2] subcutaneously or **C1 INH (Berinert®** 20 U/Kg IVI or **Cinryze®** 1,000 U IVI)[2,3]
- In children administer **C1 INH (Berinert®** 20 U/Kg IVI or **Cinryze®** 1,000 U IVI)[2,3]
- Seek urgent hospital treatment if symptoms worsen or last longer than 2 hours

**ADDITIONAL HOSPITAL TREATMENT:**

- Opiate analgesia
- 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®)**[1,2] subcutaneously or **C1 INH (Berinert®** 20 U/Kg IVI or **Cinryze®** 1,000 U IVI)[2,3]
- In children administer **C1 INH (Berinert®** 20 U/Kg IVI or **Cinryze®** 1,000 U IVI)[2,3]
- Phone ambulance - 000 (AU) or 112 (mobile)
- Seek **urgent hospital treatment**

**ADDITIONAL HOSPITAL TREATMENT:**

- Prepare for emergency intubation or cricothyrotomy
- Give 2nd dose of specific treatment if inadequate response after 1 hr

NOTE: 1. Icatibant (Firazyr) is approved for use in adults with HAE.
2. Patient's own supply either at home or at hospital
3. C1 INH (C1 inhibitor concentrate) is approved for use in children and adults with HAE.
4. Products cited in this Action Plan are TGA registered hence this information is specific for HAE treatment in Australia
5. Adrenaline, antihistamines and corticosteroids are not effective for HAE attacks.

# Hereditary Angioedema

NATIONAL BLOOD AUTHORITY AUSTRALIA

**C1 inhibitor for:**

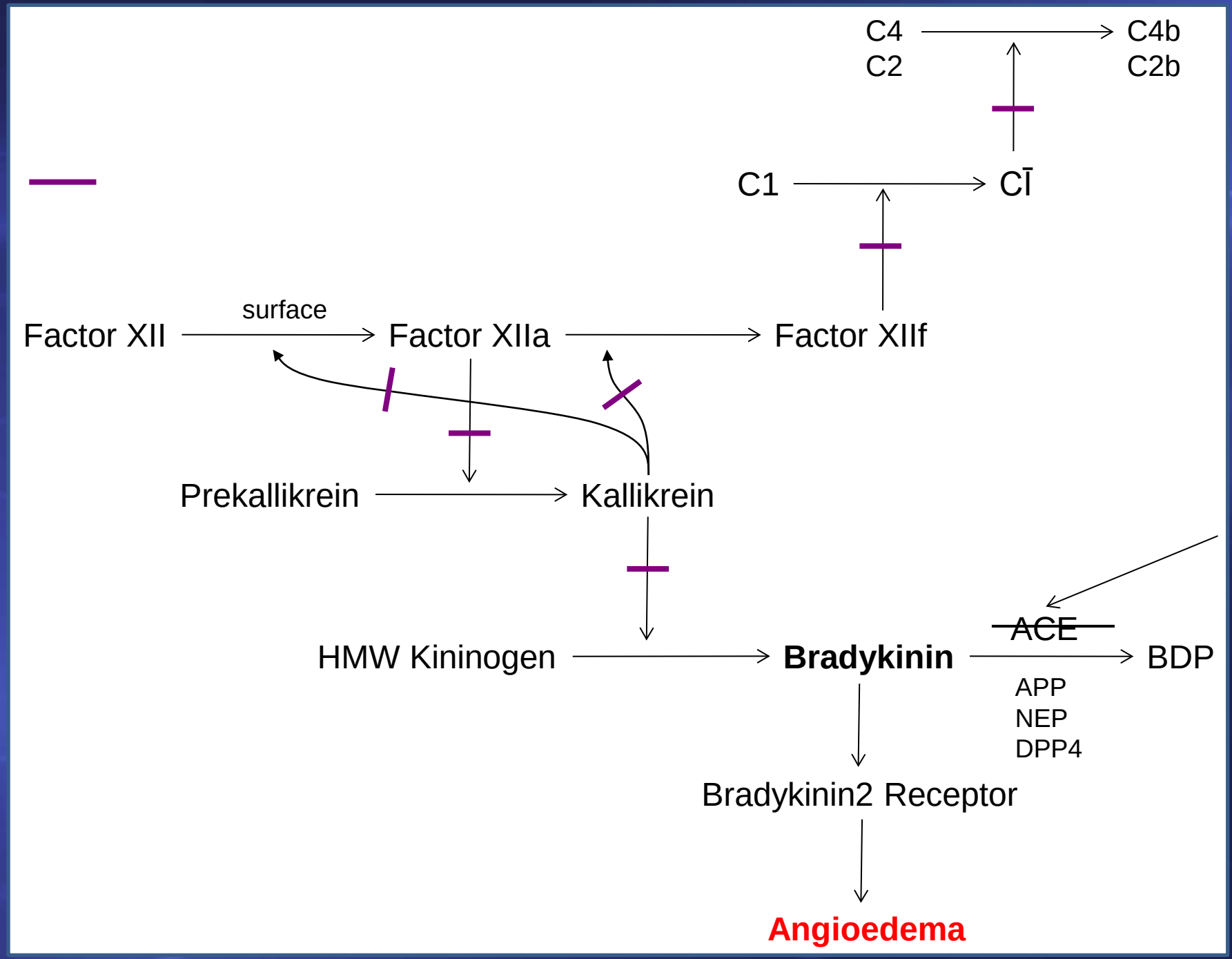
- treatment of acute HAE attacks
- pre-procedural prophylaxis (for high risk procedures)
- routine prophylaxis (for patients who experience eight or more acute attacks per month).


HAE Australasia

hope • advocacy • education

*Australasian Patient Organisation for Hereditary Angioedema*

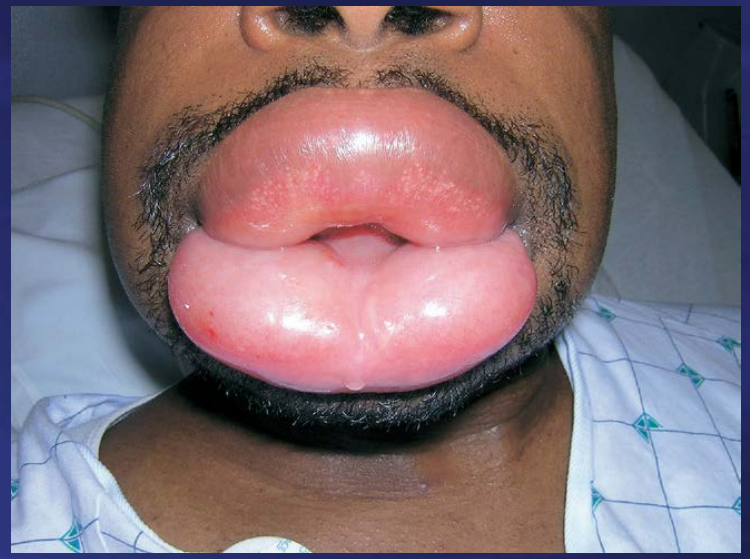
C1 inhibitor




ACE-inhibitors

# 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

INTERNAL MEDICINE JOURNAL

The NEW ENGLAND JOURNAL of MEDICINE

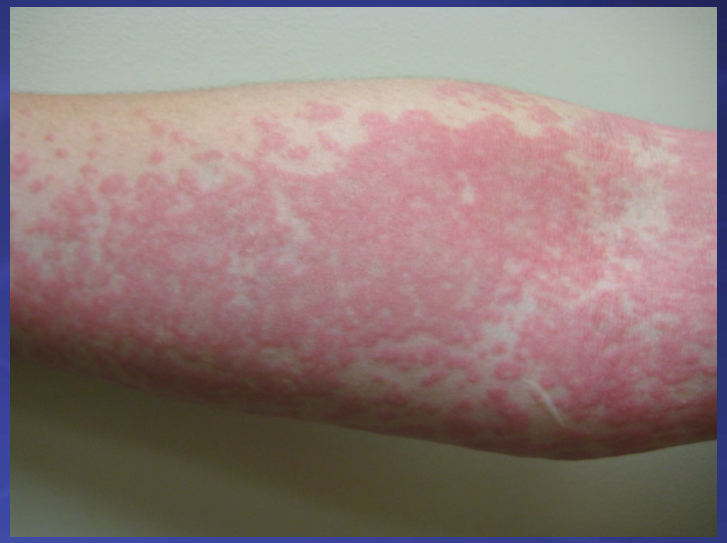
ORIGINAL ARTICLE

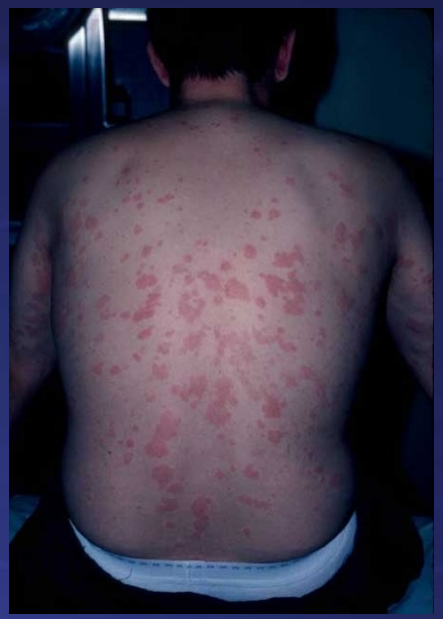
A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema

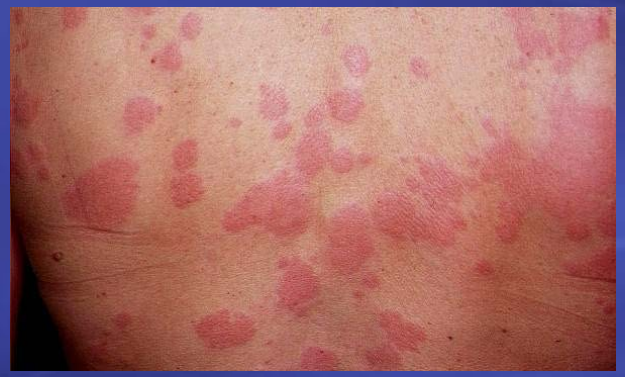
**Icatibant in angiotensin-converting enzyme (ACE) inhibitor-associated angioedema**

