Antifungal use in Allergic Fungal Disease

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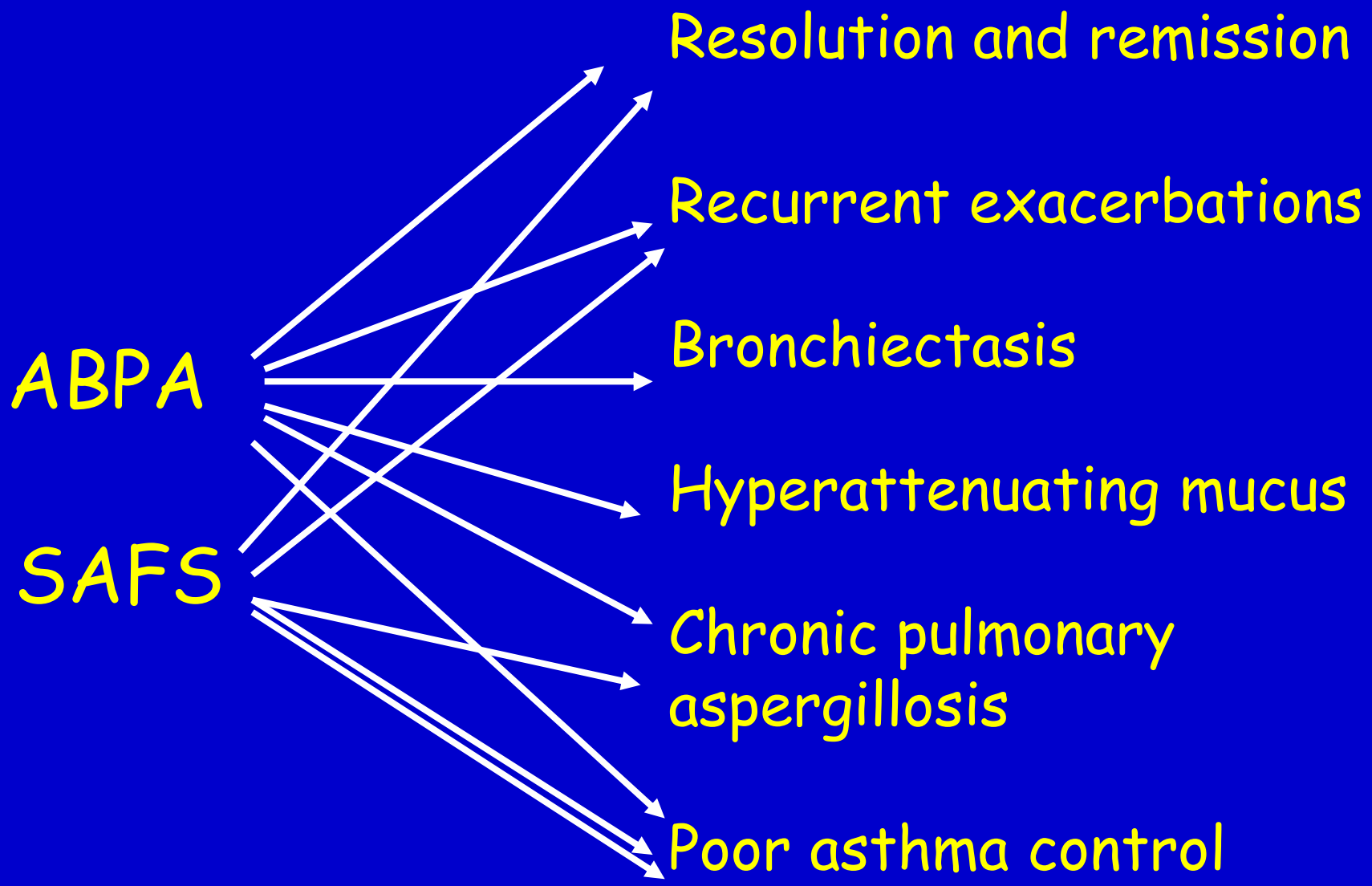
Fungal disease of the lungs in outside the hospital
'Fungal asthma'

Fungal infection	Annual burden	Annual case fatality rate	Estimated deaths
Chronic pulmonary aspergillosis	>3,000,000	~15% mortality in developed world	>450,000
SAFS	>6,500,000	<1% but no good figures	350,000 - 489,000 asthma deaths - ~50% SAFS related
ABPA (asthma)	>4,837,000	<1%	<10,000
ABPA & *Aspergillus* bronchitis (cystic firbosis)	>19,000	<1%	<100
Total	**>14 million**		**>700,000**

