The role of fungi in respiratory allergies

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**Allergic Aspergillus sinusitis**

Clinical features = nasal obstruction, recurrent sinus infections, loss of smell and nasal polyps

Aspergillus precipitins IgG antibody) positive in 85% of original series
Brazil survey

890 endoscopic sinus surgeries

62 (6.8%) had fungal rhinosinusitis

Table 4. Types of fungal rhinosinusitis.

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal ball</td>
<td>33</td>
<td>53.2</td>
</tr>
<tr>
<td>Allergic fungal rhinosinusitis</td>
<td>24</td>
<td>38.7</td>
</tr>
<tr>
<td>Indolent fungal rhinosinusitis</td>
<td>3</td>
<td>4.8</td>
</tr>
<tr>
<td>Saprophyte infection</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Invasive fungal rhinosinusitis</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Prevalence of allergic fungal rhinosinusitis

Assume 900M of all cases of allergic rhinosinusitis of all types and severities and 120M in big pharma markets

If proportion of allergic fungal rhinosinusitis is $x\%$, then caseload is:

<table>
<thead>
<tr>
<th>Proportion</th>
<th>Global</th>
<th>Pharma markets</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>90M</td>
<td>12M</td>
</tr>
<tr>
<td>6%</td>
<td>54M</td>
<td>7.2M</td>
</tr>
<tr>
<td>2.5%</td>
<td>23M</td>
<td>3M</td>
</tr>
<tr>
<td>1%</td>
<td>9M</td>
<td>1.2M</td>
</tr>
</tbody>
</table>
## Randomised studies of antifungals and rhinitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antifungal, duration</th>
<th>Benefit?</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic rhinosinusitis + nasal polyps</td>
<td>AmpB nasal, 8 wks</td>
<td>No</td>
<td>Weschta, 2004</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>AmpB nasal, 26 wks</td>
<td>Yes</td>
<td>Ponikau, 2005</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>Terbinafine, 6 wks</td>
<td>No</td>
<td>Kennedy, 2005</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>AmpB nasal, 12 wks</td>
<td>No</td>
<td>Ebbens, 2006</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>AmpB nasal, 4 wks</td>
<td>No</td>
<td>Liang, 2008</td>
</tr>
<tr>
<td>Chronic rhinosinusitis + nasal polyps</td>
<td>AmpB nasal, 52 wks</td>
<td>No</td>
<td>Gerlinger, 2008</td>
</tr>
</tbody>
</table>
Allergic bronchopulmonary aspergillosis

ABPA
ABPA - Diagnostic clues

- Asthma/CF not well controlled
- History of 'pneumonia'
- History of coughing up plugs, or paroxysms of coughing that clear when chest clears
- Central bronchiectasis on CT scan, or mucoid impaction
- Eosinophilia

Rare cases in non-asthmatics, non-CF patients
31/03/99

FEV1 = 3.00
ABPA RAST = 31
IgE = 1900.
No Rx
29/09/99

FEV1 = 1.6.
IgE=3000
RAST=52.5.
Rx Atypical Pneumonia
FEV1=3.3 (post antibiotics)
ABPA - bronchoscopy views showing mucous plugging
Mucoid impaction due to ABPA
Mucoid impaction due to ABPA
Sputum in ABPA
A. fumigatus in BAL and in Bronchial Tissue in ABPA
Effect of *A. fumigatus* proteases on bronchial epithelium - H. Kauffmann
Colonisation in 'normal' lungs

Table I. Patients and pulmonary fungal carriage.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Patients (n=74)</th>
<th>Fungal growth (n=46)</th>
<th>No fungal growth (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autopsy patients</td>
<td>18</td>
<td>11 (61.1%)</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td>Surgical patients</td>
<td>56</td>
<td>35 (62.5%)</td>
<td>21 (37.5%)</td>
</tr>
</tbody>
</table>

Table II. Presence of fungi detected.

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of patients with fungal colonization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autopsy patients (n=7)</td>
</tr>
<tr>
<td>A. fumigatus</td>
<td>6</td>
</tr>
<tr>
<td>A. flavus</td>
<td>2</td>
</tr>
<tr>
<td>A. niger</td>
<td>1</td>
</tr>
<tr>
<td>A. terreus</td>
<td>1</td>
</tr>
<tr>
<td>A. glaucus</td>
<td>0</td>
</tr>
<tr>
<td>Mucor spp.</td>
<td>2</td>
</tr>
<tr>
<td>Penicillium spp.</td>
<td>2</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>1</td>
</tr>
</tbody>
</table>

22 of 30 (73%) grew a fungus in both lung samples taken
10/30 (33%) grew >1 species

Lass-Florl et al, Br J Haematol 1999;104:745
Airborne fungal fragments

Green et al, J Allergy Clin Immunol 2005;115:1043
Summary - Immunopathogenesis of ABPA

- HLA-DR2/DR5 restriction
  - DRB1*1501, 1502, 1503, 1601
  - HLA-DR5: DRB1*1101, 1103, 1104, 1202
  - HLA-DQ2 is protective (DQB1*0201)
- IL-4Ra polymorphism
- IL-13 polymorphism
- IL-10 polymorphism
- SP-A2 polymorphism
- CFTR gene mutation
Central bronchiectasis as a complication of ABPA
Chronic cavitary pulmonary aspergillosis as a complication of ABPA
A link between airborne fungi and severe asthma?