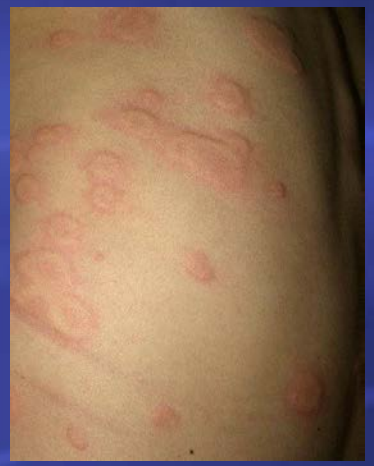
J. S. Fok,[1] C. H. Katelaris,[2,3] A. F. Brown[4,5] and W. B. Smith[1]

# Chronic Urticaria



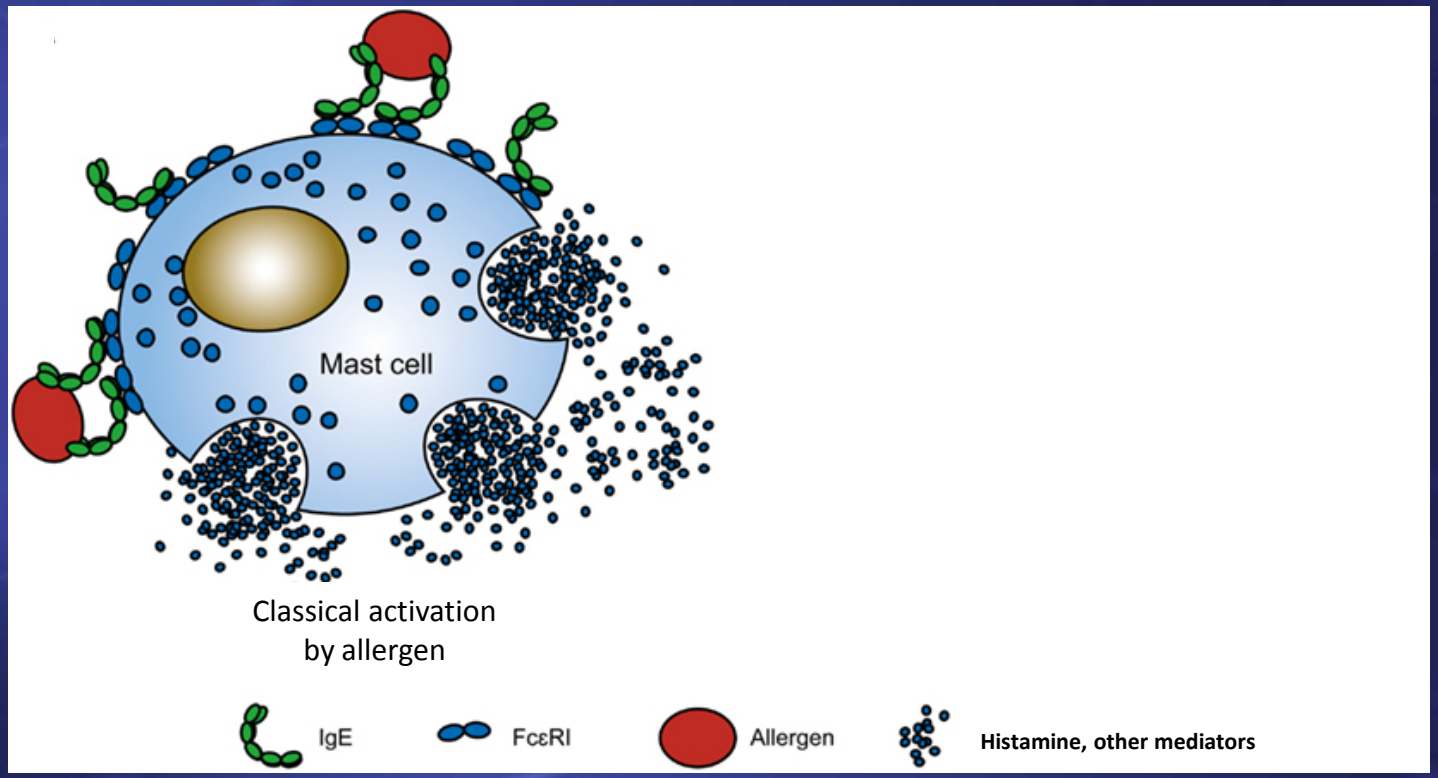






- Chronic Idiopathic Urticaria
- **Chronic Spontaneous Urticaria**

# Chronic (idiopathic) (spontaneous) urticaria



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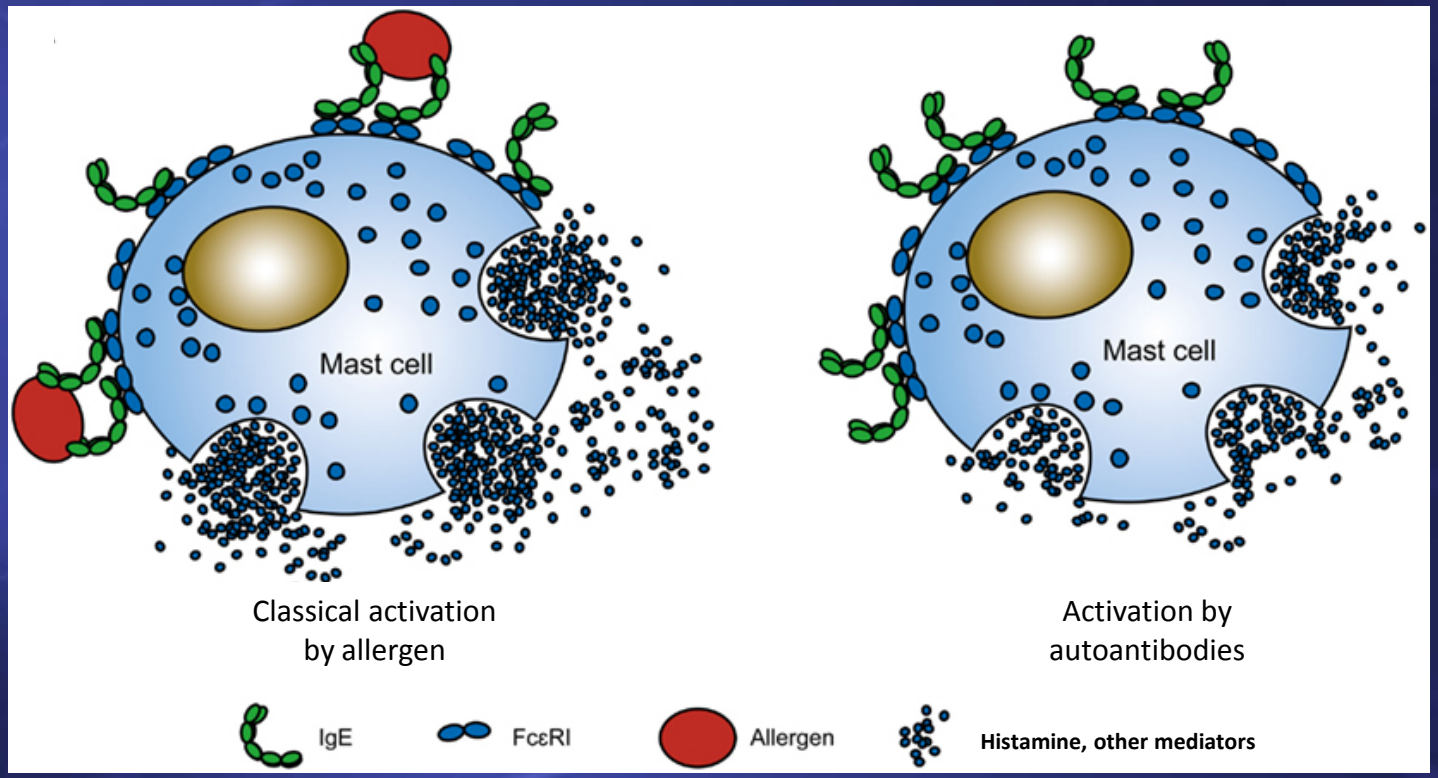

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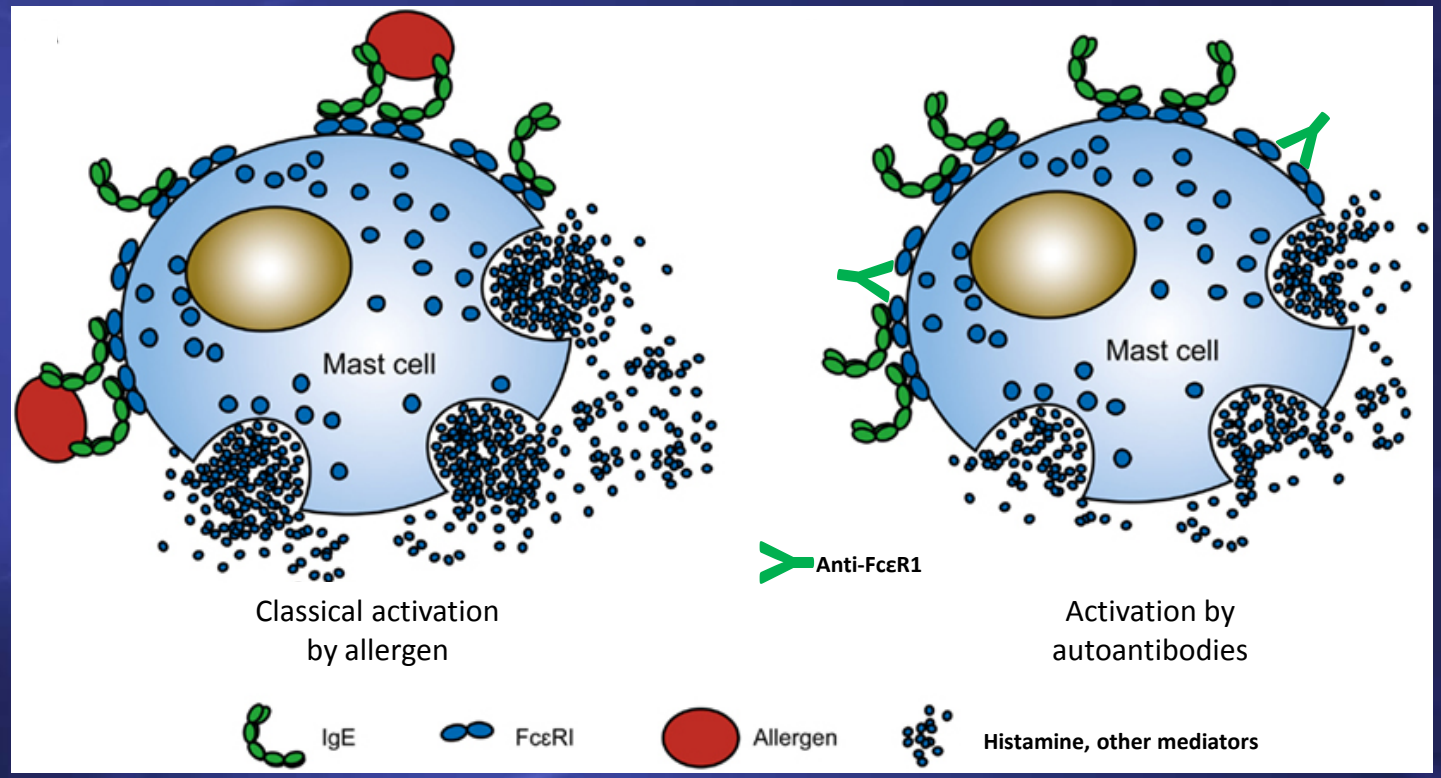

