New frontiers of asthma management

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Conflict of Interest

• AB has none to report

• Off-label and unlicensed use of medications will be described

• The presentation contains sexually explicit material, to keep you awake!
Aims of the Presentation

• Discuss the basics of bad asthma, without which new frontiers are ridiculous

• Demonstrate that we need to move beyond ‘asthma’ as the rheumatologists have moved beyond ‘arthritis’

• Discuss novel mechanisms and potential management strategies in asthma

• Show new evidence for the role of fungi in asthma

New Frontiers

• Do not KISS goodbye to the old in favour of the new!
Terminology and definitions

Problematic Severe Asthma

**NB: is it asthma?**  
**NB: is it ‘asthma plus’**

Stage 1 assessment

- **Difficult asthma (c50%)**
  - Remediable factors identified
  - Therapy adherence addressed
  - Not candidates for biologicals etc.

- **Genuine severe, therapy resistant asthma (c50%)**
  - Innovative therapies justifiable

*Lancet 2008; 372: 1019-21*

Problematic Severe Asthma

- **Umbrella term:**
  - Wrong diagnosis (‘Not asthma at all’)

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13/04/2015
Problematic Severe Asthma

• Umbrella term:
  – Wrong diagnosis (‘Not asthma at all’)
  – Co-morbidity (‘Asthma plus’)

Difficult Asthma?

• 15 year old girl

• Near Olympic standard swimmer

• Breathing difficulties towards the end of the races, impairing performance

• No response to SABA, LABA, LTRA
If treatment is not working? Do you want:

OR
‘Difficult’ vs. ‘Severe, Therapy resistant’ Asthma

• Psycho-social issues re-addressed
  – Anecdotally, more likely to ‘open up’
  – 74% referrals were after home discussions

• Adherence

• Smoking

• Allergens

• Asthma education

Arch Dis Child 2009; 94: 780-4

Did they take medications?

• 55 (77%) had a complete set of in-date, accessible medication

• N=34 (48%) medication issues contributed to poor control

Prescription Records
A More Excellent Way..?

RBH Experience

• Potentially reversible factors will be found more than half of those who are not responding to treatment

• Look for the big four: adherence, cigarettes, allergens, psychology

• Nurses find out more than Professors

• KISS – Keep It Simple, Stupid: get the basics right before going ‘beyond guidelines’

New Frontiers

• Do not KISS goodbye to the old in favour of the new!

• DO KISS goodbye to the asthma umbrella!
Begone dull asthma!

**Modified ‘Hargreave’ Phenotypes**

- **Airway inflammation**
  - Eosinophilic, neutrophilic, both
  - Neither
  - Neurogenic (?)

- **Variable obstruction to airflow**
  - Extramural – alveolar guy ropes
  - Airway wall – ASM, other
  - Intramural – mucus
  - WHEEZE MAY NOT BE BRONCHOSPASM

- **Ongoing infection**
  - Bacterial, viral, fungal

- **Fixed airflow limitation**

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**How does this work in practice?**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inflammation</th>
<th>Variable Obstruction to Airflow?</th>
<th>Fixed airflow limitation?</th>
<th>Ongoing infection?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obliterative bronchiolitis</td>
<td>No</td>
<td>Mucus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Post-RSV</td>
<td>?Neural</td>
<td>?</td>
<td>Probably</td>
<td>No</td>
</tr>
<tr>
<td>BPD</td>
<td>No</td>
<td>Yes, β-2 agonist responsive</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>EVW</td>
<td>None chronic</td>
<td>Yes, may be β-2 agonist responsive</td>
<td>Yes</td>
<td>Bacterial ?viral,</td>
</tr>
<tr>
<td>MTW +/- atopy</td>
<td>Likely</td>
<td>Yes, likely eosinophilic</td>
<td>Yes</td>
<td>Bacterial, viral</td>
</tr>
<tr>
<td>SCD</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Post-NEHI wheeze</td>
<td>No</td>
<td>Yes, may be β-2 agonist responsive</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
New Frontiers

- Do not KISS goodbye to the old in favour of the new!
- DO KISS goodbye to the asthma umbrella!
- More for the monoclonal?

Paediatric Severe, Therapy-Resistant Asthma

- No female predominance (33 males:20 females)
- 85% atopic, IgE 386 (115-1286)
- Not obese: BMI STRA 19 (11.9-36.6), Mild 19.0 (11.9-36.6), Controls 20.4 (13.95-34.1)
- Symptom duration 10.1 (9.3-12.7) years, intubation ever 11/53
- ACT 13/25 (9-17), FEV₁ %pred 69 (55-87), acute BDR (1 mg salbutamol) 15.6% (5.5-2.4), FeNO 50 50 (29-70), sputum eosinophils % 7.5 (3.2-30.4)
STRA Phenotypes: Other findings

- **BAL:**
  - EOSINS: STRA 2.7 (0-51), mild asthma 1.7 (0.7-2.7), controls 0 (0-5.7), \( p=0.0006 \) STRA vs. control
  - PMNLS: STRA 3.3 (0.3-73.7), mild asthma 2.2 (0-7.3), controls 2.35 (0.6-14), \( p=NS \)

- **CONCLUSION:** Paediatric STRA is an *eosinophilic*, not a neutrophilic disease; there is a wide spectrum of eosinophilia
Are they adult ‘Th2_{HI}?’