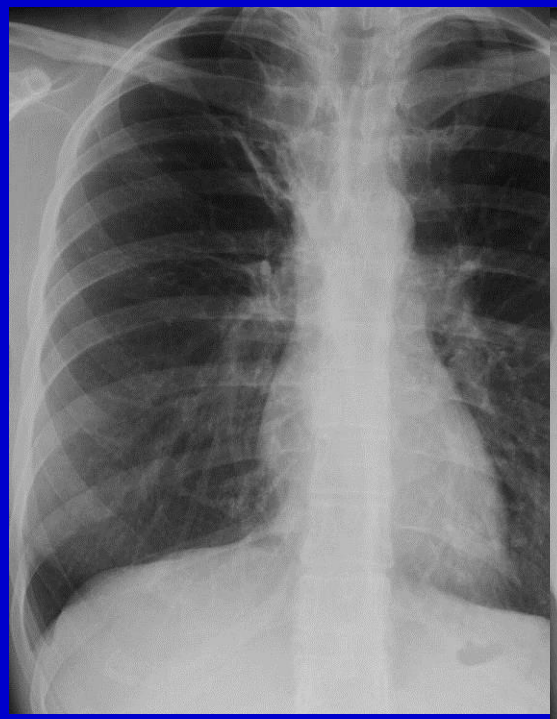
~200 million adult asthmatics

Fungal asthma in children – 2% of 100 million

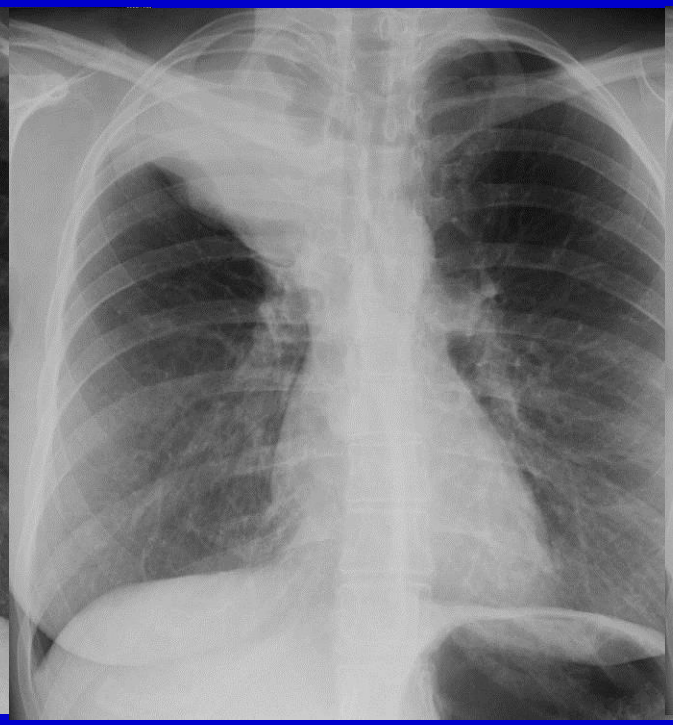
Complications of fungal asthma



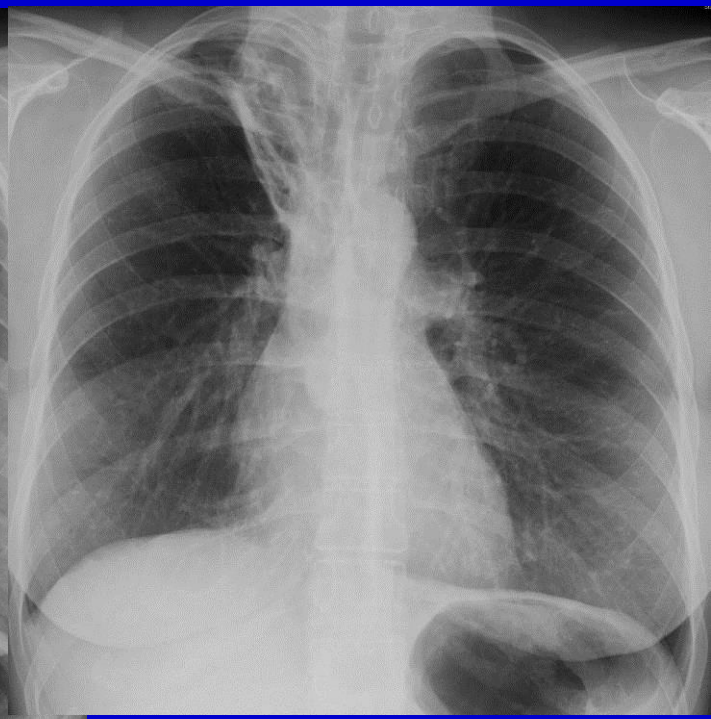
ABPA exacerbation – patient AL



May 2010



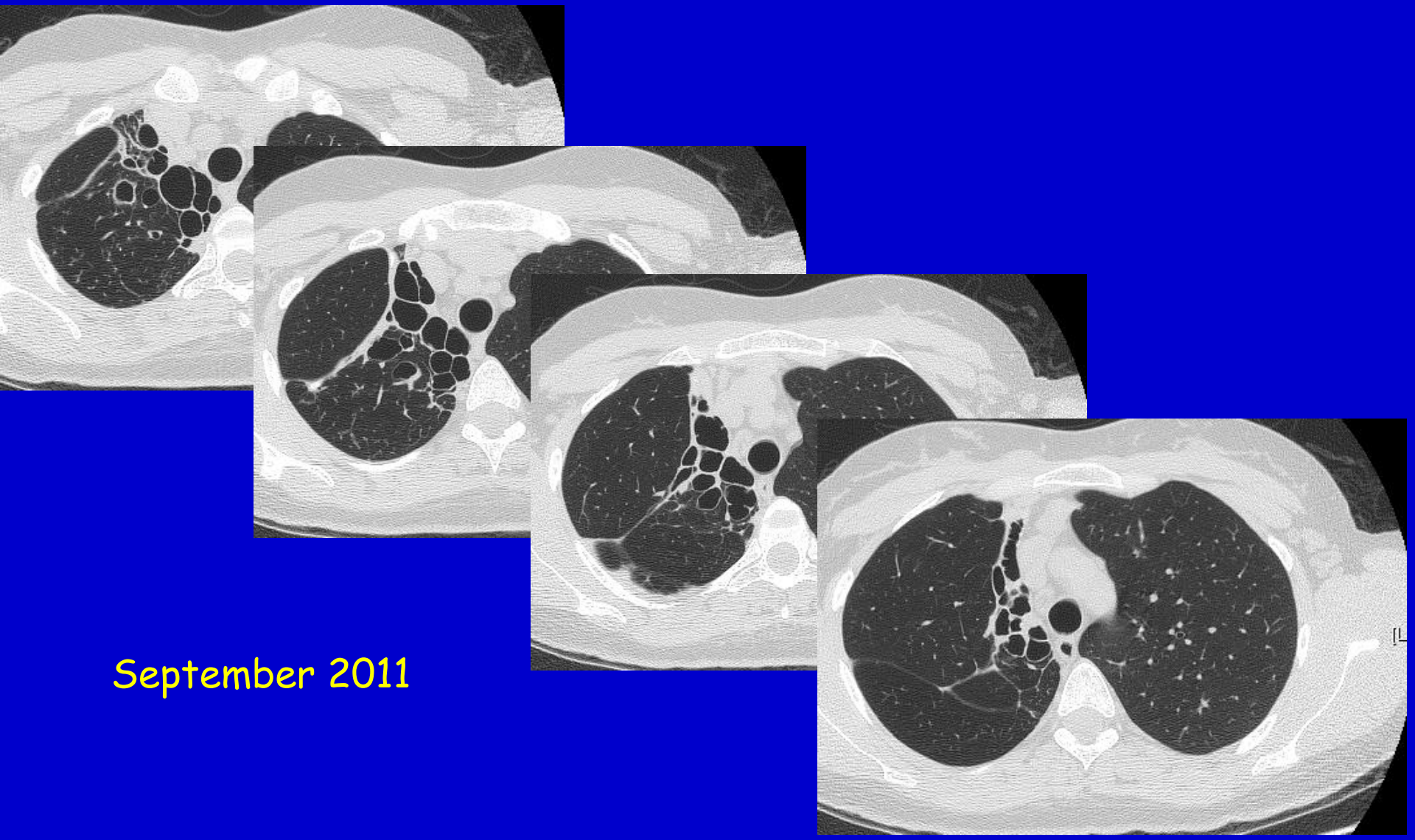
