

Fungus induced asthma - diagnosis and treatment

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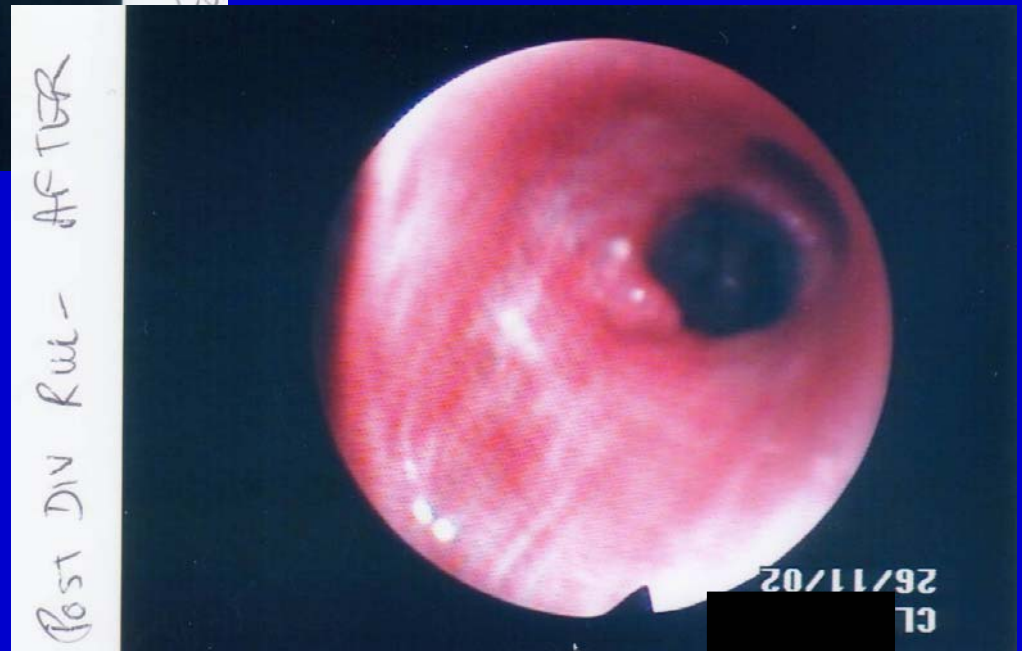
The University of Manchester

ABPA - Diagnostic clues

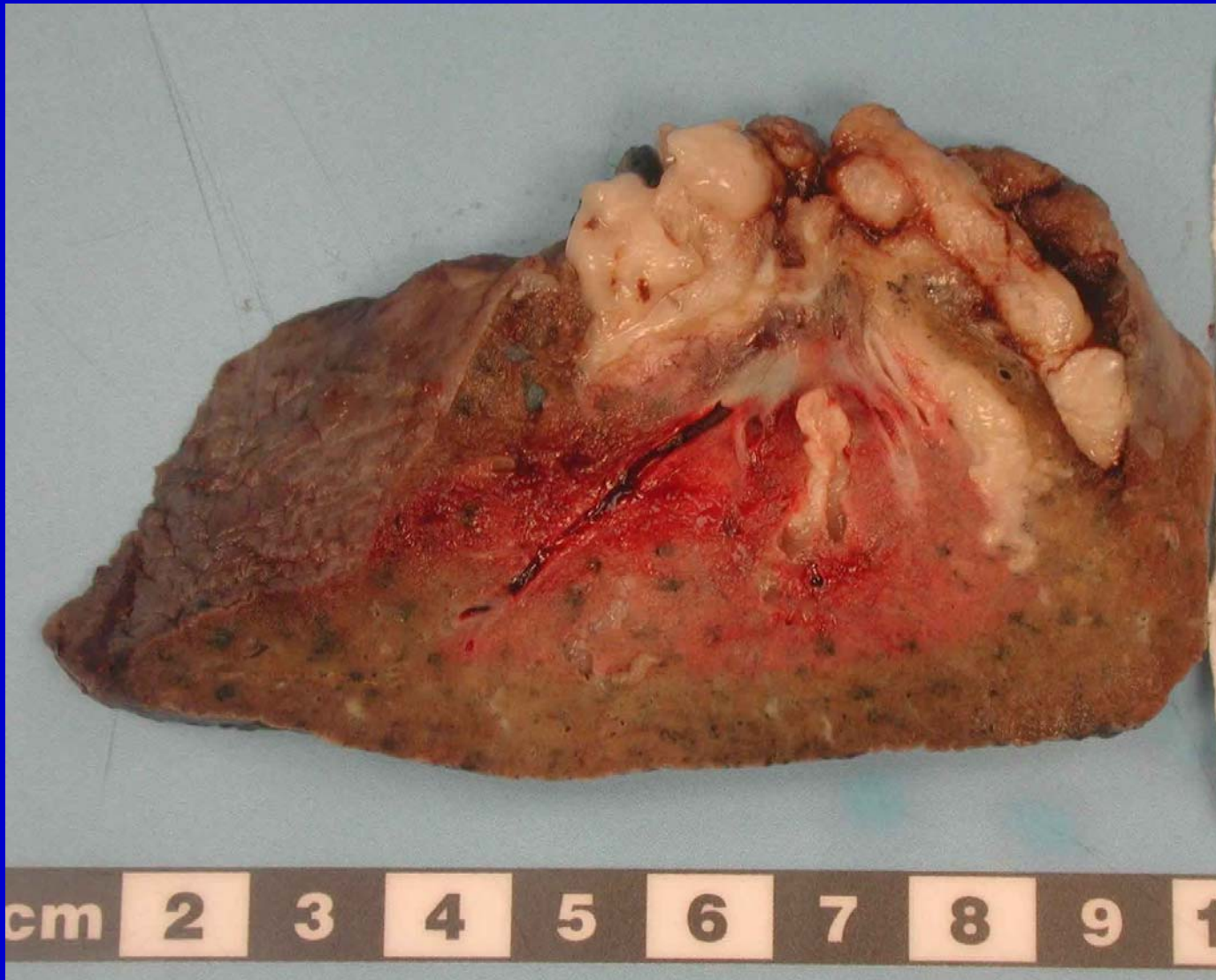
- Asthma/CF not well controlled
- History of 'pneumonia'
- History of coughing up plugs, or paroxysms of coughing that clear when chest clears
- Central bronchiectasis on CT scan, or mucoid impaction
- Eosinophilia

Rare cases in non-asthmatics, non-CF patients

ABPA - bronchoscopy views showing mucous plugging



Mucoid impaction due to ABPA



ABPA and severe asthma



Early reports of asthma exacerbated by fungi

- 1698 - 'asthmatic who fell into a violent fit, by going into a wine cellar where the must was fermenting'
- 1873 - Dr Charles Blackley self experimented with *Penicillium glaucum* which on inhalation of a large number of spores, induced hoarseness, aphonia and an attack of 'bronchial catarrh'
- 1897 - Renon noted wheezing in pigeon-crammers and hair combers exposed to *Aspergillus*
- 1924 - Cadham attributed asthma to wheat rust (*Puccinia graminis*) exposure
- 1924 - Storm Van Leeuwen showed asthma was more prevalent in the humid parts of the Netherlands, and relief with the use of filtered air

Early reports of asthma exacerbated by fungi

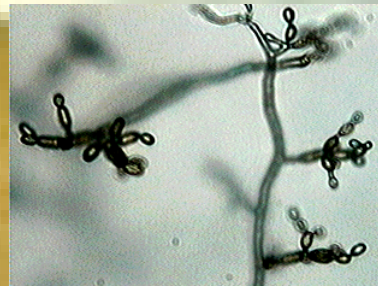
- 1925 - Van Leewen found 50% of Dutch asthmatics had mould skin sensitivity esp. to *Mucor*, *Penicillium* and *A. fumigatus*, *niger*, *flavus* and *nidulans*
- 1928 - Hansen found 15% of asthmatics had positive skin tests to *Aspergillus* or *Penicillium* grown from their environment and that inhalation challenge reproduced symptoms
- 1928 - Jimines-Diaz and Sanchez Cuenca demonstrated that 'house dust' sensitivity was often due to moulds
- 1930 - 3 separate case reports of asthma related to *Alternaria*, *A. fumigatus* and *Trichopyton*
- 1939 - Cohen showed that mattresses, pillows and furniture were potent sources of 'house dust antigen' which when removed abolished asthmatic symptoms in those with mould allergy

Fungal exposure in asthmatics is related to:

- Life-threatening asthmatic attacks (ie thunderstorm asthma)
- Severe asthma and hospital admission

Skin prick testing - scoring using wheal diameter (AllergoPharma reagents)

Cladosporium +ve



Hospital admission and sensitisation

<u>Allergen</u>	<u>Asthma, no admission (n=82)</u>	<u>Asthma, 2+ admissions (n=46)</u>
House dust mite	56 %	67 %
Grass pollen	46 %	63 %
Cat	37 %	59 %
Dog	18 %	48 %
Any non fungal allergen	70%	74%

Hospital admission and mould allergy

<u>Allergen</u>	<u>Asthma, no admission (n=82)</u>	<u>Asthma, 2+ admissions (n=46)</u>
<i>Aspergillus</i>	7 %	37 %
<i>Alternaria</i>	5 %	26 %
<i>Cladosporium</i>	1 %	41 %
<i>Penicillium</i>	2 %	30 %
<i>Candida</i>	10 %	33 %
Any fungal allergen	16%	76%

Fungal exposure in asthmatics is related to:

- Life-threatening asthmatic attacks (ie thunderstorm asthma)
- Severe asthma and hospital admission
- Increased wheezing and symptoms
- Loss of medication control
- Allergic bronchopulmonary mycosis
- Eosinophilic fungal rhinosinusitis

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)

Is

Allergic bronchopulmonary aspergillosis
(ABPA)

the same as

Severe asthma and fungal sensitisation
(SAFS)?