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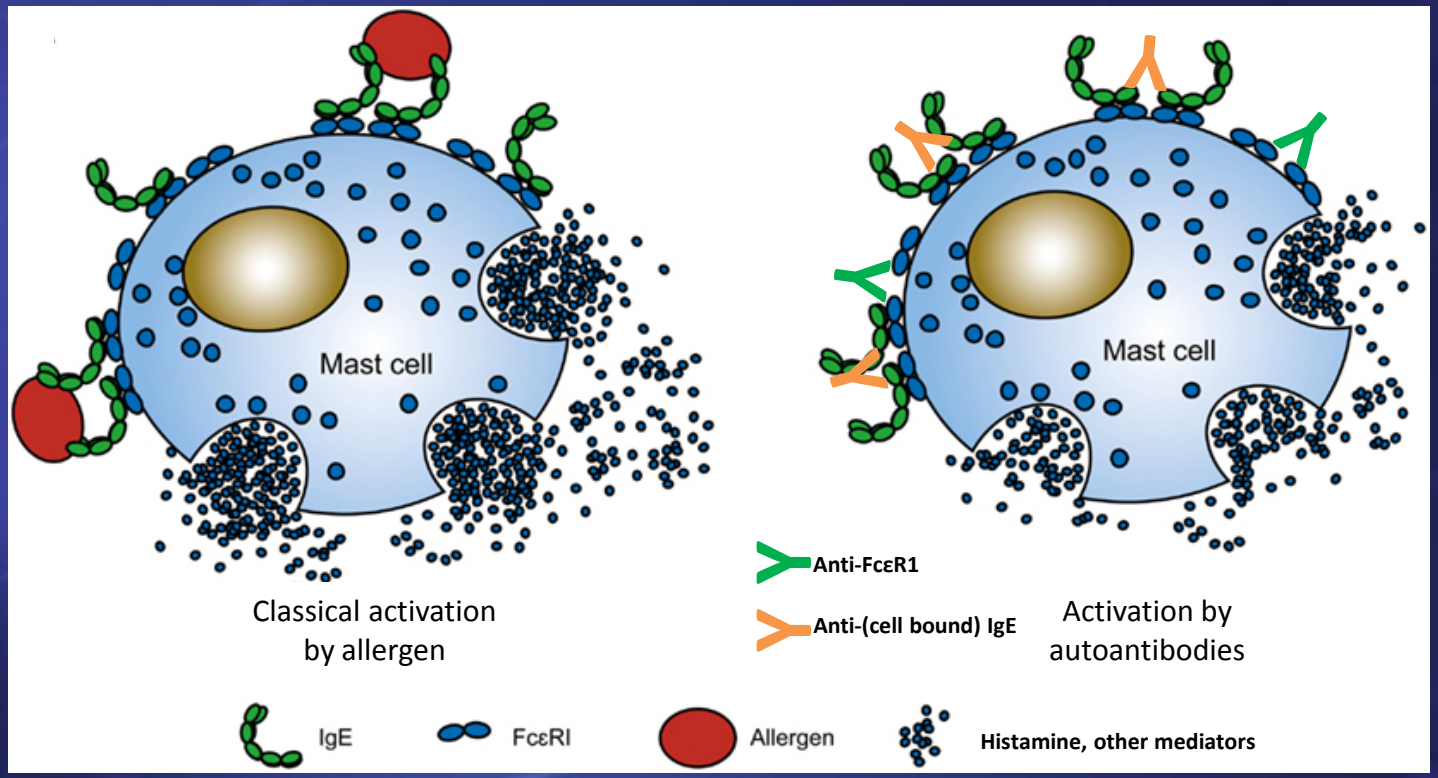


# Chronic (idiopathic) (spontaneous) urticaria

INTERNAL MEDICINE JOURNAL

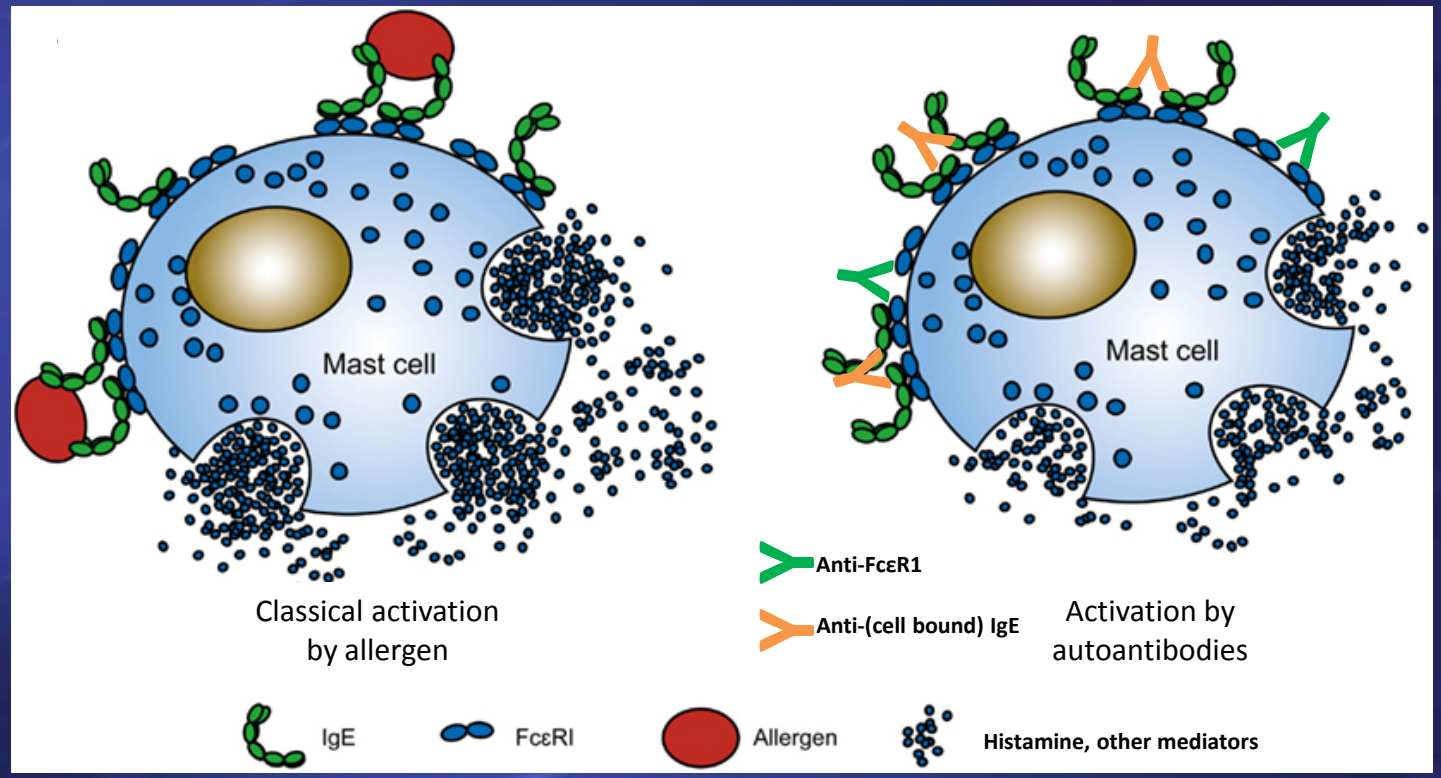
*Internal Medicine Journal* **38** (2008) 852–857

