The role of fungi in respiratory allergies

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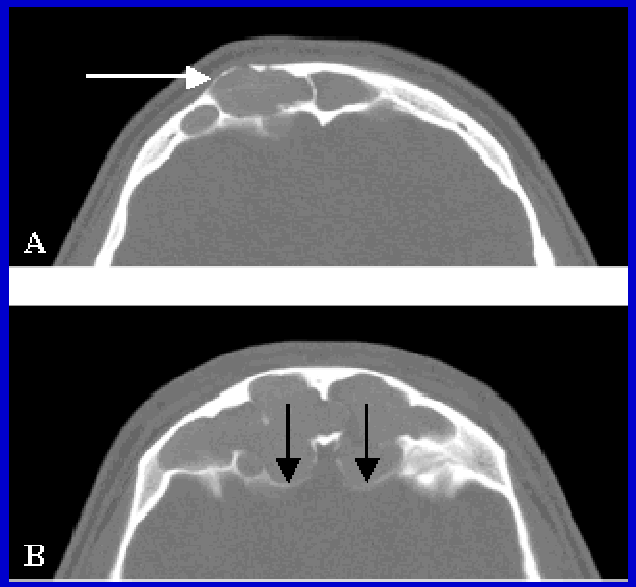
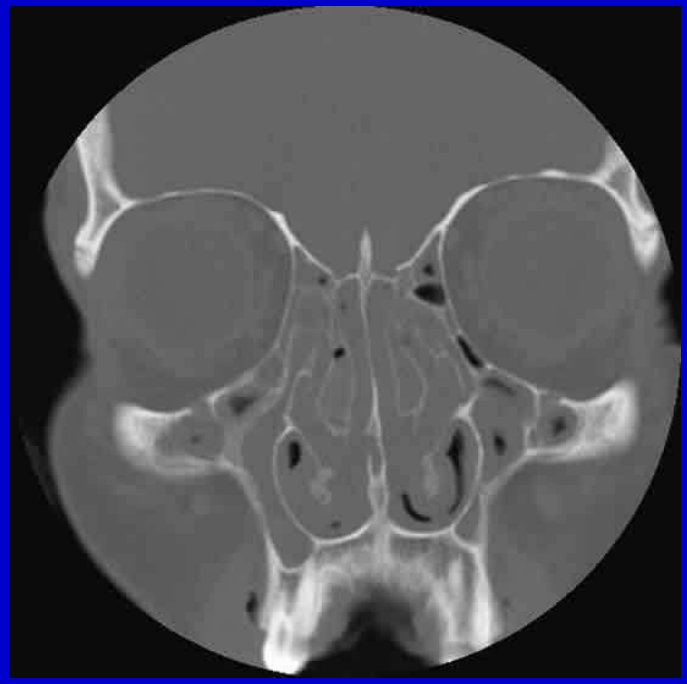
Allergic Aspergillus sinusitis





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.

	n	%
Fungal ball	33	53,2
Allergic fungal rhinosinusitis	24	38,7
Indolent fungal rhinosinusitis	3	4,8
Saprophyte infection	2	3,2
Invasive fungal rhinosinusitis	0	-
Total	62	100.0

Dall'Igna Rev Bras Otorhinolaringol 2005;71:712

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:

	Global	Pharma markets
10%	90M	12M
6%	54M	7.2M
2.5%	23M	3M
1%	9M	1.2M

Randomised studies of antifungals and rhinitis

Disease	Antifungal, duration	Benefit?	Author, year
Chronic rhinosinusitis + nasal polyps	AmpB nasal, 8 wks	No	Weschta, 2004
Chronic rhinosinusitis	AmpB nasal, 26 wks	Yes	Ponikau, 2005
Chronic rhinosinusitis	Terbinafine, 6 wks	No	Kennedy, 2005
Chronic rhinosinusitis	AmpB nasal, 12 wks	No	Ebbens, 2006
Chronic rhinosinusitis	AmpB nasal, 4wks	No	Liang, 2008
Chronic rhinosinusitis + nasal polyps	AmpB nasal, 52 wks	No	Gerlinger, 2008

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.

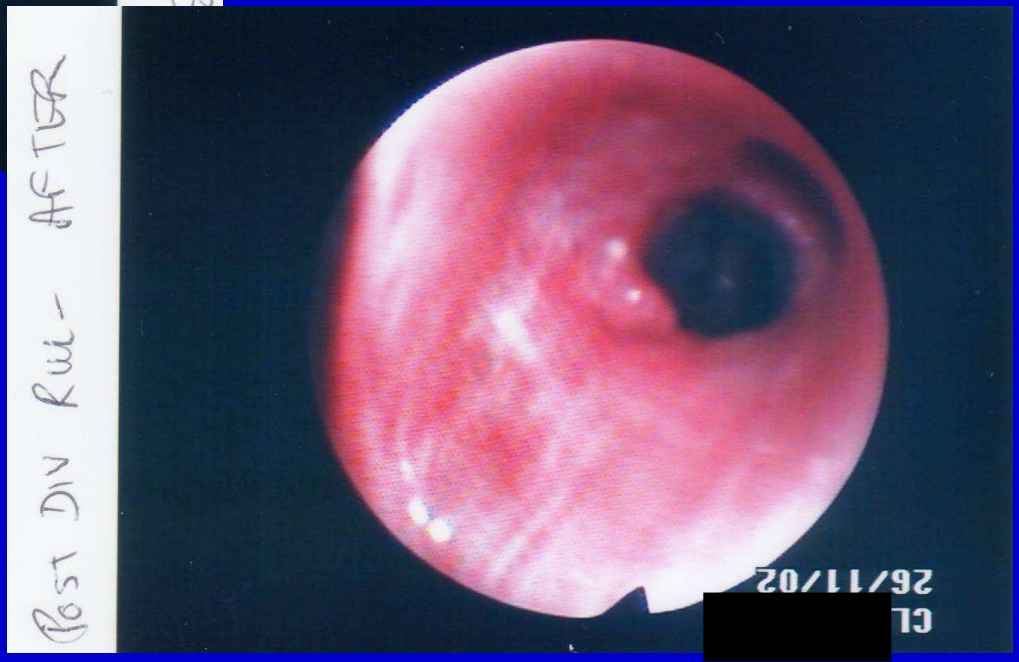
IgE=3000

RAST=52.5.