Comparison of ABPA and SAFS serology

ABPA results

normal range

date 1

date 2

Patient

1

Total IgE	KIU/l	(0.1-100.0)	1900.0	3000.0
aspergillus.f	KUa/l	(0-0.4)	41.6	49.2

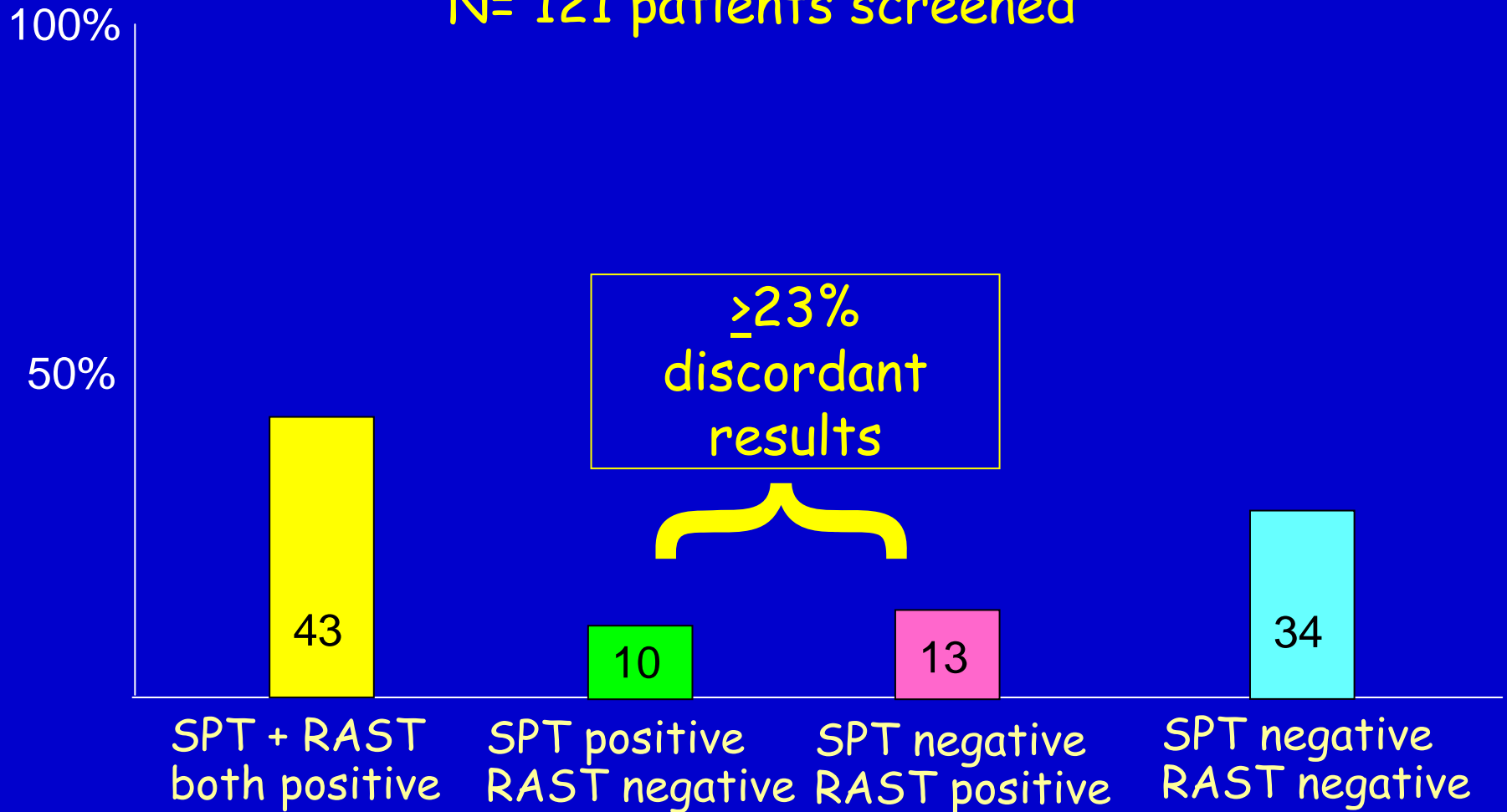
SAFS results

2

Total IgE	KIU/l	(0.1-100.0)	200.0	260.0
aspergillus.f	KUa/l	(0-0.4)	4.5	5.2

Fungal sensitisation in severe asthma - skin prick test or RAST for diagnosis?

