Stanford Children's Health | Lucile Packard Children's Hospital Stanford

What Place for Antifungals In Pulmonary Medicine?

Food and Drug Administration
Virtual Public Workshop
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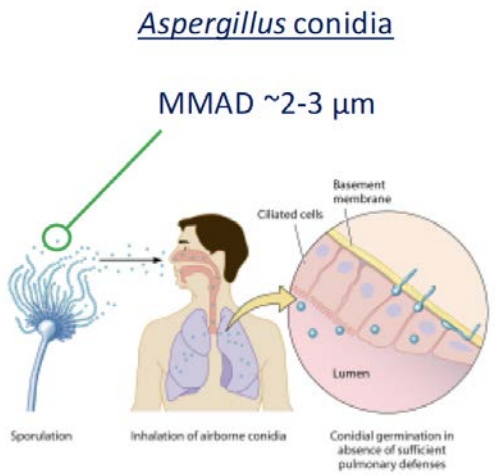
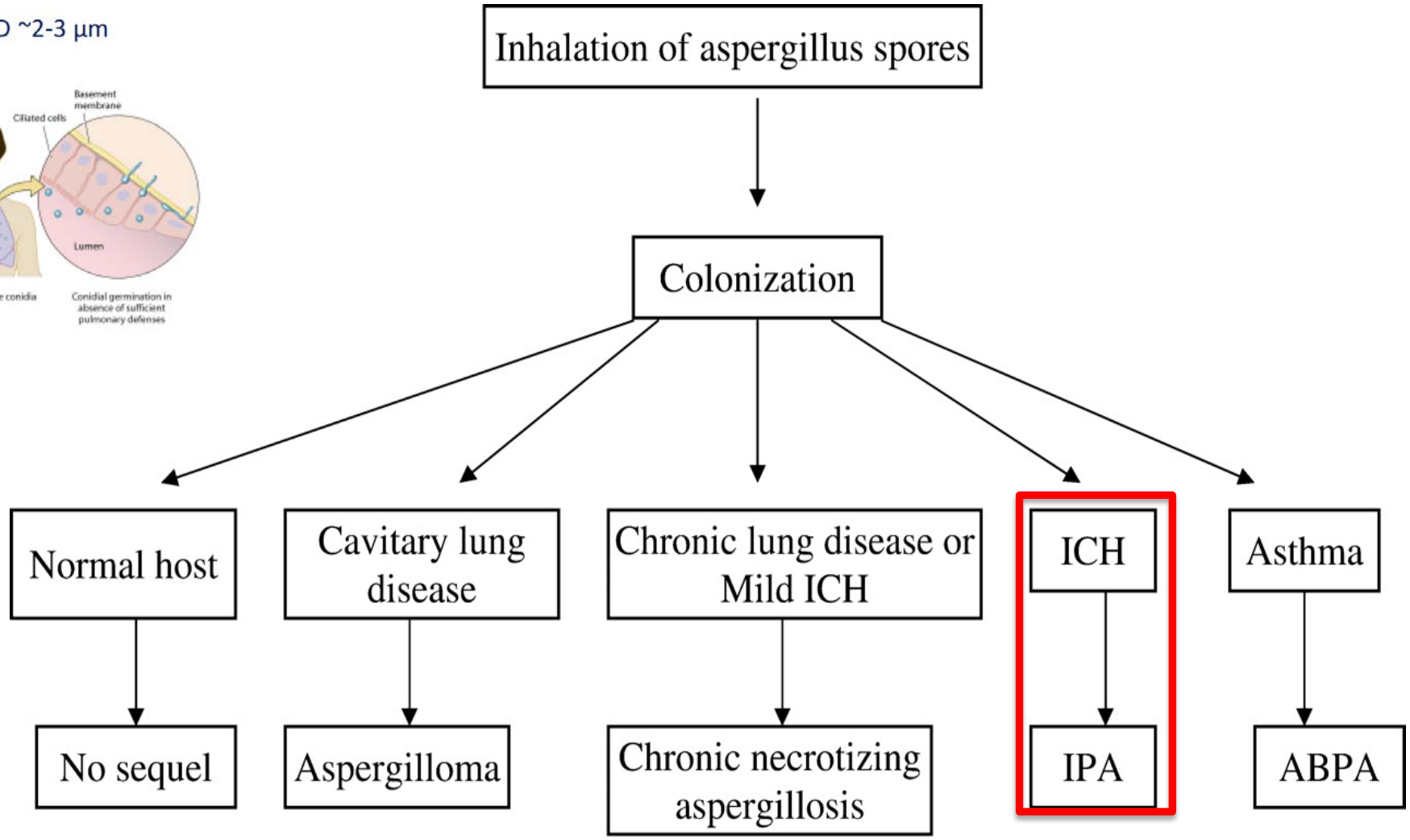
The clinical spectrum of conditions resulting from inhalation of *Aspergillus* spores: The Host Determines Risk





Zmeili OS et al, *Quart J Med* 2007;100:317

Invasive Aspergillosis in Transplant Recipients

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

Singh N & Paterson DL, *Clin Microbiol Rev* 2005;18:44-69.

