Tackling the Epidemic of Allergy & Asthma

Glenis Scadding
President BSACI
Plan of talk

- Burden of allergic disease
- Mechanisms (briefly!)
- Why such an increase?
- Presentations - children
- - adults
- Diagnosis
- Treatment
- Referral
Warning over allergy provision

Rising levels of allergies are costing the NHS £1bn a year, according to research carried out in Scotland.

The Clinical and Experimental Allergy report calls for more allergy specialists to meet increased demand.

Experts at the Universities of Edinburgh and Aberdeen say levels of asthma, eczema and hay fever have risen significantly since the 1950s.

The report warns a lack of specialist care may see sufferers seek herbalist or homeopathic treatment.

The UK has one of the highest rates of allergies in the world and Scotland has more teenage asthma sufferers than any other country.
Metro 2012

A child is admitted to hospital here because of their asthma every 17 minutes.

There are more than 1,100 deaths from asthma in the UK a year, or three deaths every day.

5.4m people in Britain suffer from asthma.

The NHS spends about £1 billion a year on asthma treatment.

4.3m adults

1.1m children

JAN 1st

More than 1 million working days are lost each year due to breathing or lung problems.

25% of Britons suffer from hayfever.

45% of Britons suffer from food intolerance.

1/3 children say their asthma means they are left out of sports at school.

Sources: Asthma UK and Allergy UK.
Trends in hospital admissions for anaphylaxis

<table>
<thead>
<tr>
<th>Year</th>
<th>Cause of anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991-2</td>
<td>Food 5, Other 1, Insect venom 1, Therapeutic drugs 2</td>
</tr>
<tr>
<td>1992-3</td>
<td>Food 6, Other 1, Insect venom 1, Therapeutic drugs 2</td>
</tr>
<tr>
<td>1993-4</td>
<td>Food 6, Other 1, Insect venom 1, Therapeutic drugs 2</td>
</tr>
<tr>
<td>1994-5</td>
<td>Food 8, Other 1, Insect venom 1, Therapeutic drugs 4</td>
</tr>
</tbody>
</table>

The allergy pyramid. Most allergy symptoms are mild and intermittent, but due to the high prevalence of allergy, severe symptoms are also common and account for most of the costs. From: The Finnish Asthma Programme [25].
Epidemiology of allergic rhinitis

Children aged 13–14 years

% 13- to 14-year-olds (n=463,801)

- Australia
- China
- France
- Germany
- Greece
- India
- Indonesia
- Singapore
- South Africa
- Spain
- Sweden
- UK
- USA

Changes in asthma and allergy prevalence in ISAAC Phase 3 vs Phase 1

Prevalence of Allergy in the 21st Century

Comparison of the burden of allergic rhinitis to other diseases

†P<0.05 for allergic rhinitis/hay fever vs other conditions.
Factors of productivity loss for patients with allergic rhinitis

- Presenteeism: 37%
- Absenteeism: 44%
- Caregiver absenteeism: 19%

Source: Hellegren et al. 2010 [26]
Grass pollen counts 2003

- English
- Maths
- Science

Pollen count/m³

29th April - 5th May
6th May - 12th May
13th May - 19th May
20th May - 26th May
27th May - 2nd June
3rd June - 9th June
10th June - 16th June
17th June - 23rd June
24th June - 30th June
1st July - 7th July
8th July - 14th July
15th July - 21st July
22nd July - 28th July
Effects of hay fever on GCSEs

• Symptomatic hayfever is associated with a 43% increase in the odds of dropping an exam grade between summer and winter

• In those taking hayfever medication and for those taking sedating medications the risk increases were 36% and 71% respectively

• The odds of dropping a grade are increased in those who report previous hayfever symptoms

• The odds of dropping a grade increase according to symptom severity on the exam day
Atopy

IgE hyper-responsiveness, representing a predisposition to develop allergic disease
Allergen

Foreign protein material that induces an allergic response

Allergy
Clinical disease related to IgE mechanisms
And similar conditions not via IgE
Including:
Atopic dermatitis, asthma, rhinitis, rhinosinusitis, urticaria, angioedema, anaphylaxis, food allergy, drug allergy, eosinophiliic oesophagitis, etc
Immunology of Allergy

- **Mast cells**
  - Histamine
  - Leukotrienes
  - Prostaglandins
  - Bradykinin, PAF etc.