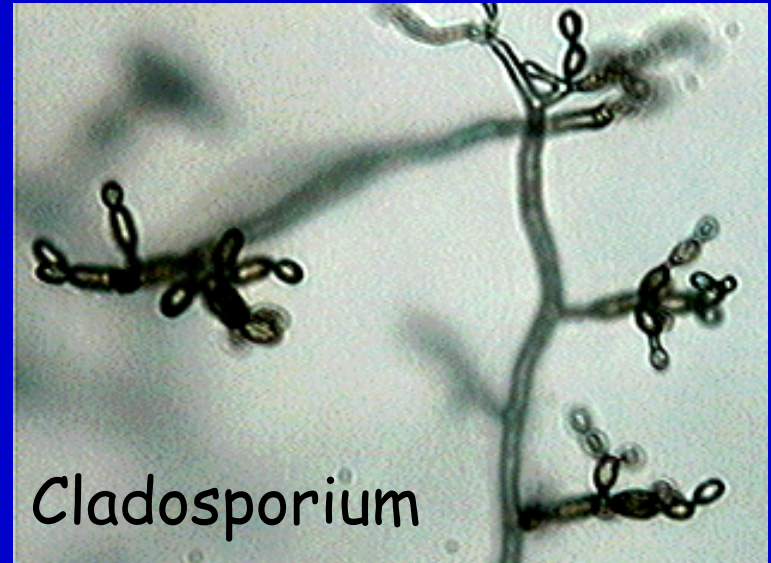
N= 121 patients screened



Other important airborne fungi



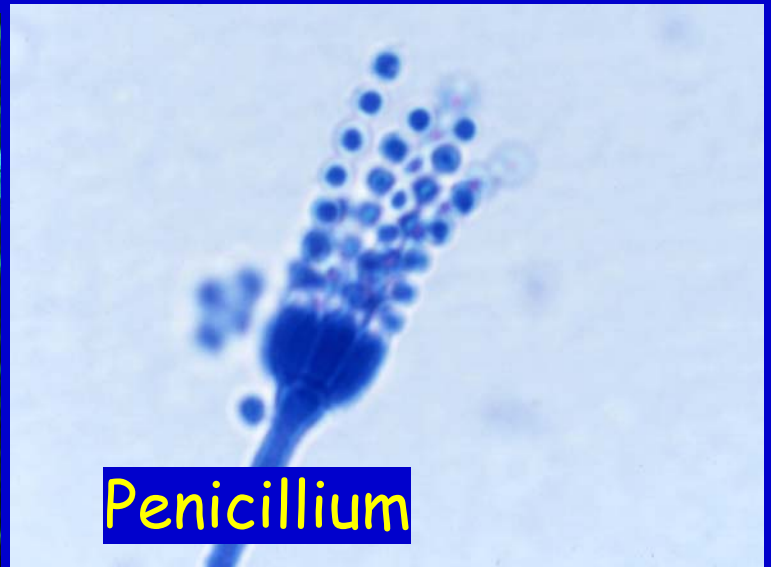
Alternaria



Cladosporium

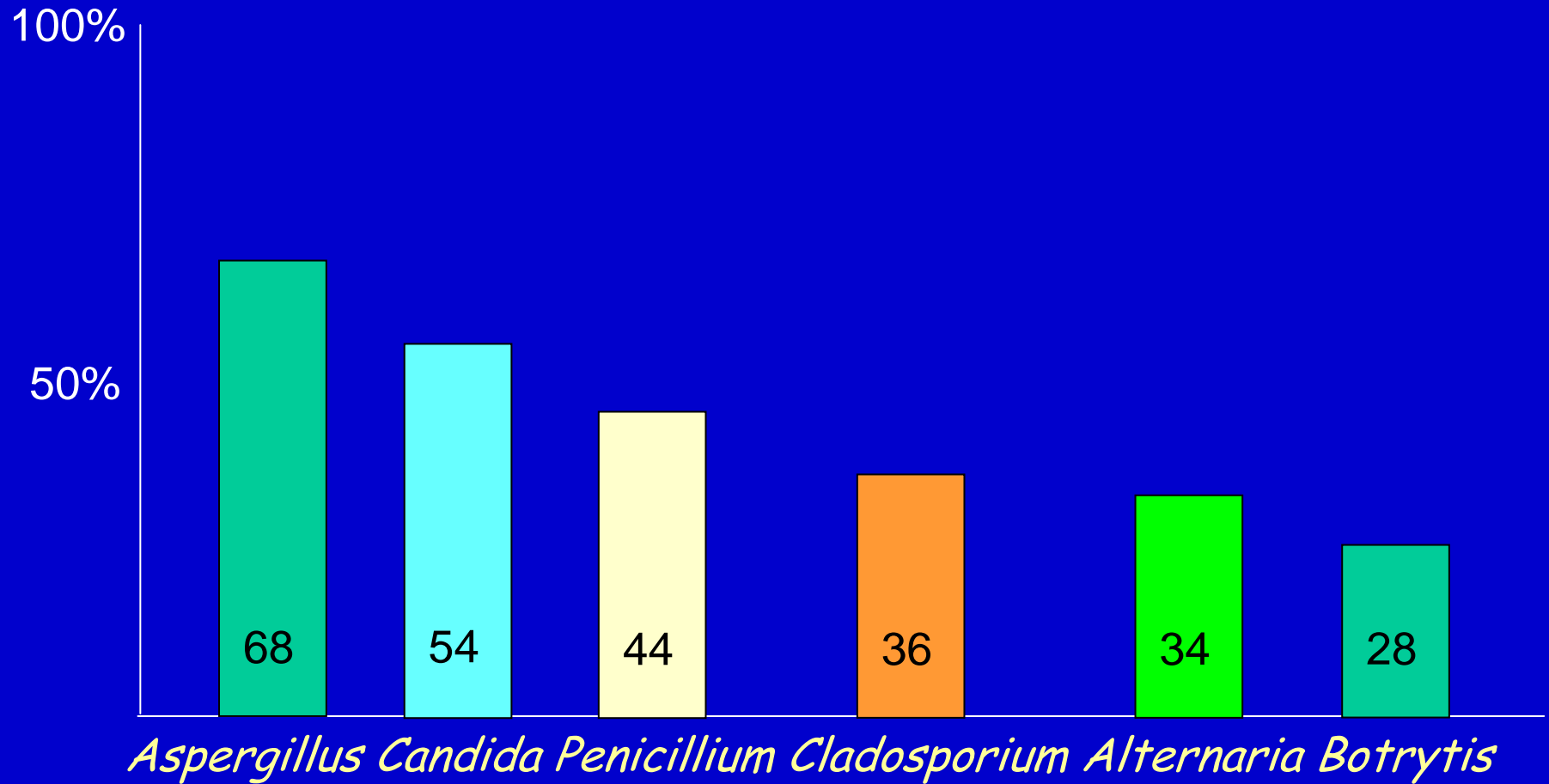


Rhizopus

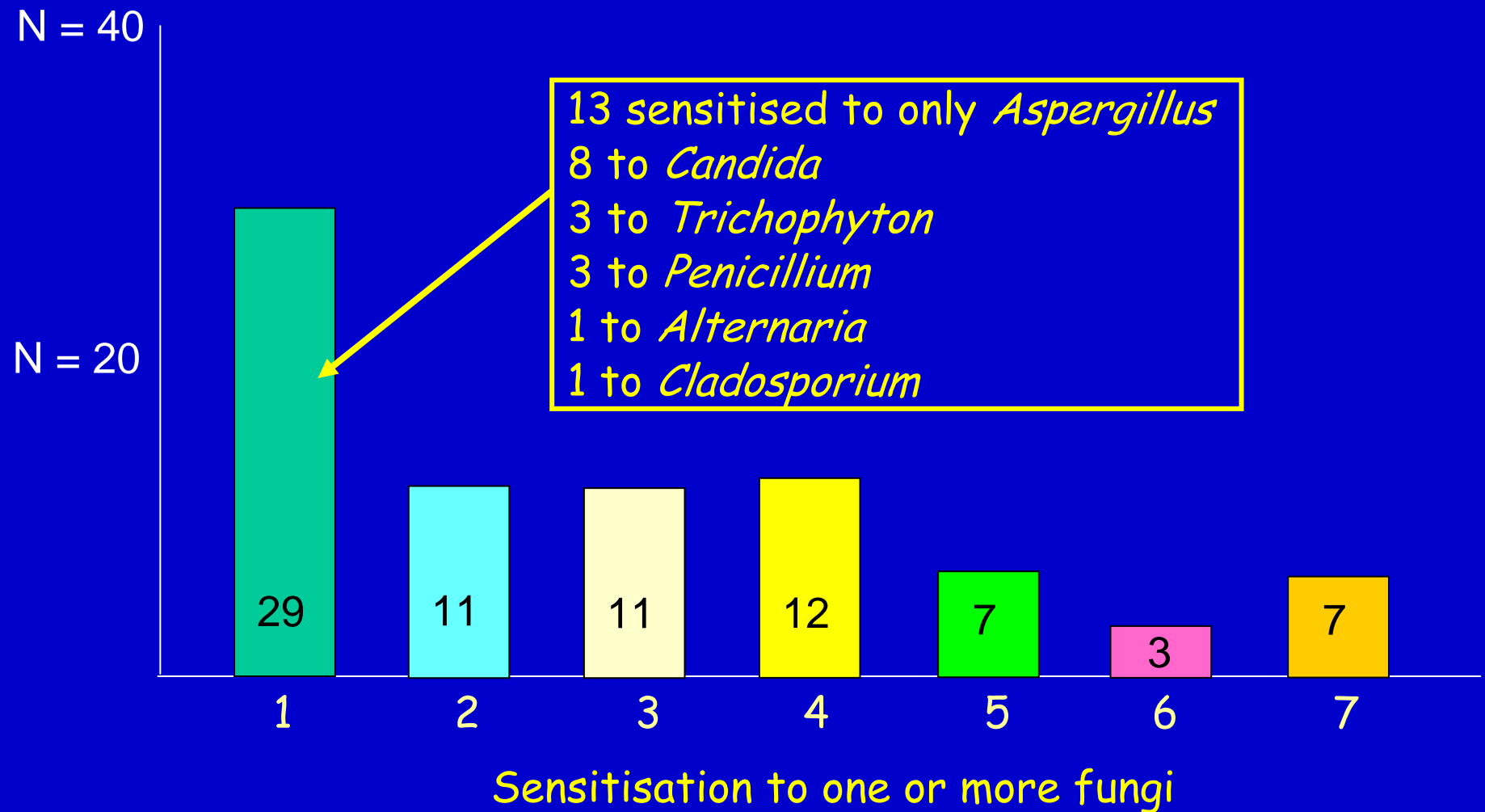


Penicillium

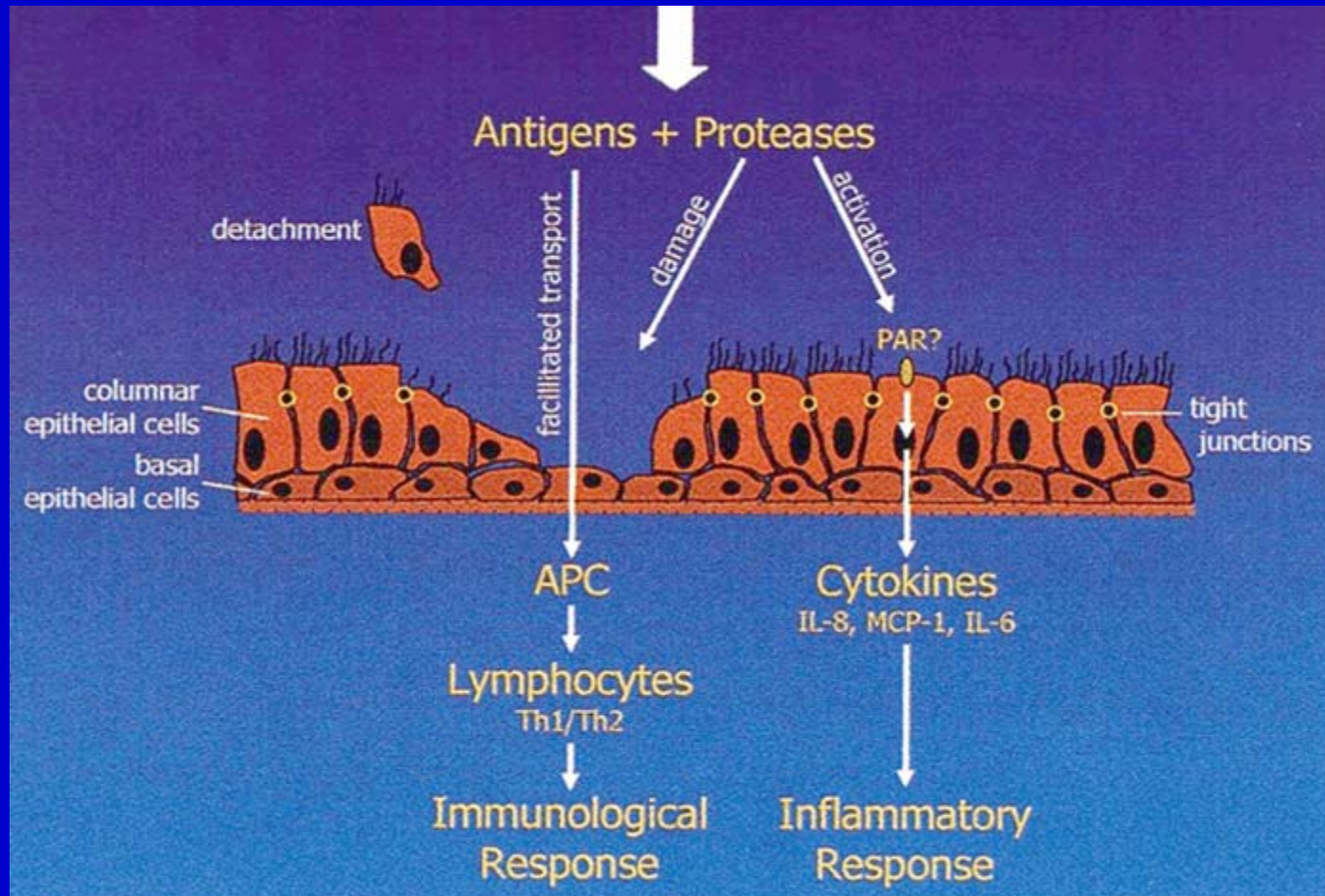
Fungal sensitisation in severe asthma - skin prick test or RAST