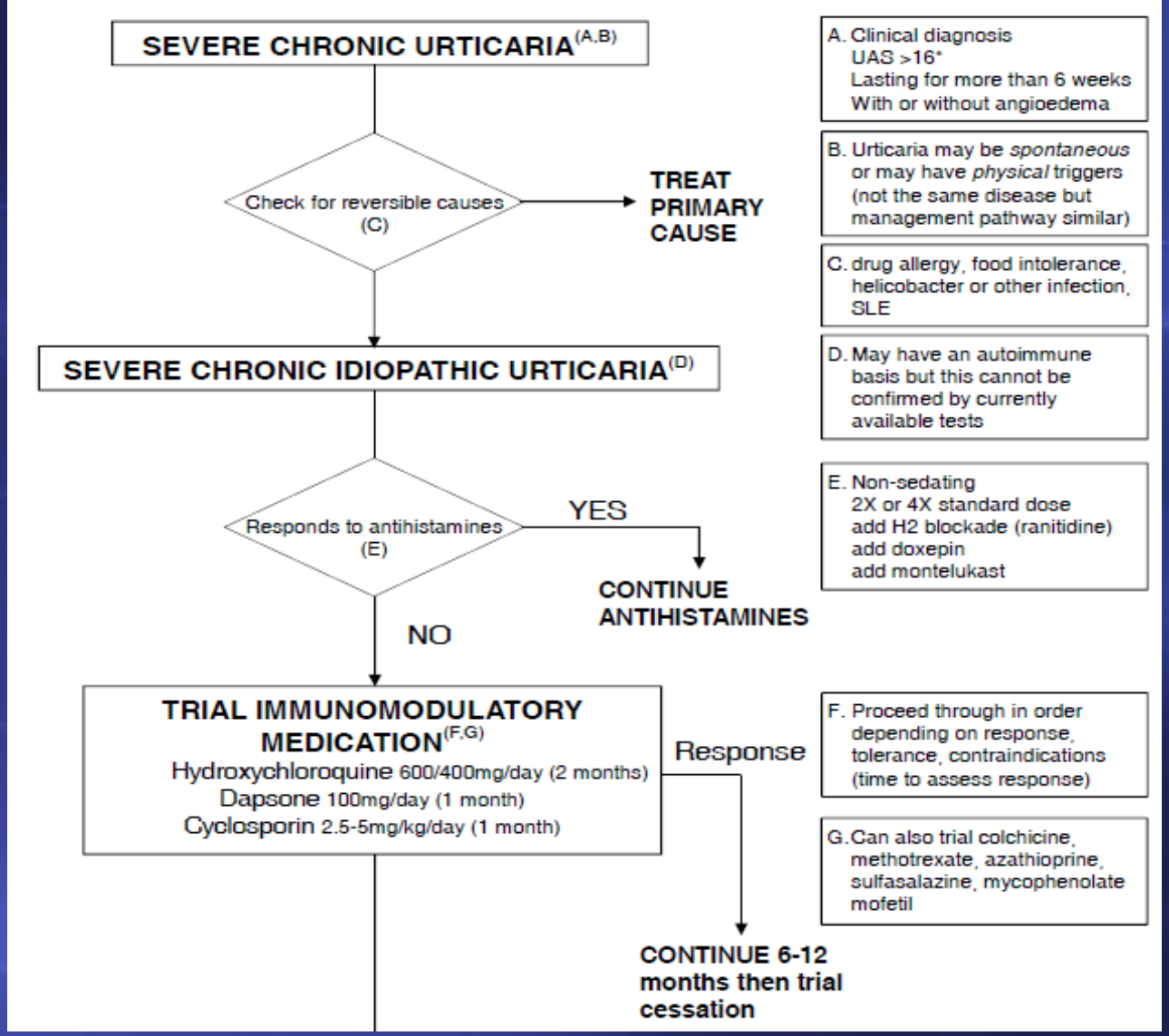
REVIEW

**Chronic urticaria: the autoimmune paradigm**

H. Philpott, F. Kette, P. Hissaria, D. Gillis and W. Smith

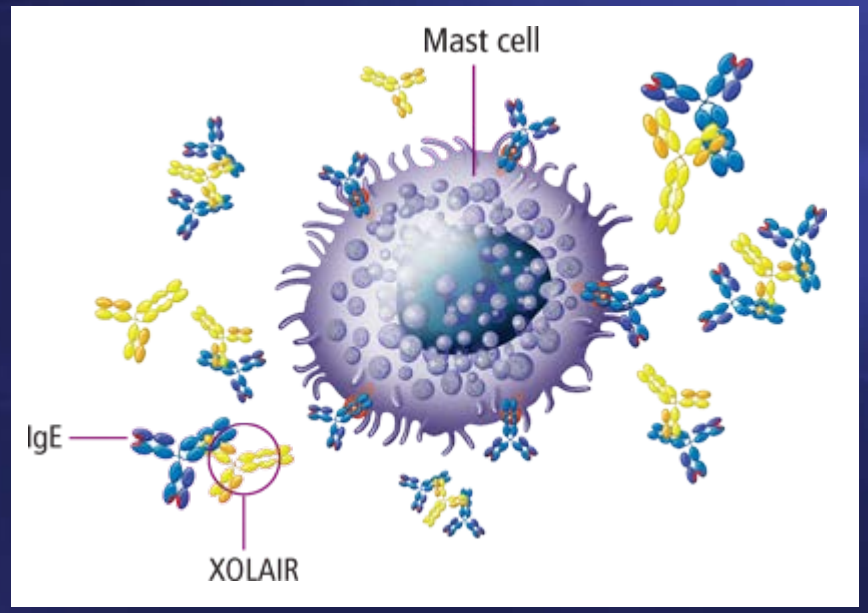
- 60% autoimmune
- 40% remain idiopathic




SEVERE CHRONIC URTICARIA(A,B)
Check for reversible causes (C)
TREAT PRIMARY CAUSE
SEVERE CHRONIC IDIOPATHIC URTICARIA(D)
Responds to antihistamines (E)
YES
CONTINUE ANTIHISTAMINES
NO
TRIAL IMMUNOMODULATORY MEDICATION(F,G)
Hydroxychloroquine 600/400mg/day (2 months)
Dapsone 100mg/day (1 month)
Cyclosporin 2.5-5mg/kg/day (1 month)
Response
CONTINUE 6-12 months then trial cessation
A. Clinical diagnosis
UAS >16*
Lasting for more than 6 weeks
With or without angioedema
B. Urticaria may be spontaneous or may have physical triggers (not the same disease but management pathway similar)
C. drug allergy, food intolerance, helicobacter or other infection, SLE
D. May have an autoimmune basis but this cannot be confirmed by currently available tests
E. Non-sedating
2X or 4X standard dose
add H2 blockade (ranitidine)
add doxepin
add montelukast
F. Proceed through in order depending on response, tolerance, contraindications (time to assess response)
G. Can also trial colchicine, methotrexate, azathioprine, sulfasalazine, mycophenolate mofetil

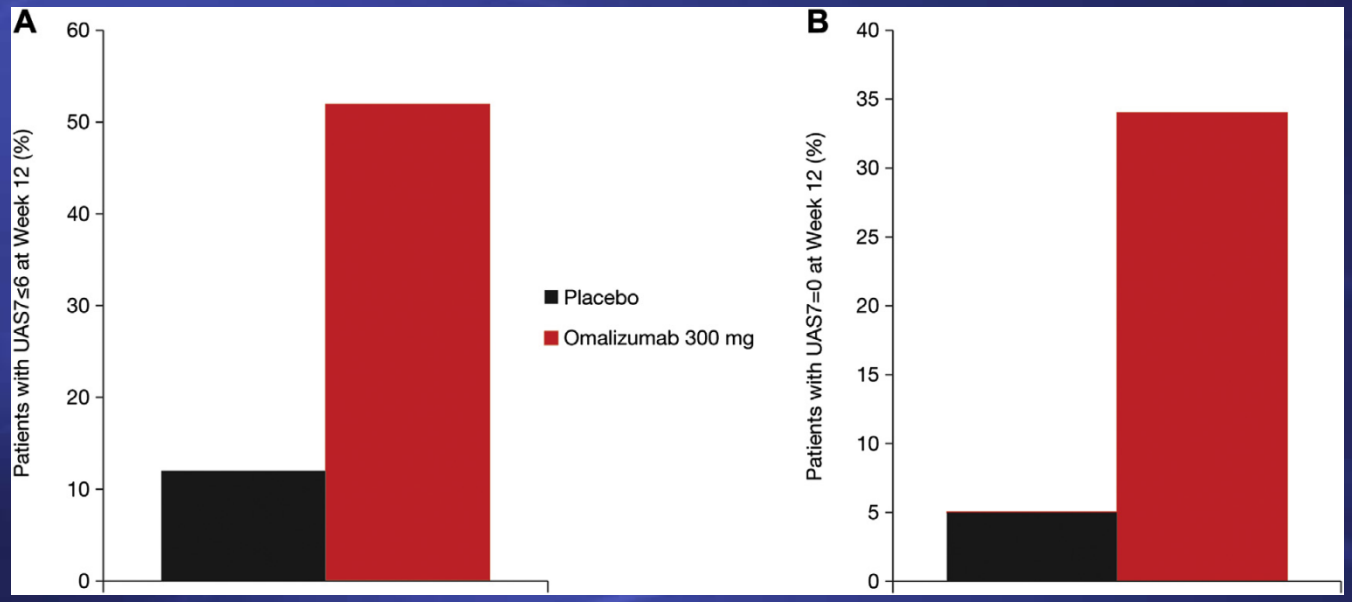
# Omalizumab- anti-IgE

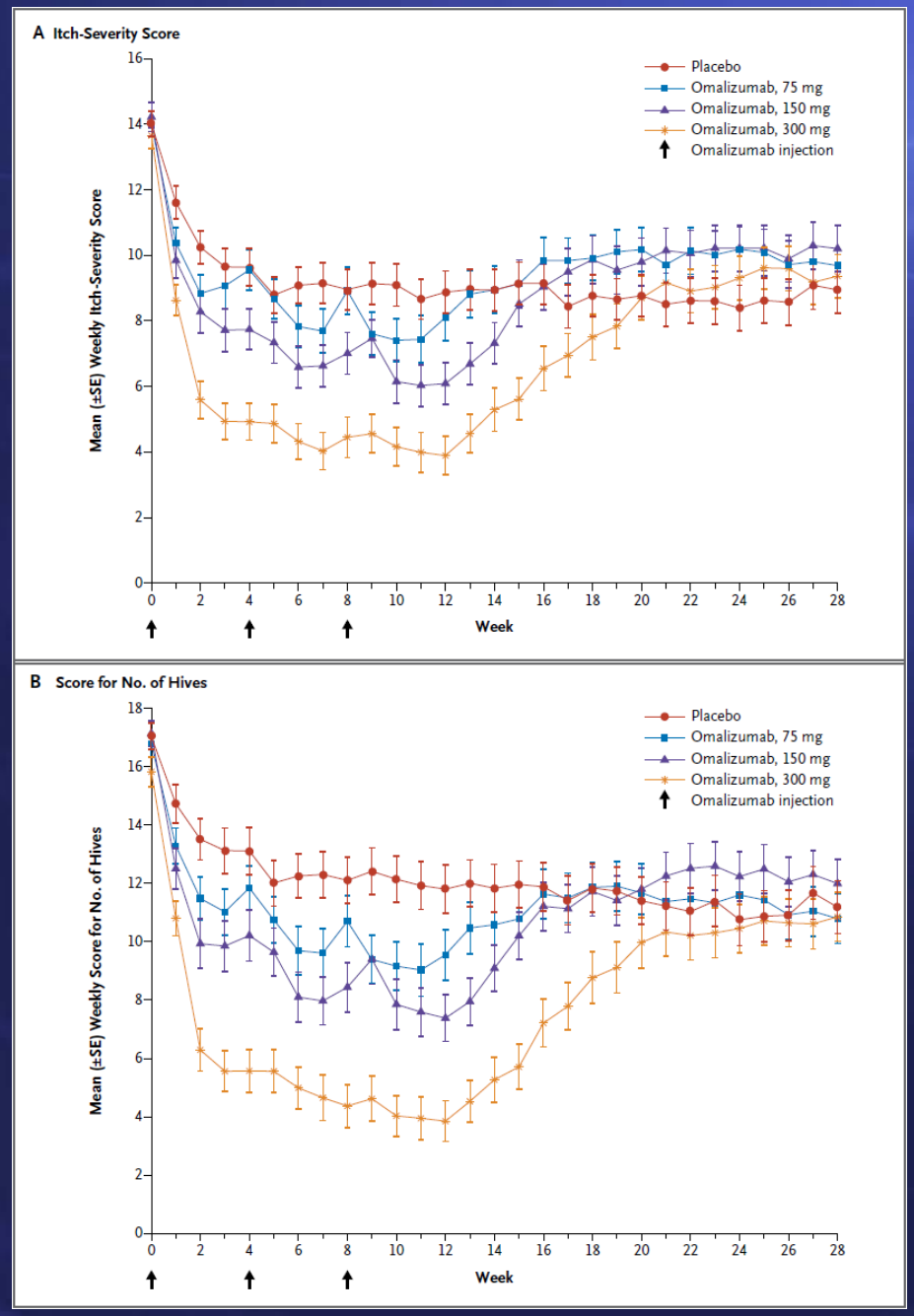
- Binds free IgE in circulation
- Anti-allergy
- Efficacy in asthma
- Other disorders-
  - Food allergy
  - Allergic rhinitis
  - Anaphylaxis
  - Adjunct to immunotherapy