S • A • C • M • M
San Antonio Center for Medical Mycology

Nebulized Voriconazole IV Solution Attenuates Murine Invasive Aspergillosis

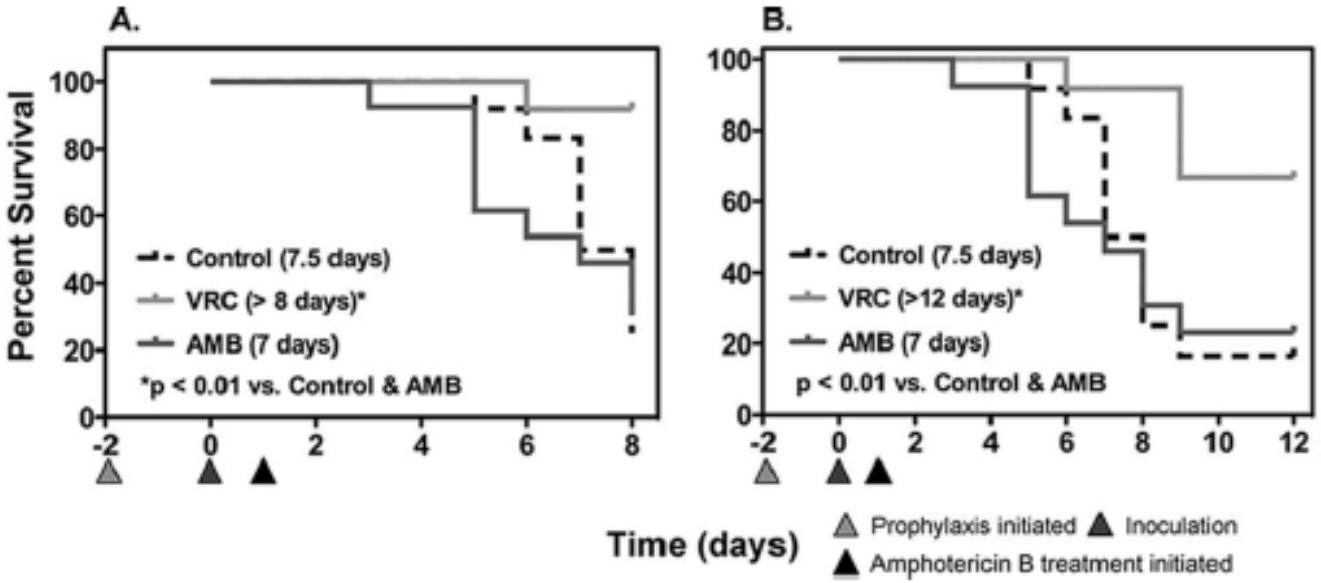
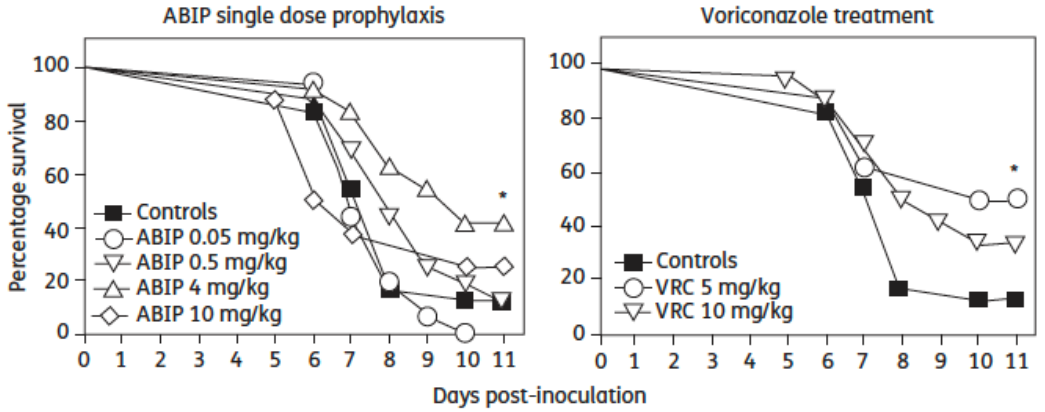


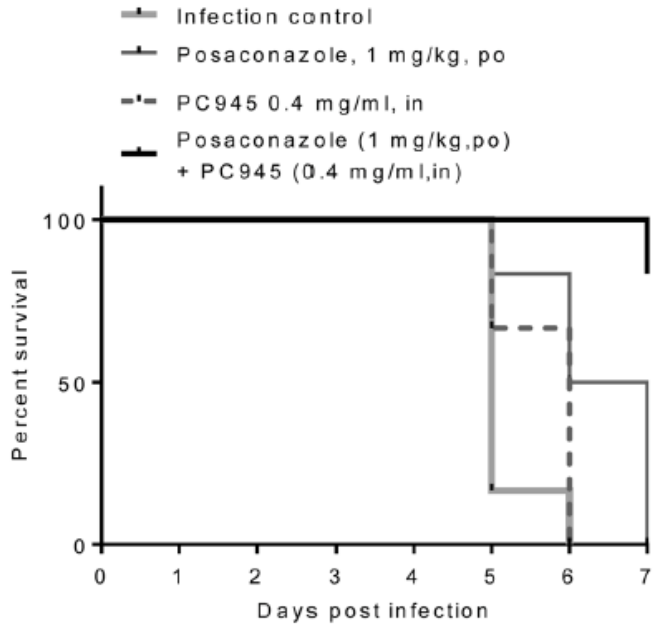
FIG. 1. Survival curves of immunosuppressed mice that received aerosolized voriconazole (VRC; 6.25 mg/ml twice daily), amphotericin B deoxycholate (AMB), or a control (aerosolized sulfobutyl ether-β-cyclodextrin sodium, 100 mg/ml twice daily) and were challenged by pulmonary inoculation with *A. fumigatus*.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