“inadequate or insufficient evidence to determine whether or not an association exists between fungal exposure and the development of asthma”

US Academy of Sciences, 2000

Pubmed search ‘Aspergillus and asthma’ = 730 papers!
Guidelines in development - Feb 2008

WHO Guidelines for Indoor Air Quality: Dampness and mould
Spore counts and asthma attacks and admission to hospital

All circumstantial evidence

- Thunderstorm asthma - linked to *Alternaria*
- Asthma deaths (Chicago) linked to high ambient spores counts and season (summer autumn) when spore counts highest
- Asthma hospital admission linked to high ambient spore counts (Derby, New Orleans, Ottawa
- Asthma hospital attendance linked to high spore counts, but not pollen counts (Canada)
- Asthma symptoms increased on days of high spore counts (California, Pennsylvania)

Fungus at home

Environmental data

• Mouldy housing associated with worse asthma, with a correlation between asthma severity and degree of dampness in the home and separately with visible mould growth

• In Germany bronchial reactivity in children was associated with damp housing

• Mouldy and damp school associated with asthma symptoms and emergency room visits

• Home exposure to Cladosporium – if doubled, risk of asthma attack ↑ by 54%

Common sources of airborne fungi - pillows?
**Fungus in the bedroom**

We examined pillows (n=10) for fungi:

<table>
<thead>
<tr>
<th>Pillow type</th>
<th>No pillows</th>
<th>Mean cfu/g pillow</th>
<th>Predominant species</th>
</tr>
</thead>
</table>
| Synthetic   | 3          | $8.6 \times 10^2 - 2 \times 10^3$ | *A. fumigatus*  
*R. mucilaginosa* |
| Feather     | 3          | $1.8 \times 10^2 - 1.8 \times 10^3$ | *A. fumigatus*  
*R. mucilaginosa* |

Other common species were other *Aureobasiuim pullulans*, *Aspergillus flavus* and other species, *Penicillium* spp., *Cladosporium* spp., *Epicoccum nigrum*, *Scopulariopsis brevicaulis*, *Botrytis cinerea*, *Pithomyces chartarum*, *Trametes* sp., *Agricakes*, *Stereum* sp., *Arthrinium phaeospermum*, *Pholiota* sp., *Candida parapsilosis* and *guilliermondii*.

Woodcock et al, Allergy 2006;61:140
Severe asthma

Bel EH, Severe asthma. Breath magazine Dec 2006
Mean sensitization score (mm) (Mean and 95% CI)

Mould allergens
- No Hospital Admission
- Single Admission

Non-Mould allergens
- No Hospital Admission
- Single Admission

P = <0.0001

O’Driscoll et al, BMC Pulmonary Medicine 2005;5:4
Severe asthma and mould sensitivity - *Alternaria* and *Cladosporium*

- **Mild asthma** - 564 (50%)
- **Moderate asthma** - 333 (29%)
- **Severe asthma** - 235 (21%)

<table>
<thead>
<tr>
<th>Region</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK and Republic of Ireland</td>
<td>2.29 (0.88 to 5.99)</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>4.66 (1.75 to 12.43)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1.60 (0.37 to 6.96)</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>6.36 (0.93 to 43.41)</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>1.45 (0.69 to 3.05)</td>
</tr>
<tr>
<td>United States</td>
<td>13.07 (0.86 to 199.22)</td>
</tr>
<tr>
<td>Combined</td>
<td>2.56 (1.49 to 4.40)</td>
</tr>
</tbody>
</table>

Severe asthma and fungal sensitisation (SAFS)

Criteria for diagnosis

- Severe asthma (BTS step 4 or 5) AND
- RAST (IgE) positive for any fungus OR
- Skin prick test positive for any fungus AND
- Exclude ABPA (ie total IgE <1,000 iu/mL

Denning et al, Eur Resp J 2006; 27;27:615
Skin prick testing - example of SAFS result

Cladosporium +ve
Comparison of ABPA and SAFS serology

<table>
<thead>
<tr>
<th></th>
<th>ABPA results</th>
<th>normal range</th>
<th>date 1</th>
<th>date 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IgE</td>
<td>KIU/l</td>
<td>(0.1-100.0)</td>
<td>1900.0</td>
<td>3000.0</td>
</tr>
<tr>
<td>aspergillus.f</td>
<td>KUa/l</td>
<td>(0-0.4)</td>
<td>41.6</td>
<td>49.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SAFS results</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IgE</td>
<td>KIU/l</td>
<td>(0.1-100.0)</td>
<td>200.0</td>
<td>260.0</td>
</tr>
<tr>
<td>aspergillus.f</td>
<td>KUa/l</td>
<td>(0-0.4)</td>
<td>4.5</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Fungal sensitisation in severe asthma - skin prick test or RAST for diagnosis?

