

# Pulmonary fungal infections and susceptible hosts

David W. Denning

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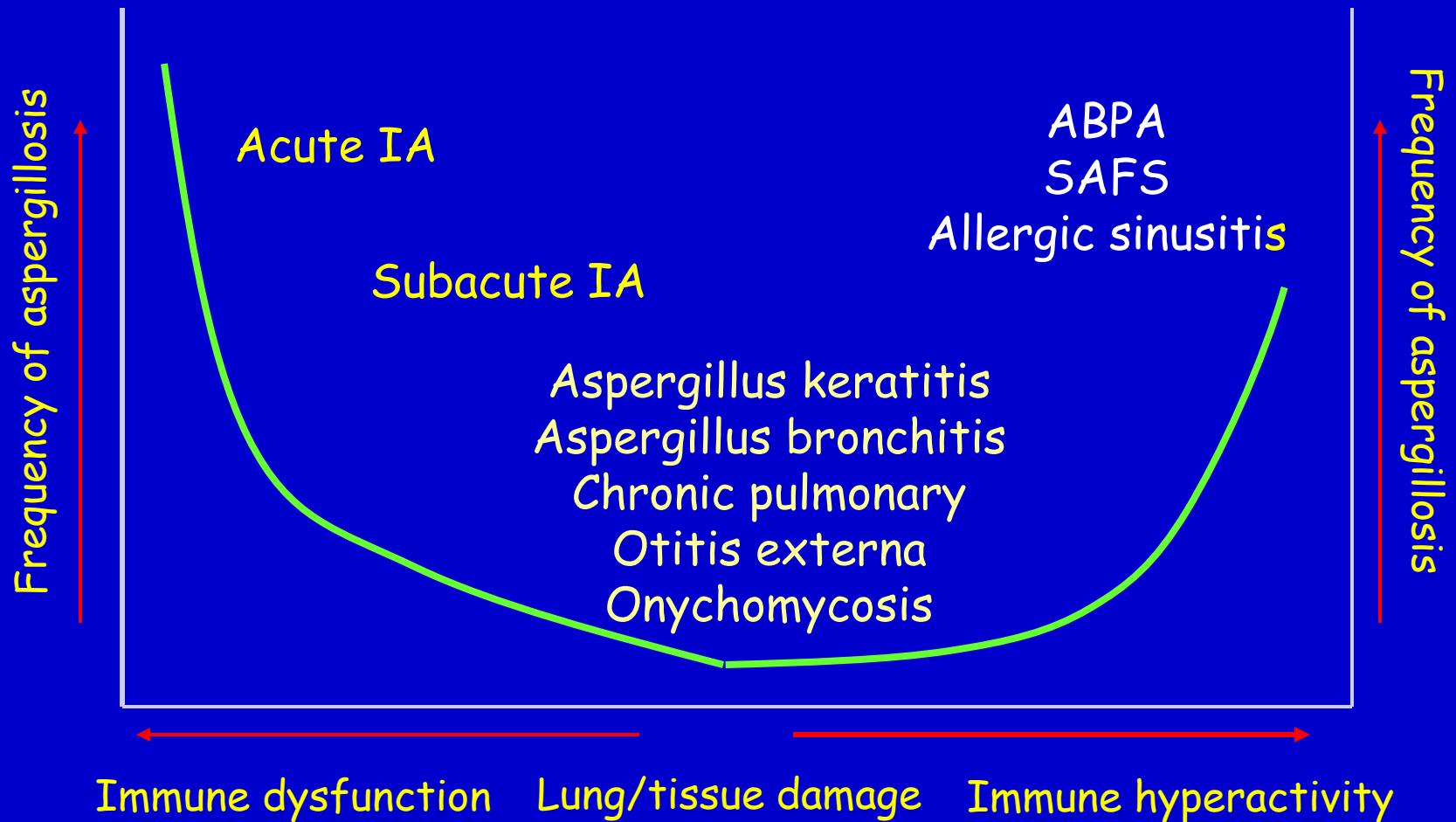
University Hospital of South Manchester