Tolman JA et al, *Antimicrob Agents Chemother* 2009;72:199

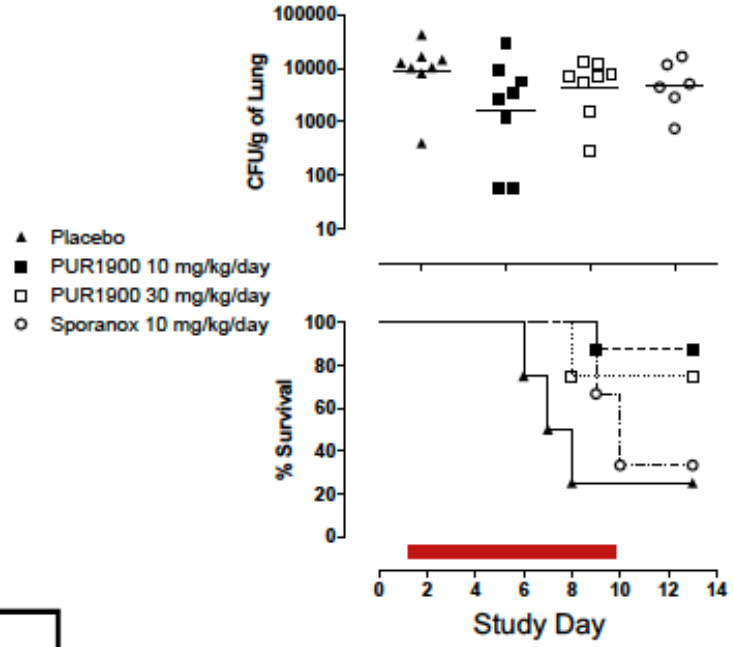
Preclinical *in vivo* Efficacy of Novel Inhalational Antifungals vs *A. fumigatus*



Kirkpatrick WR et al*, J Antimicrob Chemother* 2012;67:970



Colley T el al, *Sci Rep* 2019;9:9482



Curran AK et al, AAAAI 2018

Inhaled Antifungals in Nonallergic (Immunocompromised) Lung Disease

- 1. Anti-fungal prophylaxis in lung transplantation. Off-label use of IV formulations. Mainly nebulized ampho B; case reports with vori. Often for *Aspergillus*, combined with oral fluconazole for *Candida*.
    - 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.

Drew RH et al, *Transplantation* 2004;77:232
Hilberg GR & Lewis JS. *Eur Respir J* 2012;40:271
Holle J et al, *J Cyst Fibros* 2014;13:400
Peghin M et al, *Transpl Intl* 2016;29:51
Qiao W et al, *J Thorac Dis* 2019;11:1554

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

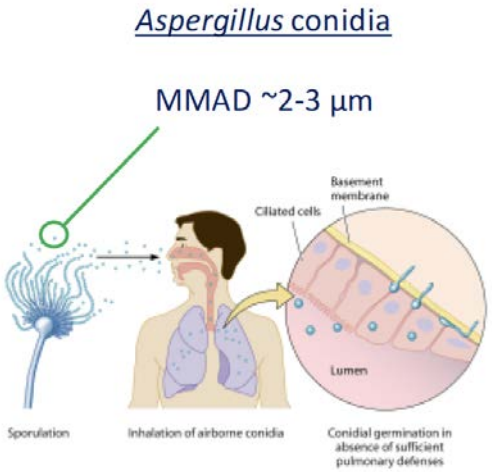
Sole A et al, *Am J Transplant* 2018;18:504

Inhaled Antifungals in Nonallergic Immunocompromised) Lung Disease 2

- 3. *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.

Schwartz S et al, *Blood* 1999;93:3654
Rijnders B et al, *Clin Infect Dis* 2008;46:1401
Patterson T et al, *Clin Infect Dis* 2016;63:e1
Duckwall MJ et al, *Microbiol Insights* 2019;12:1

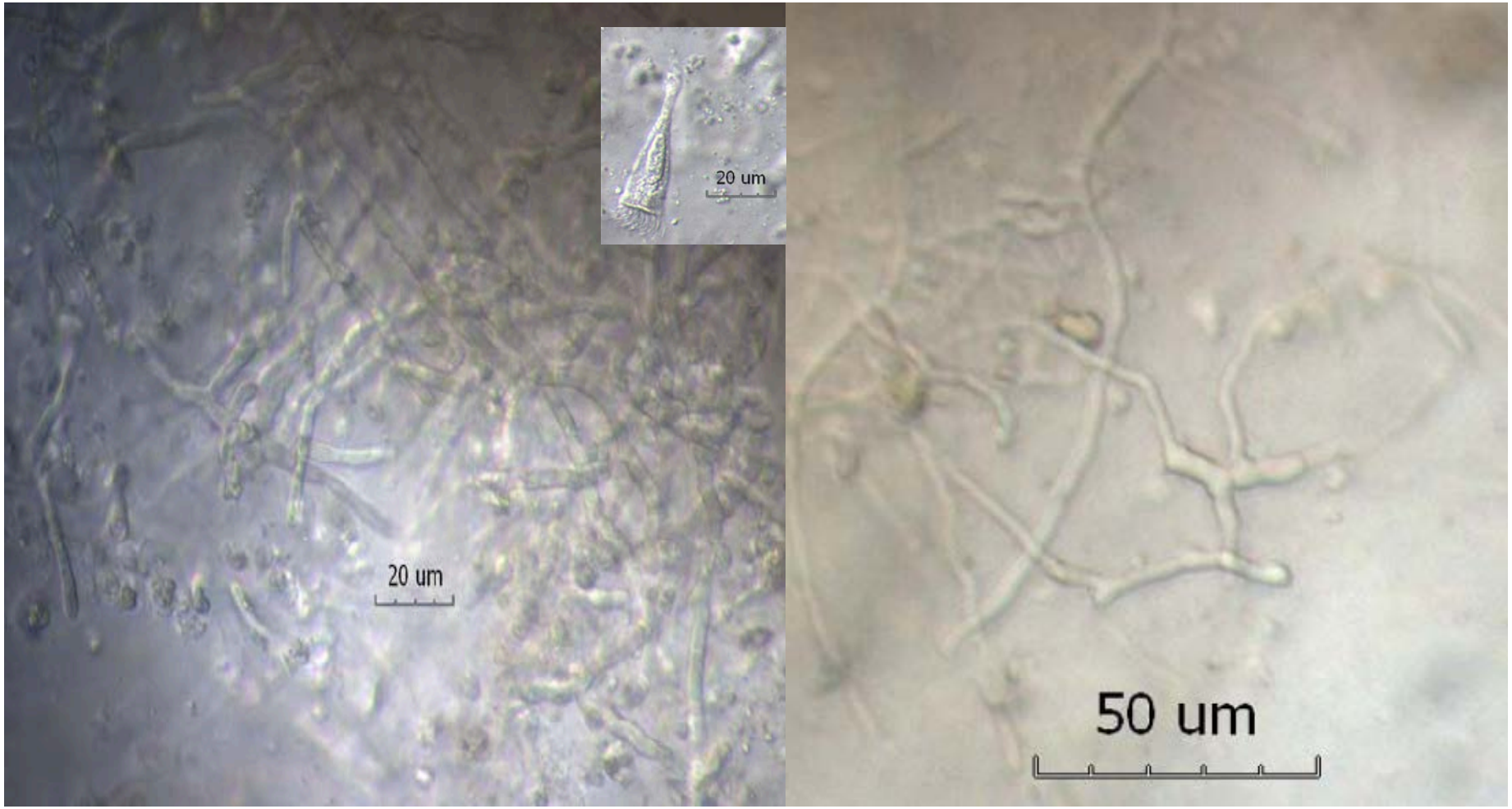
The clinical spectrum of conditions resulting from inhalation of *Aspergillus* spores: The Host Determines Risk