N = 121 patients screened

FAST study

N% discordant results

- 43 (SPT + RAST both positive)
- 10 (SPT positive, RAST negative)
- 34 (SPT negative, RAST negative)
- 13 (SPT negative, RAST positive)

≥23% discordant results
Fungal sensitisation in severe asthma - skin prick test or RAST

Aspergillus 68%
Candida 54%
Penicillium 44%
Cladosporium 36%
Alternaria 34%
Botrytis 28%

FAST study
Fungal sensitisation in severe asthma - number sensitised to one or more fungi

N = 40

13 sensitised to only *Aspergillus*
8 to *Candida*
3 to *Trichophyton*
3 to *Penicillium*
1 to *Alternaria*
1 to *Cladosporium*

N = 20

12
7
3
7

Sensitisation to one or more fungi
Severe asthma and fungal sensitisation (SAFS)

Does antifungal therapy work?
### Open trial of itraconazole in ABPA - 1991

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th></th>
<th>After</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (mg/d)</td>
<td>43</td>
<td>↓</td>
<td>24*</td>
<td></td>
</tr>
<tr>
<td>Total IgE</td>
<td>2462</td>
<td>↓</td>
<td>525*</td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>1.48</td>
<td>↑</td>
<td>1.79*</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>2.3</td>
<td>↑</td>
<td>2.9</td>
<td></td>
</tr>
</tbody>
</table>

*p=0.04

Only 1 patient failed - he had low itraconazole levels.

Denning et al, Chest 1991; 35:1329
Randomised trial of itraconazole in ABPA - results

Corticosteroid dependant ABPA with asthma

Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks

<table>
<thead>
<tr>
<th></th>
<th>Itra</th>
<th>Placebo then Itra</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td>13/28 (46%)</td>
<td>5/27 (19%)</td>
</tr>
<tr>
<td></td>
<td><em>p=0.04</em></td>
<td></td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior response</td>
<td>4/13 (31%)</td>
<td>8/20 (40%)</td>
</tr>
<tr>
<td>(n=33)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
Antifungal treatment of severe asthma with fungal sensitisation (SAFS)

11 patients with Trichophyton skin test allergy and moderate/severe asthma,

Rx with fluconazole or placebo for 5 months, then all received fluconazole.

Fluconazole v. placebo at 5 months

- Bronchial hypersensitivity reduced (p = 0.012)
- Steroid requirements reduced (p = 0.01)

Peak flow increased in 9/11 at 10 months
Proof of concept RCT of antifungal Rx in SAFS - key results

Patients enrolled & randomised N = 58

Active (itraconazole) N = 29

Placebo N = 29

Withdrawal in ≤4 weeks

Active N= 3   Placebo N=1 (p=0.60)

Withdrawal 4-32 weeks

Active N= 8   Placebo N=5 (p=0.25)

MITT analysis set (active) N =26

MITT analysis set (placebo) N =28

P=0.014
AQLQ Δ = 0.82

P=0.002
AQLQ Δ = 1.18

Per protocol analysis set (active) N= 18

Per protocol analysis set (placebo) N=23

Proof of concept RCT of antifungal Rx in SAFS - AQLQ change

RCT of anti-IgE (omalizumab) v. placebo, moderate and severe asthma

Improvement in AQLQ
$\Delta = \sim 0.4$
Proof of concept RCT of antifungal Rx in SAFS - improvement in rhinitis

Retrospective comparison of antifungal treatment of SAFS with ABPA

22 patients with SAFS were compared with 11 with ABPA

Pasquallotto et al, unpublished data
Randomised studies of antifungals and ABPA and/or asthma

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antifungal, duration</th>
<th>Benefit?</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPA</td>
<td>Natamycin inh, 52 wks</td>
<td>No</td>
<td>Currie, 1990</td>
</tr>
<tr>
<td>ABPA</td>
<td>Itraconazole, 32 wks</td>
<td>Yes</td>
<td>Stevens, 2000</td>
</tr>
<tr>
<td>ABPA</td>
<td>Itraconazole, 16 wks</td>
<td>Yes</td>
<td>Wark, 2003</td>
</tr>
<tr>
<td>“Trichophyton” asthma</td>
<td>Fluconazole, 20 wks</td>
<td>Yes</td>
<td>Ward, 1999</td>
</tr>
<tr>
<td>SAFS</td>
<td>Itraconazole, 32 wks</td>
<td>Yes</td>
<td>Denning, 2009</td>
</tr>
</tbody>
</table>
Likely SAFS caseload

In 2002 - 15,960,496 adults with self-reported asthma in the USA

In Europe - >17,000,000 adults with asthma

~20% have severe asthma = 6,600,000 adults

20-50% of severe asthmatics have SAFS

SAFS cases (US +EU) = 1,320,000 - 3,300,000