The University of Manchester

Global Action Fund for Fungal Infections

# Interaction of *Aspergillus* with the host

## A unique microbial-host interaction



After Casadevall & Pirofski, Infect Immun 1999;67:3703



# Burden of fungal diseases in Pakistan

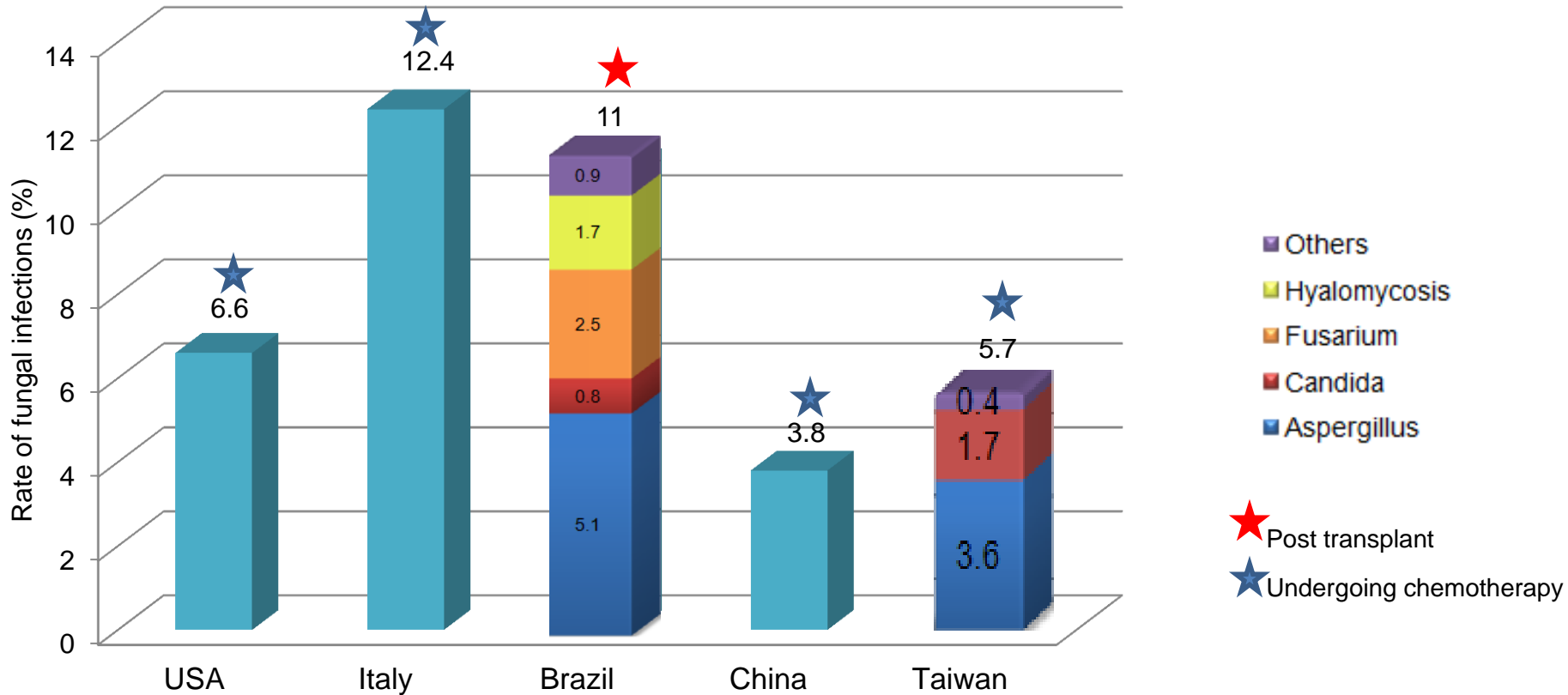
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<i>Pneumocystis pneumonia</i>	2200	–	2200	–	–	–	1.2
Oesophageal candidiasis	3231 <sup>a</sup>	–	3231 (1925–4537)	–	–	–	1.7
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Intra-abdominal candidiasis	148	–	–	–	–	148	0.08
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Mucormycosis	25,830	–	–	–	–	–	14
Recurrent vaginal candidiasis (4×/year)	2,821,440	2,821,440	–	–	–	–	3036 <sup>d</sup>
ABPA	94,358	–	–	92,697 + 1661 <sup>b</sup>	–	–	51
SAFS	129,776	–	–	129,776	–	–	70
Chronic pulmonary aspergillosis	72,438	–	–	71,932 + 506 <sup>c</sup>	–	–	39
Fungal keratitis	80,553 <sup>a</sup>	80,553 <sup>a</sup> (21,845–139,260)	–	–	–	–	44
Mycetoma	92 <sup>a</sup>	92 <sup>a</sup> (18–185)	–	–	–	–	0.05
Total burden estimated	3,280,554						1778

# Invasive aspergillosis

>99% mortality if not treated

# IFI in AML/MDS patients

425,000 new cases annually

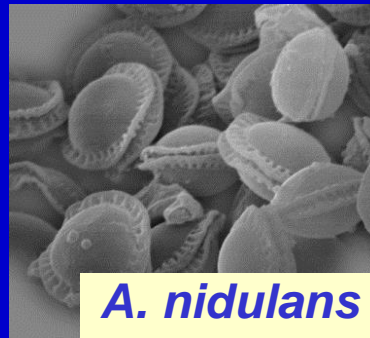
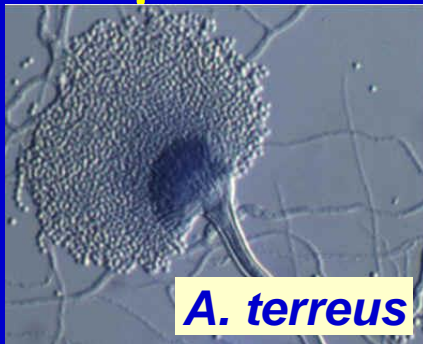


Ref. - Am. J. Hematol. 88:283–288, 2013.  
 Clin Microbiol Infect 2013; 19: 745–751  
 PLoS ONE. 2015 10(6): e0128410.