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



Effect of *A. fumigatus* proteases on bronchial epithelium - H. Kauffmann



Colonisation in 'normal' lungs

Table I. Patients and pulmonary fungal carriage.

Study group	Patients (n = 74)	Fungal growth (n = 46)	No fungal growth (n = 28)
Autopsy patients	18	11 (61.1%)	7 (38.9%)
Surgical patients	56	35 (62.5%)	21 (37.5%)

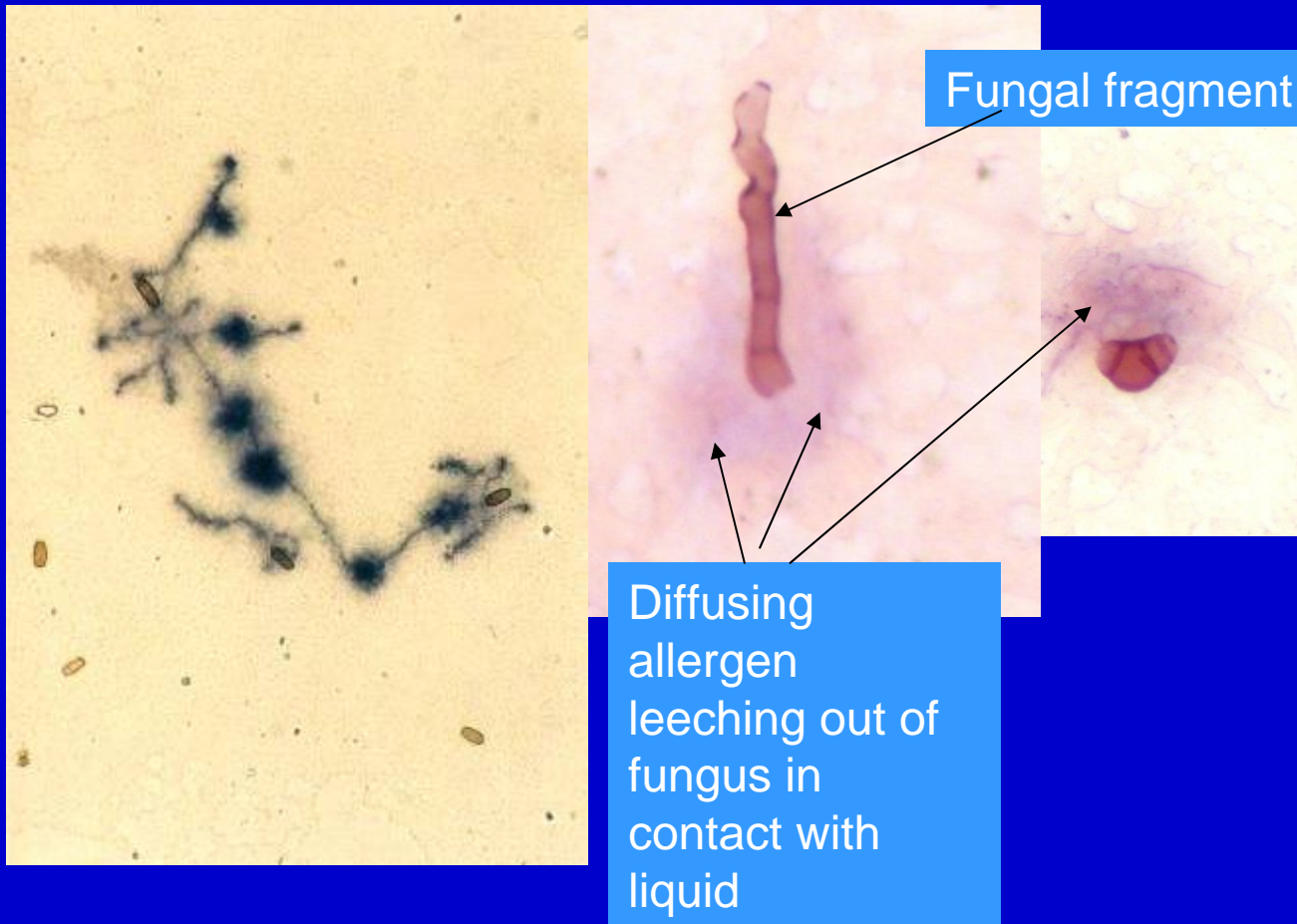
22 of 30 (73%) grew a fungus
in both lung samples taken

10/30 (33%) grew >1 species

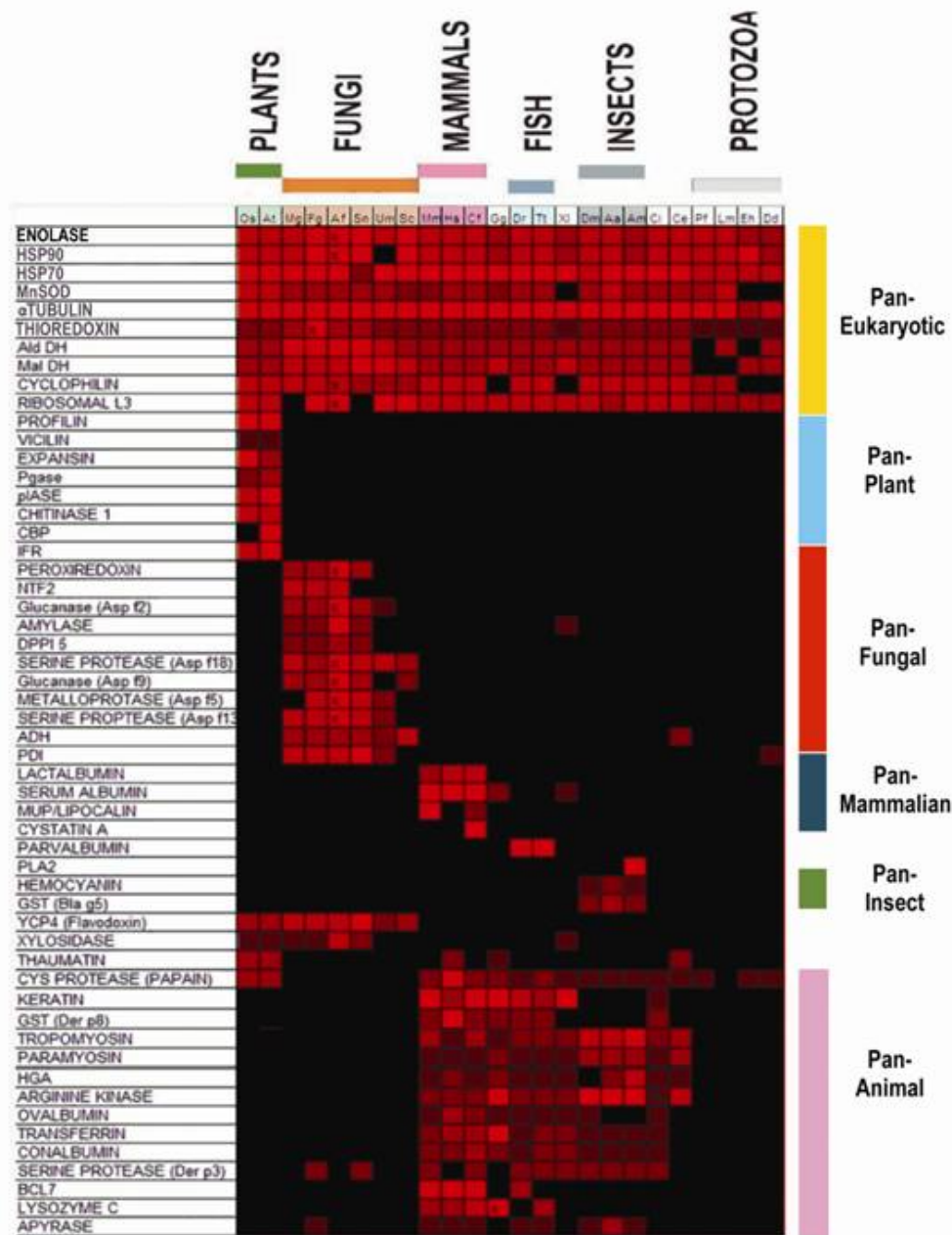
Table II. Presence of fungi detected.