Zmeili OS et al, *Quart J Med* 2007;100:317

Aspergillus Grows in Mucus Plugs

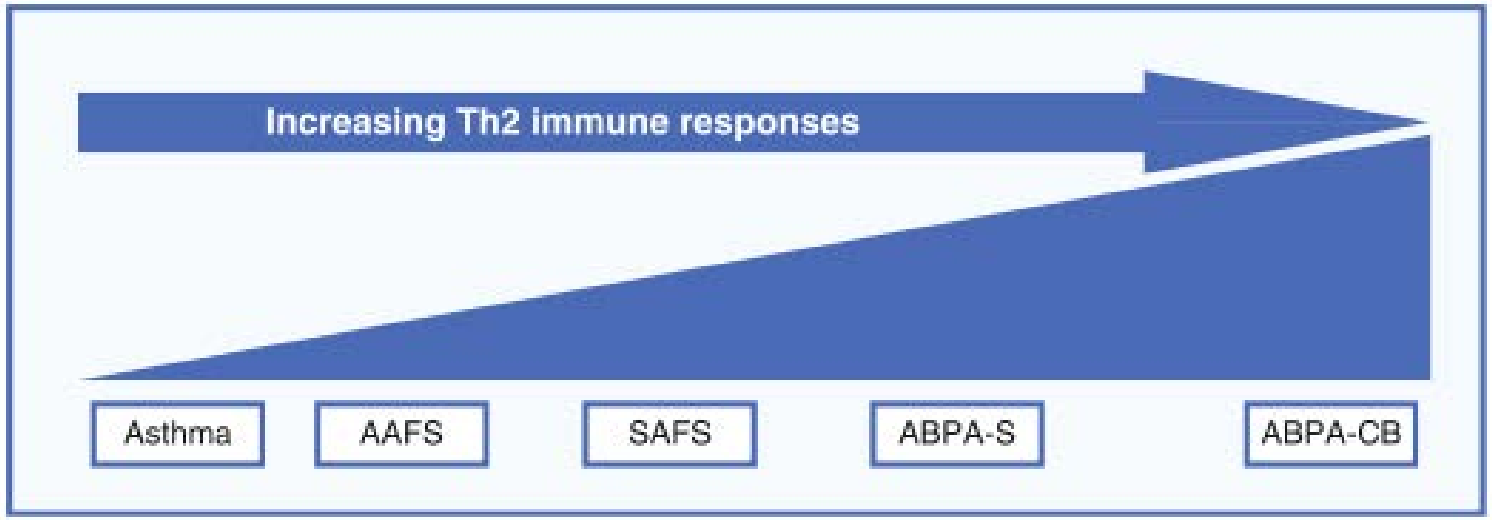
Branching filaments (hyphae) of *A. fumigatus* in sputum



Key elements: Muco-obstructive disease (asthma, CF, COPD), luminal fungal growth, endobronchial inflammation