May 2011



June 2011
After prednisolone

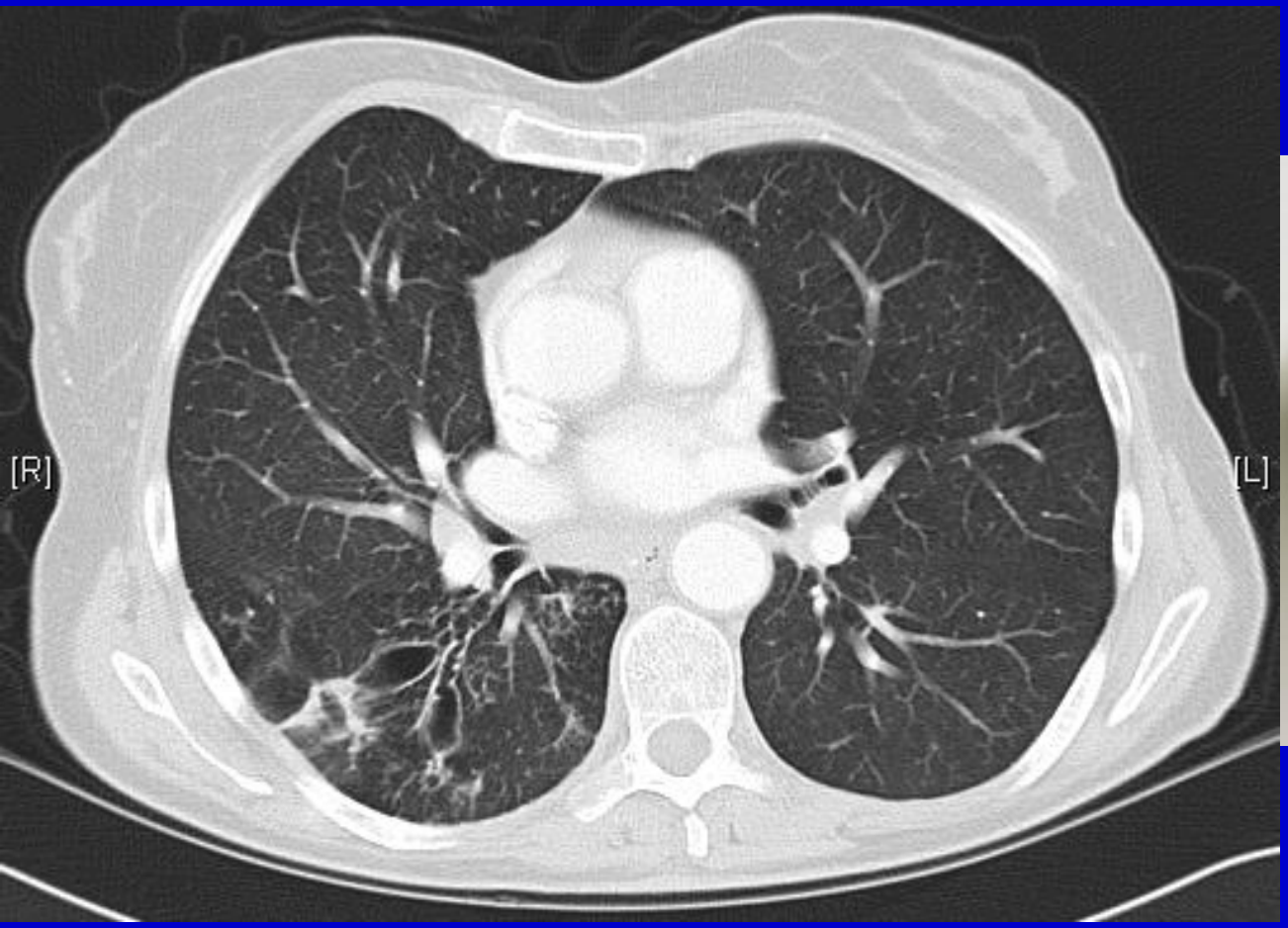
Exacerbation of ABPA

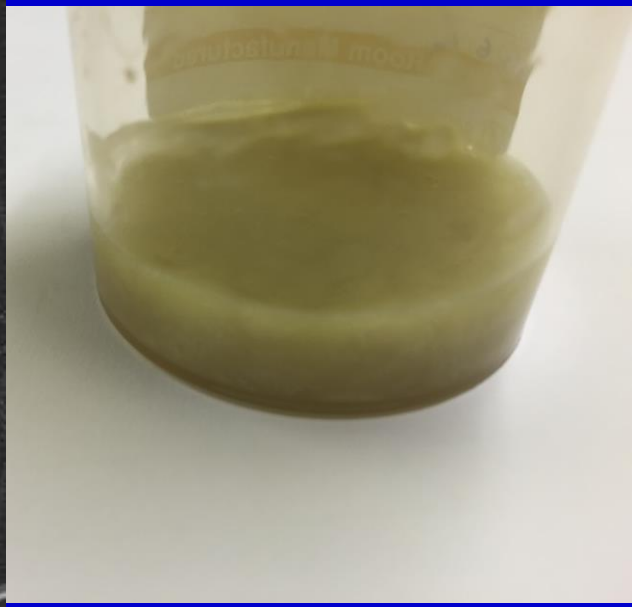
Patient AL



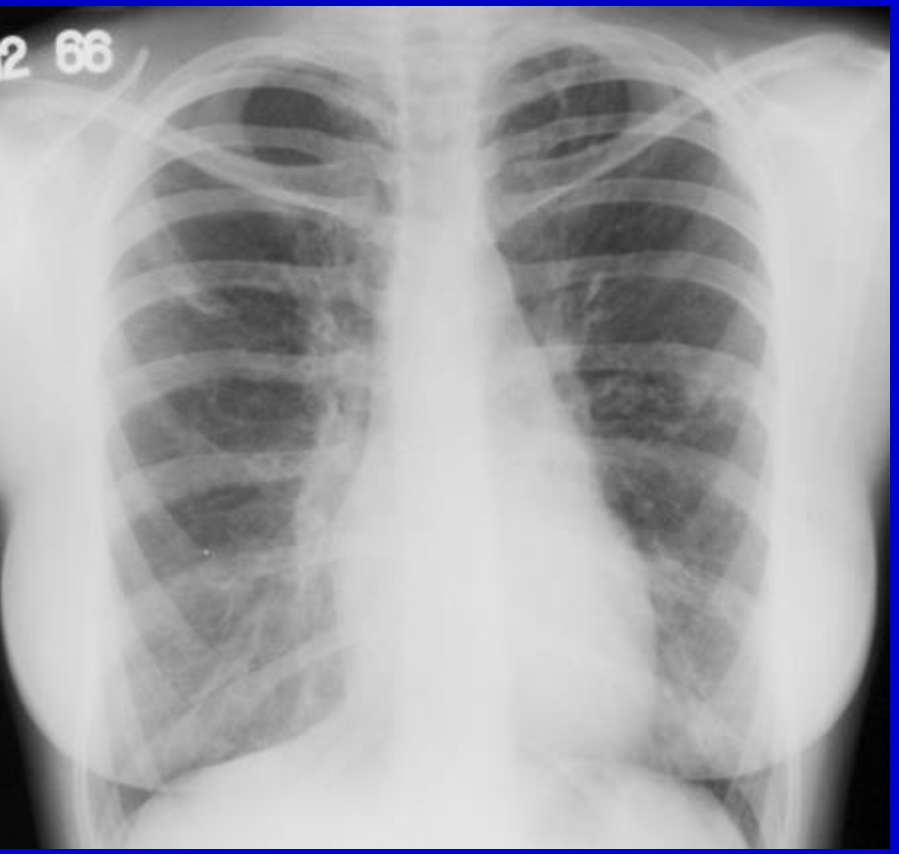
September 2011

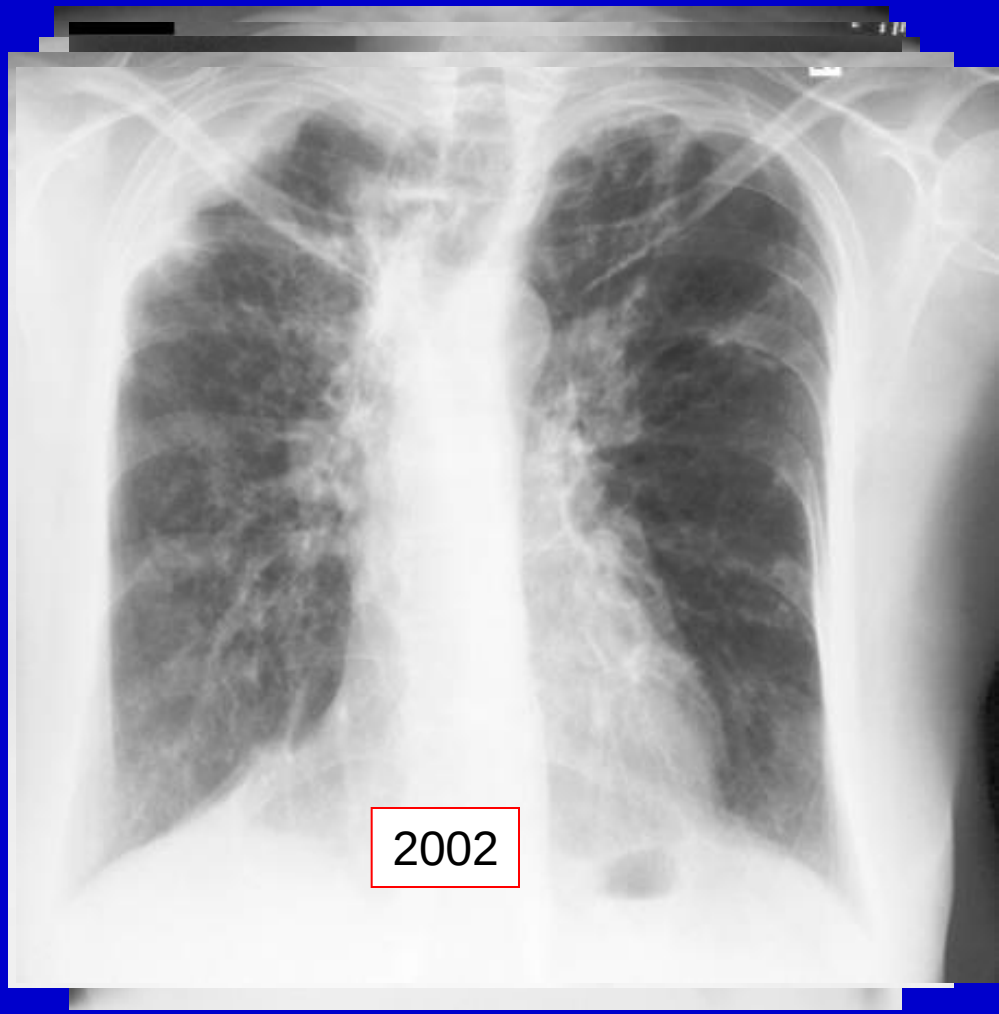
Central bronchiectasis as a complication of ABPA



