Outline

- occupational asthma recognition/diagnosis management outcomes
- when it's not so simple...
- preventing occupational asthma (surveillance)

Occupational asthma

- appropriate history of exposure to an airborne sensitising agent
- typical symptoms:
  - specific immunology
  - serial peak flow measurement
  - (specific provocation testing)
- management of confirmed case by avoidance
John, age 23
18 - started work in a bakery
20 - rhinitis
21 - wheezy during football
22 - symptoms related to work

Occupational asthma
- appropriate history of exposure to an airborne sensitising agent
- typical symptoms:
  - work-related
  - eye/nasal symptoms "constant cold" "hay fever all year round"
  - keep having "chest infections"
- specific immunology
- serial peak flow measurement

Occlusion of time since first exposure

- sensitised

Occupational asthma
- appropriate history of exposure to an airborne sensitising agent
- typical symptoms:
  - work-related
  - eye/nasal symptoms "constant cold" "hay fever all year round"
  - keep having "chest infections"
- specific immunology
- serial peak flow measurement

Peak flow measurements
- every 2-3 hours
- 4 weeks
- at work and days off
- best of 3 blows

- lowest peak flow
- mean of all readings that day
- best peak flow

Work day
Day off
Specific inhalation testing (controlled provocation)

- when you need a diagnosis
- where all else fails
- new or specific agents
- not for legal reasons
- specialist++ (3 centres in the UK)

• single blind challenge series
• exposure chamber
• exposed: 15 - 25 minutes - separate days
• monitored symptoms, FEV₁ and PC₂₀

Managing a case

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th></th>
<th>mid-term</th>
<th></th>
<th>socio-economic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>continuing exposure causes continuing symptoms</td>
<td></td>
<td>most patients improve after exposure ceases</td>
<td></td>
<td>avoidance of exposure requires ‘relocation’</td>
</tr>
<tr>
<td></td>
<td>continuing exposure causes worse symptoms</td>
<td></td>
<td>specific IgE antibodies fall after exposure ceases</td>
<td></td>
<td>re-employment more difficult (1/3 unemployed up to 6y later)</td>
</tr>
<tr>
<td></td>
<td>protective equipment rarely satisfactory</td>
<td></td>
<td>improvement plateaus at 2 years?</td>
<td></td>
<td>earnings often lower</td>
</tr>
<tr>
<td></td>
<td>medical treatment usually unhelpful</td>
<td></td>
<td></td>
<td></td>
<td>dependent on occupational mobility</td>
</tr>
</tbody>
</table>

bronchial provocation test
- bakers’ amylase

<table>
<thead>
<tr>
<th>% CHANGE IN BASELINE FEV₁</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase 0.1% 15 mins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase 1% 15 mins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase 2.5% 10 mins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROYAL BROMPTON HOSPITAL
high risk occupations - high molecular mass allergens

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Allergen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker</td>
<td>Flour, fungal α-amylase, hemicellulase</td>
</tr>
<tr>
<td>Laboratory animal worker</td>
<td>Mouse urinary proteins, Guinea pig epithelial proteins, other mammal/insect/fish proteins</td>
</tr>
<tr>
<td>Health care worker</td>
<td>Rat urinary proteins, mouse urinary proteins</td>
</tr>
<tr>
<td>Detergent manufacturer</td>
<td>Detergent protease, Detergent amylase, Detergent cellulase, Detergent lipase</td>
</tr>
<tr>
<td>Tea packer</td>
<td>Herbal tea dusts, crab proteins, other shellfish/fish proteins</td>
</tr>
<tr>
<td>Seafood processor</td>
<td>Prawn proteins, other shellfish/fish proteins</td>
</tr>
<tr>
<td>Other foods</td>
<td>Flour, latex, eggs, etc.</td>
</tr>
<tr>
<td>Factory workers</td>
<td>Latex, latex, etc.</td>
</tr>
</tbody>
</table>

- all IgE associated

atopy increases risk
Skin prick testing

Benefits:
- quick
- inexpensive
- safe
- easy to perform
- not painful
- Platinum – no IgE test