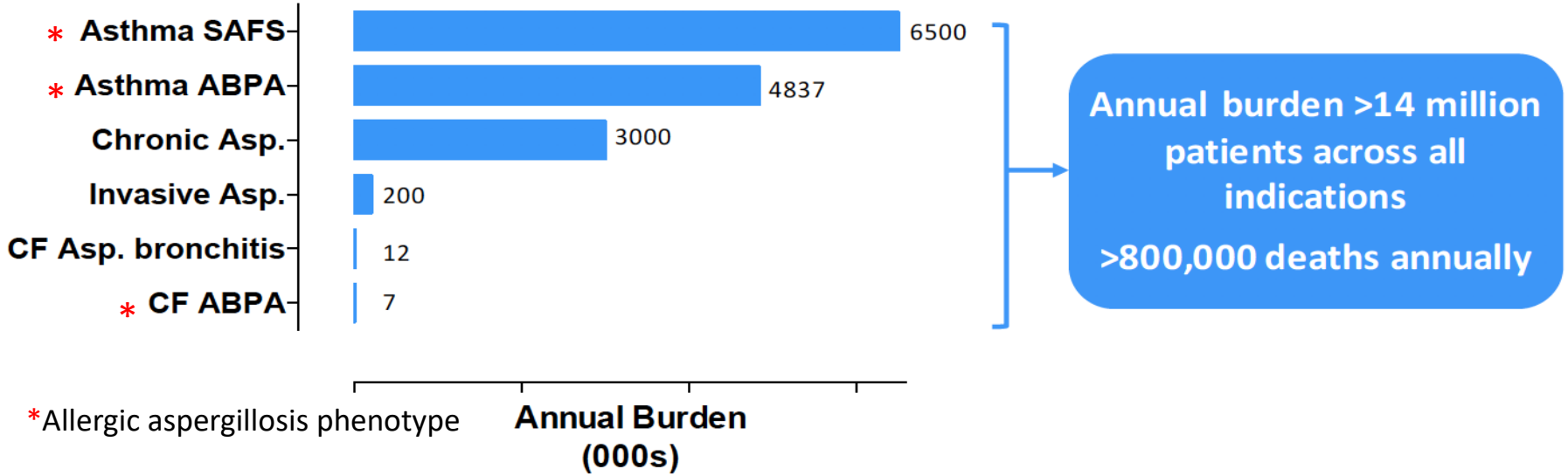
Moss RB, *Eur Respir J* 2014;43:1487

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

Agarwal R, *Curr Allergy Asthma Rep* 2011;11:403
Woolnough K et al, *Curr Opin Pulm Med* 2015;21:39



*Allergic aspergillosis phenotype

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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

	Other asthma (n = 753)		Severe asthma according to different criteria: GINA (n = 50)		ERS/ATS (n = 39)		SARP (n = 29)		Difference (*P*-value[a]) compared to other asthma		
	n	%	n	%	n	%	n	%	GINA	ERS/ATS	SARP
Any allergen	269	35.7	16	32.0	10	25.6	8	27.6	0.594	0.199	0.369
Any dust mite	44	5.8	3	6.0	3	7.7	2	6.9	0.964	0.634	0.813
Any furred animal	187	24.8	13	26.0	8	20.5	7	24.1	0.854	0.541	0.932
Any pollen	189	25.1	9	18.0	6	15.4	4	13.8	0.259	0.170	0.166
Any mould	20	2.7	5	10.0	5	12.8	5	17.2	0.004	<0.001	<0.001
Specific moulds											
Cladosporium herbarum	10	1.3	2	4.0	2	5.1	2	6.9	0.132	0.058	0.017
Aspergillus fumigatus	16	2.1	5	10.0	5	12.8	5	17.2	0.001	<0.001	<0.001
Alternaria alternata	6	0.8	2	4.0	2	5.1	2	6.9	0.027	0.008	0.001

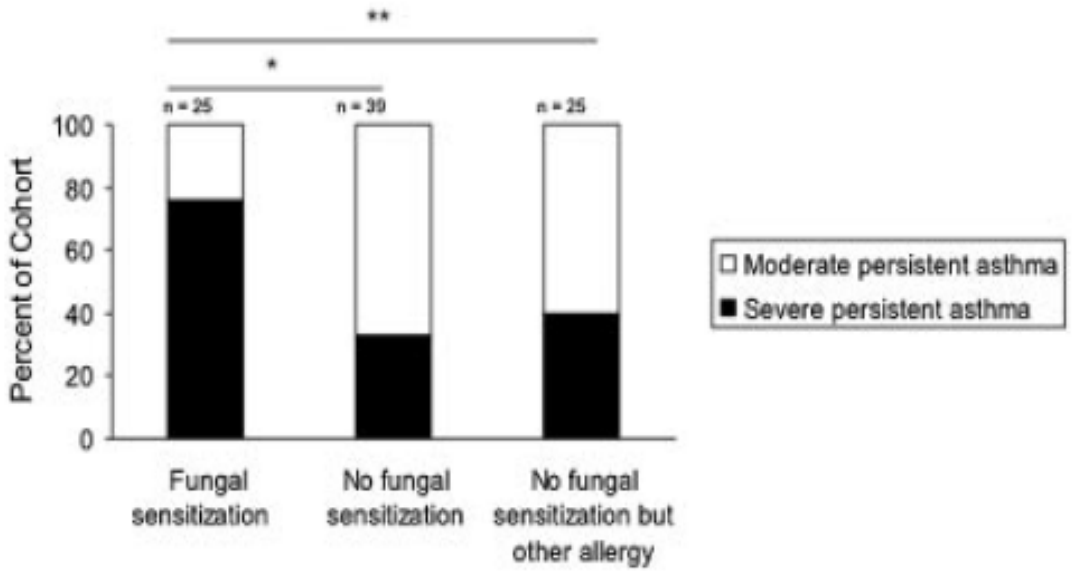
Backman H et al, *Clin Exp Allergy* 2019;49:819

Severe Asthma in Pediatrics

Role of Fungal Sensitization

	Fungal sensitization (n = 25)	No fungal sensitization (n = 39)	*P*-value	Sensitization to non-fungal allergens (n = 25[1])	*P*-value
Male:female	2.6	2.0	0.65 (NS)	1.8	0.55 (NS)
Age (years)	11 (IQR 9.5–14.5)	9 (IQR 6–12)	0.02	9 (IQR 7–15)	0.2 (NS)
IgE (IU/ml)	1,049 (IQR 566–2319)	78 (IQR 21–308)	<0.0001	257 (IQR 80–480)	<0.0001

	Fungal sensitization (n = 22)	No fungal sensitization (n = 26)	*P*-value	Sensitization to non-fungal allergens (n = 19[1])	*P*-value
FEV1 (% predicted)	81.5 (IQR 65–88)	95.5 (IQR 81–101)	0.016	96 (IQR 81–101)	0.034
FEV1/FVC	71.5 (IQR 64–78)	83 (IQR 78–88)	0.0004	82 (IQR 75–89)	0.008
FEF25–75% (% predicted)	55 (IQR 36–61)	78.5 (IQR 60–86)	0.002	74 (IQR 59–85)	0.011