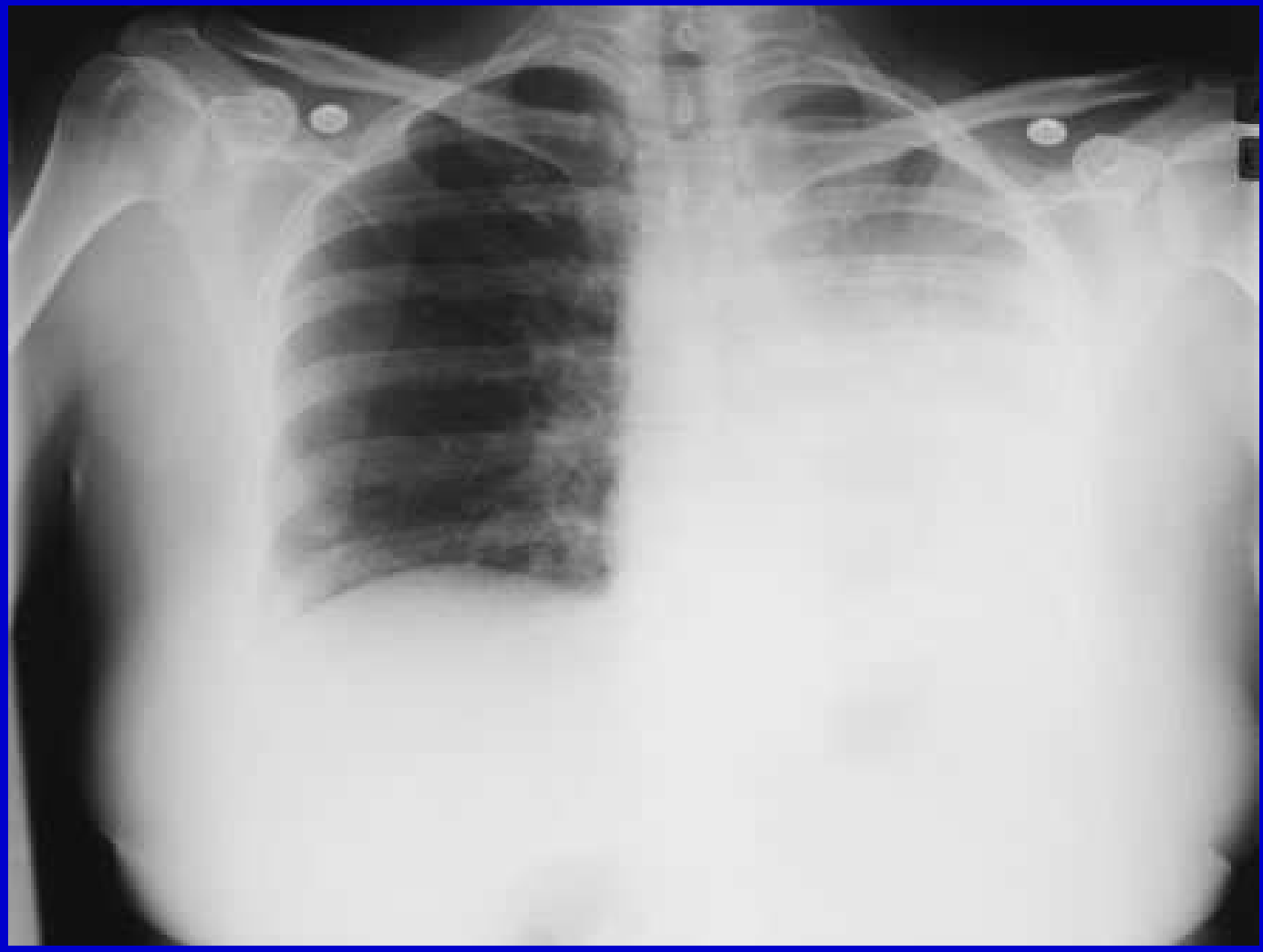
Rx Atypical Pneumonia

FEV1=3.3 (post antibiotics)

ABPA – bronchoscopy views showing mucous plugging



Mucoid impaction due to ABPA



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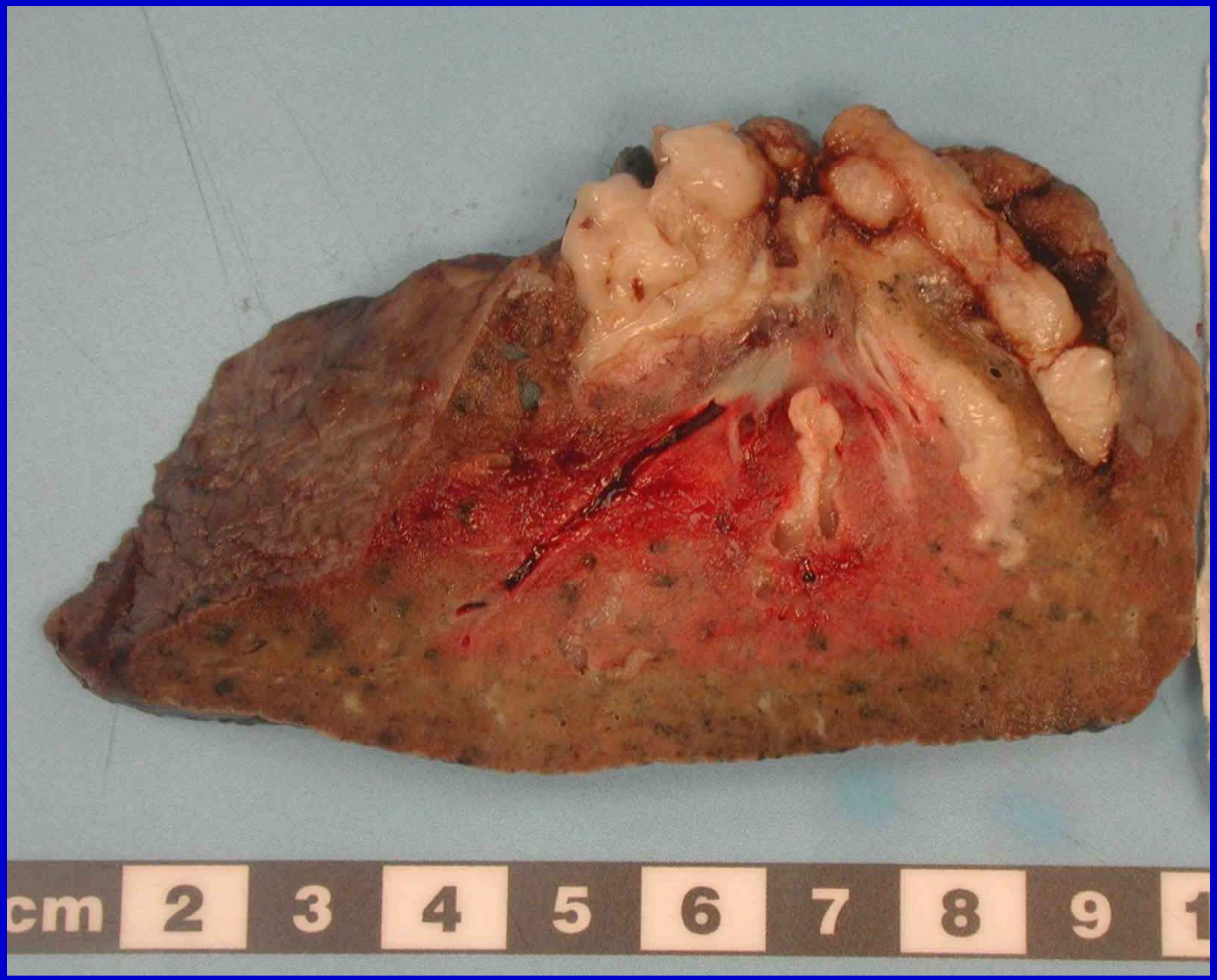
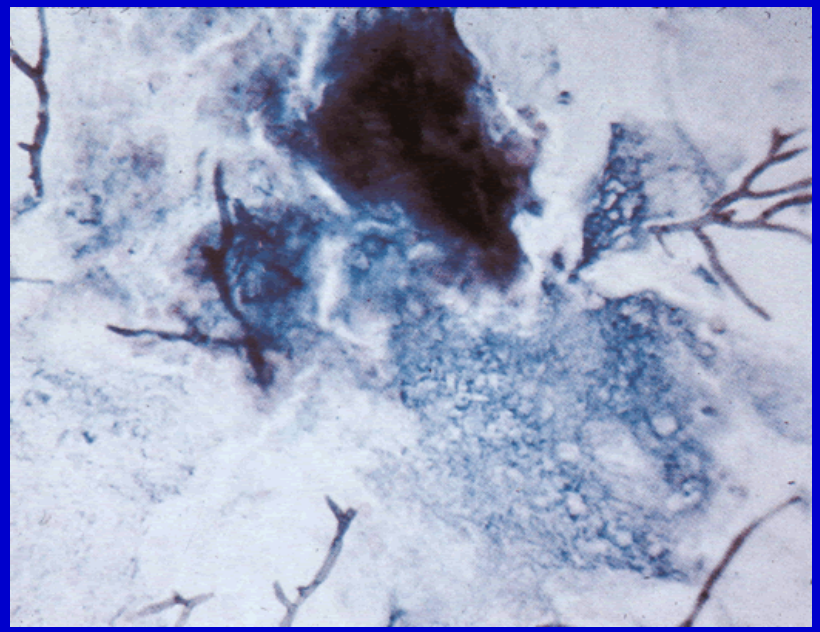
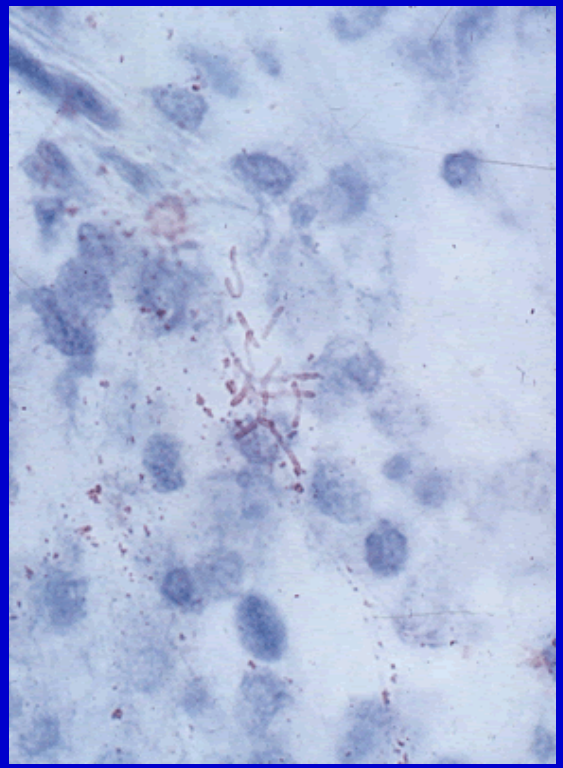