Eur J Haematol. 2008 Nov;81(5):354-63  
 Tumour Biol. 2015 Feb;36(2):757-67

# Intrinsic and acquired resistance among the *Aspergilli*

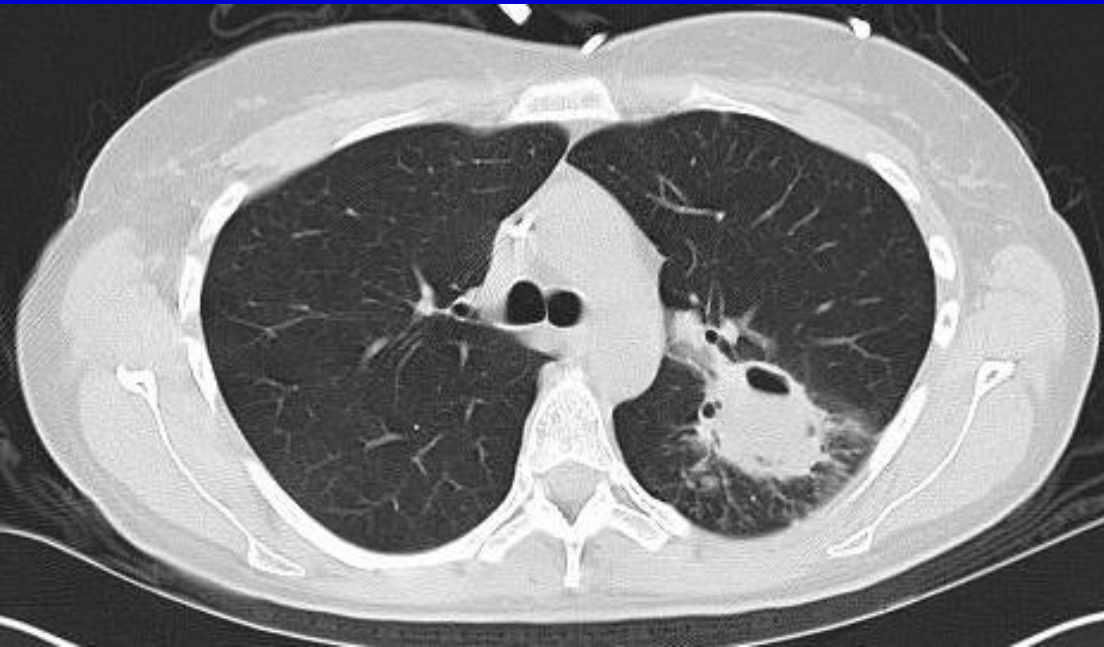
## Amphotericin B resistance



## Azole resistance



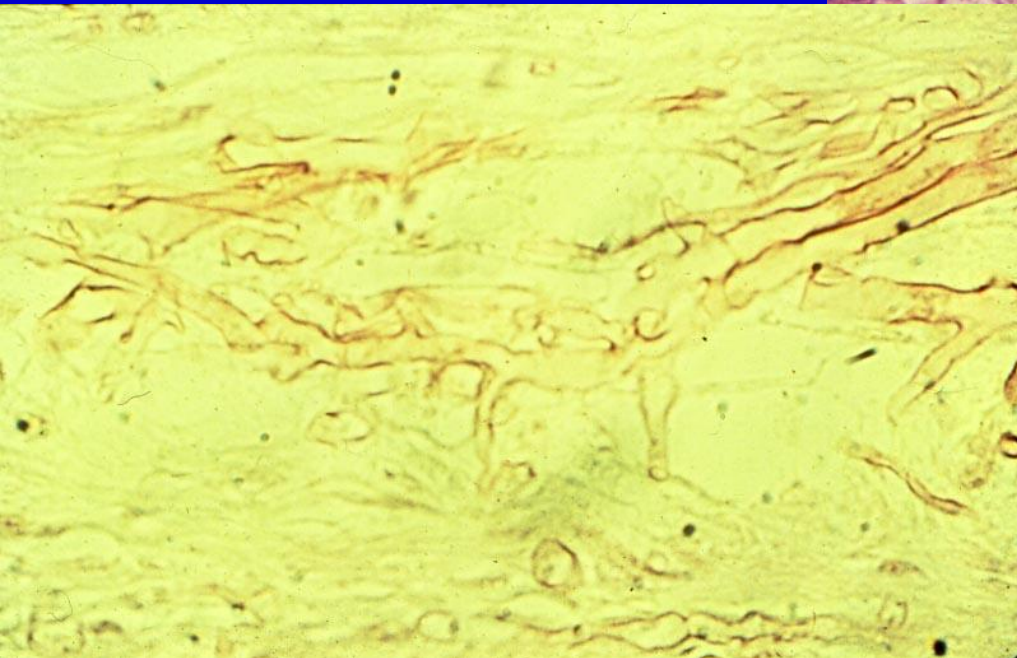
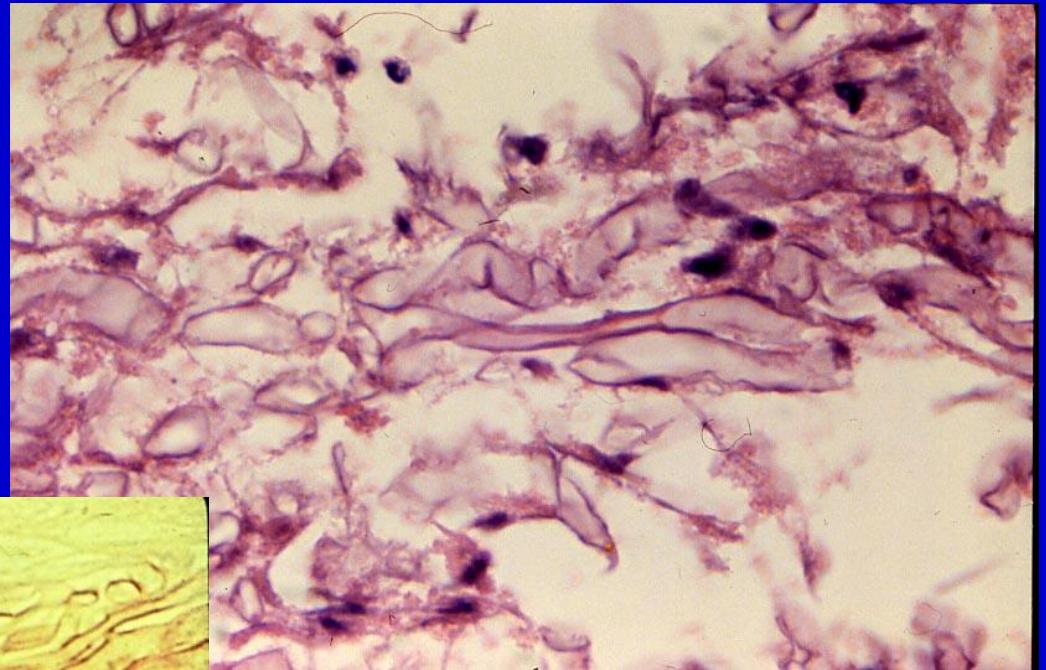
# Pulmonary mucormycosis