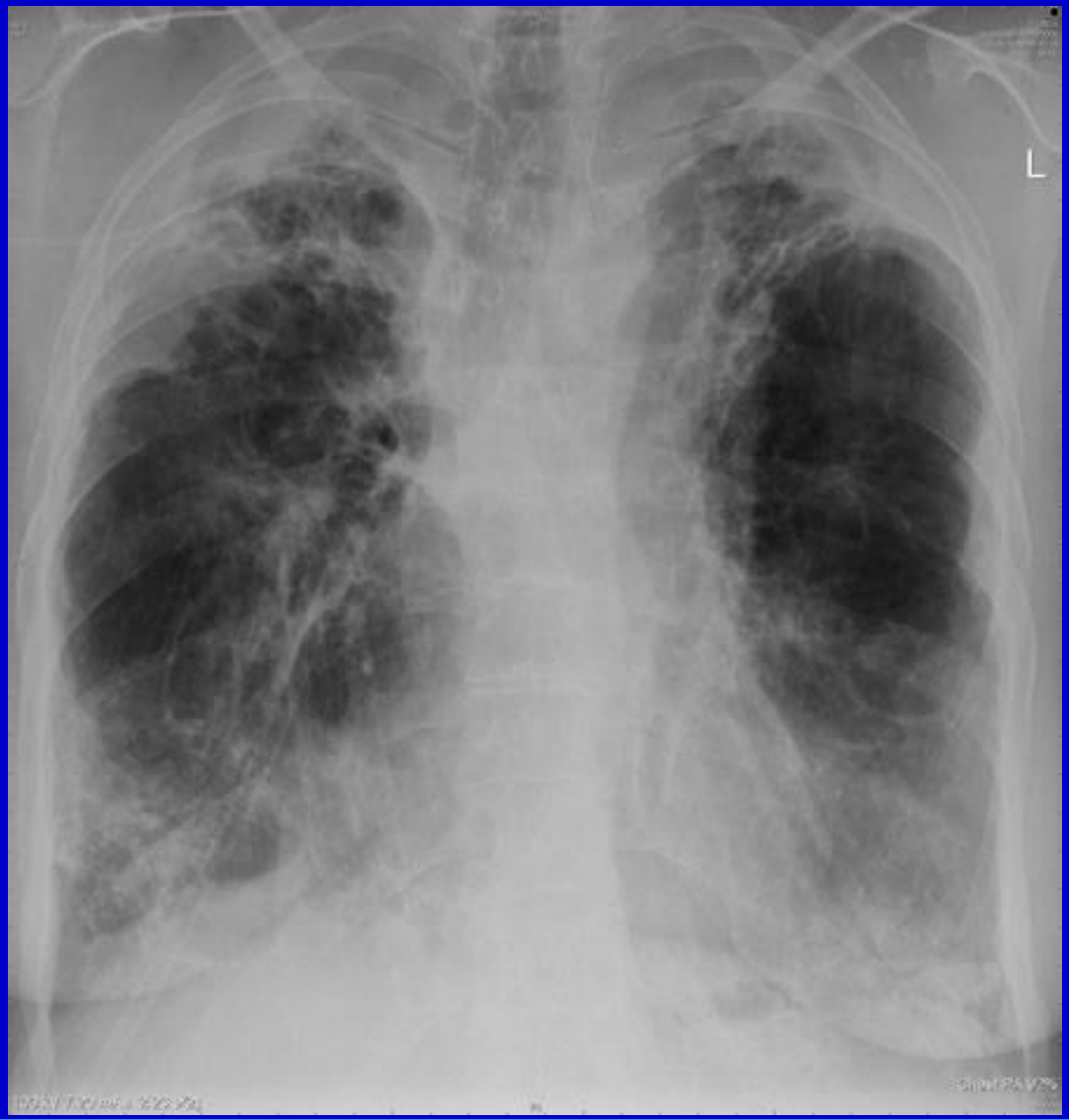


ABPA and development of CPA





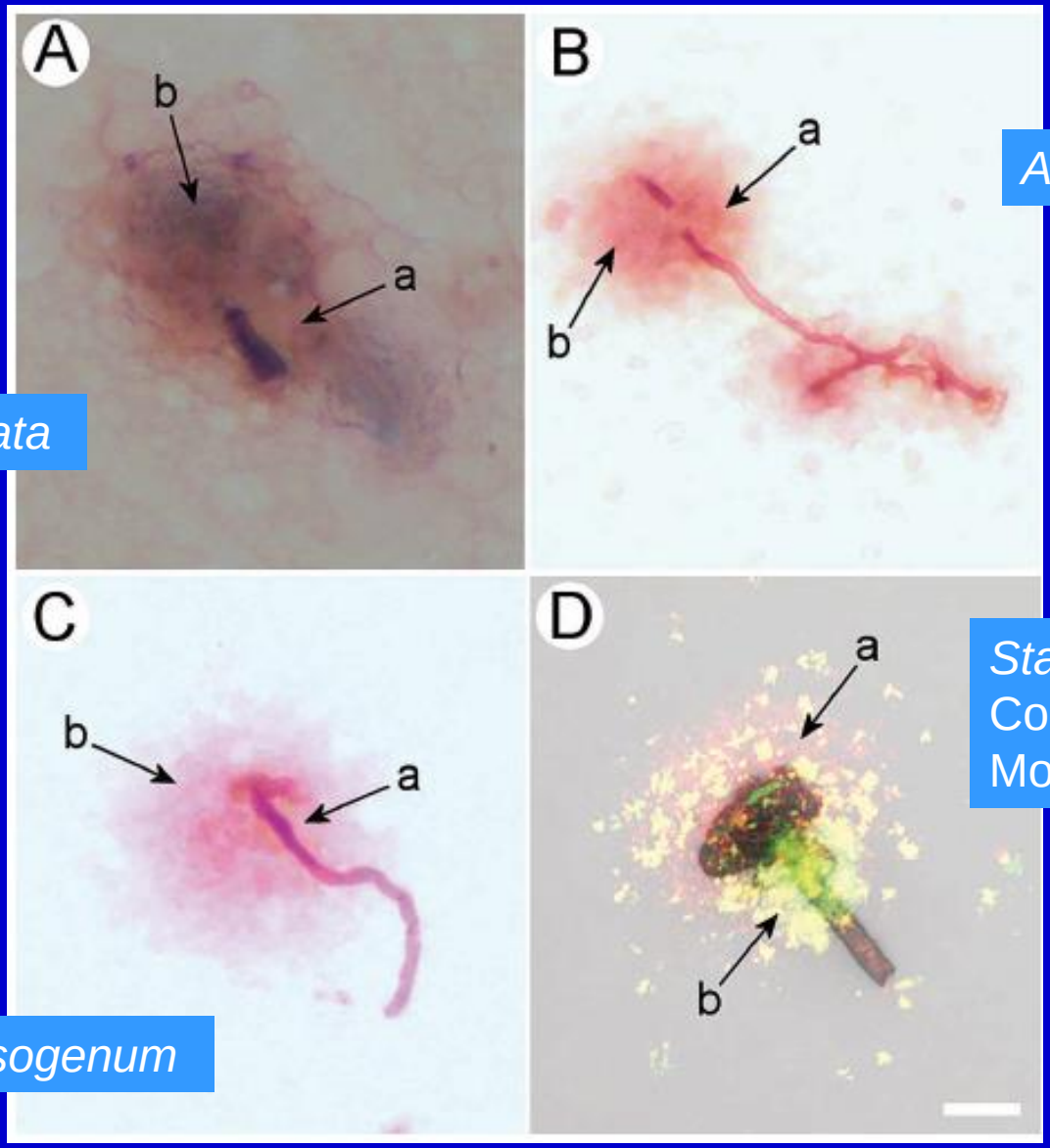
Chronic cavitary pulmonary aspergillosis as a complication of ABPA



Objectives of therapy

1. Avoidance of fungi in air
2. Control of the inflammatory response
3. Improvement of airway airflow via reduction of obstruction and mucus
4. Reduction in the fungal burden
5. Control of bacterial infection

Immunogenic airborne fungal fragments with remarkable allergens on their surface



Alternaria alternata

Aspergillus fumigatus

Penicillium chrosogenum

Stachybotris chartarum
Conidiophore
Monocolonal antibody

Green et al, Med Mycol 2006;44:S245

Randomised studies of antifungals and ABPA and/or asthma

Disease	Antifungal, duration	Benefit?	Author, year
ABPA	Natamycin inh, 52 wks	No	Currie, 1990
ABPA	Itraconazole, 32 wks	Yes	Stevens, 2000
ABPA	Itraconazole, 16 wks	Yes	Wark, 2003
"Trichophyton" asthma	Fluconazole, 20 wks	Yes	Ward, 1999
SAFS	Itraconazole, 32 wks	Yes	Denning, 2009
A. fumigatus-associated asthma	Voriconazole, 12 wks	No	Agbetile, 2014
ABPA	Amphotericin B, inh, 16 wks	Yes	Ram, 2016
ABPA exacerbations	Itraconazole, 6-12 wks	Yes	Agarwal, 2018

Open trial of itraconazole in ABPA - 1991

	Before		After
Prednisone (mg/d)	43	↓	24*
Total IgE	2462	↓	525*
FEV1	1.48	↑	1.79*
FVC	2.3	↑	2.9

*p=0.04

Only 1 patient failed – he had low itraconazole levels.

Denning et al, Chest 1991; 35:1329

Antifungal treatment of severe asthma with fungal sensitisation (SAFS)

11 patients with Trichophyton skin test allergy, dermtaphytosis 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

Ward et al, J Allergy Clin Immunol 1999;104:541;

The New England Journal of Medicine

A RANDOMIZED TRIAL OF ITRACONAZOLE IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

DAVID A. STEVENS, M.D., HOWARD J. SCHWARTZ, M.D., JEANNETTE Y. LEE, PH.D., BRUCE L. MOSKOVITZ, M.D., DENNIS C. JEROME, M.D., ANTONINO CATANZARO, M.D., DAVID M. BAMBERGER, M.D., ALLISON J. WEINMANN, M.B., B.S., CARMELITA U. TUAZON, M.D., MARC A. JUDSON, M.D., THOMAS A.E. PLATTS-MILLS, M.D., PH.D., AND ARTHUR C. DEGRAFF, JR., M.D.

Corticosteroid dependant ABPA with asthma

Phase 1 - 200mg BID v placebo, 16 weeks

Phase II - 200mg daily in all patients, 16 weeks

Stevens et al, New Engl J Med 2000; 342:756

Randomised trial of itraconazole in ABPA

TABLE 3. DEFINITION OF A RESPONSE IN THE DOUBLE-BLIND TRIAL.*

Reduction in the dose of corticosteroid by 50 percent or more
Decrease in the total IgE concentration by 25 percent or more
At least one of the following
Increase in exercise tolerance by at least 25 percent
Improvement by 25 percent in results of at least one of five pulmonary-function tests†
Resolution of infiltrates present at enrollment and attributable to allergic bronchopulmonary aspergillosis and no subsequent development of infiltrates, or absence of development of any infiltrates during the study if no infiltrates were present at enrollment‡

*Patients were considered to have had a response if they met the first two criteria and at least one of the conditions of the third. Responses were assessed by comparing values at week 0 with those at week 16.

†The following were assessed: forced expiratory volume in one second, forced vital capacity, forced expiratory flow in the midexpiratory phase, peak flow rate, and carbon monoxide diffusing capacity.

Stevens et al, New Engl J Med 2000; 342:756

Randomised trial of itraconazole in ABPA

Corticosteroid dependant ABPA with asthma
Phase 1 - 200mg BID v placebo, 16 weeks
Phase II - 200mg daily in all patients, 16 weeks

	Itra	Placebo then Itra	
	Overall 17/28 (61%) response rate		
Overall response	13/28 (46%)	5/27 (19%)	p = 0.04
	Phase 2		
No prior response	4/13 (31%)	8/20 (40%)	NS
	(n=33)		

Number needed to treat = 3.58

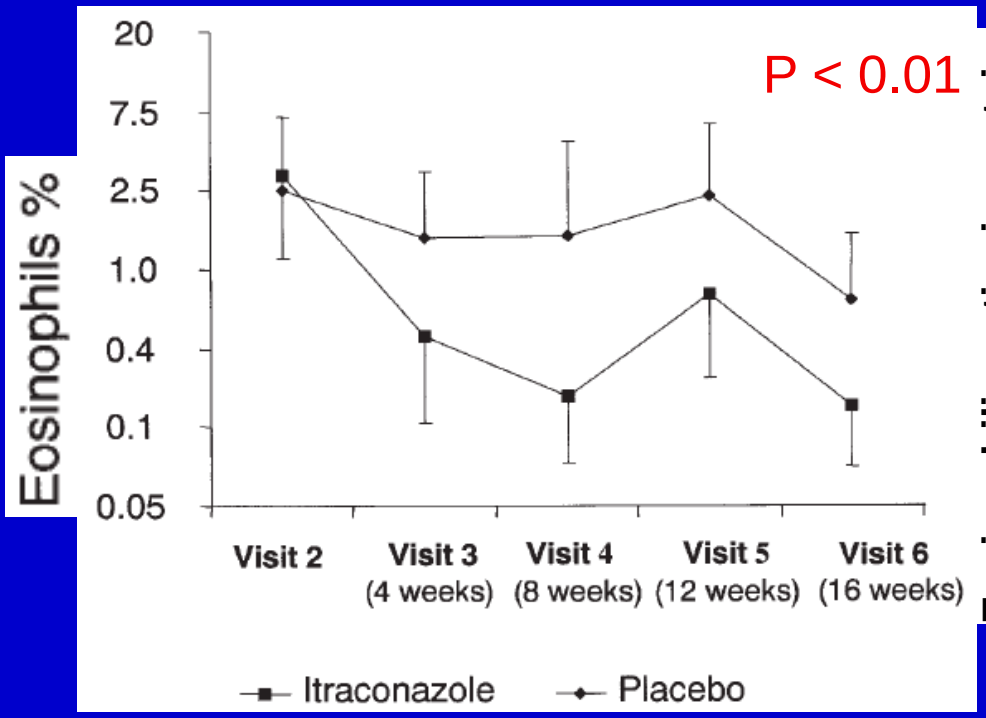
Stevens et al, New Engl J Med 2000; 342:756