Species	No. of patients with fungal colonization	
	Autopsy patients (n = 7)	Surgery patients (n = 23)
<i>A. fumigatus</i>	6	17
<i>A. flavus</i>	2	7
<i>A. niger</i>	1	3
<i>A. terreus</i>	1	1
<i>A. glaucus</i>	0	1
<i>Mucor</i> spp.	2	7
<i>Penicillium</i> spp.	2	5
<i>Candida</i> spp.	1	0

Airborne fungal fragments



Genomic analysis of allergens



Severe asthma and fungal sensitisation (SAFS)

Does antifungal therapy work?

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

	<u>Itra</u>	<u>vs</u>	<u>en Itra</u>
<u>Phase 1</u>			
Overall response	13/28 (46%)		5/27 (19%) p = 0.04
<u>Phase 2</u>			
No prior response (n=33)	4/13 (31%)		8/20 (40%) NS

60%
response
rate

Number needed to treat = 3.58

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

Inclusion criteria

- Severe asthma [BTS 4 or 5] (ie high dose inhaled steroids, continuous oral steroids for >6 mo, or 4 courses of high dose oral/IV steroids in last 12 months, or 6 courses in last 24 mo).
- +
 - Fungal sensitisation (RAST or skin test +ve) to *Aspergillus*, *Cladosporium*, *Alternaria*, *Penicillium*, *Candida*, *Trichophyton* and/or *Botrytis*

Exclusion criteria

- Not ABPA (IgE <1000IU/mL)
- Positive *Aspergillus* precipitins

Proof of concept RCT of antifungal Rx in SAFS - study plan

Study plan

Randomised to itraconazole capsules (200mg BID) or placebo for 8 months (concealed by over-encapsulating)

FU at 4 months post treatment

108 patients planned - 58 enrolled

Baseline demographics - FAST study

	Mean (range) or % (no.)	
	Active (n=29)	Placebo (n=29)
Gender (Male)	48% (14)	48% (14)
Age	49.2 (18, 79)	51.7 (19, 76)
Severity of asthma (BTS) (>4)	3% (1)	11% (3)
Baseline total serum IgE (IU/L)	212 (24,820)	245 (36,990)
Baseline eosinophilia (>0.4x 10 ⁹)/L	24% (7)	43% (12)
No. of hospitalisations last 12 months ⁴ (>1)	39%	17%

Asthma Quality of Life Questionnaire (AQLQ)

Assesses physical symptoms in asthmatics

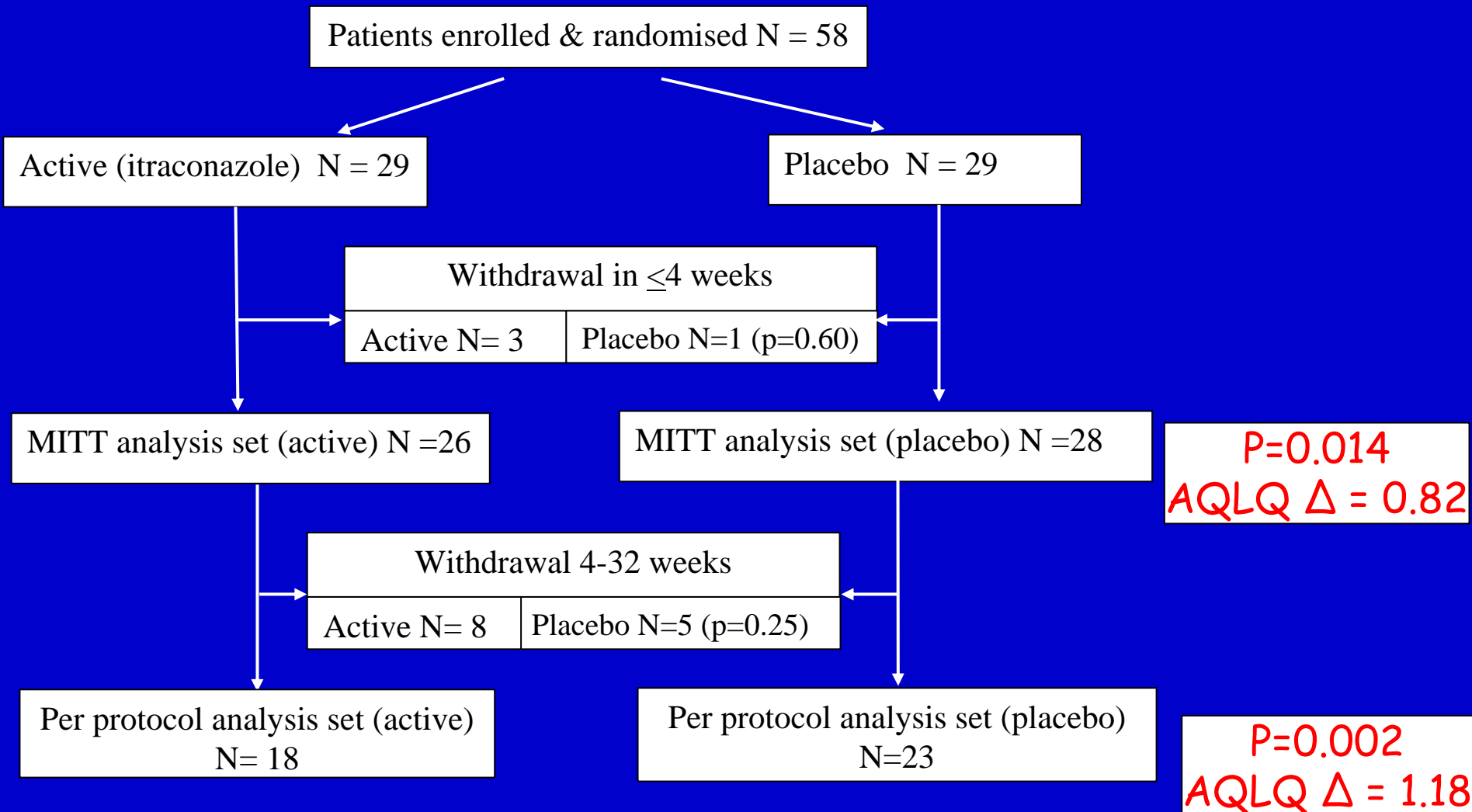
Well validated and used extensively in asthma studies

Score 1-7, with:

1 dreadful health and breathing

7 tip top shape, no problems

Proof of concept RCT of antifungal Rx in SAFS - key results

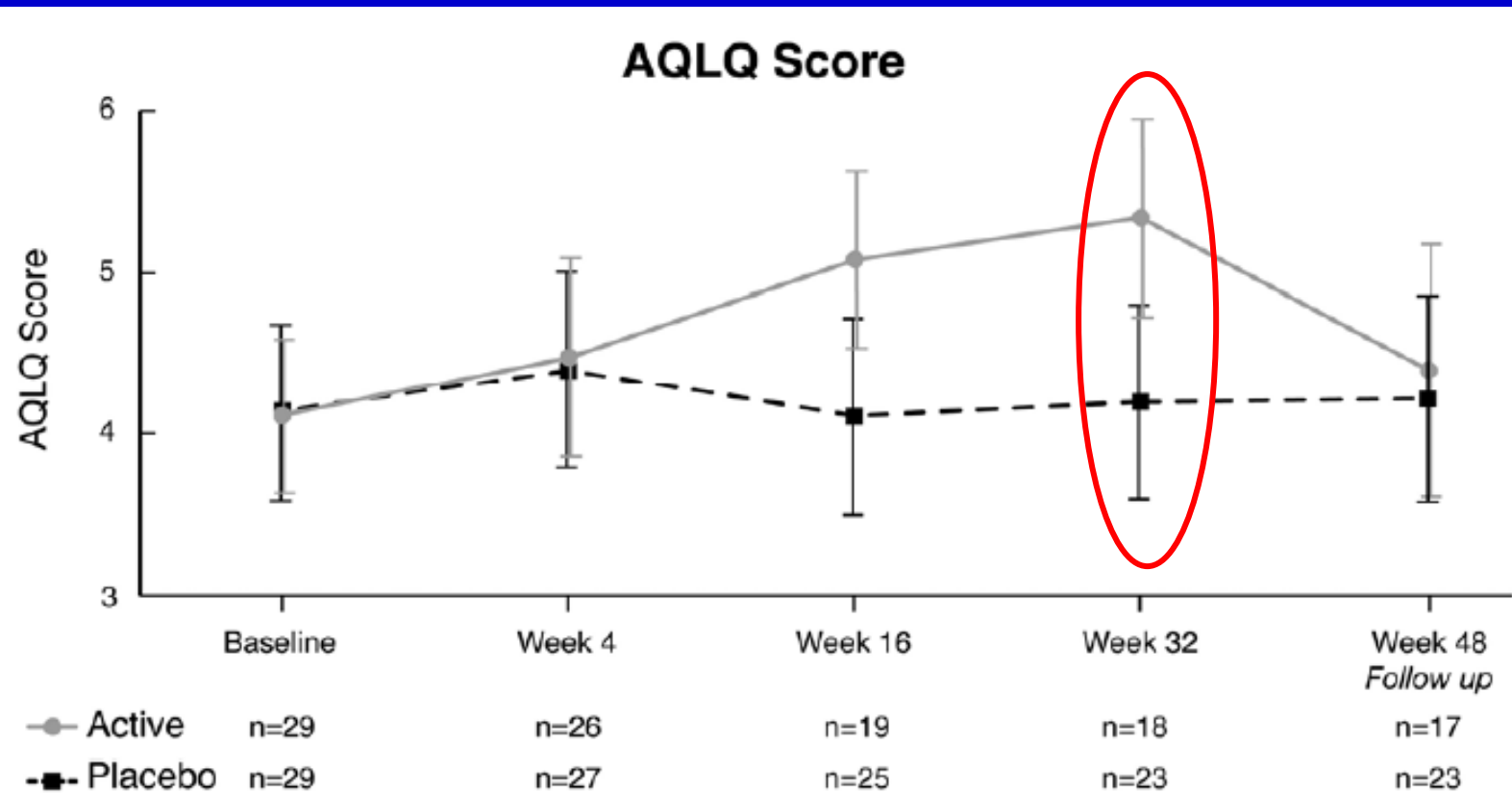


Proof of concept RCT of antifungal Rx in SAFS - outcomes at 32 weeks MITT

	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

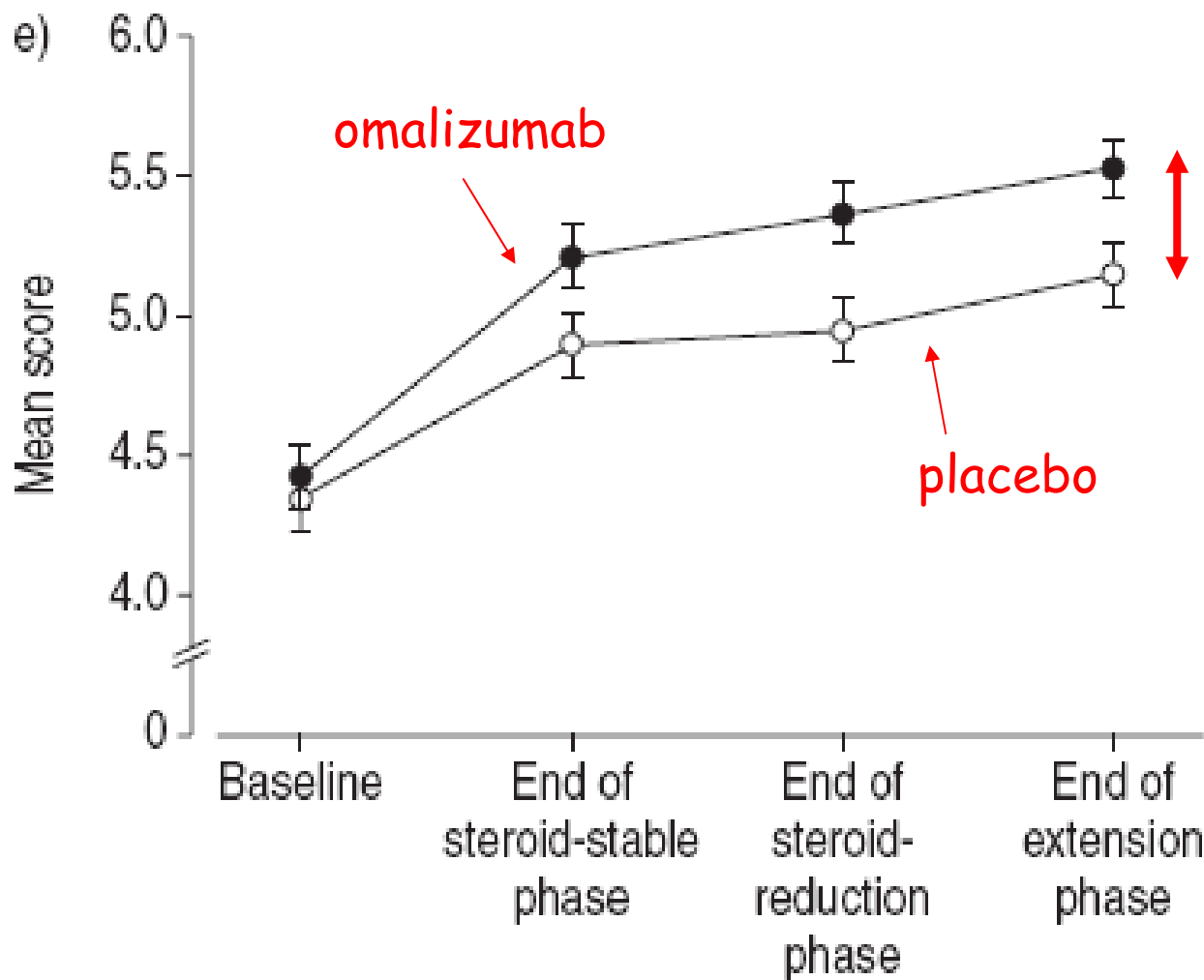
Number needed to treat = 3.22

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



P= 0.014

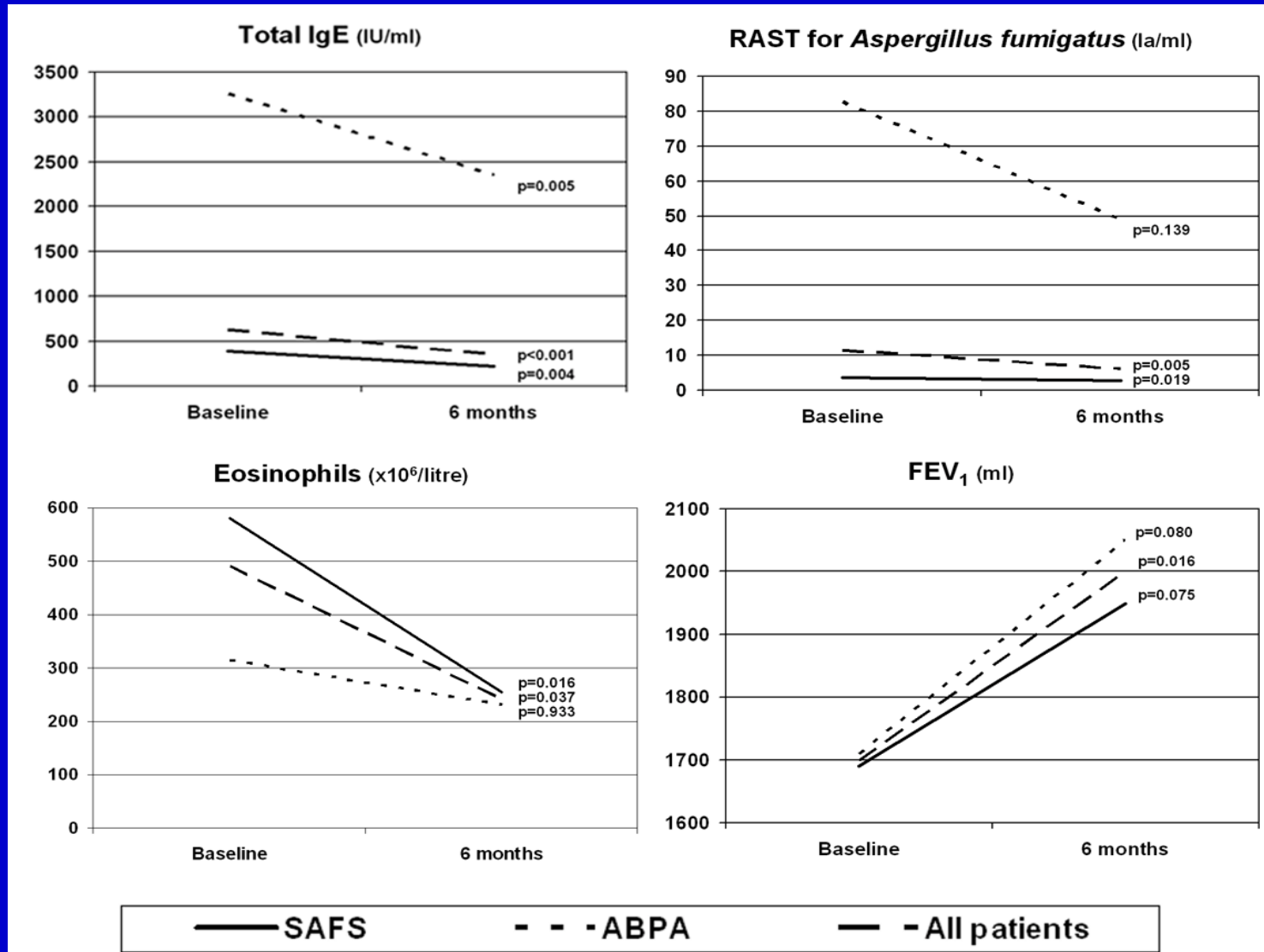
RCT of anti-IgE (omalizumab) v. placebo, moderate and severe asthma