ALL induction  
Breakthrough infection on  
voriconazole prophylaxis



# Microscopy of mucormycosis





# Frequency of mucormycosis in leukaemia

391 pts with leukaemia (225 with AML) and a filamentous fungal infection

80% neutropenia for >14 days

85% pulmonary infection

Antemortem diagnosis in 79%

Aspergillus 296 (76%)

Mucorales 45 (11.5%)

Fusarium 6

Other 4

Unidentified in 40

Overall mortality in 3 months 74%, 51% attributable

# Clinical Characteristics of 45 Patients With Invasive Pulmonary Aspergillosis

Retrospective Analysis of 1711 Lung Cancer Cases

Xi Yan, MD; Mei Li, MD; Ming Jiang, MD; Li-qun Zou, MD; Feng Luo, MD; and Yu Jiang, MD

2.63%, proven in 10 (22%)

Risk factors were:

Stage 4 disease

Chemotherapy

Corticosteroids for >2 days

But not age, sex, tumour type or radiotherapy

6800 lung cancer patients in Pakistan annually,  
178 IA cases each year

RESEARCH

Open Access

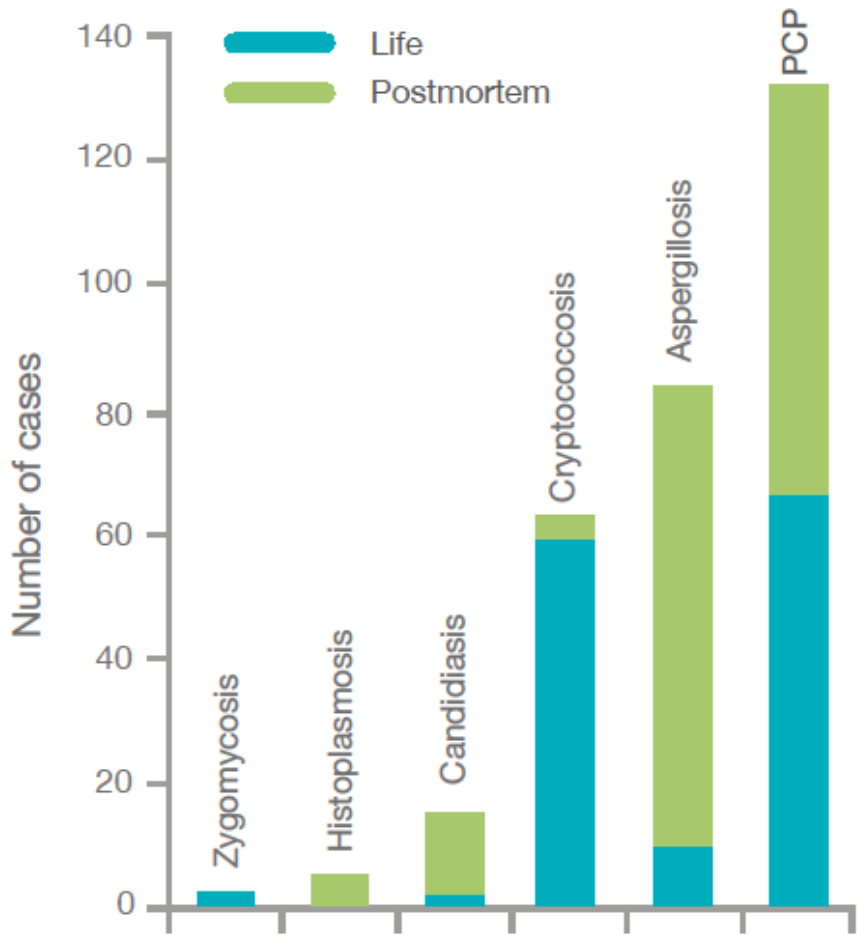
# Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes

Fabio Silvio Taccone<sup>1</sup>, Anne-Marie Van den Abeele<sup>2</sup>, Pierre Bulpa<sup>3</sup>, Benoit Misset<sup>4</sup>, Wouter Meersseman<sup>5</sup>, Teresa Cardoso<sup>6</sup>, José-Artur Paiva<sup>7</sup>, Miguel Blasco-Navalpotro<sup>8</sup>, Emmanuel De Laere<sup>9</sup>, George Dimopoulos<sup>10</sup>, Jordi Rello<sup>11</sup>, Dirk Vogelaers<sup>12</sup>, Stijn I Blot<sup>12,13\*</sup>, on behalf of the AspICU Study Investigators

563 ICU patients with positive *Aspergillus* culture  
266 colonised  
203 (36%) had putative IA  
94 (17%) proven IA



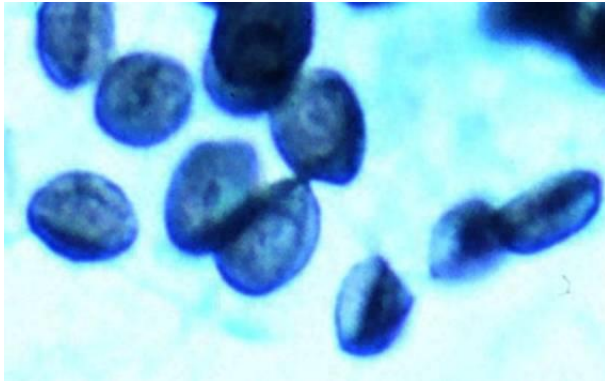
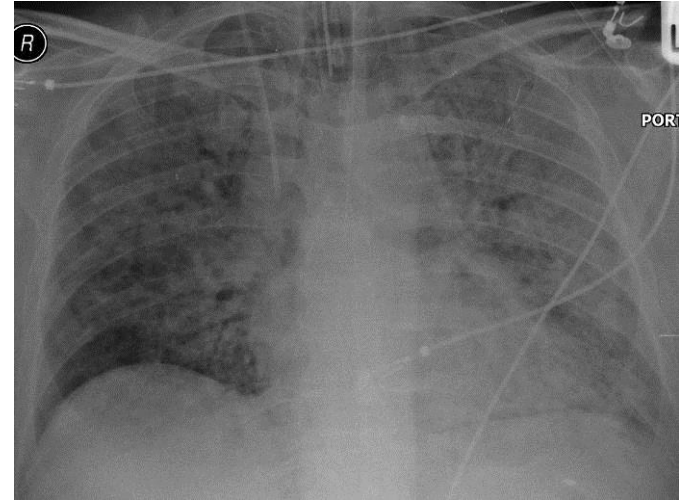
# Missed diagnoses in AIDS – including PCP