- **Allergen**
- **B-lymphocytes**
  - IL-4
  - VCAM-1

- **T-lymphocytes (mast cells)**
  - IL-3, IL-5
  - GM-CSF

- **Eosinophils**

**Immediate symptoms**
- Wheeze, Itch, sneeze
- Bronchospasm
- Watery discharge
- Congestion

**Chronic symptoms**
- Airway reduction
- Sticky Mucus
- Loss of smell
- “hyper-reactivity”
Risk factors - some genetic
Susceptibility to asthma /AD

- Genes - epithelial cells in skin and lung
- TSLP
- SOCS3
- Microbial receptors - NOD, TLRs
- Filaggrin
- Jones G Curr Allergy Asthma Rep 2007
Environmental problems
ENVIRONMENTAL EFFECTS
Decline in Infectious Diseases Coincides with Rise in Asthma

Adapted from Armstrong et al., JAMA 1999;281; 61-6.
## Table 3. Significant Predictors of Asthma in 926 Children

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Relative Risk (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each additional older sibling</td>
<td>0.8 (0.7–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Entry into day care at ≤6 mo of age</td>
<td>0.4 (0.2–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.5 (1.1–2.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>History of asthma in the mother</td>
<td>2.3 (1.6–3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of asthma in the father</td>
<td>1.6 (1.1–2.4)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Allergic Inflammation and the Hygiene Hypothesis

- APC
- T Cell
- Th1
- IFN-γ
- Th2
- IL-4
- IL-5
- IL-3
- Mast Cell
- Eosinophil
- Leukotrienes (and others)
- MBP, ECP, EPO
- Histamine
- Bronchoconstriction
- Mucous Secretion
- Epithelial Damage
- Airway Inflammation and Hyperresponsiveness

Infections
Endotoxin
Mycobacteria
GI flora
Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? (n=1206 age 7-8)

Table 2. Association of antibiotics use in 1st year with asthma and allergy outcome variables; odds ratios (95% CI) of use of antibiotics in first year, adjusted for area, gender, parental asthma, parental hay fever, ≥ 2 older siblings, maternal smoking in pregnancy, exposure to smoke in first 6 months and LRI in infancy

<table>
<thead>
<tr>
<th></th>
<th>N*</th>
<th>Asthma (n = 53)</th>
<th>Hay fever (n = 66)</th>
<th>Eczema (n = 230)</th>
<th>N*</th>
<th>Atopy (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antibiotics</td>
<td>805</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>450</td>
<td>1</td>
</tr>
<tr>
<td>Antibiotics 1st year</td>
<td>375</td>
<td><strong>1.7 (1.0–3.1)</strong></td>
<td><strong>2.3 (1.3–3.8)</strong></td>
<td><strong>1.3 (1.0–1.8)</strong></td>
<td>210</td>
<td><strong>1.1 (0.7–1.7)</strong></td>
</tr>
</tbody>
</table>

*Number of subjects in each antibiotics subgroup (atopic diseases and atopy, respectively).
Vitamin D and its role in allergic disease.

• Incidence of atopy and allergic diseases is high and rising.

• Epigenetic or nutritional factors might be important in pathogenesis.

• Vitamin D - the 'sunshine hormone' - exerts profound effects on both adaptive and innate immune functions.

• The incidence of vitamin D insufficiency is surprisingly high in the general population.

• Correcting vitamin D levels [measured as serum 25 hydroxy vitamin D -25(OH)D] beneficial or even protective?
Asthma, allergy and respiratory infections: the vitamin D hypothesis.