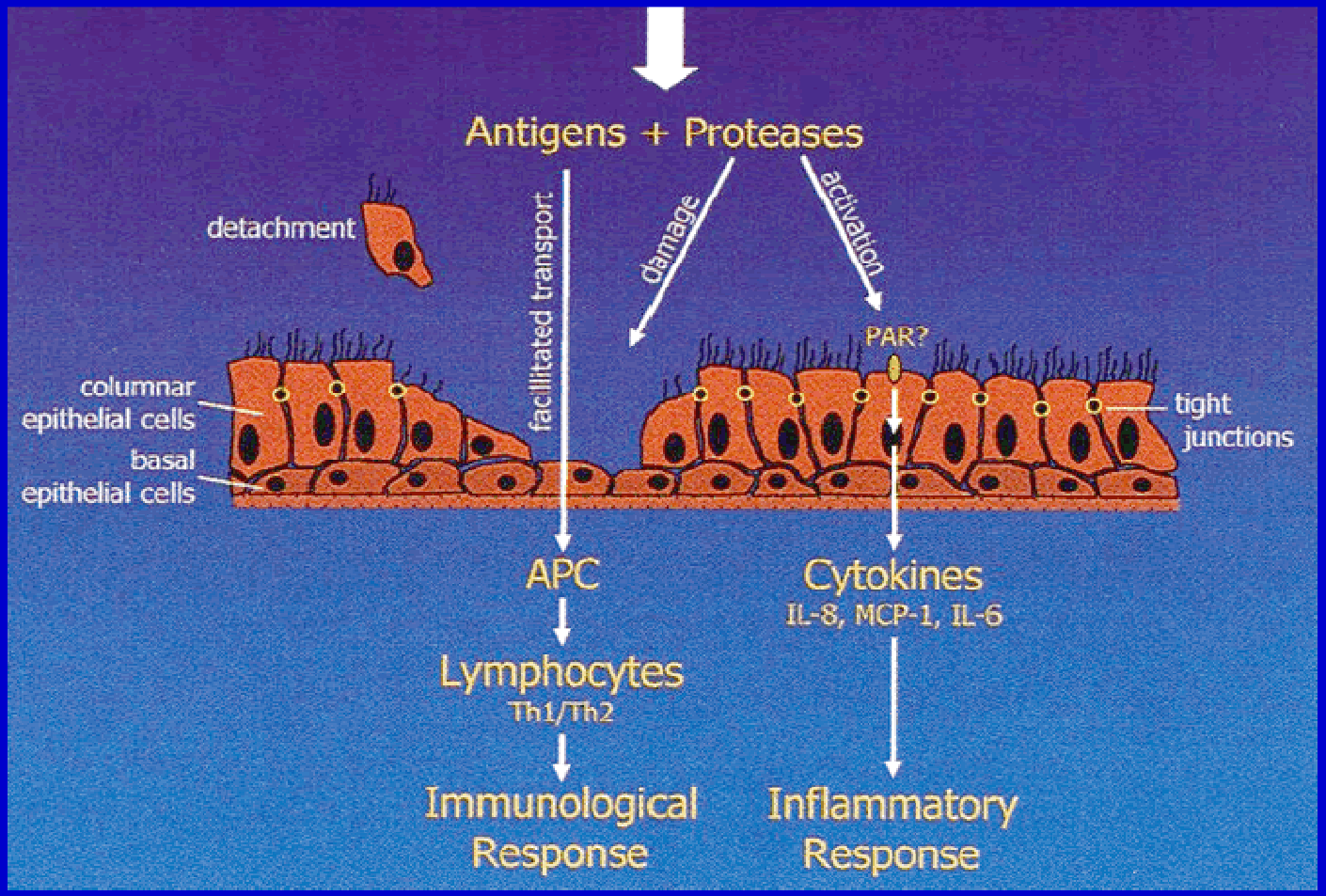
Sputum in ABPA

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.

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

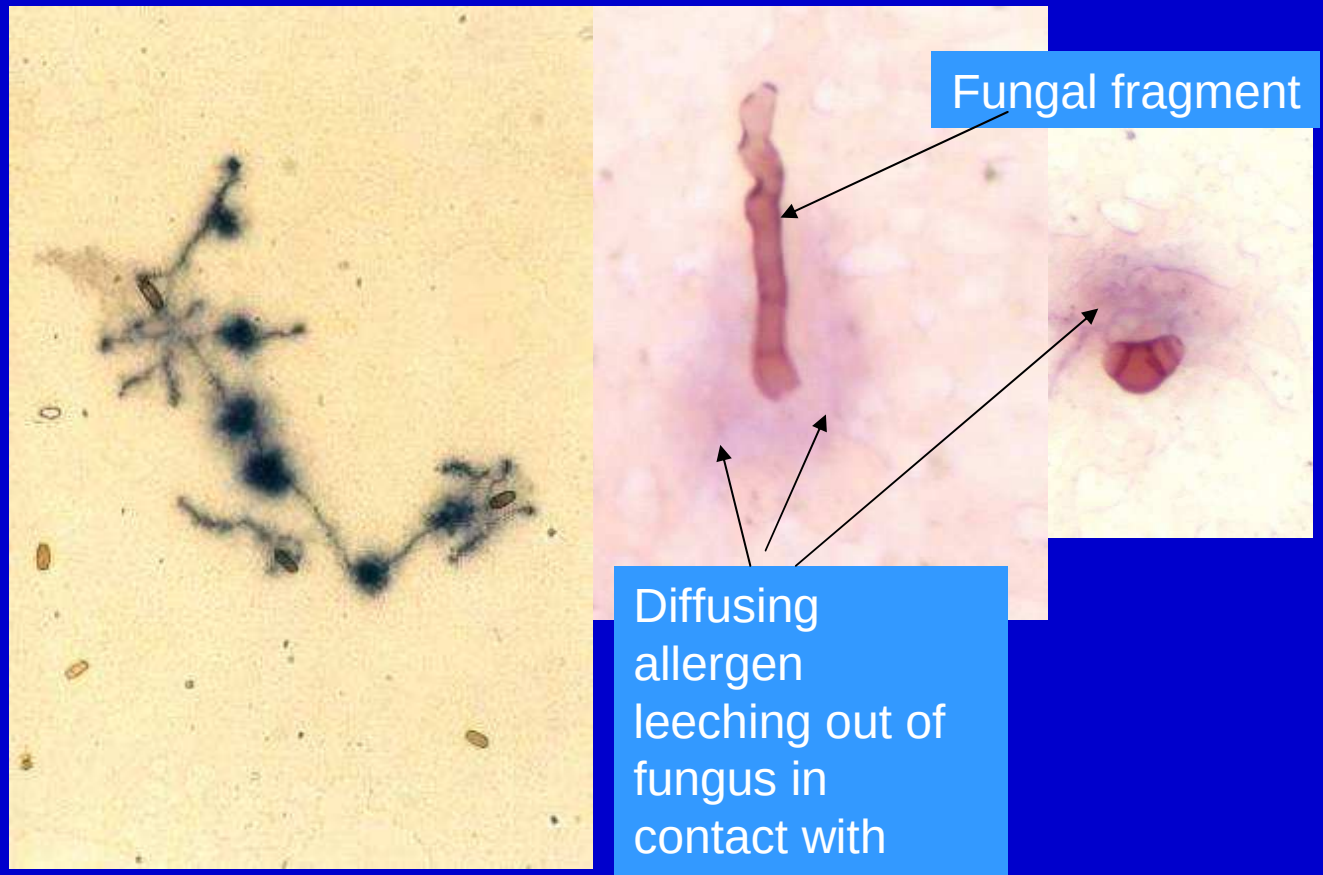
10/30 (33%) grew >1 species

Table II. Presence of fungi detected.