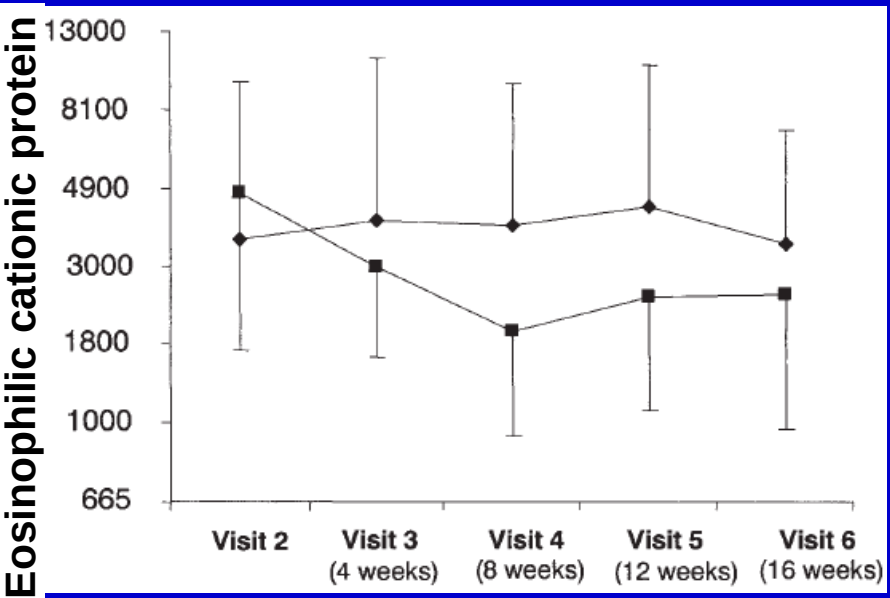
Randomised trial of itraconazole in ABPA

ABPA with asthma, n = 29

Phase 1 - 200mg BID v placebo, 16 weeks

Primary outcome measure – Sputum eosinophil count





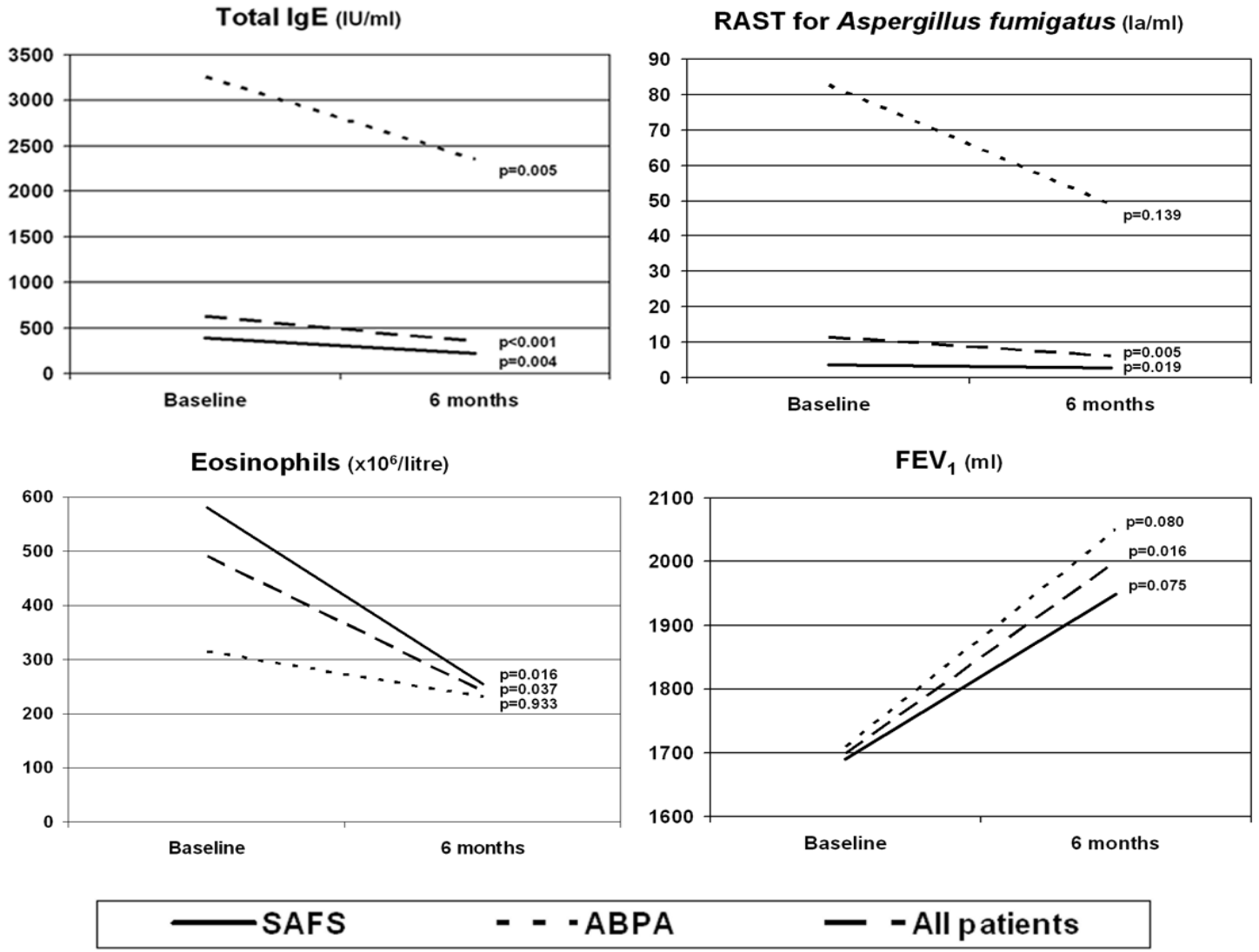
Reduced exacerbation rate

No change in FEV1 or PEF

Wark et al, J Clin All Immunol 2003; 111:952

Retrospective comparison of antifungal treatment of SAFS with ABPA

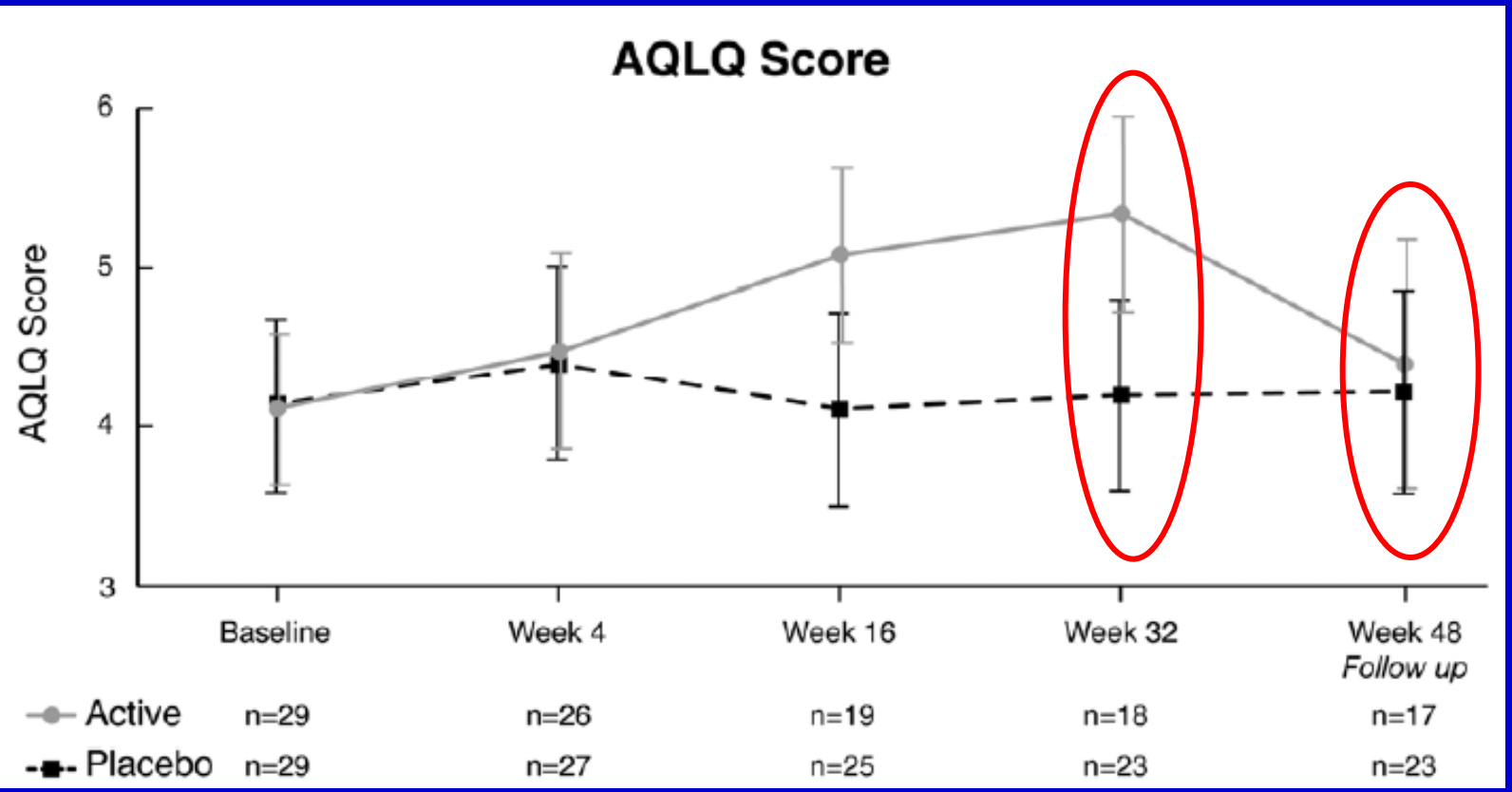
22 patients with SAFS were compared with 11 with ABPA