- Every body tissue has vitamin D receptors
- Vitamin D has pleiotropic effects
- Low levels - higher risk of upper and lower respiratory infections in children
- and may contribute to asthma symptoms and morbidity
- Associations between childhood asthma, fetal lung and/or immune development, and maternal vitamin D intake.
- Insufficiency implicated in the onset of childhood atopy and food allergies.
- Controlled, prospective studies on vitamin D
Decreased Prevalence of Sensitization to Cats with High Exposure to Cat allergen
JACI 2001;108:537(n=2502)
Oral tolerance induction

• Allergenic food avoidance in pregnancy, lactation and weaning has not reduced allergy

• Early cutaneous exposure via inflamed skin leads to food allergy

• Whereas early oral exposure leads to tolerance?

• UNDER INVESTIGATION- LEAP STUDY

• Lack G Nestle Nutr Wkshop Ser Paed Program 2007 59,63-8
The Allergic March

Development of allergic symptoms – Allergic march

German MAS cohort

% period prevalence

Age (mo)

Atopic dermatitis
Asthma
Rhinoconjunctivitis

Prevalence rates up to 12 years

Co-morbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>1 year</th>
<th></th>
<th>2 years</th>
<th></th>
<th>4 years</th>
<th></th>
<th>8 years</th>
<th></th>
<th>12 years</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Eczema only</td>
<td>397</td>
<td>14</td>
<td></td>
<td>487</td>
<td>17</td>
<td>403</td>
<td>14</td>
<td>245</td>
<td>8</td>
<td>196</td>
</tr>
<tr>
<td>Asthma only</td>
<td>63</td>
<td>2</td>
<td></td>
<td>106</td>
<td>4</td>
<td>105</td>
<td>4</td>
<td>81</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>Rhinitis only</td>
<td>72</td>
<td>2</td>
<td></td>
<td>74</td>
<td>3</td>
<td>174</td>
<td>6</td>
<td>244</td>
<td>8</td>
<td>404</td>
</tr>
<tr>
<td>Eczema and asthma</td>
<td>22</td>
<td>1</td>
<td></td>
<td>32</td>
<td>1</td>
<td>31</td>
<td>1</td>
<td>20</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Eczema and rhinitis</td>
<td>15</td>
<td>1</td>
<td></td>
<td>19</td>
<td>1</td>
<td>94</td>
<td>3</td>
<td>60</td>
<td>2</td>
<td>92</td>
</tr>
<tr>
<td>Asthma and rhinitis</td>
<td>10</td>
<td>0</td>
<td></td>
<td>15</td>
<td>1</td>
<td>28</td>
<td>1</td>
<td>46</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>Eczema, asthma and rhinitis</td>
<td>6</td>
<td>0</td>
<td></td>
<td>4</td>
<td>0</td>
<td>18</td>
<td>1</td>
<td>30</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>No disease (not shown in figure)</td>
<td>2331</td>
<td>80</td>
<td></td>
<td>2179</td>
<td>75</td>
<td>2063</td>
<td>71</td>
<td>2190</td>
<td>75</td>
<td>2035</td>
</tr>
</tbody>
</table>
WHICH ALLERGENS MATTER?

- EARLY childhood - foods
- LATER childhood - inhalants, some foods
- ADULT - inhalants, occupational, foods
Point prevalence of sensitisation to food

% period prevalence

Age (months)

- Hen's egg
- Cow's milk
- Wheat
- Soy
SENSITIZATION

- ALSPAC study
- population based
- birth cohort
- 13638 singletons
- SPT age 7 years
- to 29 allergens
- valid data from 6412

- Peanut 1.4%, tree nut 1%
- Peanut sensitization associated with AD and use of arachis oils on skin

- Lack G. NEJM 2003
SENSITIZATION

- ALSPAC study
- population based
- birth cohort
- 13638 singletons
- SPT age 7 years
- to 29 allergens
- valid data from 6412

- Aeroallergens commonest
- GP 8.5%, Dp 7.8%
- Cat 4.9%, Dog 2.7%
- Horse & Rabbit 1.4%
- 95% of +ves included GP,Dp,Cat.
## Allergic diseases in childhood, prevalence of sensitization