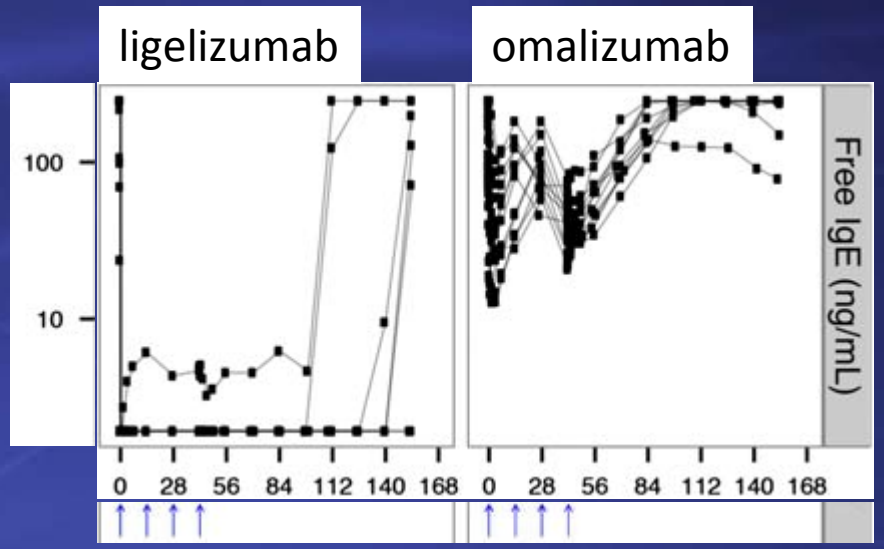
# Omalizumab for CU

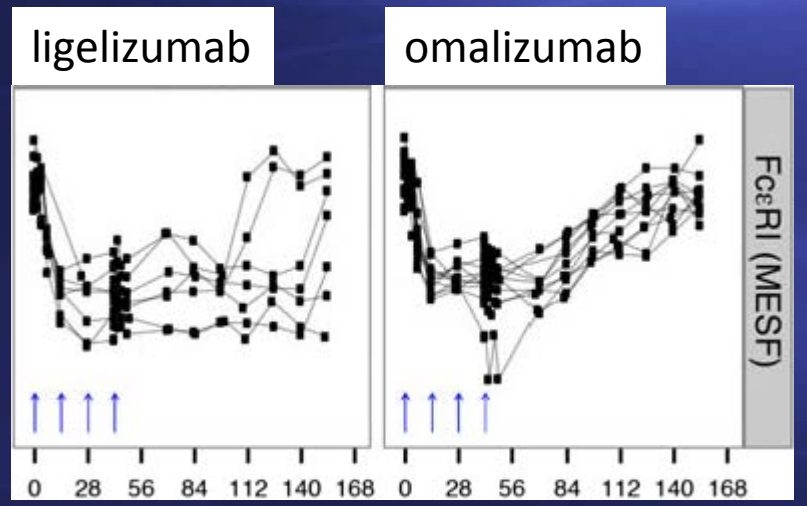
- Case reports
  - (antihistamine-resistant cases)
- Now large RCT (4 trials, >1,000)
- Mechanism? (mast cell FcεR1)