Antinori S et al, *Am J Clin Pathol* 2009;132 :221



# Pneumocystis pneumonia in AIDS



**Human only pathogen**

**Microscopy 75% sensitive**

**Real time PCR 98% sensitive**

**$\beta$ -D-Glucan 96% sensitive**

# Typical presentation of PCP

## All patients:

Shortness of breath

Hypoxaemia, or major dip in pO<sub>2</sub> on limited exercise

Raised LDH

## AIDS:

- Chest unremarkable on clinical examination
- 10% have normal chest Xrays, typically mid zone fluffy infiltrates

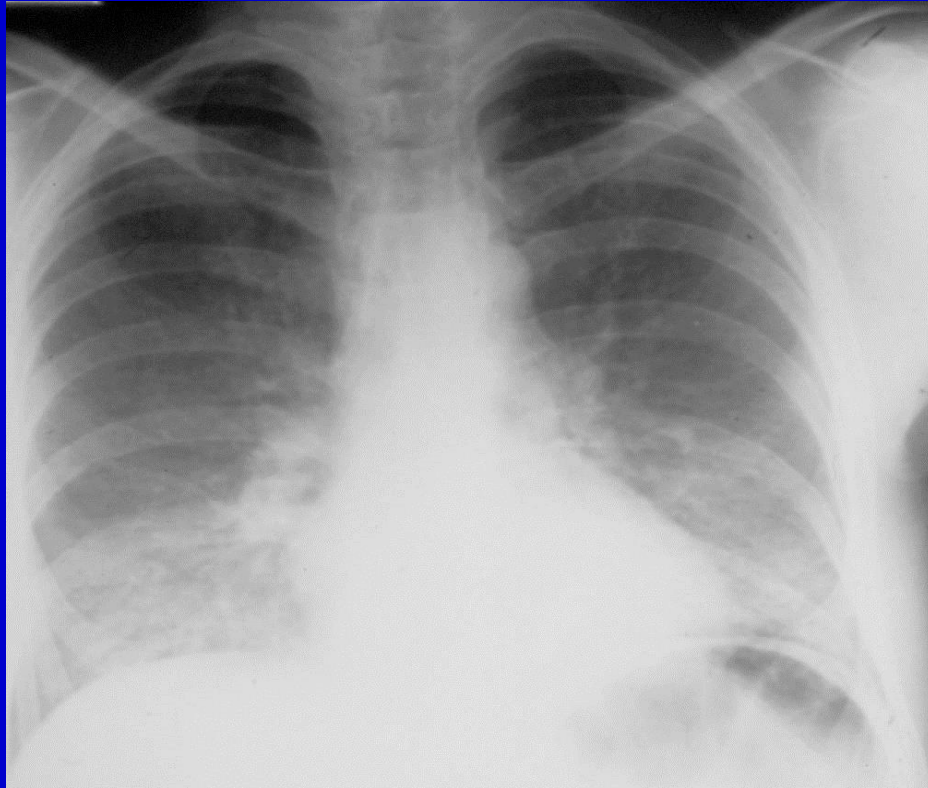
## Non-AIDS:

- Wheezes and crackles on clinical examination
- Extensive infiltrates - wide spectrum of appearances

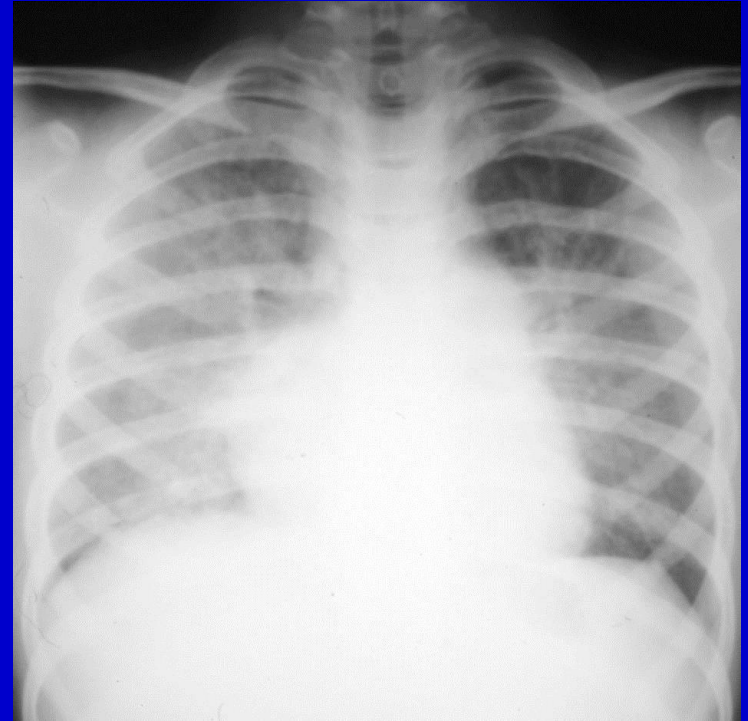
# Hypoxia and respiratory failure in PCP