<table>
<thead>
<tr>
<th>Age</th>
<th>Diagnosis</th>
<th>Prevalence</th>
<th>IgE – sensitization</th>
<th>Statement of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early childhood</td>
<td>Food allergy</td>
<td>7-8%</td>
<td>40-60%</td>
<td>II</td>
</tr>
<tr>
<td>School age</td>
<td>Food allergy</td>
<td>1-2%</td>
<td>60-70%</td>
<td>II</td>
</tr>
<tr>
<td>Childhood</td>
<td>Atopic dermatitis</td>
<td>15-20%</td>
<td>33-40%</td>
<td>II</td>
</tr>
<tr>
<td>Early Childhood</td>
<td>Recurrent wheeze/asthma</td>
<td>21-34%</td>
<td>30-60%</td>
<td>II</td>
</tr>
<tr>
<td>School age</td>
<td>Asthma</td>
<td>7-10%</td>
<td>70-90%</td>
<td>II</td>
</tr>
<tr>
<td>Childhood</td>
<td>Rhinitis and conjunctivitis</td>
<td>10-15%</td>
<td>60-80%</td>
<td>II</td>
</tr>
</tbody>
</table>

Høst et al. Allergy 2003
Allergy testing

- Skin prick testing
- Measurement of specific IgE in blood
  - ‘RAST’ testing
- Challenge testing (Day ward)
  - Food challenges
Increasing prevalence of specific IgE in an adult population
Linneberg et al, J Allergy Clin Immunol 2000

15-41 yr adults
Same subjects studied 8 yrs apart
Increase in rhinitis associated with increase in IgE
Allergic Marches?
Scadding, CEA 2007

1. Genetic
   - Environmental

2. Environmental
   - Genetic
Can Seasonal Allergic Rhinitis Cause Allergy to Fruit?
Silver Birch Tree
Oral Allergy Syndrome

- Symptoms of oral itch, swelling to fresh fruits/vegetables
- in c. 40% of birch-sensitized patients.
- Common allergens involved- including profilin = heat labile, cooked fruit tolerated.
- Other allergens eg lipid transfer proteins can give more severe reactions
Late Onset Severe Food Allergy

- Six adults with recent onset of anaphylaxis to previously tolerated foods
- Seafood, fig, celery-spice, birch-apple
- In four cases, sensitization was probably via respiratory tract
- Possibly similar to oral allergy syndrome
- Scadding et al, BSACI poster 2007
INTERACTION WITH INFECTION

• ASTHMA TRIGGERS:
  • Allergen
  • Virus
  • Both = synergy
Sensitisation, Exposure and the Risk Hospital Admission Children

![Bar chart showing odds ratio with p-values](chart.png)

- S: p = 0.42
- V: p = 0.15
- S/E: p = 0.12
- S/V: p = 0.09
- S/E/V: p < 0.0001
- ICS use: p = 0.004

Murray, Custovic et al 2005
RHINITIS TREATMENT BENEFITS ASTHMA

- Reduction of ER visits, OR 0.5 \(^1\)
- Reduction of hospitalization- 61% \(^2\)
- Reduction of both \(^3\)

1. Adams et al JACI 2002
2. Crystal- Peters, JACI 2002
3. Corren, JACI 2004
RHINITIS IS STILL.....

• IGNORED

• UNDERDIAGNOSED

• MISDIAGNOSED

• & MISTREATED
Burden of Allergic Rhinitis in US and Europe: 2005

Estimated incidence in **USA**: 62.6 million cases
- 29% Diagnosed
- 71% Undiagnosed

Estimated incidence in **Europe**: 61.6 million cases
- 23% Diagnosed
- 77% Undiagnosed

Source: *Decision Resources Report.*
ALLERGY DIAGNOSIS - WHY MISSED?