Limitations:
- retest required if further allergens later identified
- not (truly) quantitative
- anti-histamines
- dermographism
- Operator dependent
- some allergens not suitable for spt – irritant / acidic

Major limitation = lack of commercial allergens for occupational SPT

Medicine – regulation (strict)

Measurement of Specific IgE in Serum

- Ability to detect small amounts of IgE
- Small volume of blood
- Lack of interference from high total IgE
- High precision and linearity
- Reproducible and standardised between laboratories
- Relevant and standardised allergens
- Blood can be sent through post at room temperature
- External quality assurance scheme

Not so basic: change of focus

Case: 45M

New diagnosis of adult onset asthma
Referred by OHP
Works in QC at a contact lens factory
Employed since 2007 as a Technical Operative

Checking and monitoring the production of contact lenses within one of the factory areas
- supervise and monitor the technical operation of the machines (QC)
- desk based role at the end of the production line, which is arranged around his desk, within the factory
- overalls, gloves and a (FFP2) mask

Manufacture and Environment

- machine dispenses small doses of pre-mixed liquid solution into wells for pressing
- product is checked then cured using UV light
- desk right next to UV light machine
- periodically replenish the liquid supply
- supplied in a sealed bottle – inserts into the machine (pierced internally)

Protection/Environment

- ingredients (unaware of integral components) have a “strong smell”
- episodes of acute self-limiting respiratory symptoms

Various narratives

Patient
“work is harming my health”
others affected

OHP
“I am only aware of two other employees who work in a similar area with symptoms... this is not a widespread problem.”
one known asthmatic, other work-related rhinitis under local hospital
“Neither of these employees work with sensitisers but do work with methacrylates”
no concerns about risk controls where he works having visited it, and checked the environmental monitoring results

Respiratory Physician, Local Hospital
“oh yes I know that factory, I have seen a number of people who work there with respiratory (mainly airway) symptoms”

Workplace surveillance

<table>
<thead>
<tr>
<th>Date</th>
<th>PEF</th>
<th>FEV/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 2008</td>
<td>496</td>
<td>59%</td>
</tr>
<tr>
<td>March 2009</td>
<td>630</td>
<td>68%</td>
</tr>
<tr>
<td>September 2009</td>
<td>636</td>
<td>61%</td>
</tr>
<tr>
<td>March 2011</td>
<td>506</td>
<td>54%</td>
</tr>
<tr>
<td>July 2011</td>
<td>577</td>
<td>58%</td>
</tr>
<tr>
<td>May 2013</td>
<td>334</td>
<td>46%</td>
</tr>
<tr>
<td>June 2013</td>
<td>337</td>
<td>47%</td>
</tr>
<tr>
<td>June 2014</td>
<td>424</td>
<td>48%</td>
</tr>
</tbody>
</table>
Ingredients

Asthma Hazard Index (HI)

- Computer generated probability that a given compound is asthmagenic

- The computer uses a logistic regression equation to make a quantitative link between structure (molecular descriptors) and activity (asthmagenic or not)
Asthma Hazard Index (HI)

- Computer generated probability that a given compound is asthmagenic
- The computer uses a logistic regression equation to make a quantitative link between structure (molecular descriptors) and activity (asthmagenic or not)
- The mathematical relationship is defined by the statistical comparison of molecular descriptors present in asthmagens vs controls
- Hazard ranges from 0 (not likely) to 1 (extremely likely)

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>CAS</th>
<th>Structure</th>
<th>MW</th>
<th>HI (Jarvis et al 2005 model)</th>
<th>HI (Jarvis et al 2015 model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Vinyl-N-Methylacetamide</td>
<td>3195-78-6</td>
<td></td>
<td>99</td>
<td>0.29</td>
<td>0.37</td>
</tr>
<tr>
<td>Hydroxybutyl methacrylate</td>
<td>29008-35-3</td>
<td></td>
<td>158</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>Polyethylene Glycol Substituted Polysiloxanyl Macromer</td>
<td>697234-74-5</td>
<td>Polymer</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Polydimethylsiloxane methacrylate derivative</td>
<td>697234-76-7</td>
<td>Polymer</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>1-Vinyl-2-Pyrrolidone</td>
<td>88-12-0</td>
<td></td>
<td>111</td>
<td>0.32</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Literature: cases and chemistry