# Typical CXR appearances in PCP - bilateral mid zone patchy shadowing



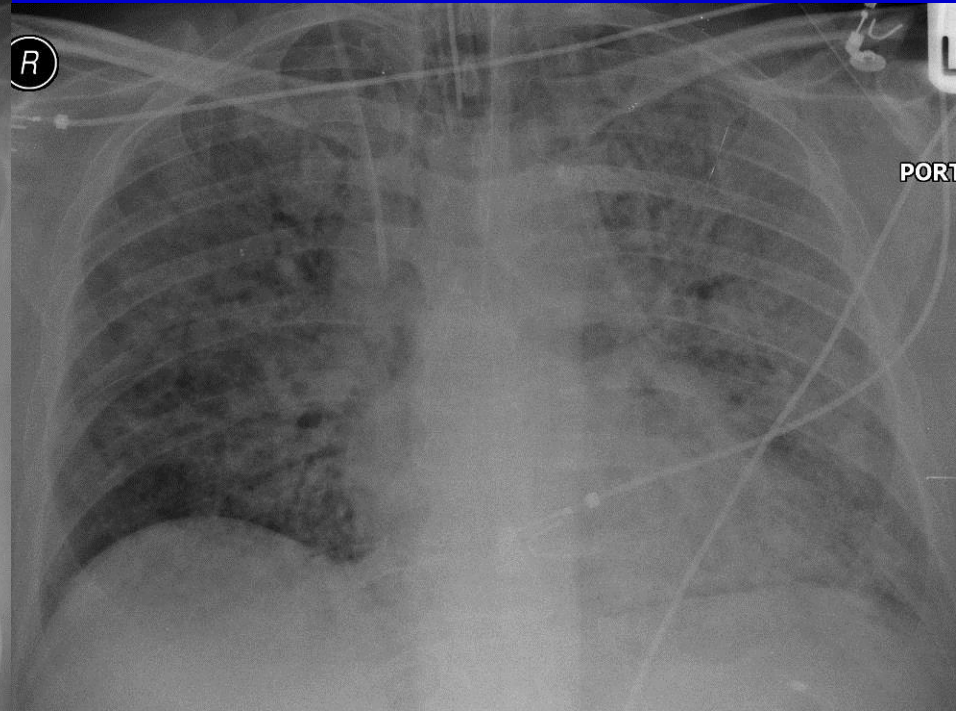
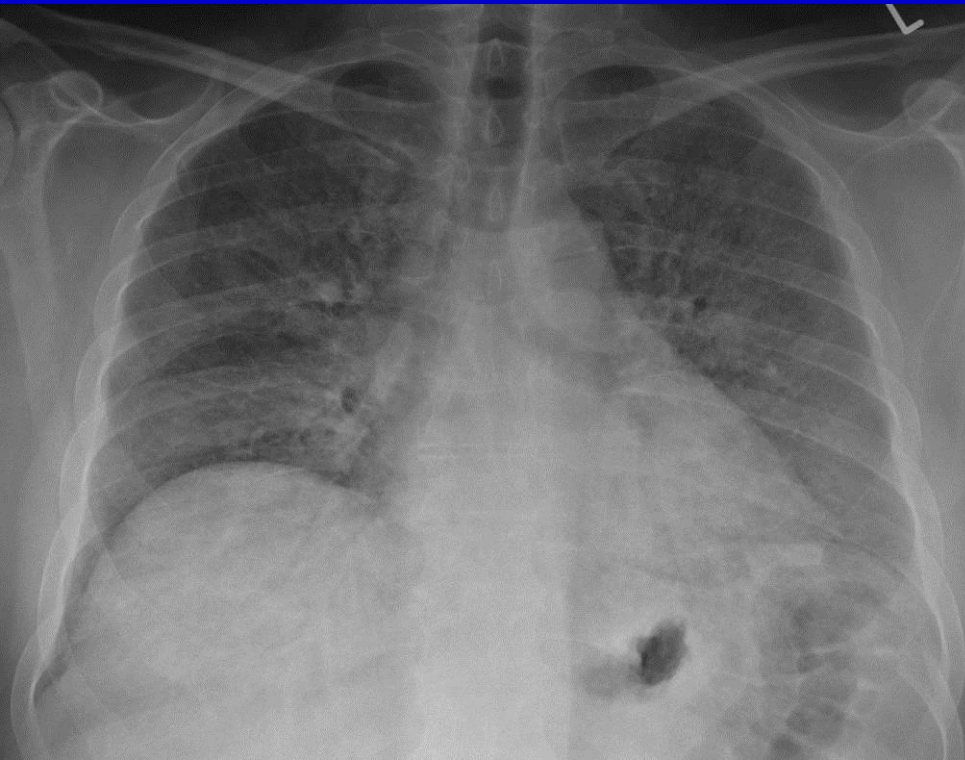
Adult with AIDS and PCP