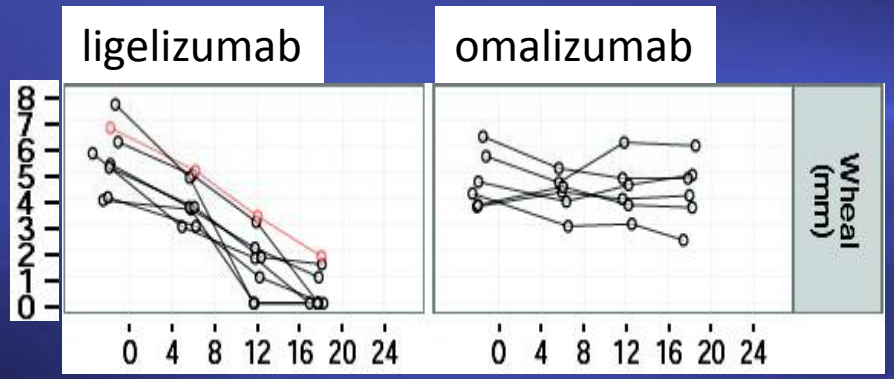


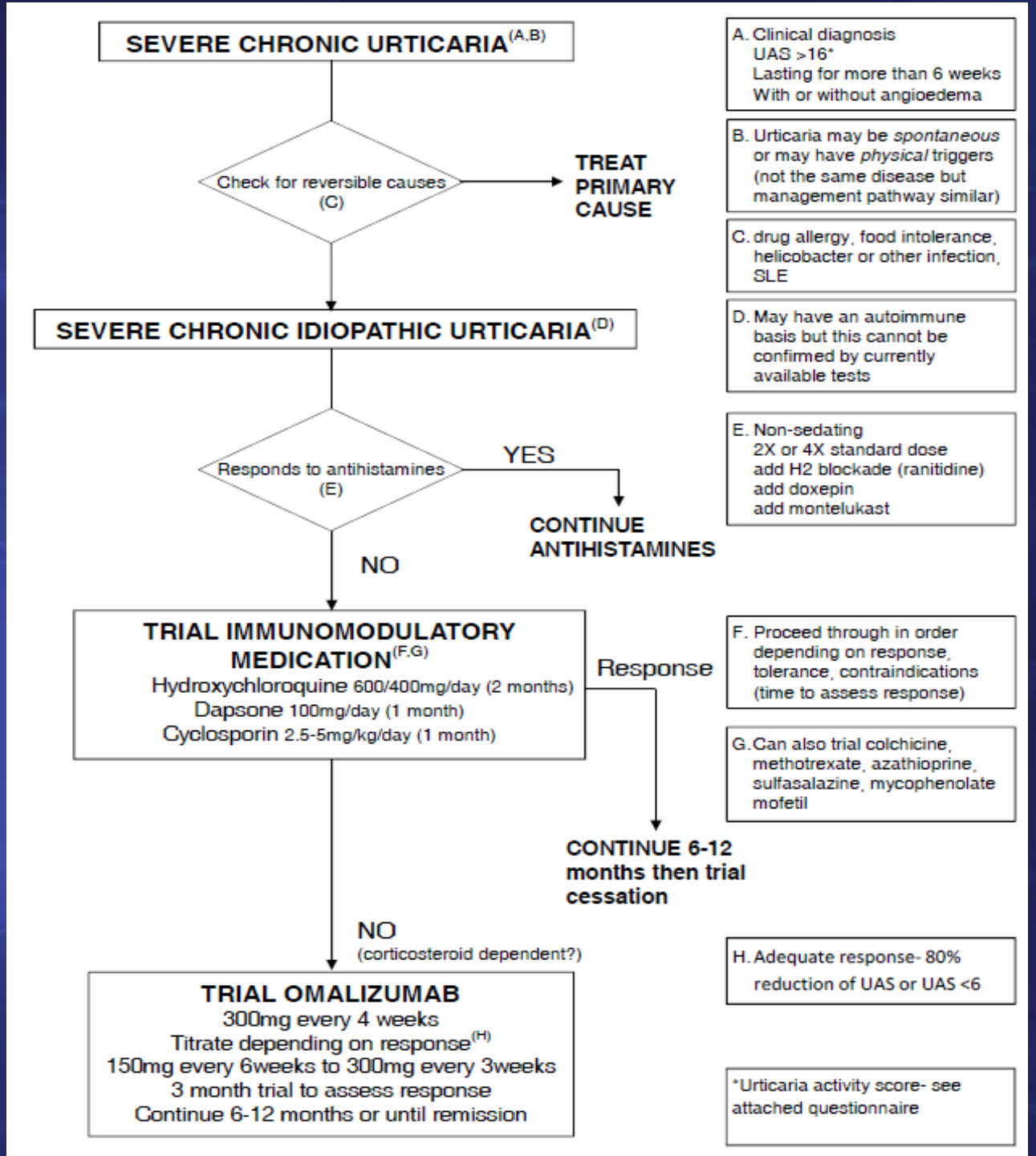



# High-affinity anti-IgE






**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

# Spectrum of WHEAT HYPERSENSITIVITY/intolerance

- 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

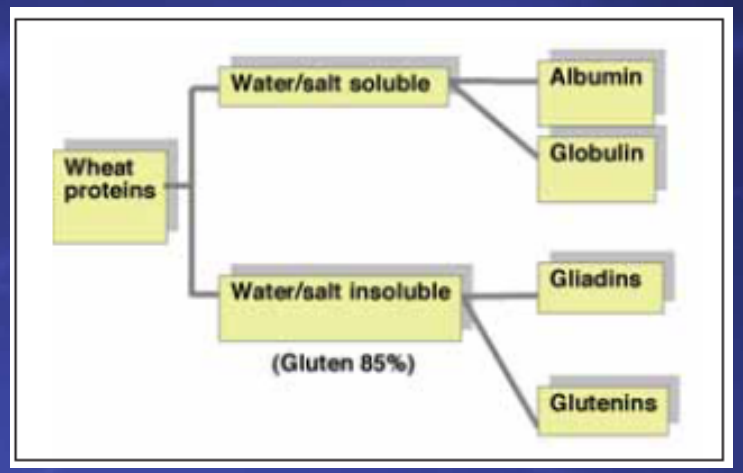
# Anaphylaxis **Cofactors**

**Factors may modify/potentiate/trigger anaphylaxis:**

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

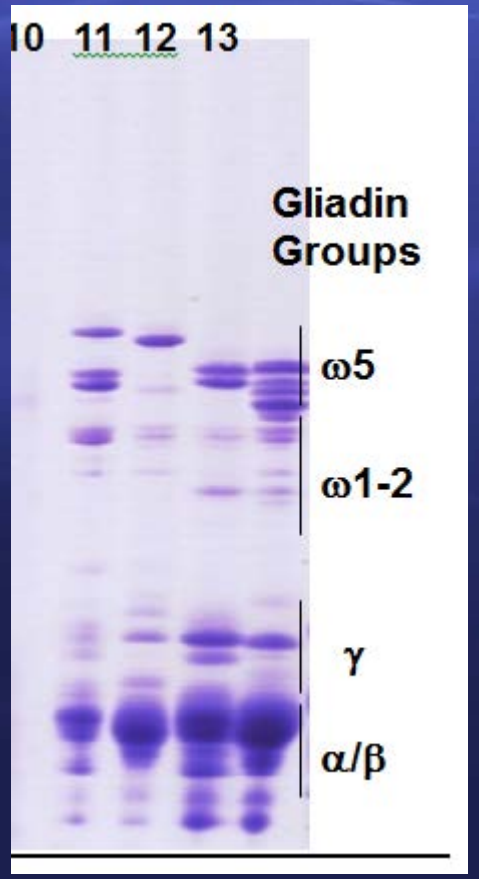
- Food-dependent exercise-induced anaphylaxis (FDEIA)
  - **Wheat**, Shellfish, any allergenic food
- Food usually tolerated, unless followed by exercise

# Wheat structure/components



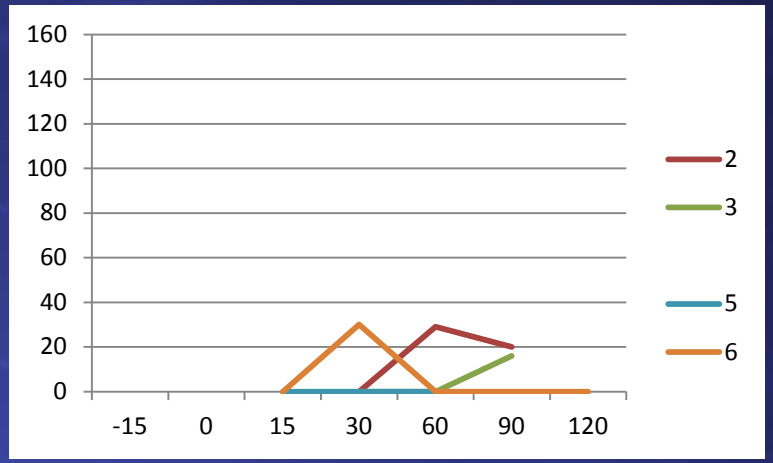

- Wheat seed = 10-15% protein
- Proteins divided into fractions:
  - Water soluble (Albumins)
  - Salt soluble (Globulins)
  - ETOH soluble (Gliadins)
  - Insoluble (Glutenins)
- Gliadins + Glutenins = Gluten
- Gliadins (wheat), secalins (rye), hordein (barley) -> 'Glutens'
- Gliadins -> α/β, γ, ω -> ω1- ω5

