What Place for Antifungals In Pulmonary Medicine?

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The clinical spectrum of conditions resulting from inhalation of *Aspergillus* spores:
The Host Determines Risk

Inhalation of aspergillus spores → Colonization

- Normal host → No sequel
- Cavitary lung disease → Aspergilloma
- Chronic lung disease or Mild ICH → Chronic necrotizing aspergillosis
- ICH → IPA
- Asthma → ABPA

Zmeili OS et al, Quart J Med 2007;100:317
## Invasive Aspergillosis in Transplant Recipients

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Incidence Range, % (Mean)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>3-14% (6%)</td>
<td>68%</td>
</tr>
<tr>
<td>Liver</td>
<td>1-8 (2)</td>
<td>87</td>
</tr>
<tr>
<td>Heart</td>
<td>1-15 (5)</td>
<td>78</td>
</tr>
<tr>
<td>Kidney</td>
<td>0-4 (1)</td>
<td>77</td>
</tr>
<tr>
<td>Small bowel</td>
<td>0-10 (2)</td>
<td>66</td>
</tr>
<tr>
<td>Allogeneic stem cell</td>
<td>5-26 (10)</td>
<td>78-92</td>
</tr>
<tr>
<td>Autologous stem cell</td>
<td>2-6 (5)</td>
<td>78-92</td>
</tr>
<tr>
<td>Nonmyeloblatative stem cell</td>
<td>8-23 (11)</td>
<td>63-67</td>
</tr>
</tbody>
</table>

Nebulized Voriconazole IV Solution Attenuates Murine Invasive Aspergillosis

FIG. 1. Survival curves of immunosuppressed mice that received aerosolized voriconazole (VRC; 6.25 mg/ml twice daily), amphotericin B deoxycholate (AMB), or a control (aerosolized sulfobutyl ether-β-cyclodextrin sodium, 100 mg/ml twice daily) and were challenged by pulmonary inoculation with *A. fumigatus*. (A) Survival on therapy (day 7; *n* = 24 per study group). (B) Survival after therapy was discontinued (*n* = 12 per study group).

Preclinical *in vivo* Efficacy of Novel Inhalational Antifungals vs *A. fumigatus*


Curran AK et al, *AAAAI* 2018

Inhaled Antifungals in Nonallergic (Immunocompromised) Lung Disease

   - Liposomal ampho B better tolerated vs deoxycholate
   - Similar or reduced incidence of invasive disease (5-14% vs 3-35%), unclear effect on anastomotic disease.
   - No direct comparative trials vs oral azoles.

2. Add-on treatment to systemic anti-fungals for resistant or recalcitrant lung transplant infections. Mainly for emergent fungi eg *Scedosporium*, *Zygomycetes*, *Fusarium*.

Hilberg GR & Lewis JS. *Eur Respir J* 2012;40:271

Inhaled Antifungals in Nonallergic Immunocompromised Lung Disease 2

- **Aspergillus** prophylaxis with inhaled amphotericin B in hematologic disease. Usually targeted to extended neutropenia in high-risk patients where oral azole prophylaxis is problematic.
  - Relative risk reduction of 40-60% vs no prophylaxis in RCTs
  - No direct comparison trials to oral azoles
  - Liposomal ampho B preferred
  - Discontinuation due to adverse effects ~10% (cough, taste, nausea)
  - Current recommendations (IDSA 2016) focus on patients with hematologic malignancy and stem cell transplants in areas of high azole resistance or with contraindications to oral azole prophylaxis.

Patterson T et al, *Clin Infect Dis* 2016;63:e1
The clinical spectrum of conditions resulting from inhalation of Aspergillus spores: The Host Determines Risk

Aspergillus conidia
MMAD ~2-3 μm

Inhalation of aspergillus spores

Colonization

Normal host
No sequel

Cavitary lung disease
Aspergilloma

Chronic lung disease or Mild ICH
Chronic necrotizing aspergillosis

ICH
IPA

Asthma

ABPA

Zmeili OS et al, Quart J Med 2007;100:317
Aspergillus Grows in Mucus Plugs

Branching filaments (hyphae) of *A. fumigatus* in sputum

Key elements: Muco-obstructive disease (asthma, CF, COPD), luminal fungal growth, endobronchial inflammation
Allergic Fungal Airway Disease Phenotypes