Several cases of acrylate-induced asthma have been described (1981–):
- Plexiglass powder (poly(methyl methacrylate))
- Dentists
- Workers using acrylate-containing glues or paints
- Late asthmatic response common after bronchial challenge

Used in a large variety of products
- Glues, solvents, paints, printing ink, soft contact lenses, porcelain nails, superglues,
- Original synthesis in 1940s – gun sights

Advantages
- Transparency, resistance to breakage, and elasticity

Several types of acrylic compounds:
- Acrylates
- Cyanoacrylates (tissue adhesives and home glues)
- Methacrylates (prostheses and dental and orthopedic fillings)

A little bit of chemistry

ACRYLATE          METHACRYLATE          CYANOACRYLATE

- Common monomers in polymer plastics, forming the acrylate polymers
- Acrylates easily form polymers because the double bonds are very reactive
- "Promising candidate monomers to prepare any hybrid polymer nanocomposites"
Challenge test

• PC20 3.9mg/ml histamine (bronchial hyper-reactivity prior to challenge)
• No change from baseline with control challenge
• Immediate fall in FEV₁ after challenge with 4 min of stirring solution
• Drop to 50% at 10 minutes post exposure
• Reproduced on the subsequent day, following 1 min exposure
• Drop to 26% at 15 mins post exposure
• No late response on either day
• PC20 fell steadily to 0.58mg/ml (increasing hyper-reactivity)

Diagnosis: Occupational Asthma

Patient input

“Health surveillance needs to be used efficiently and strategically to reduce or minimise possible incidences of occupational asthma” (Szram and Cullinan, via Google)

“This has great resonance in my case. I started on the agency and worked for about a year before becoming permanent. Agency workers were not included in the health surveillance programme. Hindsight is another wonderful thing and, had I had more of it 9 years ago, I would have asked questions as to why this did not happen. Many agency workers go on to permanent roles and a baseline figure for lung function testing could only be beneficial to all parties.”

There were two years in which I did not get tested at all two occasions when I was tested twice in a year but this was only in response to my increasingly poor performance. There was a clear downward trend. It may be that the drops were only small but I didn’t notice a big decline in my health until quite late in the day.

One of the questions I asked myself after seeing this graph was that it seemed pointless doing these tests if no discernable action was taken despite having increasingly poor results. It seems that the tests were only done to tick all the boxes with no material regard to the results themselves.

23 year old engineer
• frequent exposure to fuel, oil, lubricants
• childhood asthma, eczema, hayfever
• June 2013 – 3 months after starting training – wheeze, nocturnal cough, chest tightness
• rapidly and well controlled on inhaled steroid and salbutamol
• September 2013: substantial improvement on holiday – stopped all treatment
• peak flow normal (600l/min)

Questions:
• does he have occupational asthma?
• does he have asthma?
• future work/deployment?

Case history: asthma?

Case history: asthma?

RBH November 2013
• symptoms coincided with pollen season
• holiday coincided with end of pollen season
Atopic – positive skin test to grass pollen

Spirometry:

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th>Pre-BD</th>
<th>Post-BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>%predicted</td>
<td>%change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁</td>
<td>4.66</td>
<td>5.16</td>
<td>5.35</td>
</tr>
<tr>
<td>FVC</td>
<td>5.32</td>
<td>6.1</td>
<td>114%</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>87%</td>
<td>72%</td>
<td></td>
</tr>
</tbody>
</table>
December 2013: peak flow record

histamine PC20: normal

Case history: asthma?

Thorny issue: confusing ‘occupational’ and ‘work-exacerbated’ asthma

- occupational asthma: ‘induced by work’
- work-exacerbated asthma: ‘provoked by work’

<table>
<thead>
<tr>
<th></th>
<th>Occupational asthma</th>
<th>Work-exacerbated asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>latency (minimum)</td>
<td>yes (6-24 months)</td>
<td>no</td>
</tr>
<tr>
<td>latency (maximum)</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>work-relationship</td>
<td>no clear differences</td>
<td>no clear relationship</td>
</tr>
<tr>
<td>eye/nose symptoms</td>
<td>yes (HMW)</td>
<td>no clear relationship</td>
</tr>
<tr>
<td>‘out of context’ Sx</td>
<td>both (non-specific hyper-reactivity)</td>
<td></td>
</tr>
</tbody>
</table>
The Not So Basics...