Pasquallotto et al, Respirology 2009;14:1121

Proof of concept RCT of antifungal Rx in SAFS

AQLQ change of 0.8 to 1.2



P= 0.014

Denning et al, Am J Resp Crit Care Med 2009; 179:11

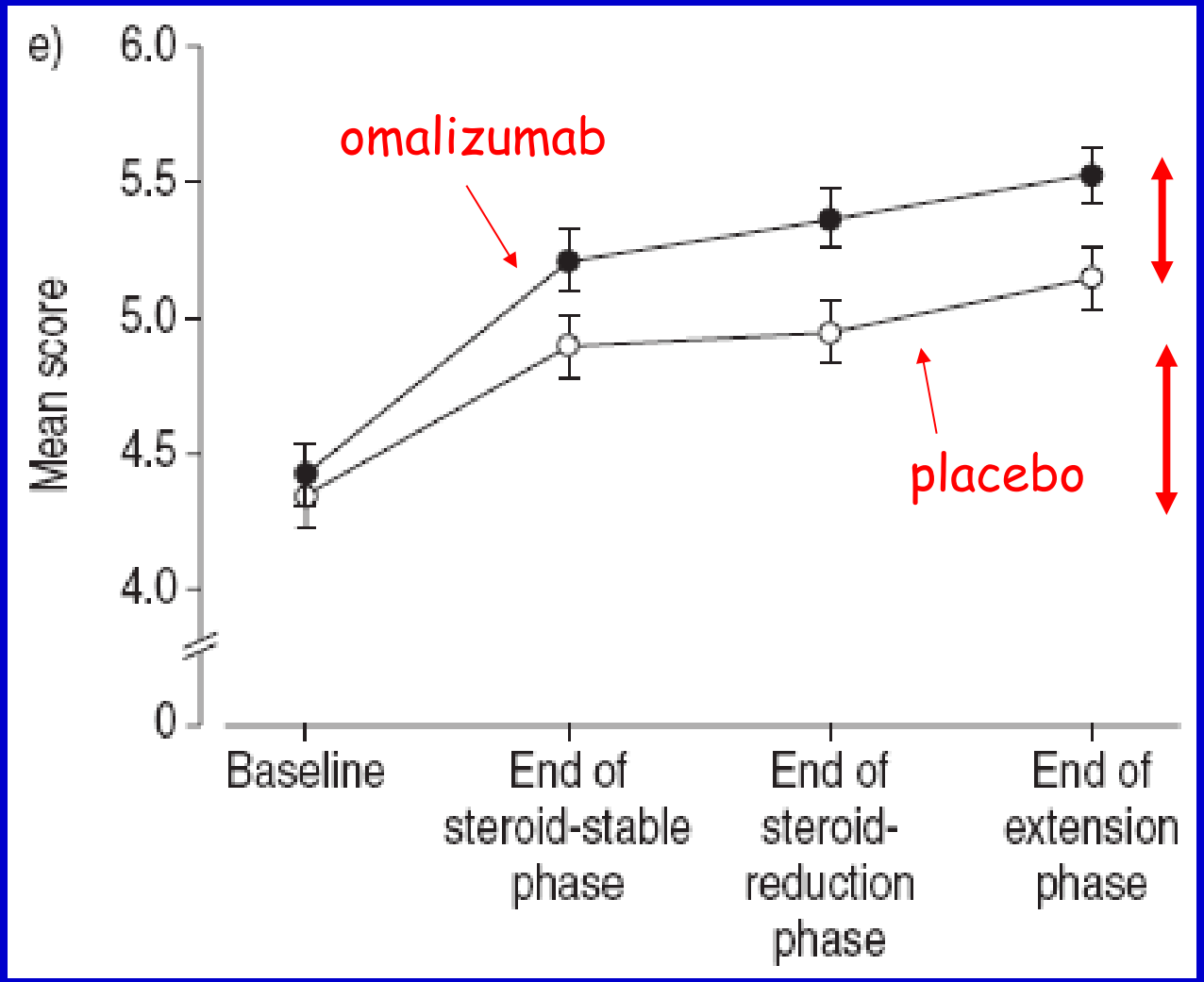
Proof of concept RCT of antifungal Rx in SAFS – outcomes at 32 weeks MITT

	Mean (95% CI) or % (n)		P-value
	Active	Placebo	
Change in AQLQ score	+0.85 (0.28, 1.41)	-0.01 (-0.43, 0.42)	0.014
Improvement in AQLQ score of >0.75	54% (14)	18% (5)	0.013