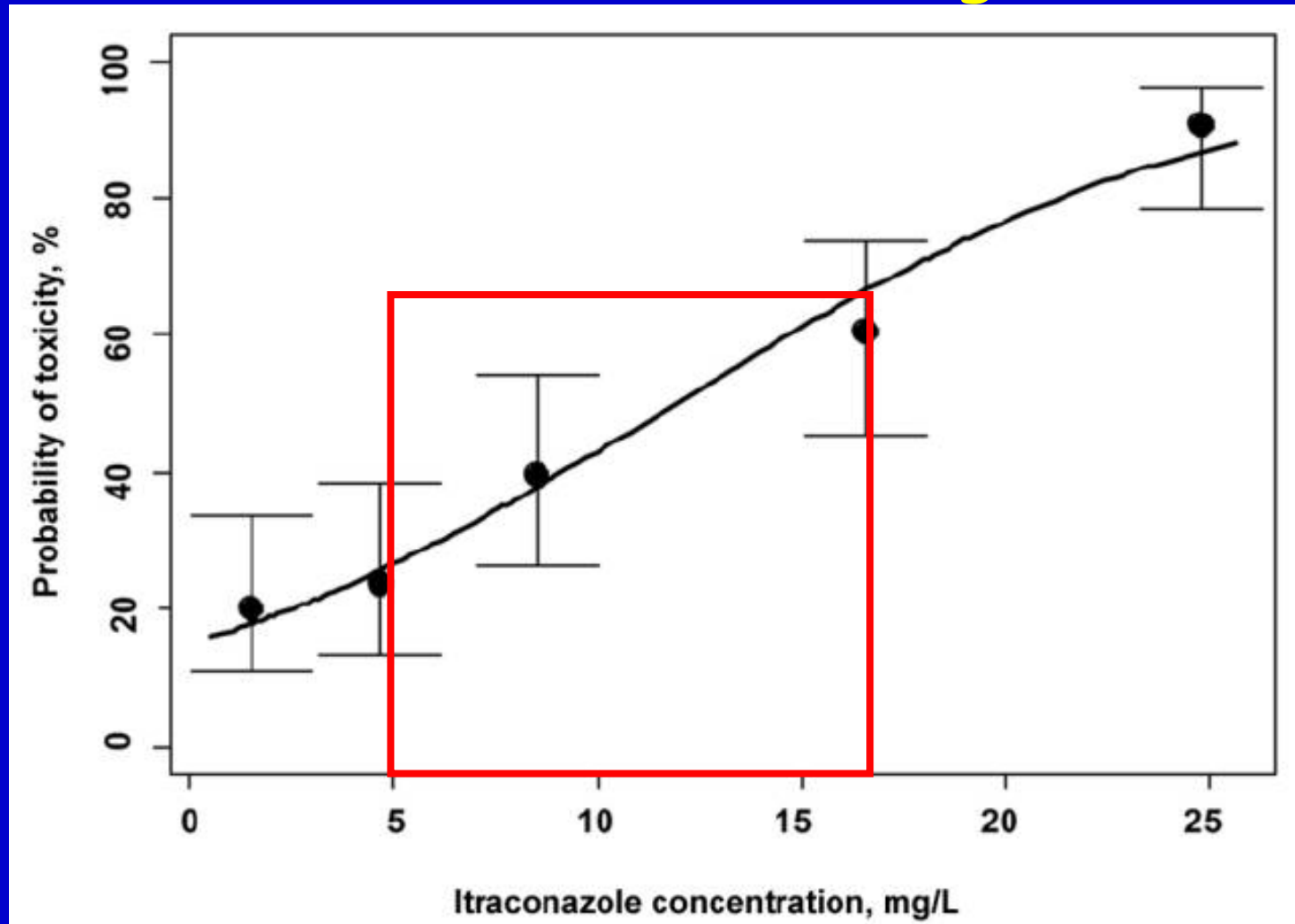
Improvement in
AQLQ
 $\Delta = \sim 0.4$

Retrospective comparison of antifungal treatment of SAFS with ABPA

22 patients with SAFS were compared with 11 with ABPA



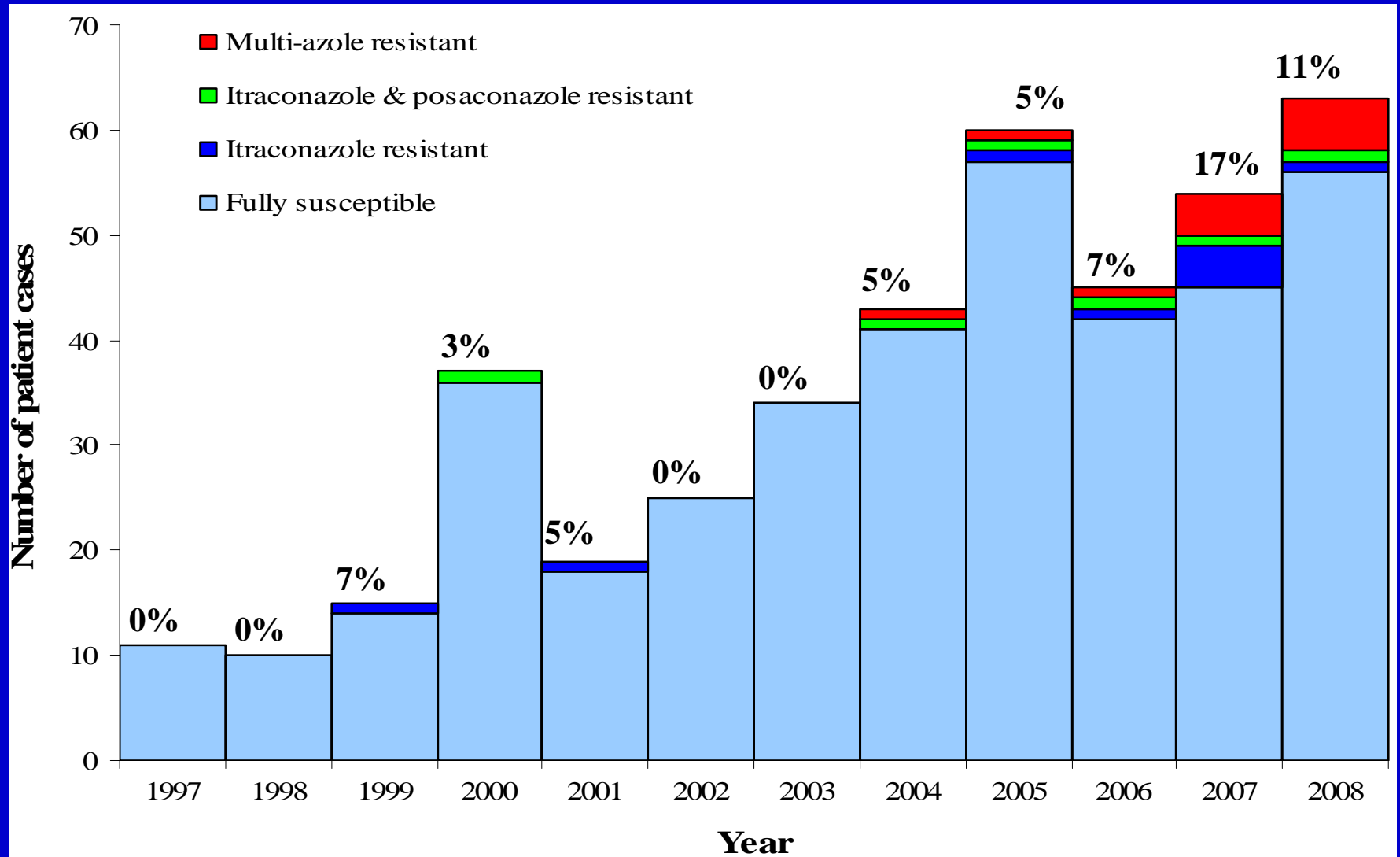
Optimising itraconazole levels - aim between 5 and 17 mg/L



Itraconazole inhaled steroid interaction in 50% of patients, with complete suppression of cortisol