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)

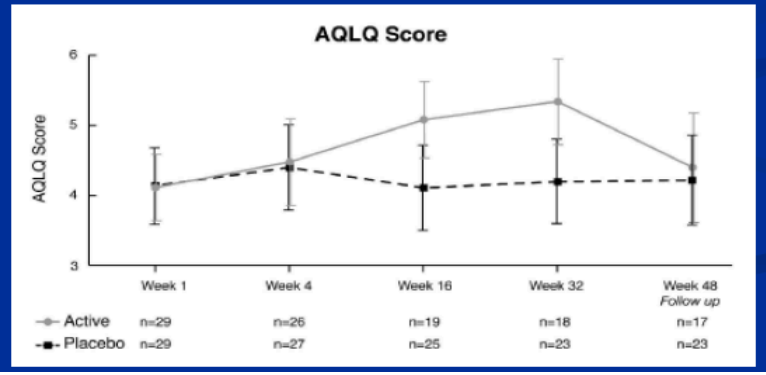
Severe asthma, mold allergic, but not meeting diagnostic criteria for ABPA

- 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

- AQLQ - ↑ 0.85
- IgE level - ↓ 27%; 187 IU/ml → 136 IU/ml
- FEV-1 – no change
- PF - ↑ 20.8 L/min

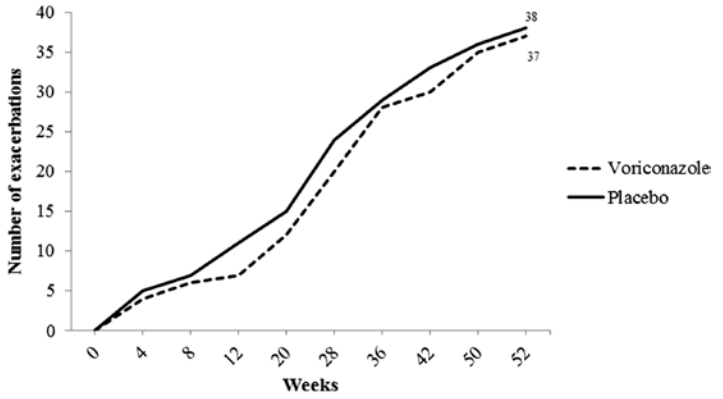


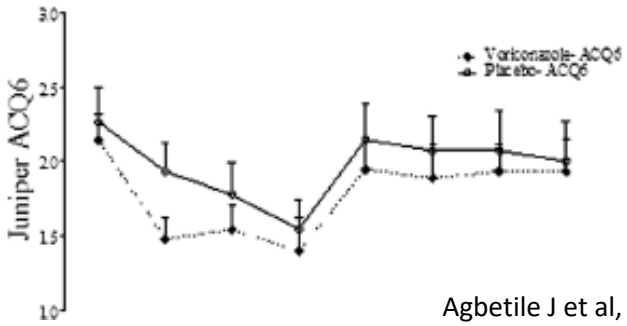
Denning DW et al, *AJRCCM* 2009;179:11

EVITA3 Study

UK adults active SAFS sensitized to *A. fumigatus*

12 week RCT with voriconazole





Agbetile J et al, *JACI* 2014;134:33

Role of azoles in SAFS unresolved

ABPA in Asthma – Scope of Problem

ASTHMA	US	Europe	US + Europe
Prevalent asthma population	25,700,000	30,000,000	55,700,000
% with severe asthma	5 – 10%	5 – 10%	5 – 10%
Diagnosed and treated severe asthma population	1,285,000 – 2,570,000	1,500,000 – 3,000,000	2,785,000 – 5,570,000
% of diagnosed severe asthma with ABPA	5%	5%	5%
Diagnosed severe asthma patients with ABPA	64,250 – 128,500	75,000 – 150,000	**139,250 – 278,500**

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)

Kuiper L & Ruijgrok EJ, *J Aerosol Med Pulm Drug Deliv* 2009;22:213

Nebulized Amphotericin Reduced Exacerbations at One Year in ABPA

	Experimental arm ($n = 12$)	Control arm ($n = 9$)	p value
Primary outcomes			
Time-to-first exacerbation, in days	351 (351–351)	170.3 (85.9–254.8)	0.126
Secondary outcomes			
No. of patients with exacerbations at 12 months	1 (8.3%)	6 (66.7%)	0.019
ACQ7			
Baseline	2.5 (1.27–3.73)	3.78 (1.42–6.14)	0.862
Twelve months	3.4 (1.26–5.54)	4 (0.38–7.62)	
FEV1 values			
Baseline	80.1 (68.9–91.3)	70.7 (52.3–89.1)	0.291
Twelve months	76.3 (58.8–93.9)	63.9 (26.9–100.9)	
Adverse effects			
Immediate bronchospasm	3 (25%)	–	0.114
Bad after taste	4 (33.3%)	–	0.052
Nausea	4 (33.3%)	2 (22.2%)	0.419

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

Table 1 Different formulation of amphotericin B (AMB)

Formulation	Carrier	Colloidal type	Size (μm)
AMBd	Deoxycholate	Micelle	0.035
L-AMB	Phosphatidylcholine, distearoylphosphatidylglycerol, cholesterol	Liposome	0.08
ABLC	Phospholipids	Lipid ribbon	1.6–11
ABCD	Cholesteryl sulphate	Lipid disc	0.11–0.12

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)