Number needed to treat = 3.22

Denning et al, Am J Resp Crit Care Med 2009; 179:11

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

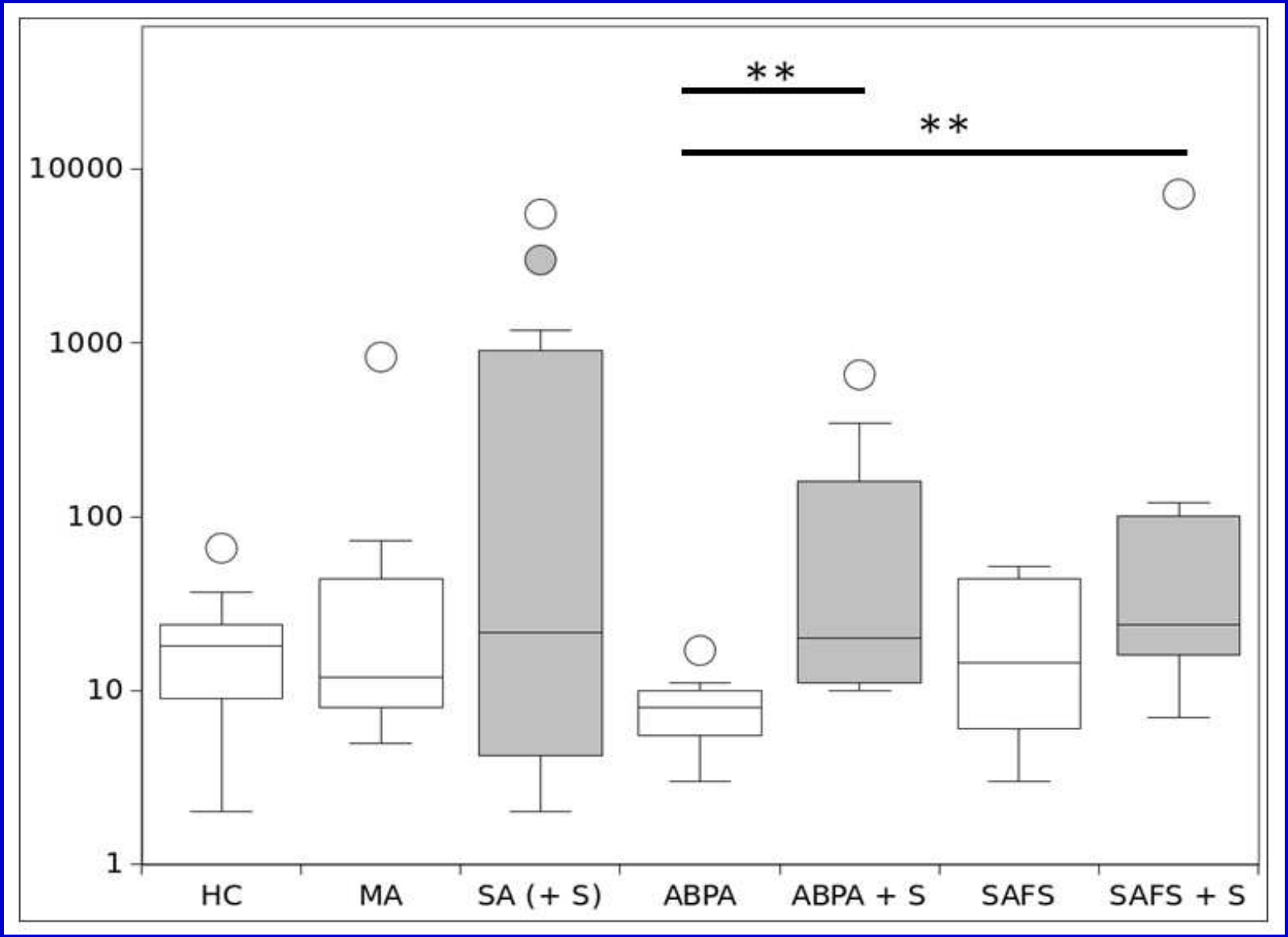


Omalizumab mprovement in AQLQ = ~0.4

Steroids improvement in AQLQ = ~0.6

Buhl et al Eur Resp J 2002;20:1088

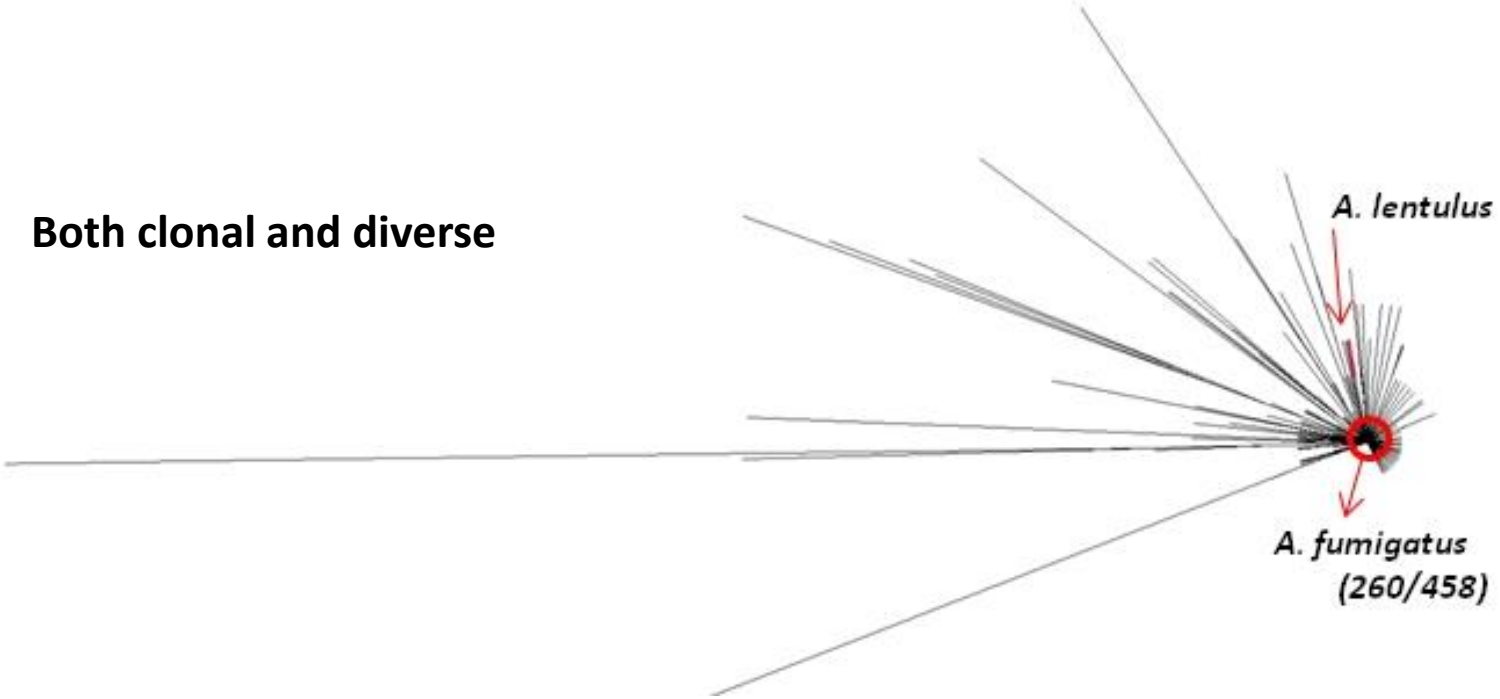
Steroids are the only factor statistically linked to higher levels of *Aspergilli* & *Penicillia*



Fraczek et al, J Clin All Immunol 2018; in press

Population structure:

Both clonal and diverse



Fraczek et al, J Clin All Immunol 2018; in press

Second and third line antifungal therapy for ABPA and/or asthma

- 26 patients, ABPA (n = 21) or SAFS (n = 5).
- All patients had failed itraconazole (n=14) or developed adverse events (AEs) (n=12)
- 34 courses of therapy, 25 with voriconazole and 9 with posaconazole.

Chishimba et al, J Asthma 2012;49:423

Impact of voriconazole and posaconazole on ABPA and SAFS - retrospective

		Clinical outcome of courses of therapy (%)		
		3 months	6 months	12 months
ABPA				
Voriconazole	Improved	13/20 (65)	11/15 (73)	9/13 (69)
	Stable	2/20 (10)	2/15 (13)	2/13 (15)
	Failure	1/20 (5)	0/15	2/13 (15)
	Discontinued (AEs)	4/20 (20)	2/15 (13)	0/13
Posaconazole	Improved	7/9 (78)	7/9 (78)	7/9 (78)
	Stable	2/9 (22)	2/9 (22)	0/9
	Failure	0/9	0/9	2/9 (22)
	Discontinued (AEs)	0/9	0/9	0/9
SAFS				
Voriconazole	Improved	4/5 (80)	4/5 (80)	3/4 (75)
	Stable	1/5 (20)	1/5 (20)	1/5 (20)
	Failure	0/5	0/5	0/5
	Discontinued (AEs)	0/5	0/5	0/5

Notes: AEs, adverse events; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitization. () indicates %.

Chishimba L J Asthma 2012;49:423

Second and third line antifungal therapy for ABPA and/or asthma

- 26 patients, ABPA (n = 21) or SAFS (n = 5).
- All patients had failed itraconazole (n=14) or developed adverse events (AEs) (n=12)
- 34 courses of therapy, 25 with voriconazole and 9 with posaconazole.

- 73-80% improved at 6 months.
- 18/24 (75%) discontinued oral corticosteroids, 12 of them within 3 months of starting antifungal therapy

- 4 relapsed (57%), 1 at 3 months and 3 at 12 months after discontinuation.

Chishimba et al, J Asthma 2012;49:423

Nebulised conventional amphotericin B

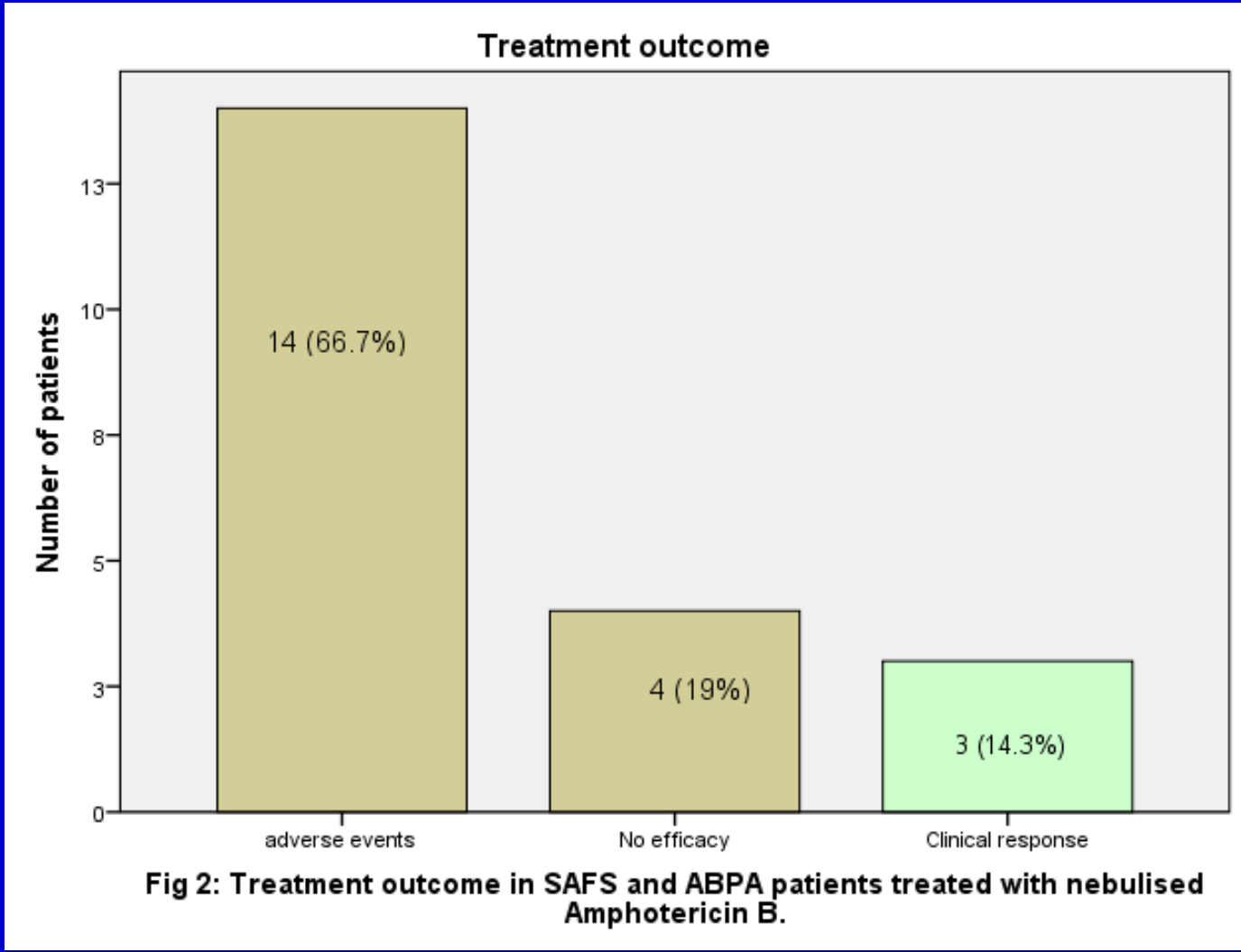
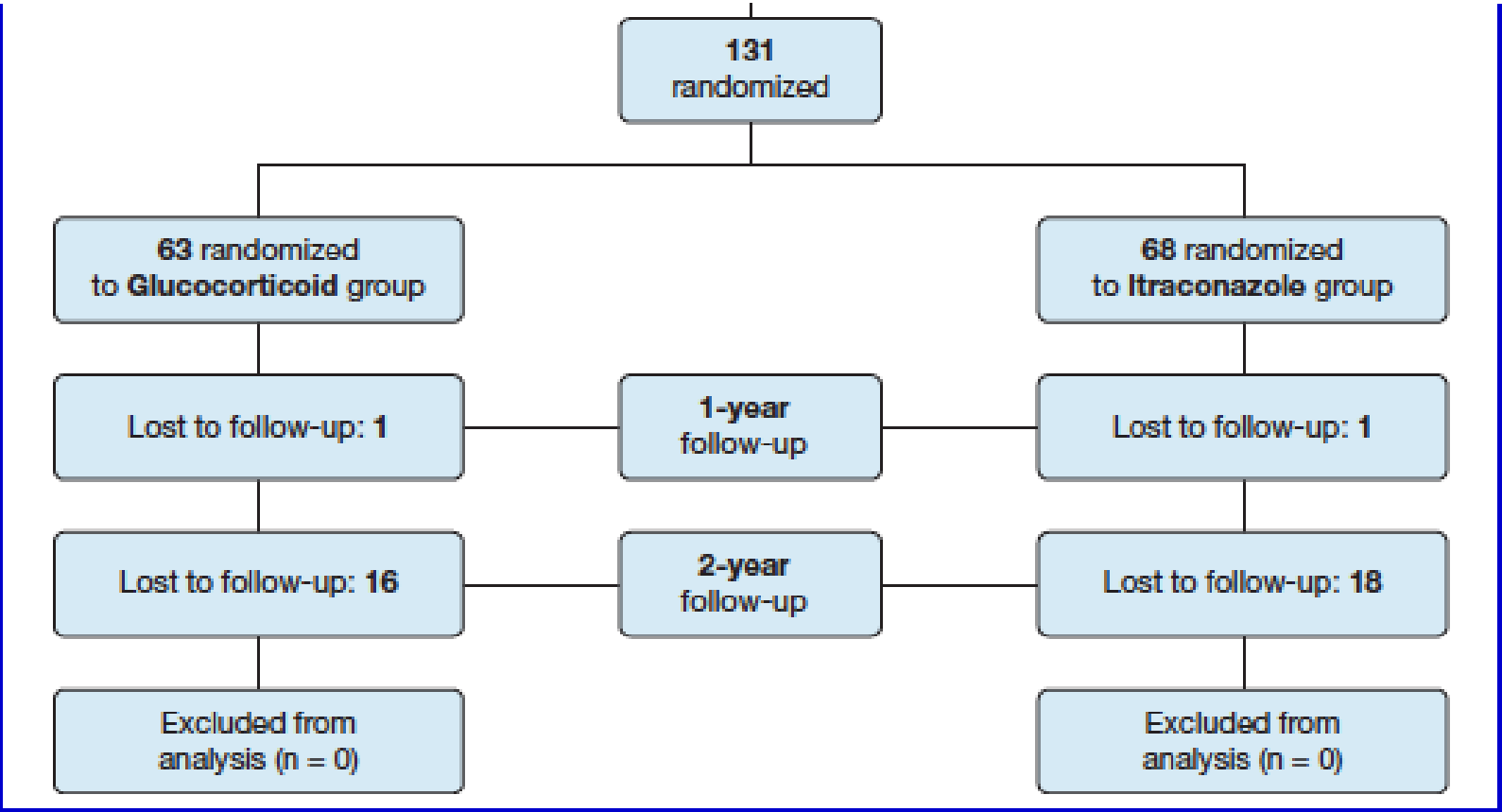