AAFS—asthma associated with fungal sensitization
SAFS—severe asthma with fungal sensitization
ABPA-S—seropositive allergic bronchopulmonary aspergillosis
ABPA-CB—allergic bronchopulmonary aspergillosis with central bronchiectasis

*Allergic aspergillosis phenotype

Annual burden >14 million patients across all indications
>800,000 deaths annually

Agarwal R, Curr Allergy Asthma Rep 2011;11:403
Woolnough K et al, Curr Opin Pulm Med 2015;21:39
# Allergic Sensitization in Severe vs Non-Severe Asthma

Swedish current asthma population cohort n=830  
Severe asthma 3.6% by SARP, 4.8% by ERS/ATS, 6.1% by GINA

<table>
<thead>
<tr>
<th>Allergen Type</th>
<th>Other Asthma (n = 753)</th>
<th>Severe Asthma according to different criteria</th>
<th>Difference (P-value) compared to other asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>GINA (n = 50)</td>
</tr>
<tr>
<td>Any allergen</td>
<td>269</td>
<td>35.7</td>
<td>16</td>
</tr>
<tr>
<td>Any dust mite</td>
<td>44</td>
<td>5.8</td>
<td>3</td>
</tr>
<tr>
<td>Any furred animal</td>
<td>187</td>
<td>24.8</td>
<td>13</td>
</tr>
<tr>
<td>Any pollen</td>
<td>189</td>
<td>25.1</td>
<td>9</td>
</tr>
<tr>
<td>Any mould</td>
<td>20</td>
<td>2.7</td>
<td>5</td>
</tr>
<tr>
<td>Specific moulds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cladosporium herbarum</td>
<td>10</td>
<td>1.3</td>
<td>2</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>16</td>
<td>2.1</td>
<td>5</td>
</tr>
<tr>
<td>Alternaria alternata</td>
<td>6</td>
<td>0.8</td>
<td>2</td>
</tr>
</tbody>
</table>

Backman H et al, Clin Exp Allergy 2019;49:819
Severe Asthma in Pediatrics
Role of Fungal Sensitization

Fungal sensitivities:
Aspergillus 84%, Alternaria 72%, Candida 52%, Cladosporium 36%, Mucor 32%, Penicillium 16%

Similar results in UK study

Vicencio AG et al, Pediatr Pulmonol 2014;49:8
Castanhinha S et al, JACI 2015;136:312
Oral Azoles for Severe Asthma with Fungal Sensitization (SAFS)

Severe asthma, mold allergic, but not meeting diagnostic criteria for ABPA

- Fungal Asthma Sensitization Study – UK adults
  Sensitivities: *Aspergillus* 72%, *Candida* 59%, *Cladosporium* 40%, *Penicillium* 41%, *Alternaria* 40%, *Trichophyton* 22%, *Botrytis* 29%
  32 week RCT with itraconazole – improved asthma quality of life

- EVITA3 Study
  UK adults active SAFS sensitized to *A. fumigatus*
  12 week RCT with voriconazole

- **AQLQ** - ↑ 0.85
- **IgE level** - ↓ 27%; 187 IU/ml → 136 IU/ml
- **FEV1** - no change
- **PF** - ↑ 20.8 L/min

Denning DW et al, AJRCCM 2009;179:11

Role of azoles in SAFS unresolved

Agbetile J et al, JACI 2014;134:33
### ABPA in Asthma – Scope of Problem

<table>
<thead>
<tr>
<th>ASTHMA</th>
<th>US</th>
<th>Europe</th>
<th>US + Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent asthma population</td>
<td>25,700,000</td>
<td>30,000,000</td>
<td>55,700,000</td>
</tr>
<tr>
<td>% with severe asthma</td>
<td>5 – 10%</td>
<td>5 – 10%</td>
<td>5 – 10%</td>
</tr>
<tr>
<td>Diagnosed and treated severe asthma population</td>
<td>1,285,000 – 2,570,000</td>
<td>1,500,000 – 3,000,000</td>
<td>2,785,000 – 5,570,000</td>
</tr>
<tr>
<td>% of diagnosed severe asthma with ABPA</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Diagnosed severe asthma patients with ABPA</td>
<td>64,250 – 128,500</td>
<td>75,000 – 150,000</td>
<td>139,250 – 278,500</td>
</tr>
</tbody>
</table>
**Therapeutic Approaches for ABPA**