**Critical Component ω5-**
**Omega-5-gliadin (O5G)**

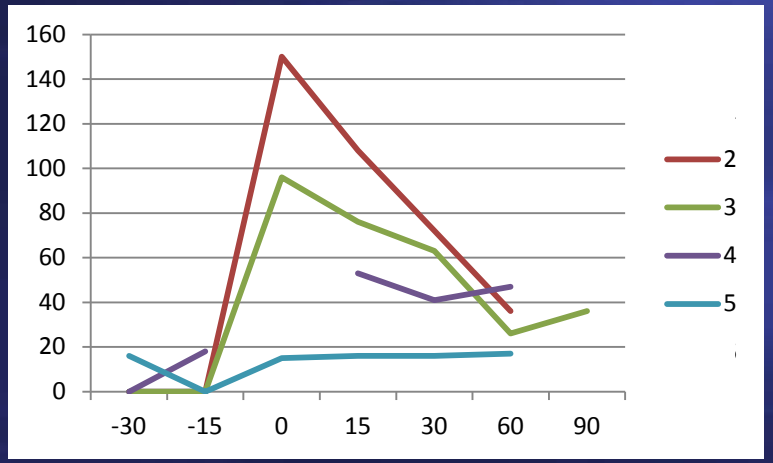


# Serum gliadin levels

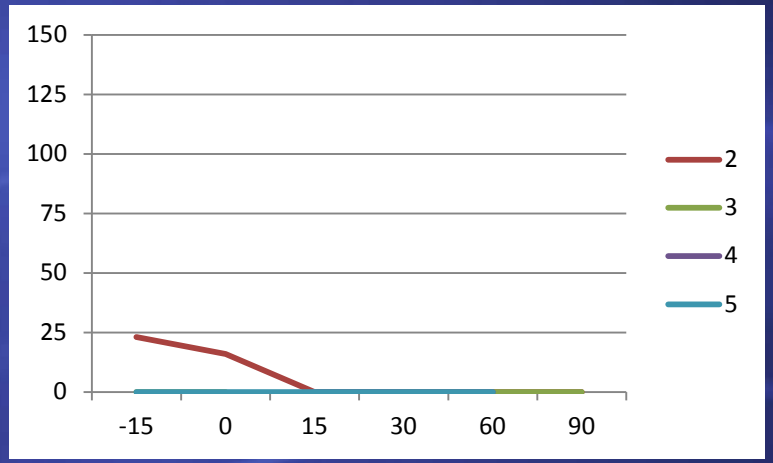
Wheat alone



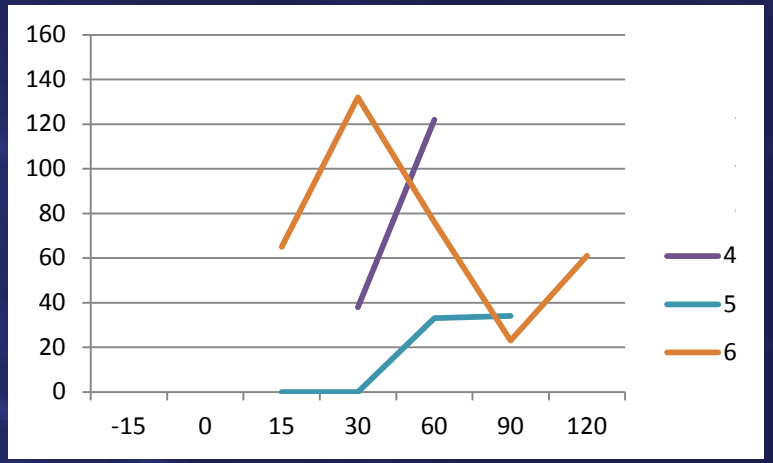

Wheat + exercise




Exercise alone




Wheat + aspirin

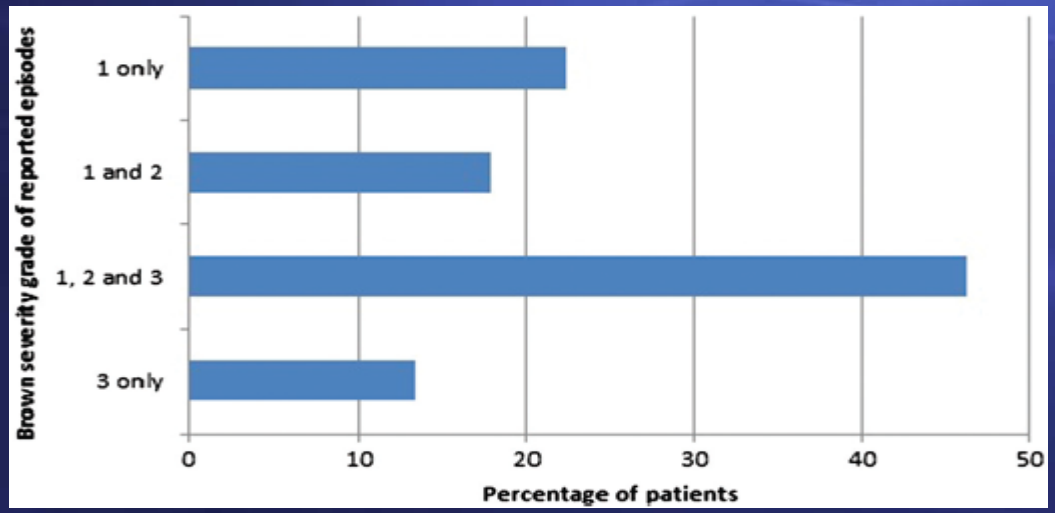


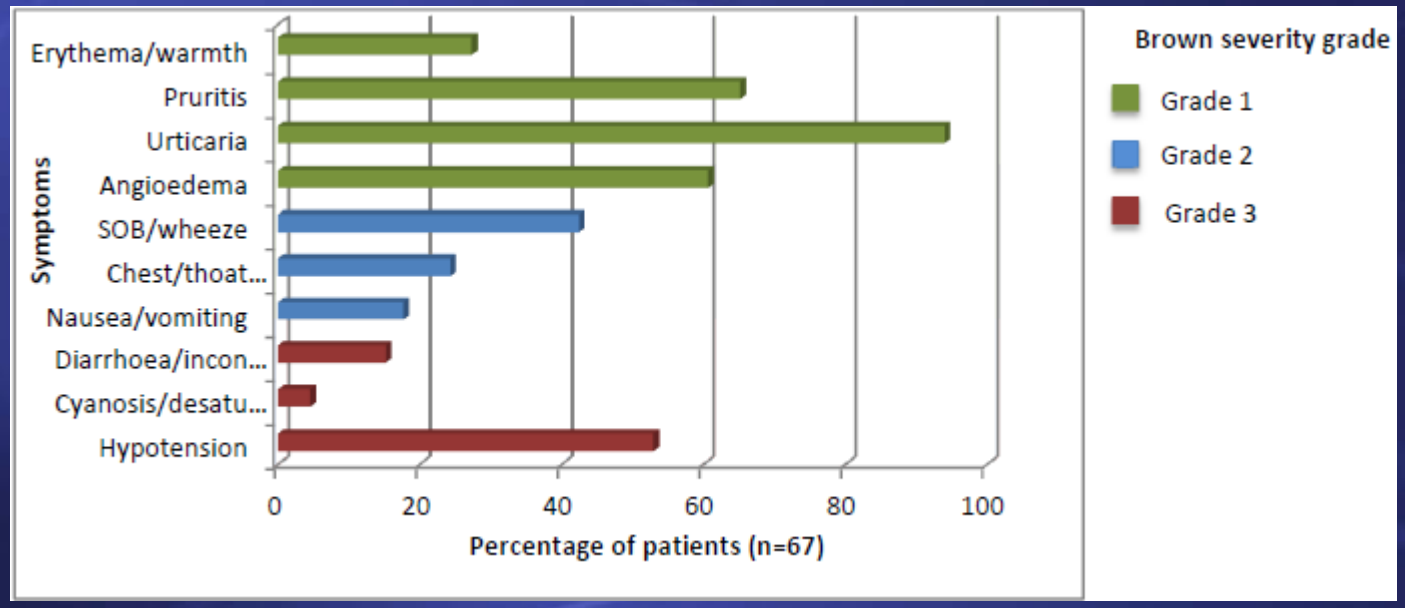
# WDEIA

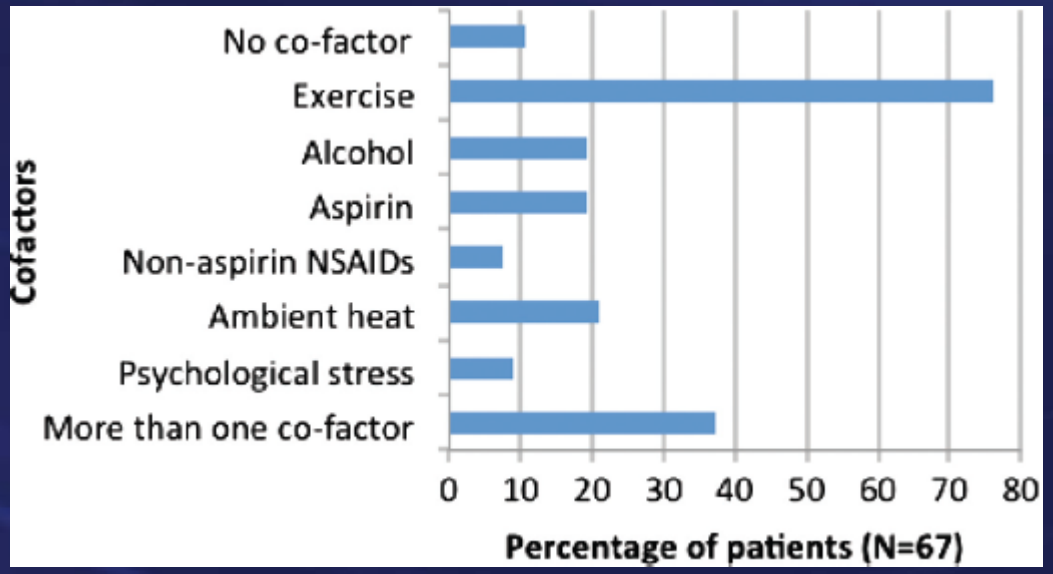
- Wheat-Dependent Exercise-Induced Anaphylaxis
- Specific IgE to O5G (Immunocap assay)
- 2007-2013- 67 individuals with positive tests (SA Pathology)
  - Age 22-84 (median 44)
  - Male 60%
  - Symptom onset to diagnosis 0.5-14 years (median 2.6)
- Survey of presenting clinical features & cofactors- clinical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

# O5G allergy

| Initial presentation pattern | No. of pts (*N* = 67) |
|---|---|
| Wheat-dependent exercise-induced urticaria or anaphylaxis (WDEIU/A) | 13 |
| Food-dependent exercise-induced allergy (FDEIA) | 13 |
| Exercise-induced urticaria or anaphylaxis (EIU/A) | 16 |
| Idiopathic anaphylaxis (IA) | 10 |
| Food-induced allergy (FIA) | 10 |
| Recurrent acute urticaria (RAU) | 5 |



# O5G allergy

- **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

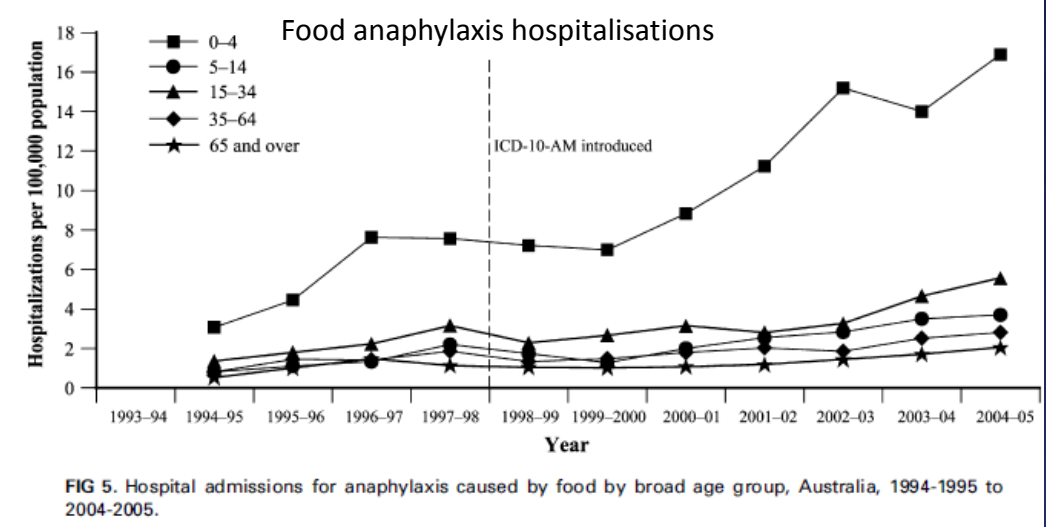



FIG 5. Hospital admissions for anaphylaxis caused by food by broad age group, Australia, 1994-1995 to 2004-2005.

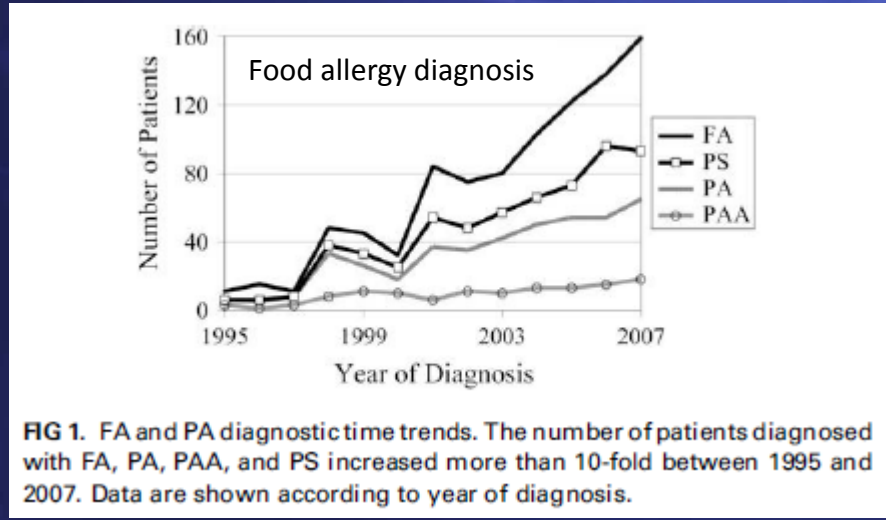



FIG 1. FA and PA diagnostic time trends. The number of patients diagnosed with FA, PA, PAA, and PS increased more than 10-fold between 1995 and 2007. Data are shown according to year of diagnosis.

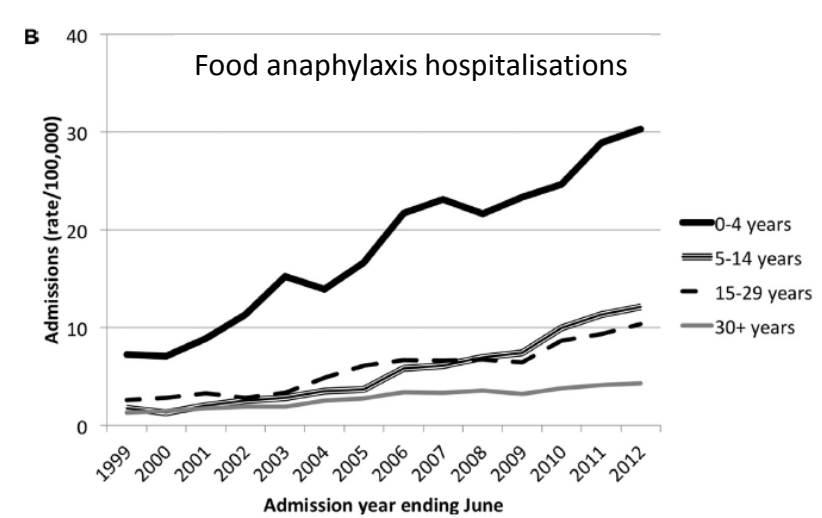
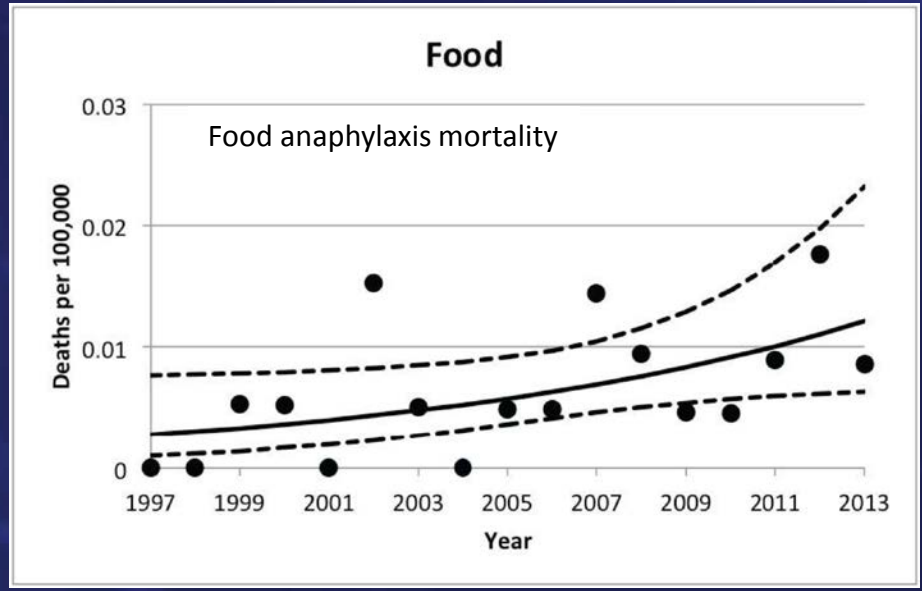



FIG 2. Australian hospital morbidity data: 1998-1999 to 2011-2012. Age-specific admission rates to Australian hospitals (per $10^5$ population per year) for total anaphylaxis (A) and food-related anaphylaxis (B) are shown.