Child with ALL given only trimethoprim prophylaxis

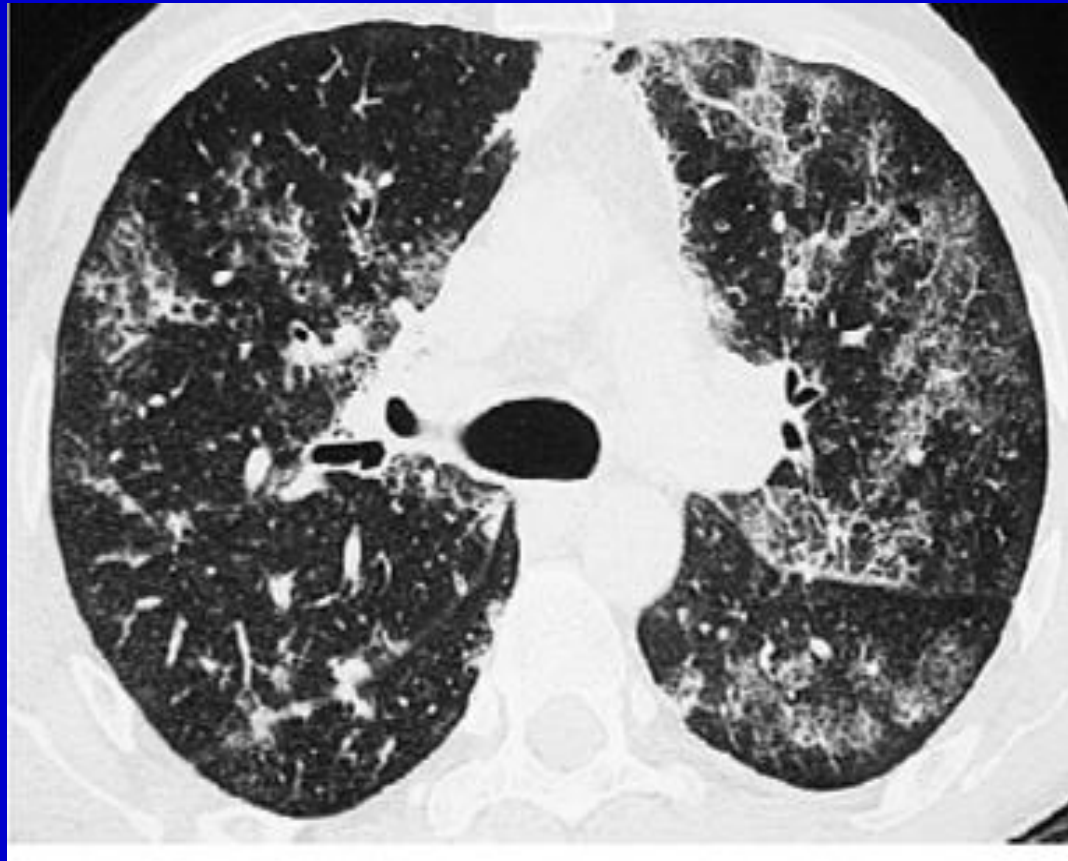


# Characteristic CXR appearances in PCP - with progression



Progression over 10 days

# Typical CT appearances in PCP - bilateral ground glass patchy shadowing



# Invasive pulmonary aspergillosis in AIDS

## Presenting features (in 78 patients)

Cough	92 %
Fever	91 %
Dypsnoea	65 %
Chest pain	24 %
Haemoptysis	9 %

Subacute  
invasive  
pulmonary  
aspergillosis in  
AIDS, showing  
upper lobe  
cavities





# Fungal infections in AIDS

## Pakistan

HIV+ and CD4 <200, not on ARVs = 27,500

Estimated PCP cases = 2,200 cases

Estimated 6,900 HIV+ with TB, so 620 CPA cases

Estimated 5,500 AIDS deaths, so 220 IA cases

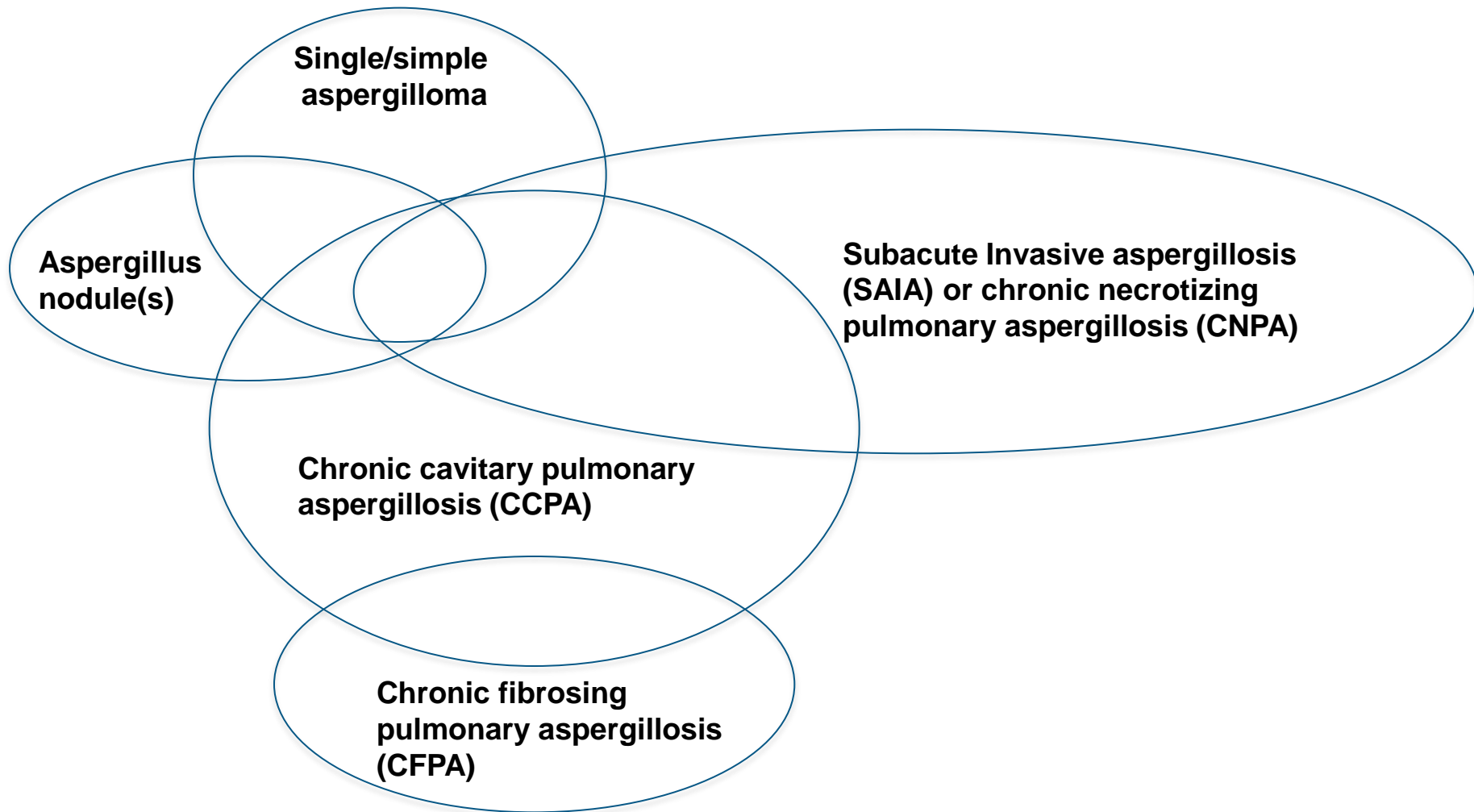
<i>Pneumocystis pneumonia</i>	>400,000	15% with best treatment	>200,000
Disseminated histoplasmosis	>100,000	15-30%, if diagnosed and treated	>80,000
Chronic pulmonary aspergillosis	>185,000	15-40% mortality in HIC	>100,000
Invasive aspergillosis	>45,000	30% mortality if treated in HIC	>30,000
<i>T. marneffeii</i> infection	>8,000	18-33%	>2,000
Mucosal and skin fungal infection	>10,120,000	<1%	<1,000
<b>Total</b>	<b>&gt;11.22 million</b>		<b>&gt;535,000</b>