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

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

Airborne fungal fragments

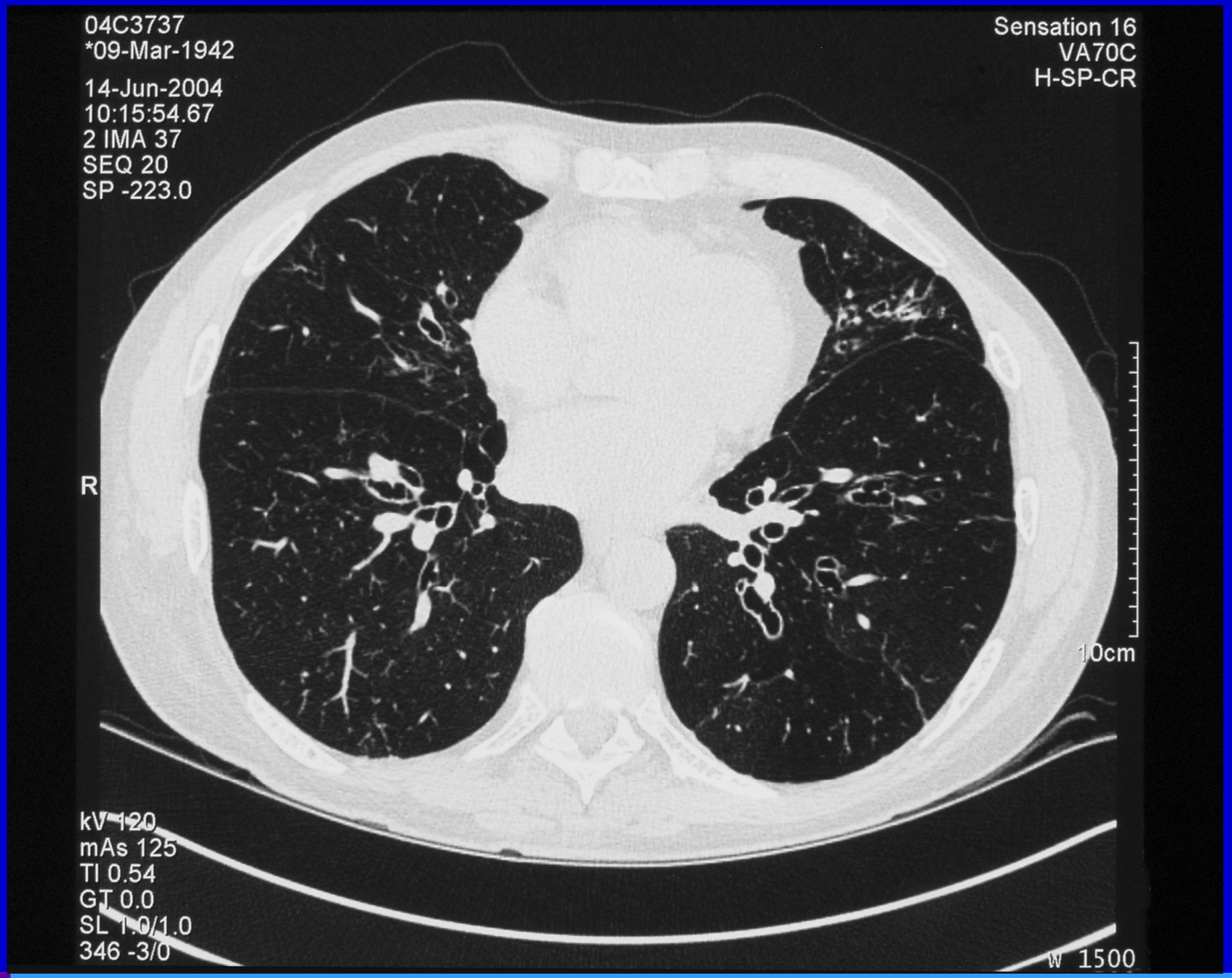


Green et al, J Allergy Clin Immunol 2005;115:1043

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

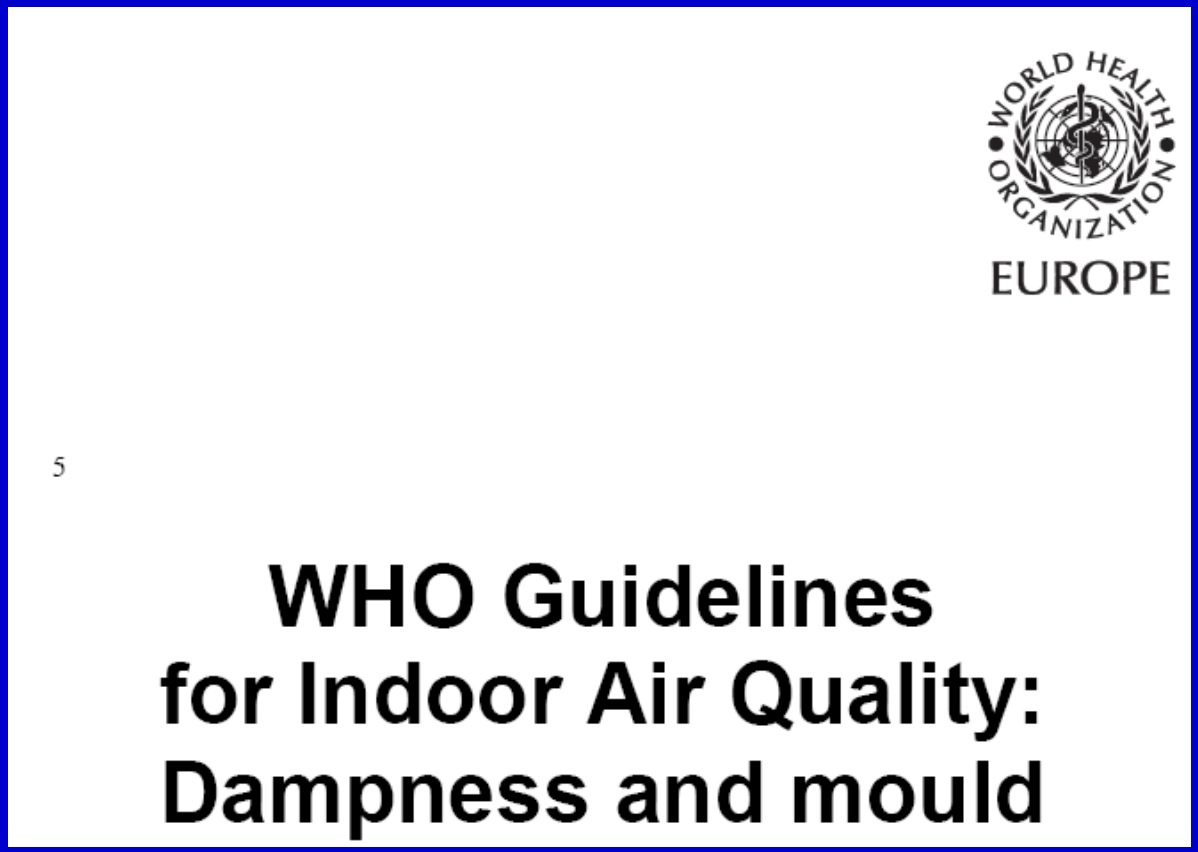
A link between airborne fungi and severe asthma?

"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



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)

O'Hollaren, N Engl J Med 1991; 324: 359; Newson, Occup Environ Med 2000; 57: 786-92.

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%

Williamson, Thorax 1997;52:229. Taskinen, Acta Paediatr 1999;88:1373. Matheson, Clin Exp All 2005;35:907

Common sources of airborne fungi – pillows?

Fungus in the bedroom

We examined pillows (n=10) for fungi:

Pillow type	No pillows	Mean cfu/g pillow	Predominant species
Synthetic	3	8.6×10^2 - 2×10^3	*A. fumigatus* *R. mucilaginosa*
Feather	3	1.8×10^2 - 1.8×10^3	*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., *Agricales*, *Stereum* sp., *Arthrinium phaeospermum*, *Pholiota* sp., *Candida parapsilosis* and *guilliermondii*.

Woodcock et al, Allergy 2006;61:140

Severe asthma

MANCHESTER 1824

Bel EH , Severe asthma. Breath magazine Dec 2006

Mean sensitization score (mm)
(Mean and 95% CI)