- Micro-array and PCR on bronchial epithelial brushings
- Th2_{HI}; Th2_{LO} & controls the same
- Th2_{HI} were more eosinophilic and steroid responsive

*Am J Respir Crit Care Med 2009; 180: 388-95*

Treatment – adult data?

- What about these steroid-resistant, eosinophilic patients?
- Target T_{H2} cytokines? Mepolizumab?
- And the non-eosinophils?
BUT: No $T_H^2$ Cytokines!

- Induced sputum supernatant
- BAL
  - Luminex
  - CBA
- BAL ($n=50$): IL-4, $n=10$; IL-5, $n=8$; IL-13, $n=8$
- Sputum ($n=41$): only 8 had detectable IL-5
- Immunohistochemistry:

SARP: molecular profiling

- $N=31$ paed STRA, $22$ paed mild-mod, $30$ non-smoking adults
- BAL and alveolar macrophage analytes
- STRA vs. mild-moderate asthma
  - GRO (CXCL1), RANTES (CCL5), IL12, IFN-γ, IL-10 best discriminants
- STRA in children neither $T_H^1$ nor $T_H^2$

*JACI 2010; 125: 851-7*
Do not ‘DREAM on’ - at least in kids!

- Anti-IL-5 mepolizumab in adults
  - 3 doses vs. placebo
- 621 adults in 81 centres
- Evidence of eosinophilia
  - IS eosins >3%
  - FeNO50 > 50
  - "asthma" blood eosin > 0.3
  - LOC if 25% less steroid

Lancet 2012; 380: 651-9

**RESULTS**

Cumulative exacerbations

Eosinophilia is not the same as TH2 cytokines

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Treatment?

- What about these non-eosinophilic patients?
- $T_h^2$ low or what? What do we do?
**Tiotropium?**

- 912 adult asthmatics receiving ICS/LABA, in two parallel RCTs
- 24 week study
- Not required to be eosinophilic
- Small improvement in FEV₁
- Small reduction in asthma attacks

*NEJM 2012; 367: 1198-1207*

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**Azithromycin?**

- N=55 AZM, N=54 placebo added to ICS and LABA
- 6 months treatment, primary end-point was severe exacerbations
- No difference in primary end-point for the whole group
- Non-eosinophilic subgroup showed marked benefit
- Shows importance of phenotyping

*Thorax 2013; 68: 322-9*
New Frontiers

- Do not KISS goodbye to the old in favour of the new!
- DO KISS goodbye to the asthma umbrella!
- More for the monoclonal?
- Is this the age of the epithelium?

If not steroid sensitive, what?

- IL-33 part of the innate immune system
- Released from epithelial and smooth muscle cells
- Implicated in causing inflammation in adults
Mouse: IL-33 levels persist longer than IL-13

- Could this persistence be important in remodelling and steroid resistance?

Mouse: rIL-33 stimulates remodeling and AHR

Bronchial hyper-responsiveness
Mouse: IL-33 receptor KOs (ST2)

AHR abrogated
No evidence of collagen deposition

Fibroblast work

- Fibroblasts cultured from airway biopsies
- IL-33 stimulated collagen secretion release is steroid non-responsive
- Airway fibroblasts express ST2, the IL-33 receptor
IL-33 is expressed in severe asthma

Conclusions

- IL-33 appears to be an important mediator in paediatric asthma
- Unlike T_{h}2 cytokines (IL-4, IL-5, IL-13) it appears to be steroid non-responsive
- Could IL-33 be a novel therapeutic target

*JACI 2013; 132: 676-85*

IL-33 & Vitamin D

- *In vitro*, Vit D stimulates TH2 cytokines! A paradox, a paradox, a most ingenious paradox!!
- Peripheral blood lymphocytes, primary (commercial) HBECs
- *In vitro* stimulation with Vitamin D, sST2 ELISA
- Conclusion: Vitamin D stimulates soluble ST-2 which may bind IL-33 and be an important effect

*Pfeffer P et al, JACI epub*
New Frontiers

• Do not KISS goodbye to the old in favour of the new!
• DO KISS goodbye to the asthma umbrella!
• More for the monoclonal?
• Is this the age of the epithelium?
• What about fungi?