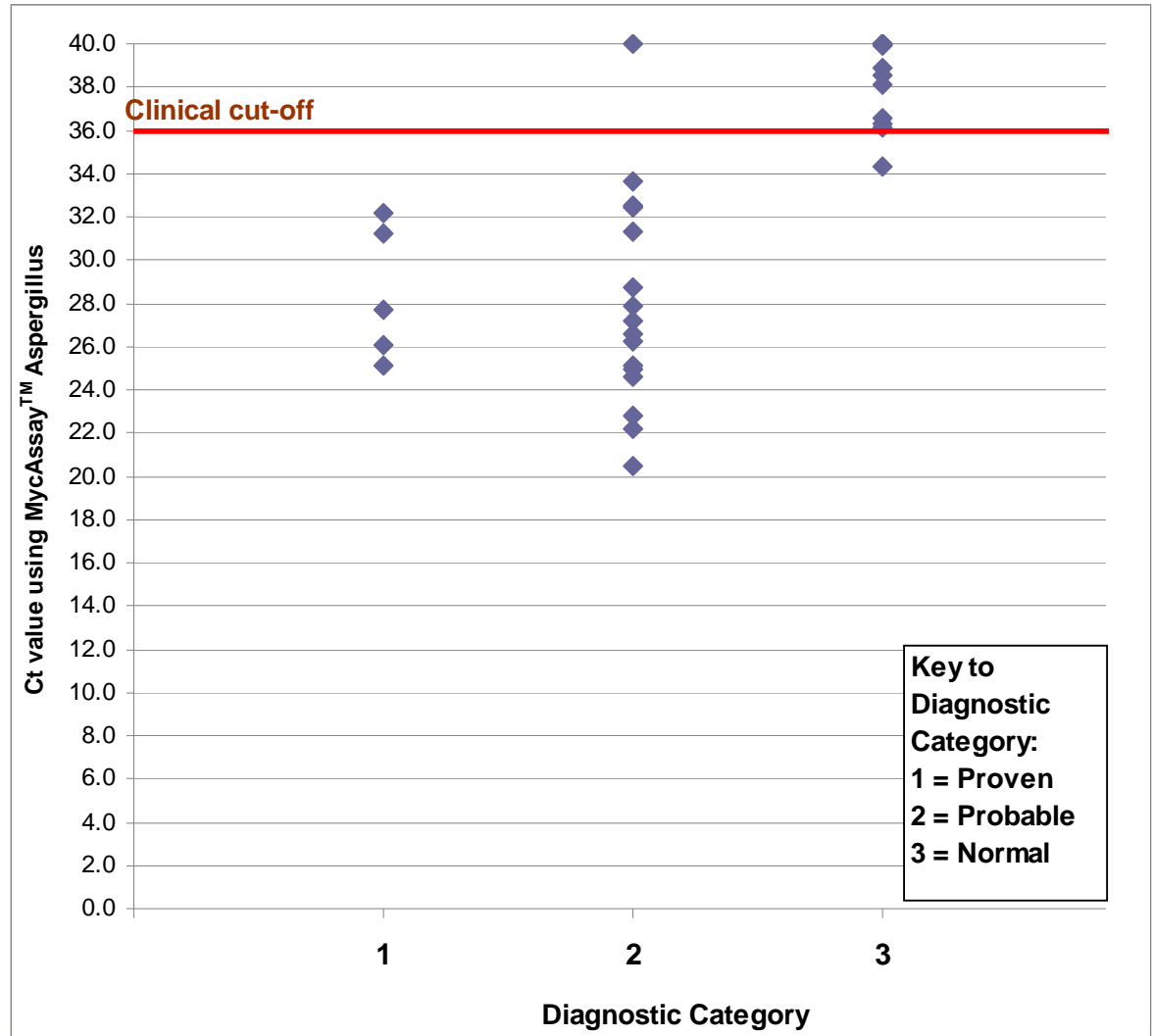
AQLQ improvements identical in those with this interaction and those without

Azole resistance in Manchester



MycAssay™: Aspergillus

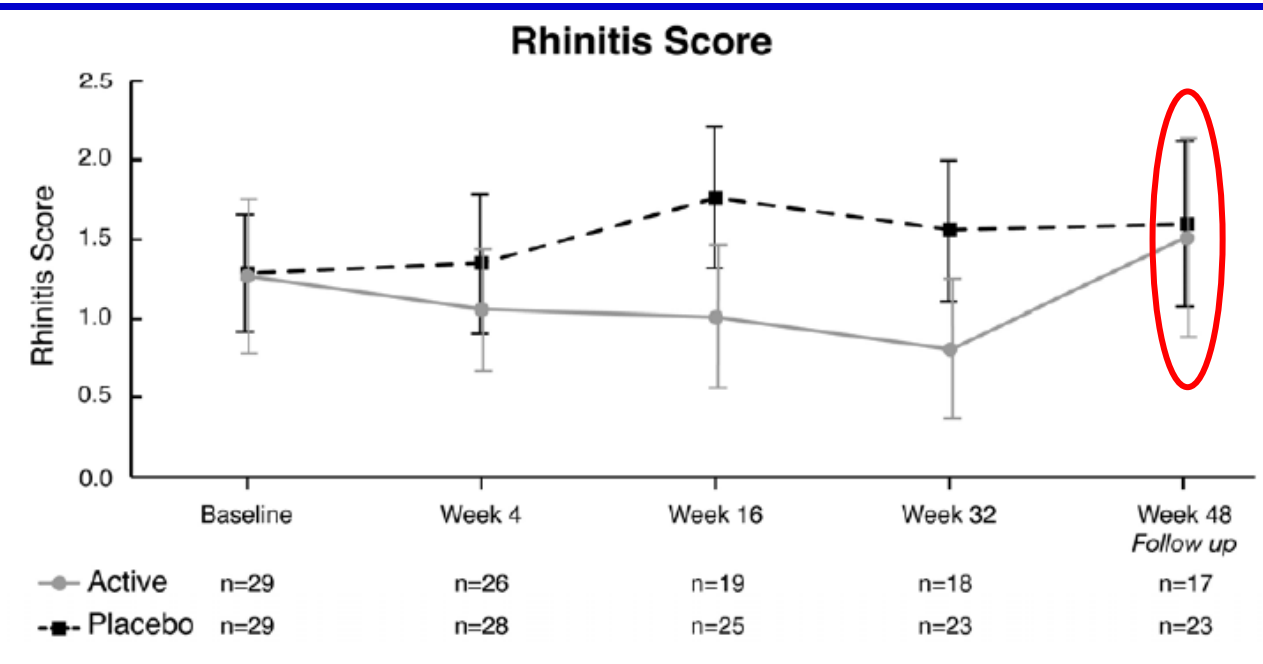
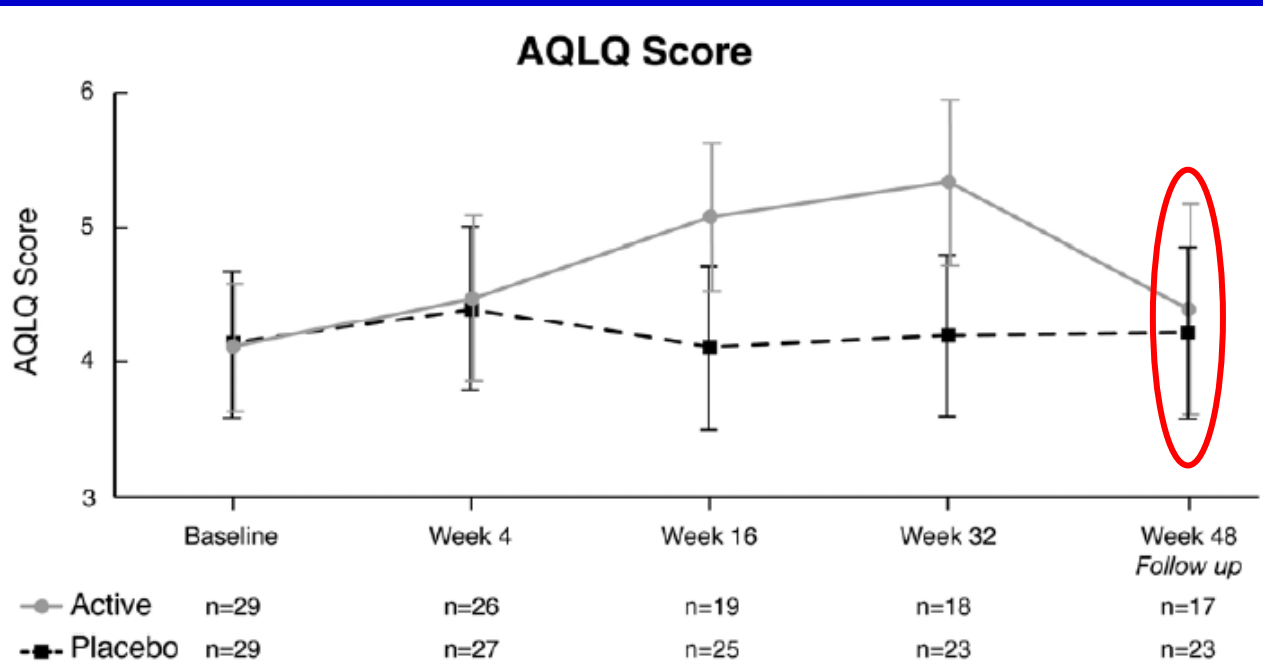
BAL samples
 Invasive aspergillosis and normal volunteers



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

Relapse after discontinuation of antifungal Rx in SAFS



Severe asthma and fungal sensitisation (SAFS)

Does antifungal therapy work?

Yes, but why?



The Aspergillus Website



www.aspergillus.org.uk



The Fungal Research Trust