37 year old researcher in biotechnology

- Long history of hayfever
- 2004: Occupational latex allergy/asthma
- Nasal symptoms disappeared on switching from latex to nitrile gloves at work
- Entire workplace went ‘latex-free’
- Growing problems with:
  - Bananas and kiwis
  - Condoms
  - Weeping figs
  - Ham sandwich
  - Other fruits
  - Raw vegetables
- Considerable difficulties with work/diet/friends

2008: Chest tightness when new floors laid at work (‘Arditex’ latex levelling compound)

“In view of her occupational asthma, is it safe for her to continue work?”

Further:

- RBH, 2008
  - SPT negative to latex (x2x2)
  - Specific IgE negative (x2)
  - Specific provocation test to latex (various) negative
  - “Not allergic to latex”
- Considerable inner turmoil...

- Letter re. original diagnosis

“One visit she mentioned that she felt she was experiencing problems with latex ... at the time RAST tests to latex were negative and skin prick tests were equivocal with 2mm. wheals. However we decided to err on the side of caution ... and advised her to practise latex avoidance.”

Consider again ...

35 year old engineer

- 17 years with large diesel engine manufacturer
- Experienced tool-setter
- Childhood wheeze – details scanty but not severe
- 2011: Asthma-like symptoms and admission for ‘chest infection’
- Off work since
- Local diagnosis of occupational asthma
- ‘To something in his place of work’
- Remained off work
- 2012: OH concerned about:
  - Firmness of diagnosis
  - Responsible agent
  - Relocation
- End of statutory sick pay

Further:

- Diagnosis based on clinical opinion and limited peak flow measurement
- Could not specify agent
- Suggest return to work in different area
- Patient declined
- Legal suit

‘Dear Paul
I think this is the third time you have written to me asking for more information about this man. I am afraid we do not have anything further than what I have already sent you. On the basis of those tests we thought it would be prudent if the patient were to avoid any further exposures at work.

If I had known what problems this would cause ….”
and once more ....

45 year old aircraft technician
- 'chest infections' as a child
- non-smoker
- fits aircraft 'crew quarters'
- variety of glues and solvents
- 2010: developed occasional wheeze at work
- no nasal or eye symptoms

- GP
  - 'occupational asthma'
  - 'allergic'
  - advised to stay away from all glues

Thorny issue: not identifying the responsible agent
- almost always possible ...
- ... with sufficient certainty (challenge test helpful)
- relocation otherwise impossible ...
- ... as is further career choice
- sometimes it doesn't matter:
  - unavoidable antigen mix
  - no likelihood of further exposure

- thinking ahead
- keeping people at work during diagnostic process
- acting fast

More complexity
- an increasing number of people report symptoms which they attribute to:
  - something or somewhere particular at work
  - strong smelling substances

- this may not appear to be, but has been labelled (by someone) as:
  - asthma
  - "allergy"
  - anaphylaxis

asthma and work; narratives and terminology 4

'I was fine until ....

- I reached 25
- I breathed in a lot of chlorine in the lab at work
  - out of the blue
  - and now I ...
  - can't breathe
  - wheeze
  - cough ...
  - whenever I come across ...
  - bleach, paint fumes, aerosols, cleaners, deodorants, perfumes, petrol fumes, furniture polish, bonfires, barbecues
  - so now I can't ...
  - work
  - use any of these things at home
  - go on public transport
  - go out
  - go out without my girlfriend walking 25 yards in front of me
  - go anywhere air-conditioned
  - go down the washing powder aisle at the supermarket
  - and my asthma pumps don't do the trick (any more)
Case A....