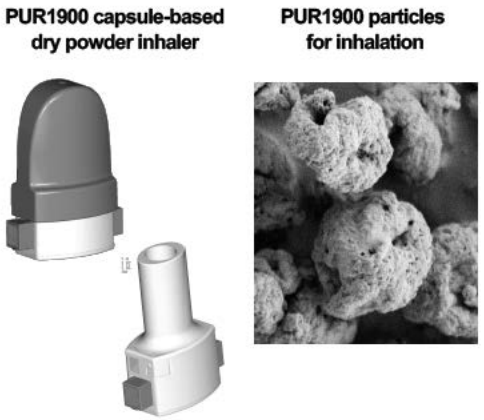
Author	Year of publication	AMB formulation	AMB dosage	Concomitant systemic antifungals	Number of patients	Type of patients
Tiddens[28]	2003	L-AMB	50 mg once a week	None	5	CF
Laoudi[29]	2008	Nbud+AMBd	5 mg twice a day	None	3	CF children
Hayes[30]	2010	AMBd	10 mg twice a day	Itraconazole	1	CF child
Proesmans[14]	2010	AMBd or ABLC	AMBd: 20 mg, thrice a week ABLC: 50 mg, twice a week	Itraconazole, voriconazole, or posaconazole	7	CF (3 adults, 4 children)

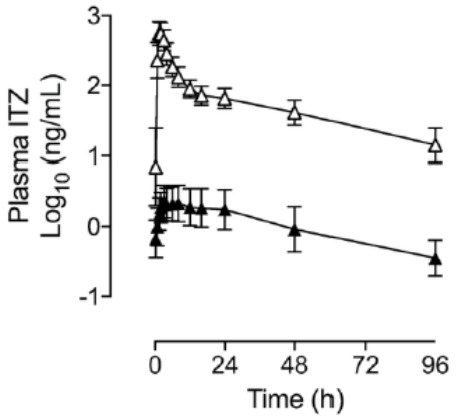
L-AMB: liposomal amphotericin B; Nbud: nebulized budesonide; AMBd: amphotericin B deoxycholate; ABLC: amphotericin B-lipid complex; CF: cystic fibrosis.

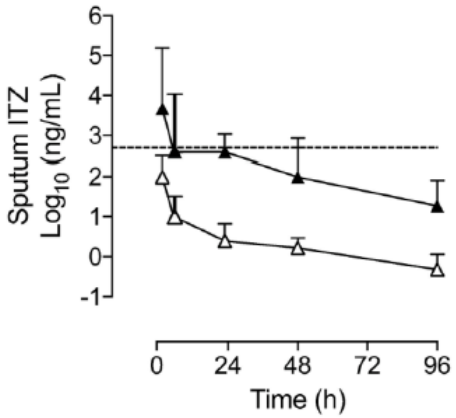
Case reports: positive clinical ± biomarker responses

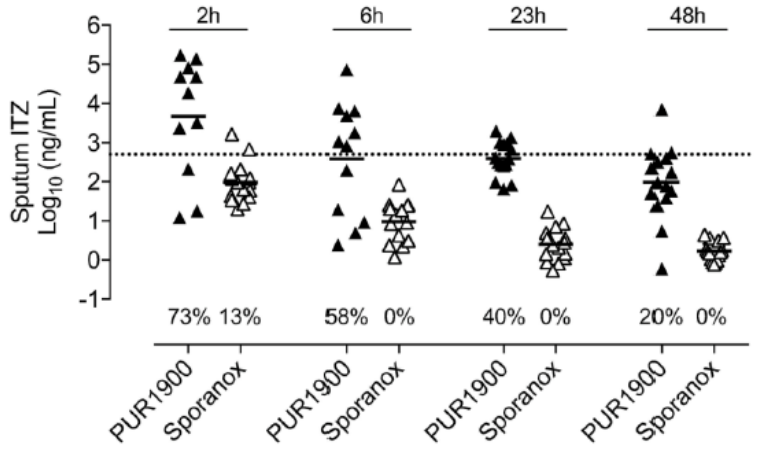
Casciaro R et al, *J Chemother* 2014;27:307

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

listory

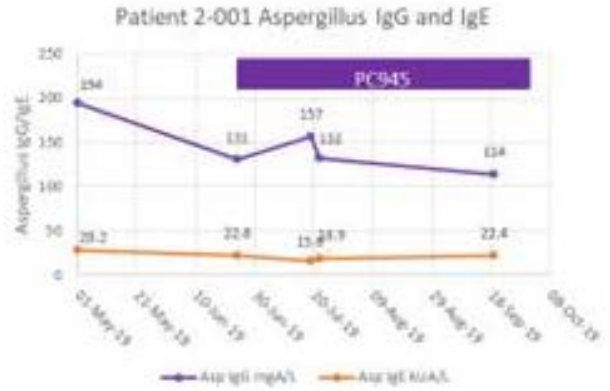
ABPA > 12 years
Multiple courses of antifungals
No response & significant side effects
Hospitalised for a week every 8 weeks for IV hydrocortisone
Symptomatic ++
A. fumigatus culture +