Fig 2: Treatment outcome in SAFS and ABPA patients treated with nebulised Amphotericin B.

Chishimba et al, J Asthma 2015; 52:289

A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma

Ritesh Agarwal, MD, DM; Sahajal Dhooria, MD, DM; Inderpaul Singh Sehgal, MD, DM; Ashutosh N. Aggarwal, MD, DM; Mandeep Garg, MD; Biman Saikia, MD; Digambar Behera, MD; and Arunaloke Chakrabarti, MD

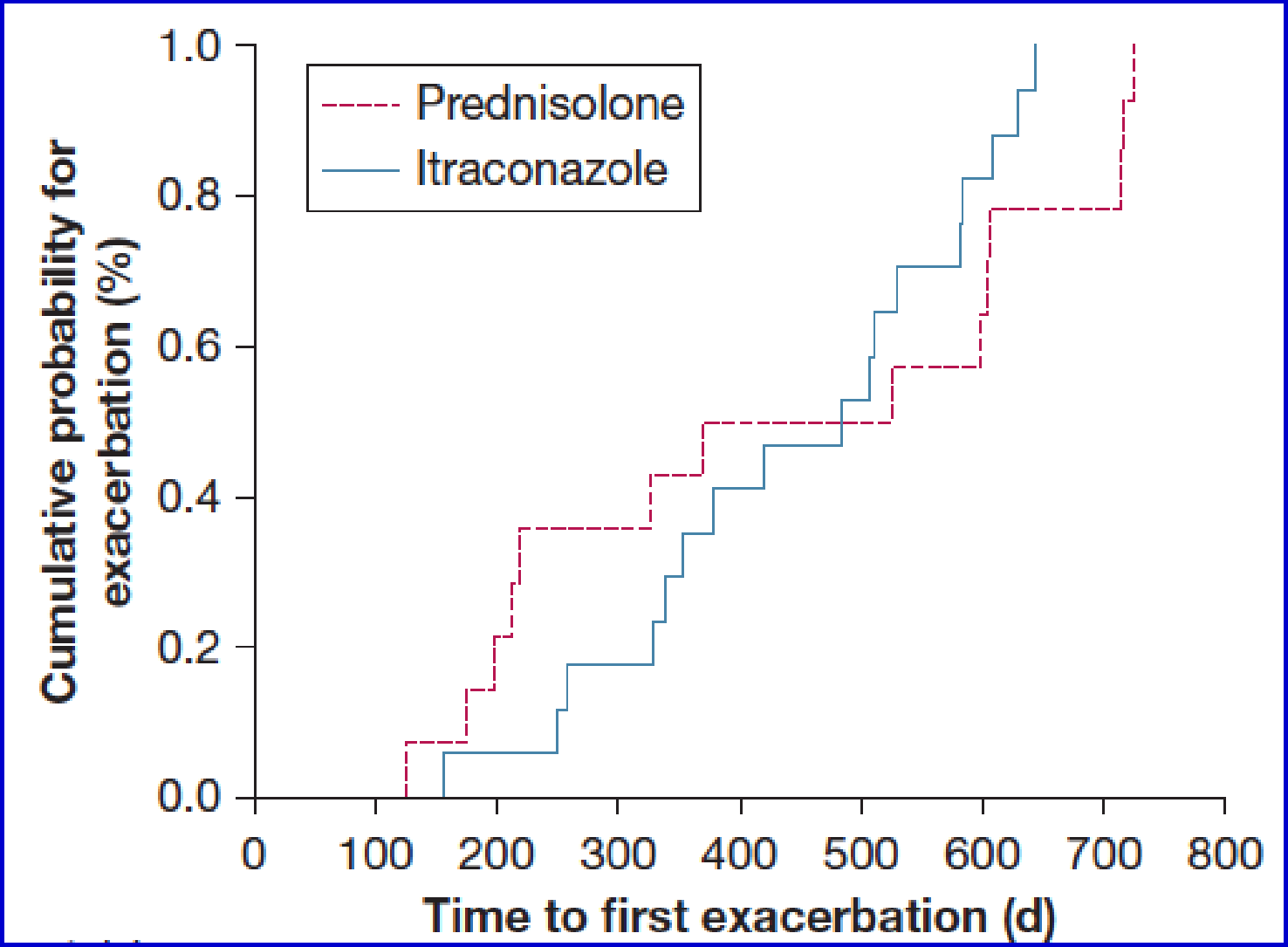


Agarwal et al, Chest 2018 in press

TABLE 2 Outcomes of Study Subjects Treated With Prednisolone or Itraconazole (N = 131)

Outcome	Prednisolone Group (n = 63)	Itraconazole Group (n = 68)	Estimated Difference (95% CI)	*P* Value
Primary outcomes				
Subjects with response following 6 wk of treatment[a]	63 (100%)	60 (88.2%)	−11.8 (−21.5 to −3.7)	.007
Subjects with response following 3 mo of treatment	63 (100%)	60 (100%)	0 (−0.06 to 0.06)	...
Complete remission following 3 mo of stopping treatment	60 (95.2%)	59 (98.3%)	−0.03 (−0.05 to 0.12)	.39
Complete remission following 6 mo of stopping treatment	58 (92.1%)	59 (98.3%)	0.05 (−0.05 to 0.14)	.13
Percentage decline in IgE following 6 wk of treatment (n = 123)	54.5 (48.9-60.1)	51.8 (42.9-60.8)	−2.7 (−7.6 to 13.4)	.87
Percentage decline in IgE following 3 mo of treatment (n = 123)	66.9 (62.0-71.8)	65.6 (59.1-72.1)	−1.3 (−6.7 to 9.3)	.80
No. of subjects experiencing exacerbation following 1 y of treatment (n = 123)	6 (9.5%)	7 (11.7%)	−2.1 (−13.8 to 9.2)	.93

4 months of therapy and then observation



Agarwal et al, Chest 2018 in press

Itraconazole inhaled steroid interaction

- Itraconazole reduces the metabolism of inhaled steroids
- Documented for beclomethasone, fluticasone
- Ciclosenide probably not
- No interaction with prednisolone, dexamethasone, hydrocortisone
- Reduces metabolism of methylprednisolone
- [Voriconazole reduces prednisolone metabolism, but probably no interaction with inhaled steroid]

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Antifungal agents	7A	We suggest antifungal agents in adults with severe asthma and recurrent exacerbations of ABPA	Conditional	Very low	The recommendation to use antifungal agents in patients with severe asthma and ABPA places a higher value on possible reduction of the risk of exacerbations and improved symptoms, and a lower value on avoiding possible adverse effects, drug interactions and increased use of resources

Chung et al, Eur Resp J 2014;43:343

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Over 300 million people are acutely or chronically infected by fungi, leading to death, long term illness, blindness, psychological problems and reduced work capacity. Many recent improvements in diagnostics and treatment have not reached treating clinicians in all countries, and access to appropriate diagnostics and simple antifungal agents is far from universal. This needs to change.

LIFE aims to provide the latest information on the most common human pathological fungi, the diseases they cause and their diagnostics and treatment. LIFE is led by Professor David Denning who has been caring for patients with fungal infection for 30 years.

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