39 year old nursery worker for 20 years
- referred by GP
- chest infection Autumn 2010 – antibiotics, then inhalers
  - increased breathlessness – GP: oral steroids, nebuliser
  - no better on discharge – home nebuliser
- returned to work – acute breathlessness on exposure to colleague’s perfume and air fresheners
- now chronic cough associated with same triggers
- several (50+) risk assessments completed by manager

-PMHx
  - past history of dystonia (R eye and face) Rx Botox (neurologist)

Tricky Issues in Occupational Asthma

Clinical:
- is it really asthma?
- making a firm diagnosis
- managing a confirmed case
- what do about rhinitis
- act fast

Pre-placement (pre-employment) assessment

Consider:
- pre-existing OA
- pre-existing asthma
- ‘atopy’

“Health practitioners should not use poorly discriminating factors – such as atopy, family or personal history of asthma, smoking and HLA phenotype – which increase individual susceptibility to exposure as a reason to exclude individuals from employment”

BOHRF Guidelines, 2010
### Surveillance for OA in the workplace: immunology

<table>
<thead>
<tr>
<th></th>
<th>Platinum refining (SPT)</th>
<th>Detergent manufacture (IgE)</th>
<th>Baking industry (IgE)</th>
<th>Animal research (IgE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High residual risk</td>
<td>High residual risk</td>
<td>High residual risk</td>
<td>High residual risk</td>
<td>High residual risk</td>
</tr>
<tr>
<td>Moderate residual risk</td>
<td>Moderate residual risk</td>
<td>High residual risk</td>
<td>High residual risk</td>
<td>High residual risk</td>
</tr>
<tr>
<td>Past epidemics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everybody, annually</td>
<td>Everybody, annually</td>
<td>Selectively, annually</td>
<td>At pre-employment</td>
<td></td>
</tr>
<tr>
<td>Individual case</td>
<td>Adjoint to exposure</td>
<td>Individual case recognition</td>
<td>Baseline for</td>
<td></td>
</tr>
<tr>
<td>recognition</td>
<td>control</td>
<td>recognition</td>
<td>reference later</td>
<td></td>
</tr>
</tbody>
</table>

### Possible interventions in bakers’ asthma:

- **Secondary prevention**
  - Workplace medical surveillance programme to detect early pre-clinical signs of asthma
    - What? Specific IgE, skin prick tests (SPT), rhinitis?
    - When? At job start (pre-exposure) and post-exposure follow-up (frequency? how long after ceasing exposure?)
    - Who? Among all bakers? Only among bakers at higher risk?

### Occupational rhinitis is a risk factor for occupational asthma: lab animal workers

#### Kaplan-Meier survival estimates

- No-rhinitis
- Rhinitis on animal exposure

**Hazard ratio = 7.39 (3.29-16.60)**

*Risk greatest within first six months of OR diagnosis*

Elliott et al. *Journal Allergy Clin Immunol* 2005
Occupational rhinitis is a risk factor for occupational asthma


Immunology in health surveillance

Surveillance
- Bakery employees
- Mandatory (routine)
- In-house
  → Identification of possible disease

Survey
- Validation of above
- External
  → Prevalence of disease

Surveillance for OA in the workplace: questionnaires

% work-related chest symptoms with sp.IgE

- Bakers
- Managers
- Confectioners

Brant et al. OEM 2005
### Outline

- occupational asthma recognition/diagnosis
- management outcomes
- when it’s not so simple...
- preventing occupational asthma (surveillance)

### References

**Guidelines:**
- www.bohrf.org

**Specialist sites:**
- www.occupationalasthma.com (Birmingham: general)
- www.remcomp.fr/asmanet/asmapro/asmawork.htm (Quebec: general)

**Review articles:**
- Szram J, Cullinan, P. Medical surveillance for prevention of occupational asthma. Current Opinion in Allergy and Clinical Immunology: April 2013 - Volume 13 - Issue 2 - p 138–144

**Book:**

### 1. Which is not a common cause of occupational asthma?

a) food processing  
b) paint spraying  
c) platinum refining  
d) air freshener manufacture
2. For an accurate assessment in the investigation of occupational asthma, the minimum number of PEF readings per days is:

a) 2  
b) 4  
c) 6  
d) 12

3. If an employee newly diagnosed with occupational asthma continues to work as before in their exposed job, it is likely that:

a) their asthma will deteriorate  
b) they will be fine as long as they take their medication  
c) they will be fine as long as they wear a mask  
d) their asthma will stay the same