- **First line: Oral glucocorticosteroids**
  - Requires months-long burst/taper: toxicity issues often unwanted or limiting
  - **Alternative:** Monthly pulse intravenous glucocorticosteroids
    - Potential for reduced steroid toxicity

- **Second line: Oral Aspergillus-active triazoles**
  - Validated by placebo-controlled trials
  - Frequent toxicities from months-long courses
  - Absorption, metabolism, drug-drug interactions mandate therapeutic drug level monitoring
  - Azole resistance increasing
  - **Alternative:** Nebulized amphotericin B
    - Multiple formulations, doses, delivery systems

- **Omalizumab (monoclonal anti-IgE)**
  - Validated by placebo-controlled trial, open-label trials
  - Expensive
  - Requires q 2-4 week office/clinic visit, observation
  - **Alternative:** Other T2-high response biologicals also in use (mepolizumab, benralizumab, dupilumab)
Amphotericin B Aerosol Therapy

First clinical neb use 1959; most experience in lung transplant & hematologic malignancy.

Four IV formulations (inhalational use off-label):
- AMB-d deoxycholate micelle
- L-AMB liposome
- ABLC lipid ribbon complex
- ABCD lipid disc

AMB-d may foam; lipids may nebulize better

Effective drug-delivery systems tested include
- AMB-d Respigard II; Pari Turbo; Aeroneb
- ABLC AeroEclipse
- L-AMB Halolite

Dosing: 5-50 mg nominal neb dose → lung dose 1.5 ≥ 3 mg

Serum concentration: usu <0.5 - 2 µg/mL (steady-state iv rx level)

Dosing regimes: bid (AMB-d) – 1-2 x/wk (liposomal forms)

Nebulized Amphotericin Reduced Exacerbations at One Year in ABPA

<table>
<thead>
<tr>
<th></th>
<th>Experimental arm (n = 12)</th>
<th>Control arm (n = 9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-to-first exacerbation, in days</td>
<td>351 (351–351)</td>
<td>170.3 (85.9–254.8)</td>
<td>0.126</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with exacerbations at 12 months</td>
<td>1 (8.3%)</td>
<td>6 (66.7%)</td>
<td>0.019</td>
</tr>
<tr>
<td>ACQ7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.5 (1.27–3.37)</td>
<td>3.78 (1.42–6.14)</td>
<td>0.862</td>
</tr>
<tr>
<td>Twelve months</td>
<td>3.4 (1.26–5.54)</td>
<td>4 (0.38–7.62)</td>
<td></td>
</tr>
<tr>
<td>FEV1 values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80.1 (68.9–91.3)</td>
<td>70.7 (52.3–89.1)</td>
<td>0.291</td>
</tr>
<tr>
<td>Twelve months</td>
<td>76.3 (58.8–93.9)</td>
<td>63.9 (26.9–100.9)</td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate bronchospasm</td>
<td>3 (25%)</td>
<td>–</td>
<td>0.114</td>
</tr>
<tr>
<td>Bad after taste</td>
<td>4 (33.3%)</td>
<td>–</td>
<td>0.052</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (33.3%)</td>
<td>2 (22.2%)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

All outcomes are based on an intention-to-treat analysis. All values are presented as n % (95% confidence intervals) or mean (95% confidence intervals), unless otherwise stated.

FEV1, forced expiratory volume in the first second; FVC, forced vital capacity

Experimental Arm: Ampho B deoxycholate 10 mg bid tiw + Budesonide 1 mg bid tiw
Control Arm: Budesonide 1 mg bid tiw

Ram B et al, J Asthma 2016;53:517

French multicenter single-blind L-AMB neb RCT in non-CF ABPA ongoing – enrollment complete

Godet C, NCT02273661
Nebulized amphotericin B for Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis

Case reports: positive clinical ± biomarker responses

### Table 1 Different formulation of amphotericin B (AMB)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Carrier</th>
<th>Colloidal type</th>
<th>Size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMBd</td>
<td>Deoxycholate</td>
<td>Micelle</td>
<td>0.035</td>
</tr>
<tr>
<td>L-AMB</td>
<td>Phosphatidylocholine, distearoylphosphatidyglycerol, cholesterol</td>
<td>Liposome</td>
<td>0.08</td>
</tr>
<tr>
<td>ABLC</td>
<td>Phospholipids</td>
<td>Lipid ribbon</td>
<td>1.6-11</td>
</tr>
<tr>
<td>ABCD</td>
<td>Cholesteryl sulphate</td>
<td>Lipid disc</td>
<td>0.11-0.12</td>
</tr>
</tbody>
</table>

AMBd: amphotericin B deoxycholate; L-AMB: liposomal amphotericin B; ABLC: amphotericin B-lipid complex; ABCD: amphotericin B cholesterol discs.