20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0

P= <0.0001

No Hospital Admission

Single Admission

Multiple Admissions

No Hospital Admission

Single Admission

Multiple Admissions

Mould allergens

Non-Mould allergens

MANCHESTER 1824

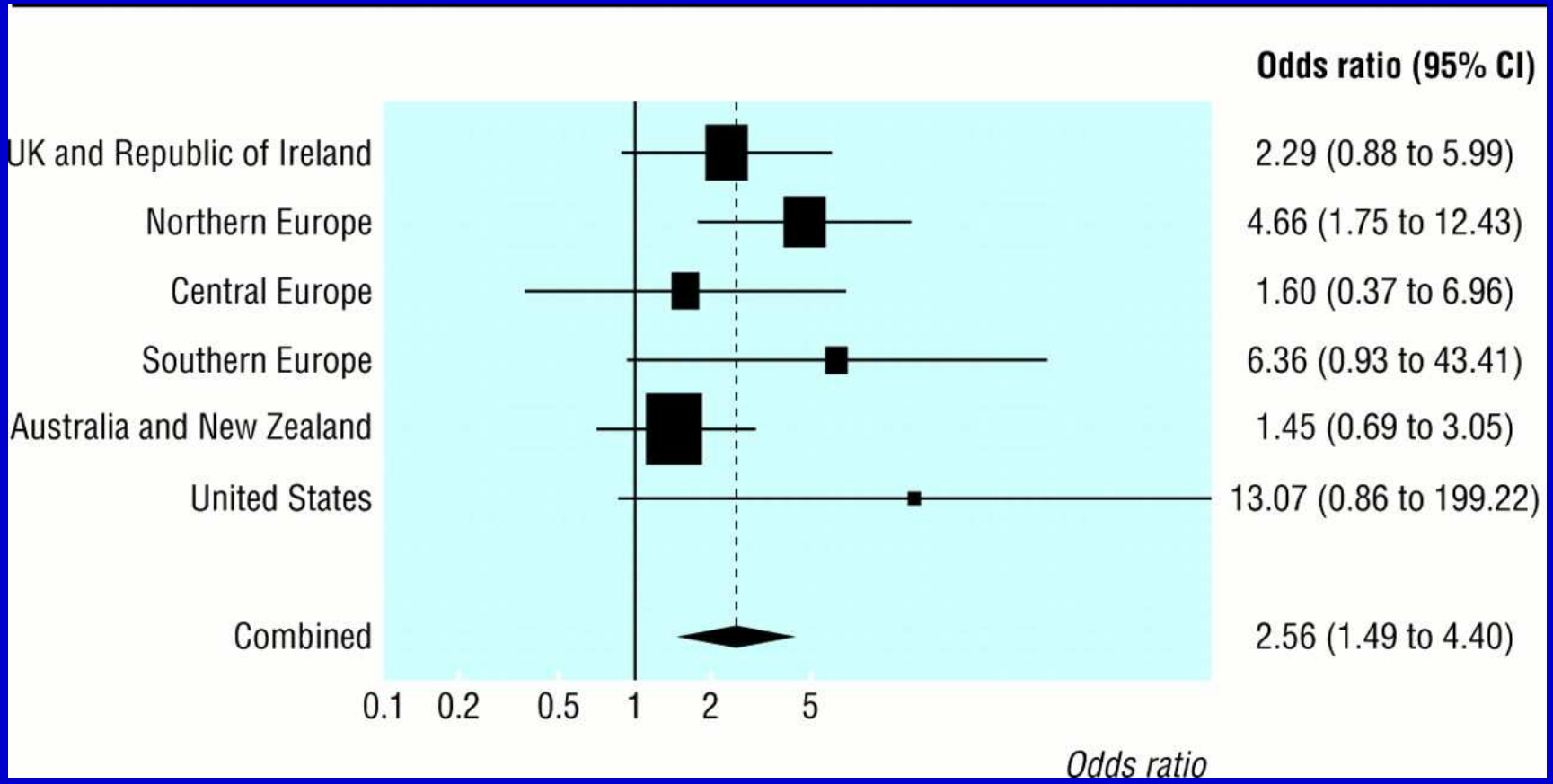
O'Driscoll et al, BMC Pulmonary Medicine 2005;5:4

Severe asthma and mould senstivity – *Alternaria* and *Cladosporium*

Mild asthma – 564 (50%)

Moderate asthma – 333 (29%)

Severe asthma – 235 (21%)



Zureik et al, Br Med J 2002;325:411

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

O'Driscoll, unpublished

Comparison of ABPA and SAFS serology

ABPA results

Patient 1

		normal range	date 1	date 2
Total IgE	KIU/l	(0.1-100.0)	1900.0	3000.0
aspergillus.f	KUa/l	(0-0.4)	41.6	49.2