# 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

# Oral immunotherapy for peanut allergy

- 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

# Immunological changes during OIT

***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

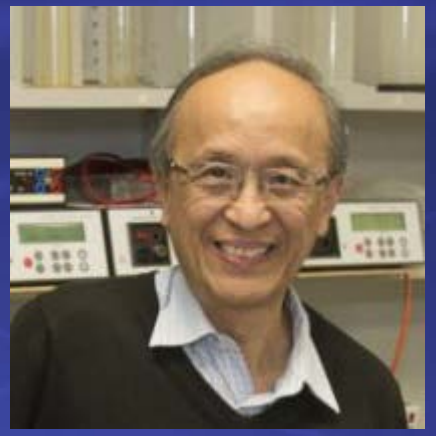
Safety-

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

Efficacy-

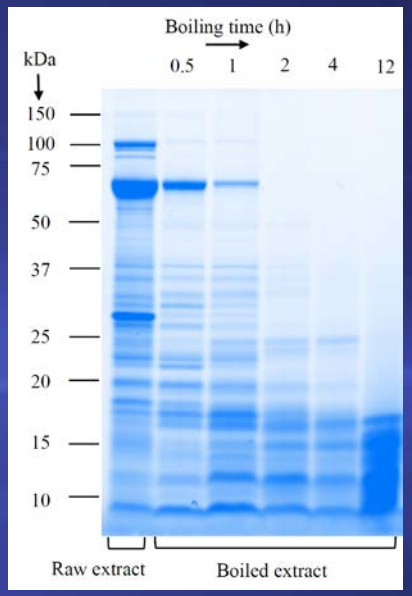
- Add probiotics
- Add adjuvants
- bacterial/viral vector for delivery of recombinant antigens

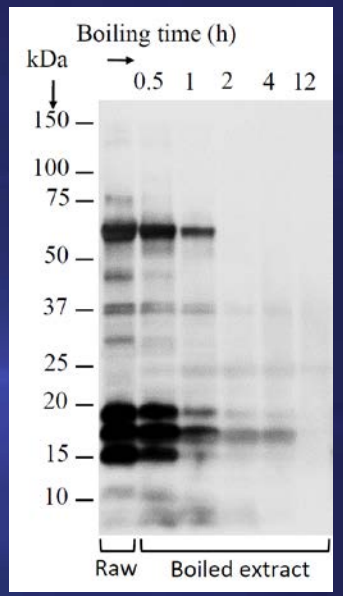
# Boiled peanut immunotherapy

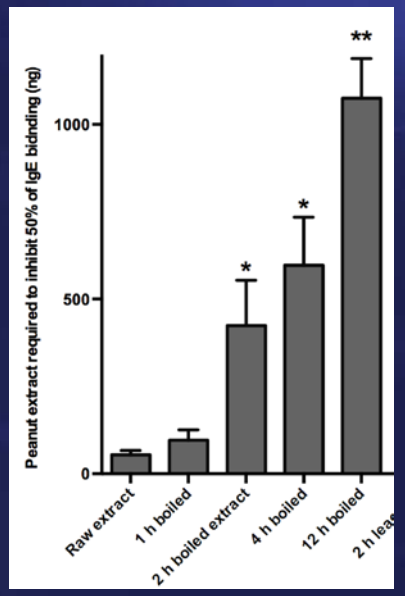


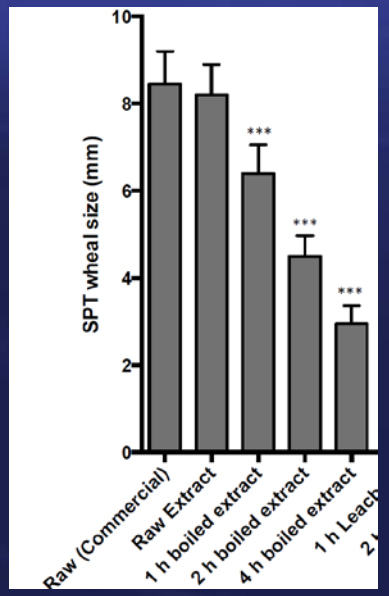
Dr Billy Tao-
Chinese have low incidence of peanut allergy
Infants and mothers consume boiled peanuts in soup

## Boiled peanuts are hypoallergenic

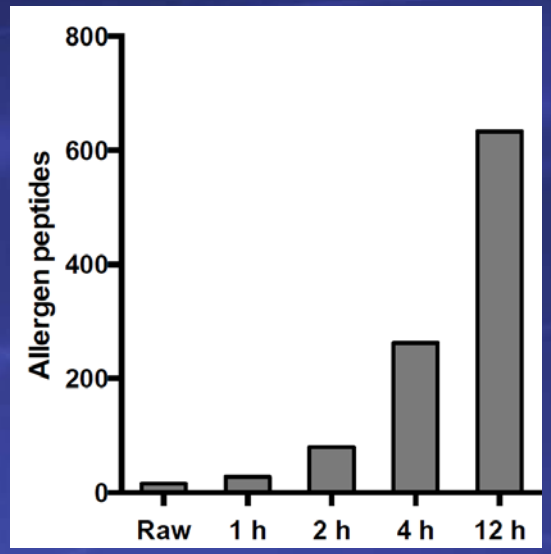


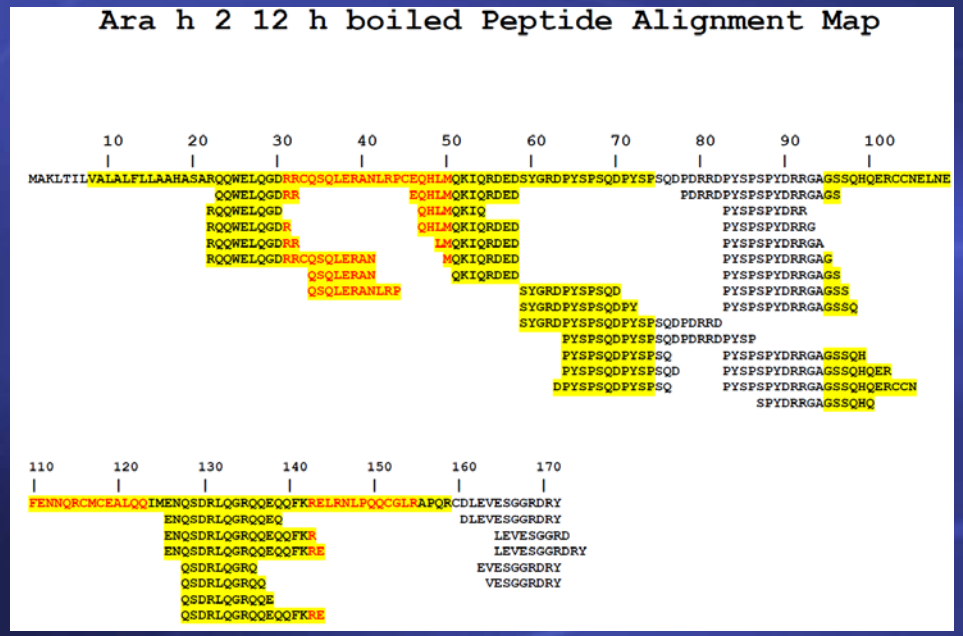



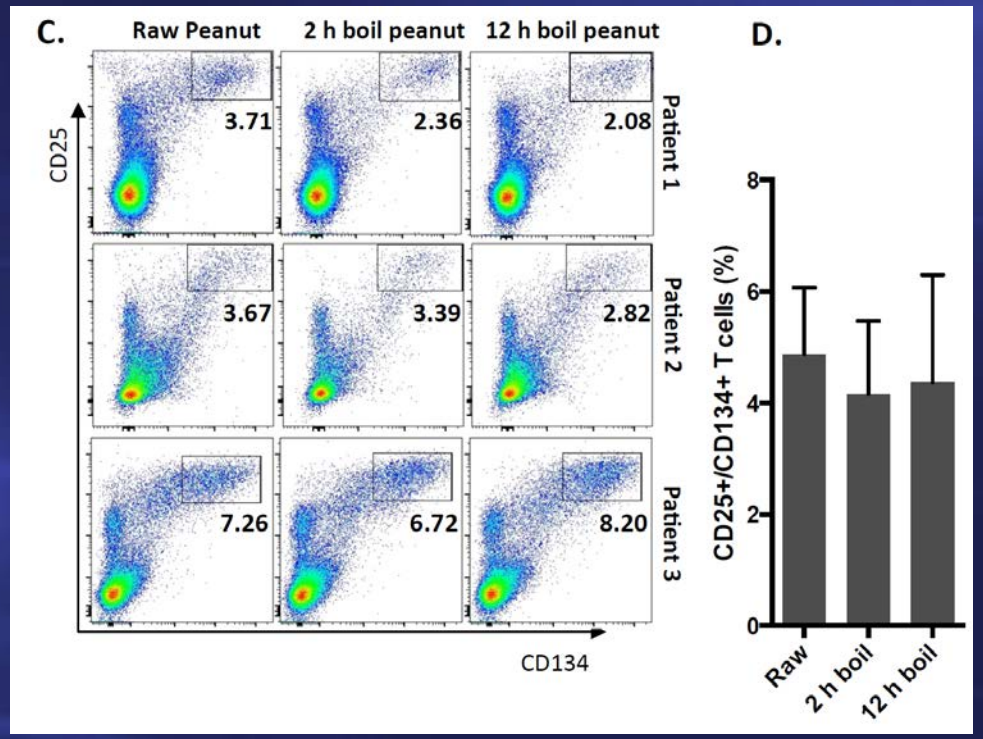
# Boiled peanut immunotherapy




Boiled peanut extracts contain T-cell reactive peptides




Boiled peanut extracts stimulate CD4 T-cell proliferation



# Boiled peanut immunotherapy

- 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

# Acknowledgements


- RAH
  - Dr Pravin Hissaria
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