### Table 2 Reported experiences about nebulized amphotericin B (AMB) treatment in cystic fibrosis (CF)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>AMB formulation</th>
<th>AMB dosage</th>
<th>Concomitant systemic antifungals</th>
<th>Number of patients</th>
<th>Type of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiddens²⁶</td>
<td>2003</td>
<td>L-AMB</td>
<td>50 mg once a week</td>
<td>None</td>
<td>5</td>
<td>CF</td>
</tr>
<tr>
<td>Laoudi²⁹</td>
<td>2008</td>
<td>Nbud±AMBd</td>
<td>5 mg twice a day</td>
<td>None</td>
<td>3</td>
<td>CF children</td>
</tr>
<tr>
<td>Hayes³³</td>
<td>2010</td>
<td>AMBd</td>
<td>10 mg twice a day</td>
<td>Itraconazole</td>
<td>1</td>
<td>CF child</td>
</tr>
<tr>
<td>Proesmans¹⁴</td>
<td>2010</td>
<td>AMBd or ABLC</td>
<td>AMBd: 20 mg, thrice a week, ABLC: 50 mg, twice a week</td>
<td>Itraconazole, voriconazole, or posaconazole</td>
<td>7</td>
<td>CF (3 adults, 4 children)</td>
</tr>
</tbody>
</table>

L-AMB: liposomal amphotericin B; Nbud: nebulized budesonide; AMBd: amphotericin B deoxycholate; ABLC: amphotericin B-lipid complex; CF: cystic fibrosis.

Itraconazole DPI for ABPA: Single Dose PK in Asthmatics

Plasma exposure 100-400x lower, sputum 70x higher, vs po itraconazole

Dotted line at 500 ng/mL = Af MIC$_{90}$

Hava DL et al, Br J Clin Pharmacol 2020;86:723
Potential for Treatment of ABPA with Inhalational Antifungal PC945

Patient 2-001 - ABPA

History
- ABPA > 12 years
- Multiple courses of antifungals
- No response & significant side effects
- Hospitalised for a week every 8 weeks for IV hydrocortisone
- Symptomatic ++
- A. fumigatus culture +

On PC945
- CT - significant improvement
- A. Fumigatus cleared
- Symptomatic improvement ++
- Improved exercise tolerance
- Serological response
- Reduced eosinophil count
- Off IV steroids

Pre-PC945 25 June 19

On PC945 29 July 19

Patient 2-001 Tot IgE

Patient 2-001 Aspergillus IgG and IgE

Courtesy Alison Murray, Pulmocide
Treatment of *Aspergillus* Lung Transplant Anastomotic Infection Tracheobronchitis with PC945

- 29 year old female. Developed invasive *A. fumigatus* 1 month post-bilateral lung transplant for cystic fibrosis
- After 2.5m on antifungal treatment (isavuconazole → posaconazole, neb amp B, caspofungin, terbinafine)
  - Anastomotic infection progressing
  - Fungus infiltrating bronchial cartilage
  - Risk of dehiscence
- PC945 added, posaconazole and terbinafine continued

- After 2 weeks of inhaled PC945 (5mg QD) the fungal mass was reduced in size
- By week 8 there was a complete clinical, mycological and radiological response and the airway had healed
- Nebs well tolerated. No adverse reactions or drug interactions
- PC945 treatment was stopped after 3 months (response)
- Patient remains *Aspergillus*-free off all antifungals for > 6 months

Pagani N et al, Fungal Update, 2019
Combination Inhaled-Systemic Azole Therapy: \textit{in vitro} Alveolus Model

Hope WW et al, \textit{J Infect Dis} 2007;195:455

Conclusions

• Because of favorable pharmacokinetics, pharmacodynamics and toxicology, specific respiratory drug-device antifungals may find validated roles in
  – Prophylaxis of pulmonary aspergillosis in lung transplant recipients
  – Prophylaxis of pulmonary aspergillosis in hematological malignancies
  – Treatment of resistant/recalcitrant fungal lung infections
  – Treatment of allergic bronchopulmonary aspergillosis
  – Treatment of severe asthma with fungal sensitization