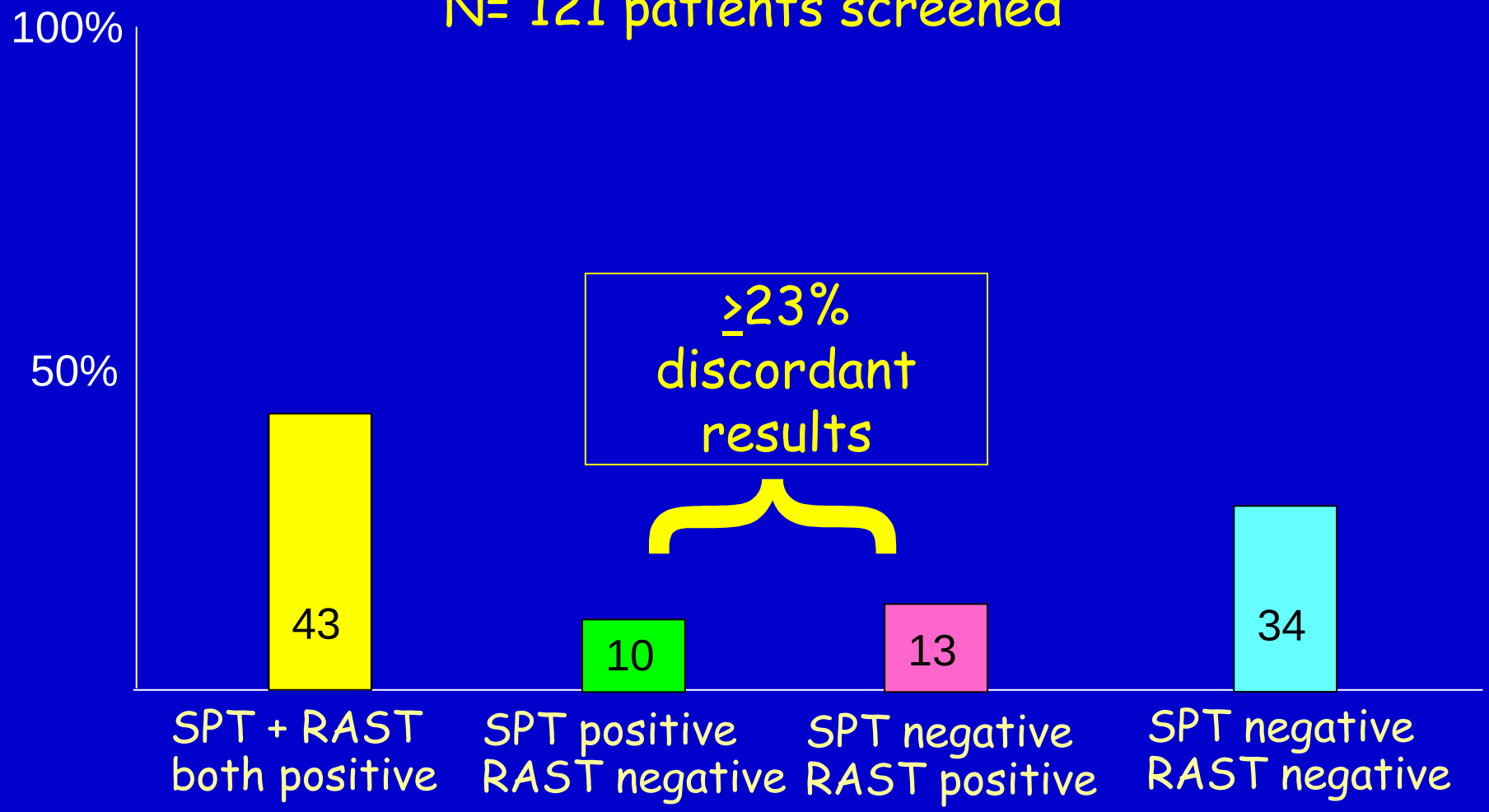
SAFS results

2

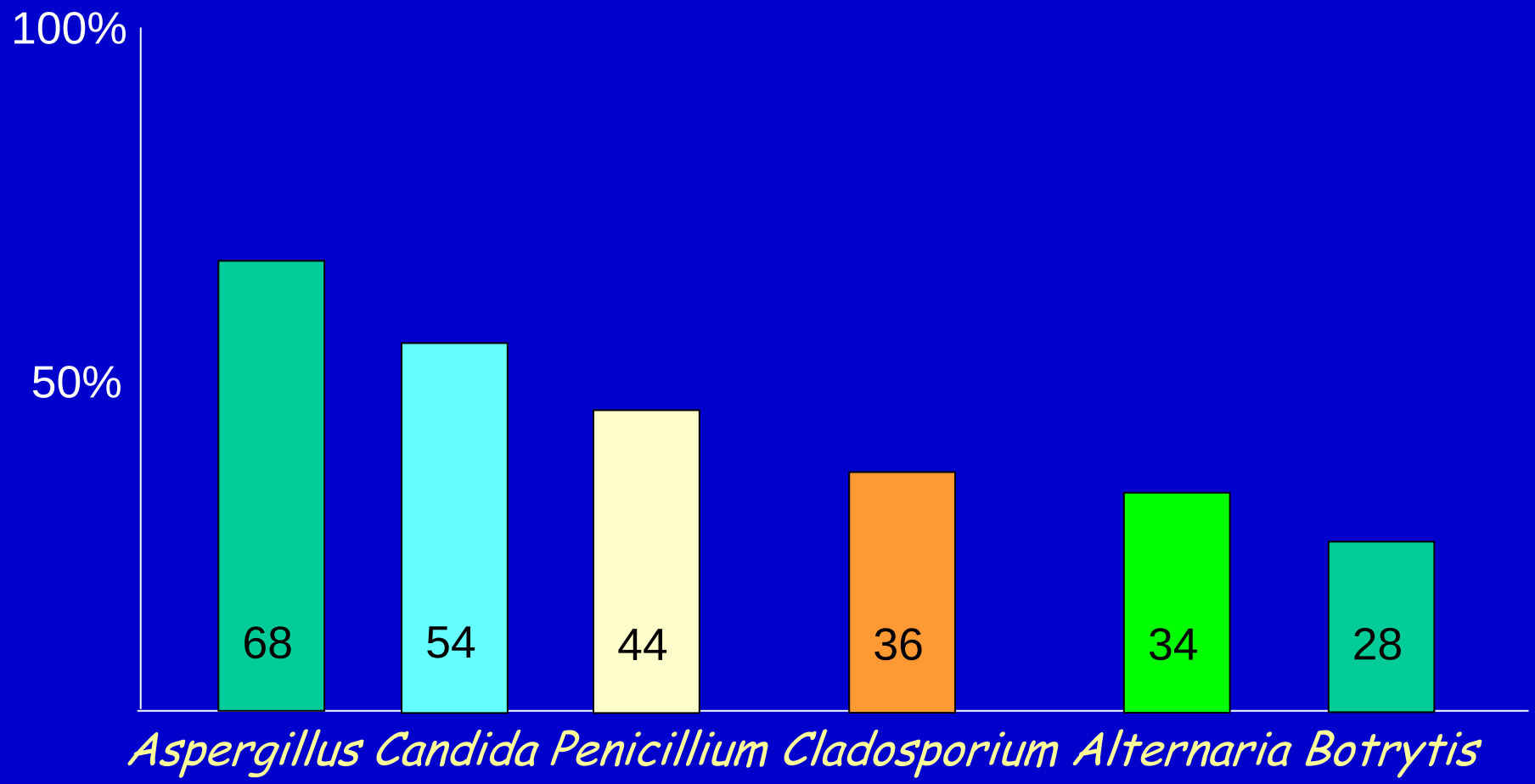
Total IgE	KIU/l	(0.1-100.0)	200.0	260.0
aspergillus.f	KUa/l	(0-0.4)	4.5	5.2

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

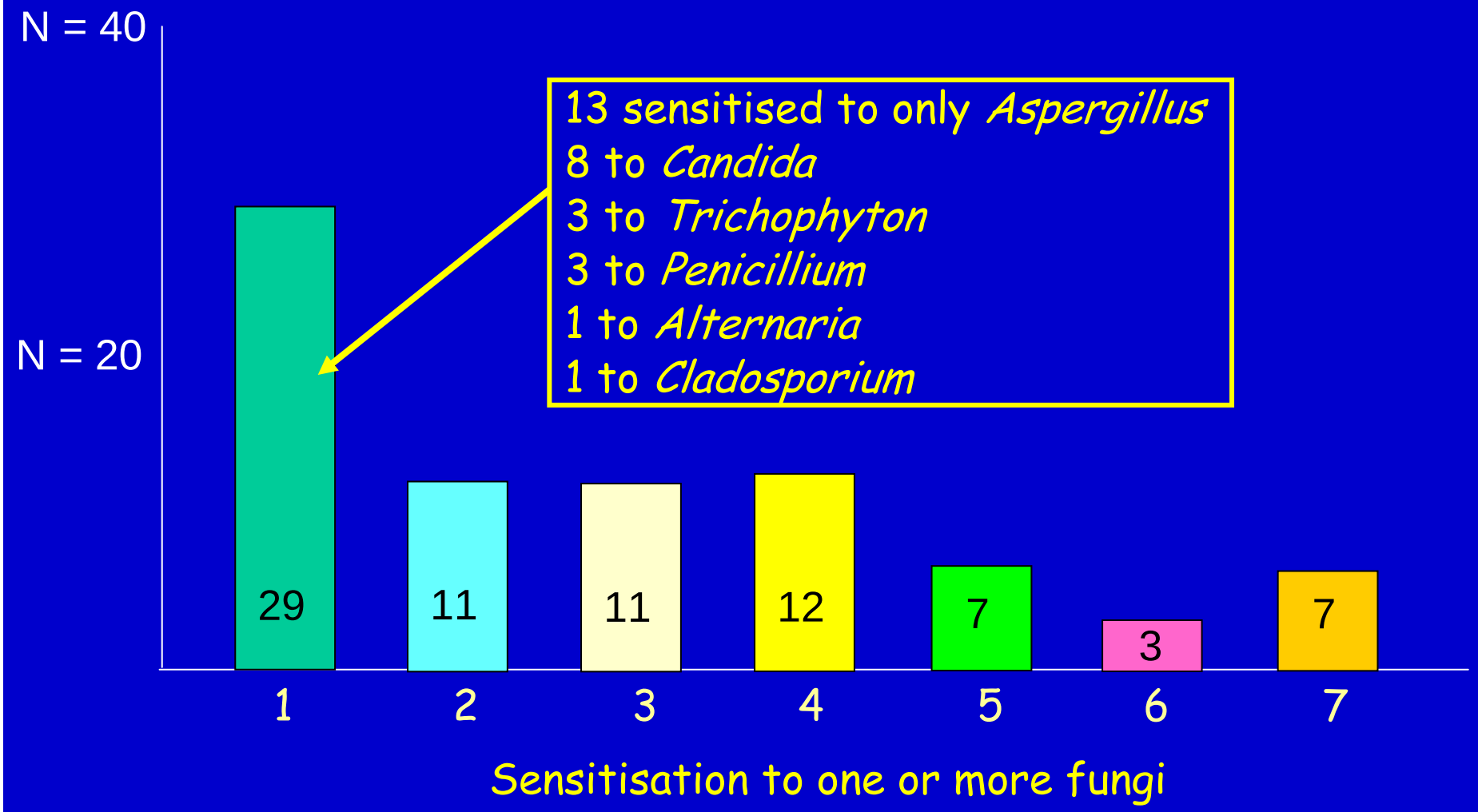
N= 121 patients screened



Fungal sensitisation in severe asthma – skin prick test or RAST



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



Severe asthma and fungal sensitisation (SAFS)

Does antifungal therapy work?

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

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

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

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

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.