• PATHOPHYSIOLOGY - hidden LPR-eg rhinitis

• MISSED concomitant diagnosis-organ specific clinics

• UNDER-APPRECIATION of co-morbidity-eg rhinosinusitis, OME

• SHEER IGNORANCE - lack of allergy education, misinformation
WHY NEGLECTED?

- THERAPEUTIC NIHILISM - “no point in diagnosing allergy because you can’t do anything about it”

- IGNORANCE - of possible treatments

- FEAR – ”Skin prick tests are dangerous” “Steroids!” “Immunotherapy kills”

- COST- Commissioners won’t like it
ALLERGY TESTING – WHY?

Allergy testing is a very important prerequisite for specific allergy treatment as regards:

A. Early identification of infants at increased risk for later development of allergic diseases

B. Specific allergy treatment
   - Specific allergen avoidance measures
   - Relevant pharmacotherapy
   - Specific allergy vaccination

Høst et al. Allergy 2003
# Indications for allergy testing

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal symptoms: Vomiting, diarrhoea, colic, failure to thrive</td>
<td>B</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>B</td>
</tr>
<tr>
<td>Acute urticaria/angioedema</td>
<td>B</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>B</td>
</tr>
<tr>
<td>Children &lt; 3-4 years of age with recurrent wheezing/asthma</td>
<td>B</td>
</tr>
<tr>
<td>Children &gt; 3-4 years and adults with asthma</td>
<td>B</td>
</tr>
<tr>
<td>Rhinitis/ rhinosinusitis</td>
<td>B</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>B</td>
</tr>
<tr>
<td>Insect sting reactions</td>
<td>B</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>B</td>
</tr>
<tr>
<td>Drug allergy</td>
<td>B</td>
</tr>
</tbody>
</table>

Høst et al. Allergy 2003, modified
Allergy referral

- Uncontrolled symptoms
- Investigation of allergens/ triggers
- Consideration of immunotherapy
- Occupational allergy
- Drug allergy
- Food allergy needing challenge
- Multisystem allergy
- Systemically unwell
- Other-if unsure please discuss
Allergen-specific immunotherapy

- Only disease-modifying treatment
- **Subcutaneous**- good efficacy, but costly, time-consuming and dangerous
- **Sublingual**- moderate efficacy, home use, no severe side effects
Cochrane Meta-analysis of Immunotherapy for Allergic Rhinitis

<table>
<thead>
<tr>
<th></th>
<th>SCIT SMD (95% CI)</th>
<th>SLIT SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>-0.73 (-0.97, -0.50)</td>
<td>-0.42 (-0.69, 0.15)</td>
</tr>
<tr>
<td>Medication</td>
<td>-0.57 (-0.82, -0.33)</td>
<td>-0.43 (-0.63, 0.23)</td>
</tr>
</tbody>
</table>

Calderon M et al. 2006  Wilson D et al. 2005
Immunotherapy prevents asthma development

- 205 children with SAR randomized to SCIT or open control group. 20% mild seasonal asthma.
- At 3&10 yrs IT group had less new asthma: OR 2.52, p<0.05

SCIT REDUCES NEW SENSITIZATION

- **Group A**
  7182 SIT 3 years, drugs 7 years

- **Group B**
  1214 drugs only

Purello-D’Ambrosio et al
CEA 2001 31, 1295-1302.

(P<0.0001)
T reg cells
A European Declaration on Immunotherapy
Combating allergy beyond symptoms
Reimbursement policies for immunotherapy in the countries surveyed

- **Sweden**: It differs in different parts of Sweden; in Stockholm it is free but not in other parts of Sweden.
- **Finland**: Allergens specific immunotherapy is partially reimbursed.
- **Germany**: Specific immunotherapy is reimbursed but physicians are restricted due to pharmaceutical budgets.
- **France**: 20% for sublingual or injection allergens; immunotherapy: 10% for sublingual tablets.
- **Italy**: Partially refunded (matching same criteria) in a few Regions.
- **Greece**: No specific reimbursement policy.
THE ANSWER

- Education
- Education
- Education
- and Interaction

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