Aspergillus Fumigatus

- An omnipresent fungus
- Grows at body temperature (37 degrees)
- MMD (2-5 microns) allows lower airway deposition
- Secretes exoproducts which are allergenic and cytotoxic (dual disease mechanisms)
- Down-regulates VDR
Fungal Airway Disease: Prevention

- Avoid damp, mouldy places, e.g. stables
- Moulds in the home?
- Check nebulizer hygiene

Severe Asthma with Fungal Sensitization (SAFS)

- Therapy with:
  - 500 mcg FP/day, or
  - Continuous oral CS, or
  - 4/6 Pred bursts in 12/24 months, AND
  - IgE < 1000
  - -ve IgG precipitins to *A. fumigatus*

- & Sensitization (SPT > 3mm, RAST > 0.4) to > one of:
  - *Aspergillus fumigatus*
  - *Cladosporium herbarum*
  - *Penicillium chrysogenum* (notatum)
  - *Candida albicans*
  - *Trichophyton mentagrophytes*
  - *Alternaria alternata*
  - *Botrytis cinerea*
Itraconazole in SAFS (Adults)

**Trial Design**

- Adult asthmatics, n=29 in each group
  - 400-4000 mcg FP/day
  - FEV1, 71%
  - AQLQ 4 (some normal!)
- Oral itraconazole or placebo
  32 weeks, then 16 week FU
- Primary end-point: AQLQ (1-7, 7=best)

*Am J Respir Crit Care Med 2009; 179: 11-8*

Voriconazole in adults with aspergillus-associated asthma (EVITA3)

Similar severe exacerbations in both groups

*Agbetile J JACI 2013; EPub*
SAFS in Children

**Diagnostic criteria?**
- Severe, therapy resistant asthma (any pattern of symptoms)
- Fungal sensitization as defined by adult criteria
- No IgE criteria (ABPA rare to non-existent in children)

**Management?**
- Minimise fungal exposure
  - Mould in house
  - Stables
  - Nebulizers?
- Oral itraconazole
  - Remember interactions with ICS

### Clinical characteristics of children with SAFS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>STRA with SAFS (n=38)</th>
<th>Non-fungal sensitised STRA (n=44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, M:F</td>
<td>30:8</td>
<td>22:22</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>(M=78.9%)</td>
<td>(M=50%)</td>
<td></td>
</tr>
<tr>
<td>Age at symptom onset, years median (range)</td>
<td>0.42 (0-12.5)</td>
<td>1 (0-12.5)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>(n=36)</td>
<td>(n=43)</td>
<td></td>
</tr>
<tr>
<td>Atopy n/total n with data available (%)</td>
<td>37:38 (97.4%)</td>
<td>33:44 (75%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Total IgE, IU/mL median (range)</td>
<td>634 (24-6737)</td>
<td>298 (7-4610)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>(n=37)</td>
<td>(n=43)</td>
<td></td>
</tr>
<tr>
<td>Sum of non-fungal inhalant SPT wheal diameter, mm median (range)</td>
<td>16 (3-38)</td>
<td>9 (0-29)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>(n=27)</td>
<td>(n=41)</td>
<td></td>
</tr>
<tr>
<td>Sum of non-fungal inhalant spIgE, IU/mL median (range)</td>
<td>68.4 (0-287)</td>
<td>30.8 (0-220.5)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(n=33)</td>
<td>(n=33)</td>
<td></td>
</tr>
<tr>
<td>Prescribed maintenance OCS n/total n with data available (%)</td>
<td>16:38 (42.1%)</td>
<td>6:42 (14.3%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Castanhinha et al JACI In press*
No difference in lung function or inflammation

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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, % pred (median (range))</td>
<td>71 (29-121) (n=38)</td>
<td>71.5 (34-99) (n=42)</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % pred (median (range))</td>
<td>94.5 (36-133) (n=38)</td>
<td>91.3 (57-123) (n=42)</td>
<td>NS</td>
</tr>
<tr>
<td>FENO, ppb (median (range))</td>
<td>30.5 (4.8-170) (n=38)</td>
<td>55.7 (3.4-231) (n=40)</td>
<td>0.012</td>
</tr>
<tr>
<td>Sputum Eosinophils, % median (range)</td>
<td>4 (0-67) (n=20)</td>
<td>6.9 (0-92) (n=22)</td>
<td>NS</td>
</tr>
<tr>
<td>Sputum Neutrophils, % median (range)</td>
<td>36 (5-86) (n=20)</td>
<td>24 (0-97) (n=22)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Chronic *alternaria* exposure in neonatal mice results in more severe atopy and inflammation, but not AHR, than HDM exposure
Similar Th2 cytokines, but significantly elevated IL-33 following *Alternaria* exposure

Lung IL-33 levels remain significantly elevated despite steroids following *Alternaria* exposure
**Alternaria** exposure results in a steroid resistant BAL eosinophilia

**Increased IL-33 in BAL and endobronchial biopsies from children with SAFS compared to those without fungal sensitisation**
New Frontiers

- Do not KISS goodbye to the old in favour of the new!
- DO KISS goodbye to the asthma umbrella!
- More for the monoclonal?
- Is this the age of the epithelium?
- What about fungi?
- Summary and conclusions

Take-home messages

- New frontiers are fine, but old ones are still important (NRAD)
- Asthma is an umbrella diagnosis like ‘anaemia’ and ‘arthritis’ (and ‘COPD’), and is not a 21st century diagnosis
- We must not assume mechanisms and hence therapies that are effective in adults will work in children
- Fungi may be a hot topic in asthma as well as CF
Thank you for listening