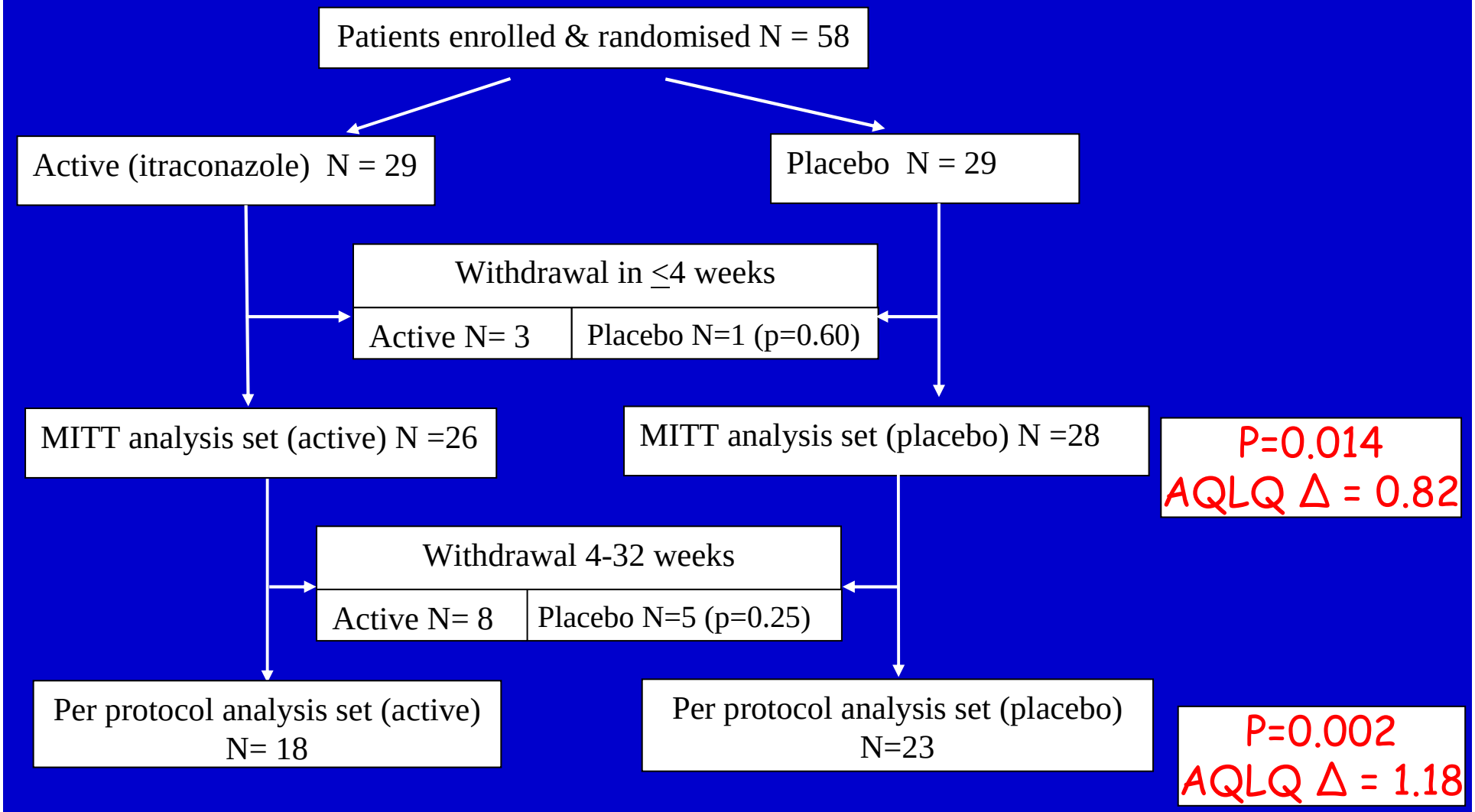
Fluconazole v. placebo at 5 months

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

Peak flow increased in 9/11 at 10 months

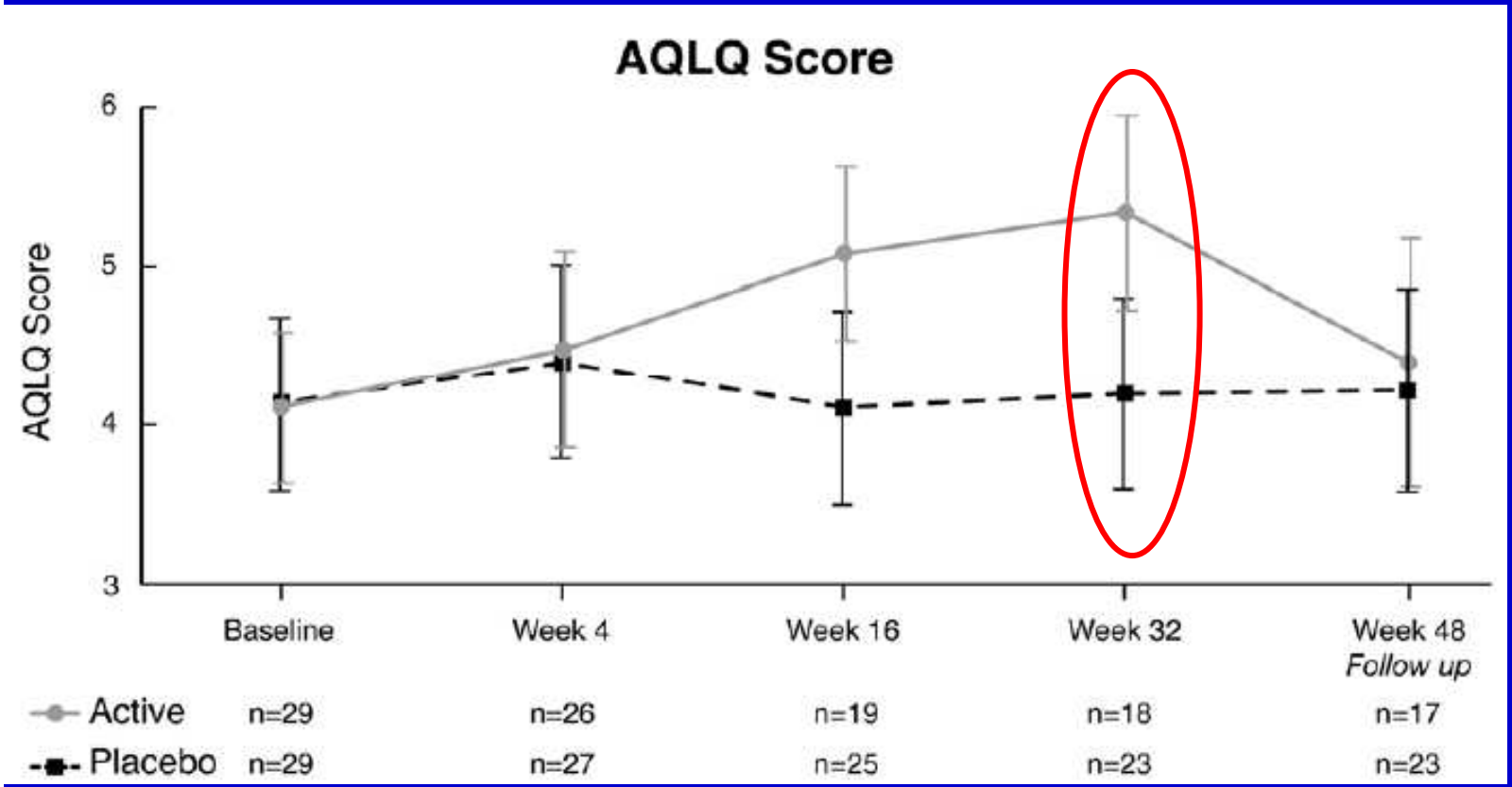
Ward et al, J Allergy Clin Immunol 1999;104:541;

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



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

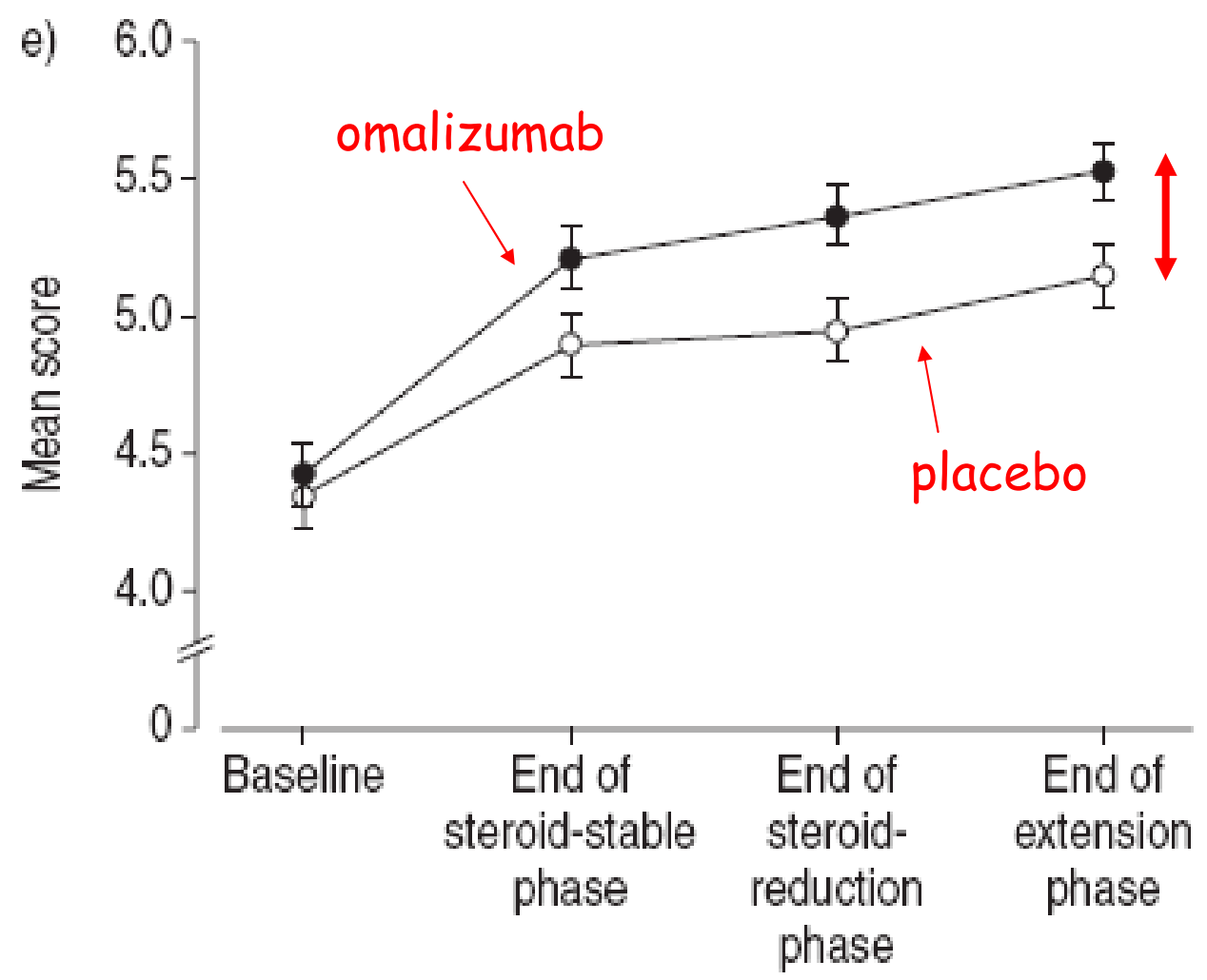
Proof of concept RCT of antifungal Rx in SAFS - AQLQ change