Pre-PC945 25 June 19

On PC945

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

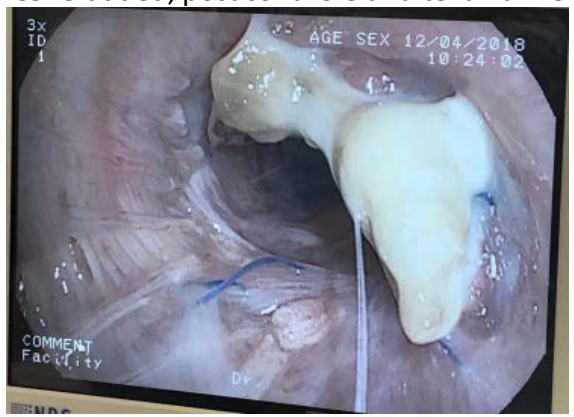
On PC945 for 4 weeks - 29 July 19



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



Refractory to available systemic & inhaled antifungals

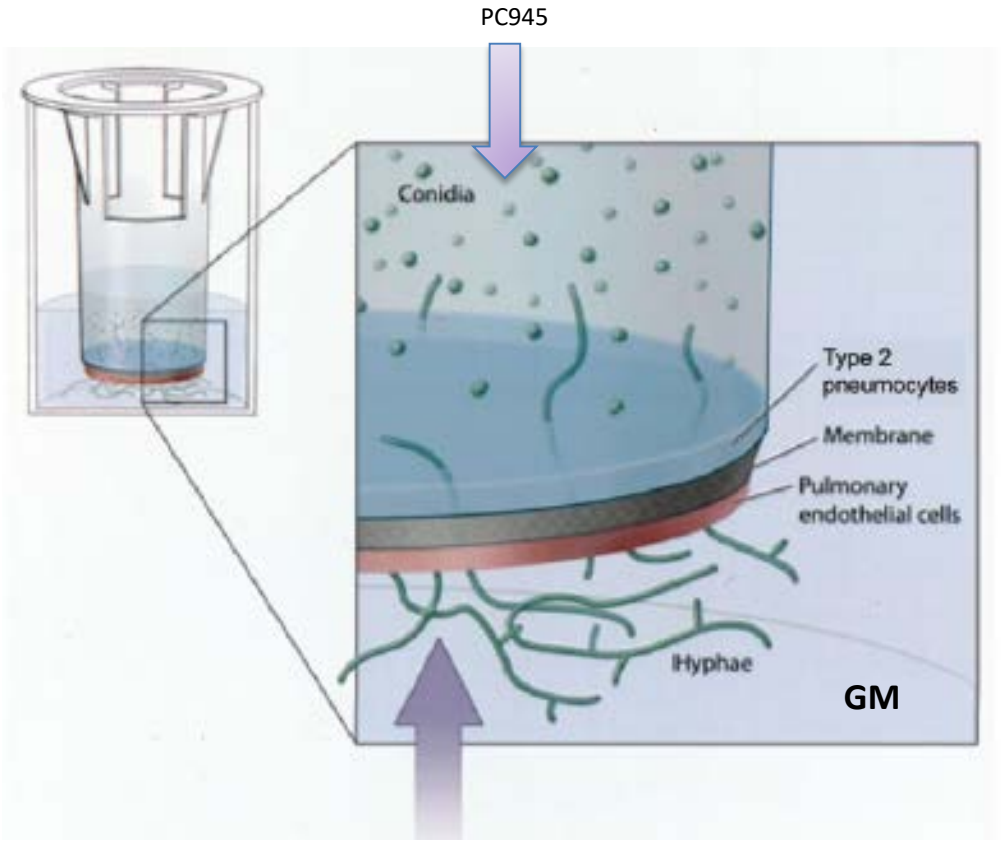
8wks

- 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

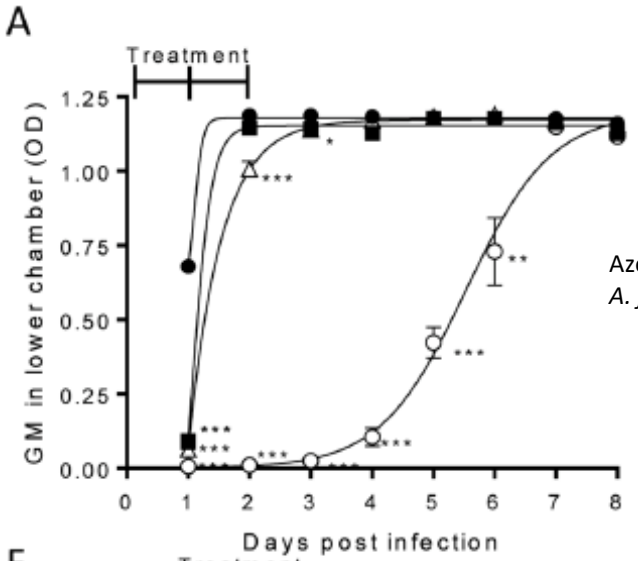
Nebulised PC945, 5mg daily added to oral antifungals

Pagani N et al, Fungal Update, 2019

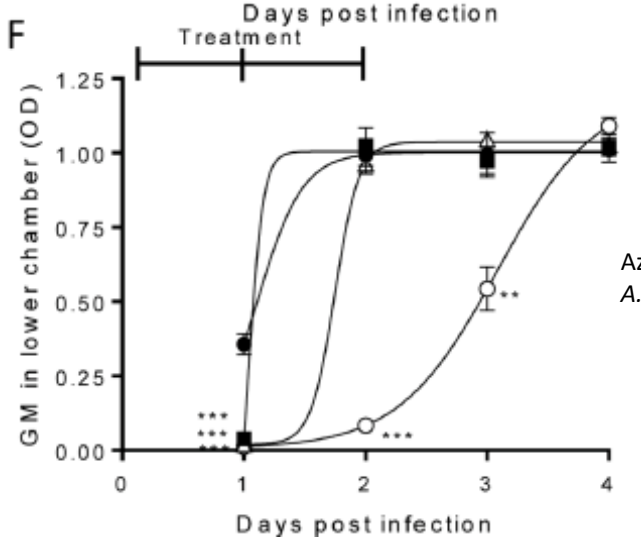
Combination Inhaled-Systemic Azole Therapy: *in vitro* Alveolus Model



Hope WW et al, *J Infect Dis* 2007;195:455



Azole-sensitive
A. fumigatus



Azole-resistant
A. fumigatus

Colley T el al, *Sci Rep* 2019;9:9482

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