P= 0.014

Denning et al, Am J Resp Crit Care Med 2008 In press

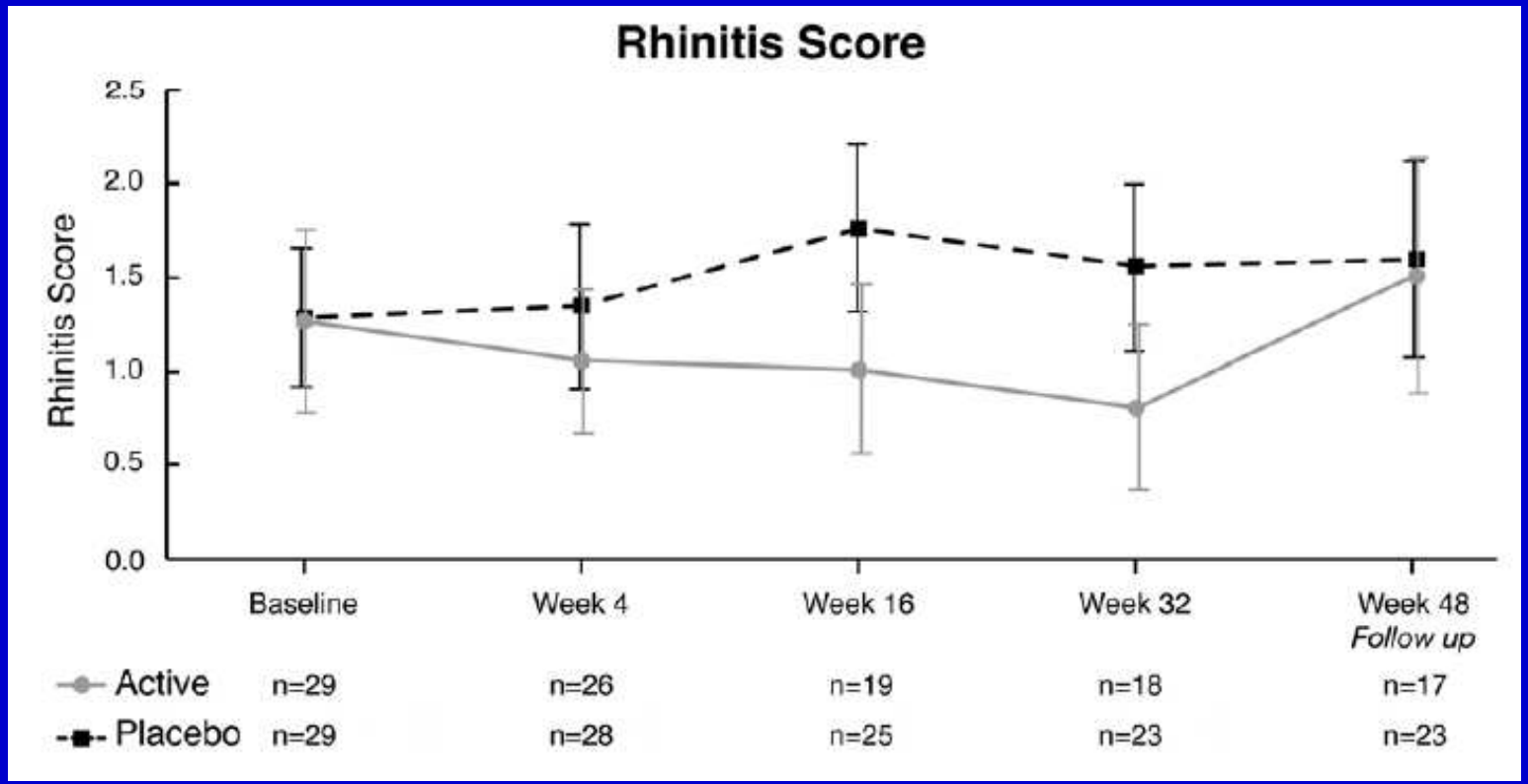
RCT of anti-IgE (omalizumab) v. placebo, moderate and severe asthma



Improvement in AQLQ
Δ = ~0.4

Buhl et al Eur Resp J 2002;20:1088

Proof of concept RCT of antifungal Rx in SAFS – improvement in rhinitis

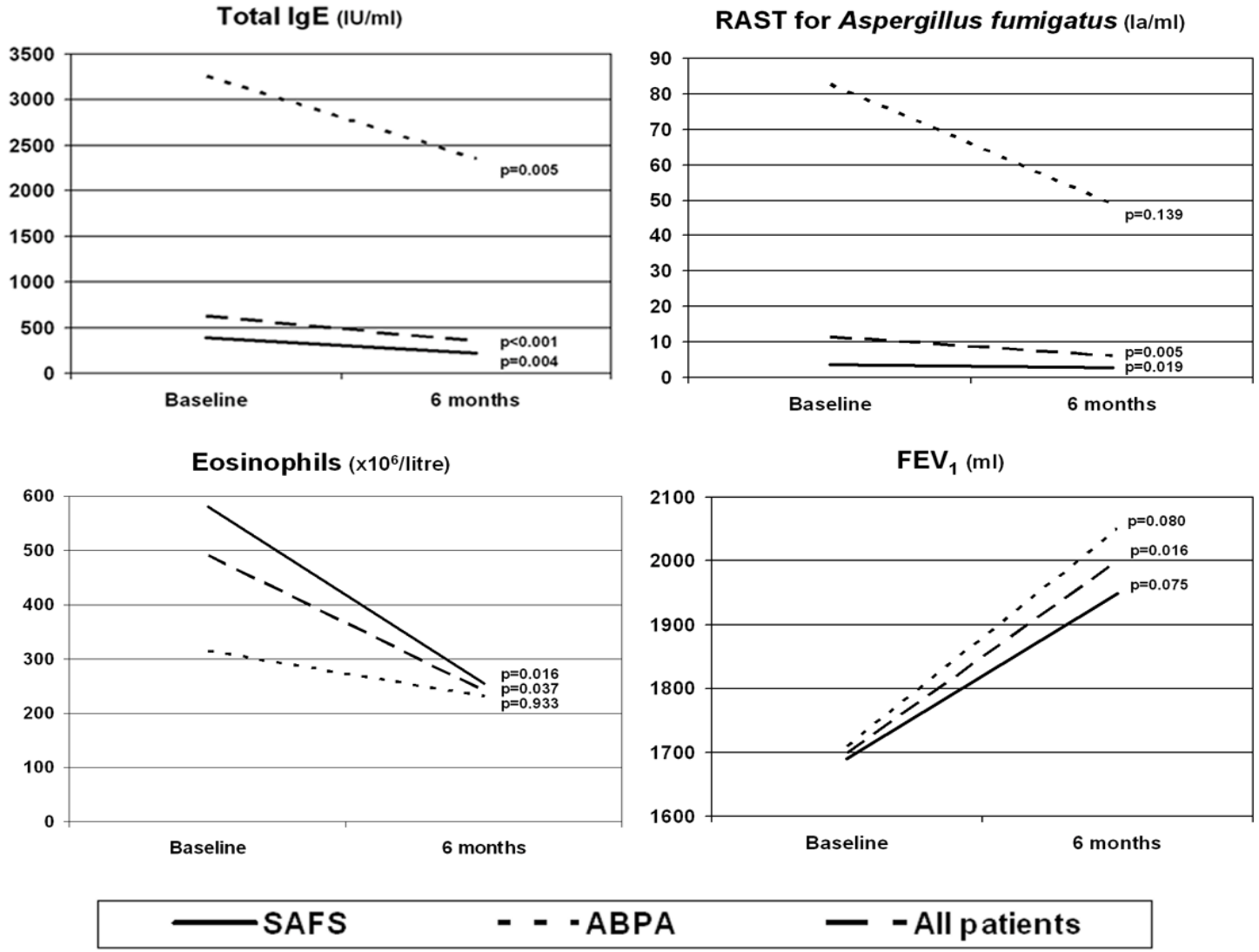


P= 0.013

Denning et al, Am J Resp Crit Care Med 2008 In press

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

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

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

www.cdc.gov/asthma/brfss/02/current/tableC1.htm; Zureik et al, Br Med J 2002;325:411