# Burden of fungal diseases in Pakistan

	Total burden	Number of infections per underlying disorder per year					Rate/100,000
		None	HIV/AIDS	Respiratory	Cancer/Tx	ICU	
Cryptococcal meningitis	794	–	790 <sup>a</sup> (344–1237)	–	4	–	0.4
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# Clinical phenotypes of chronic *Aspergillus* spp diseases





# Underlying diseases in CPA (%)

	<u>Smith</u>	<u>Others</u>
Tuberculosis	17	31-81
NTM infection	16	?
ABPA	14	12
COPD/emphysema	33	42-56
Pneumothorax	17	12-17
Lung cancer survivor	10	?
Pneumonia	22	9-12
Sarcoidosis (stage II/III)	7	12-17
Thoracic surgery	14	8-11
Rheumatoid arthritis	4	2
Asthma / SAFS	12	6-12
Ankylosing spondylitis	4	2-11
None	1	15

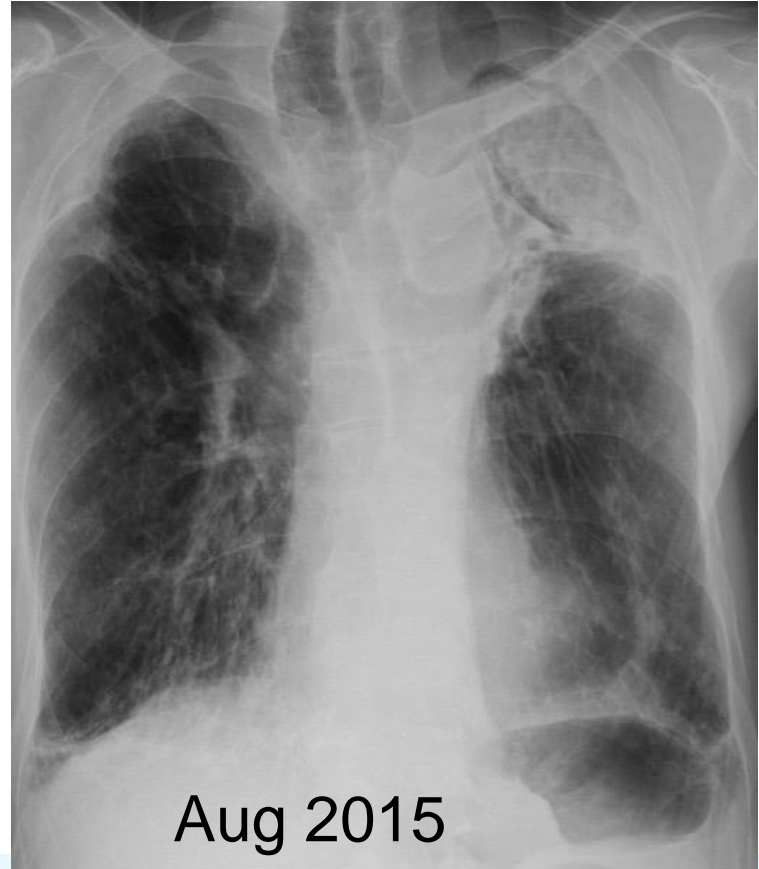




# CXRs similar to TB – aspergilloma is a late feature



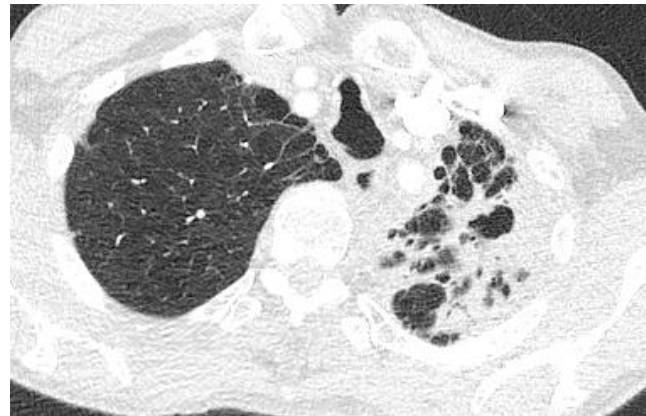
Jan 2012



Aug 2015

Chronic pulmonary aspergillosis in 2006 which improved with itraconazole for 6/12.  
In 2012, clinically relapsed, but CPA not recognised until aspergilloma seen in 2015.

# CXRs similar to TB



Recent diagnosis of CPA in context of COPD

# Multiple *Aspergillus* nodules

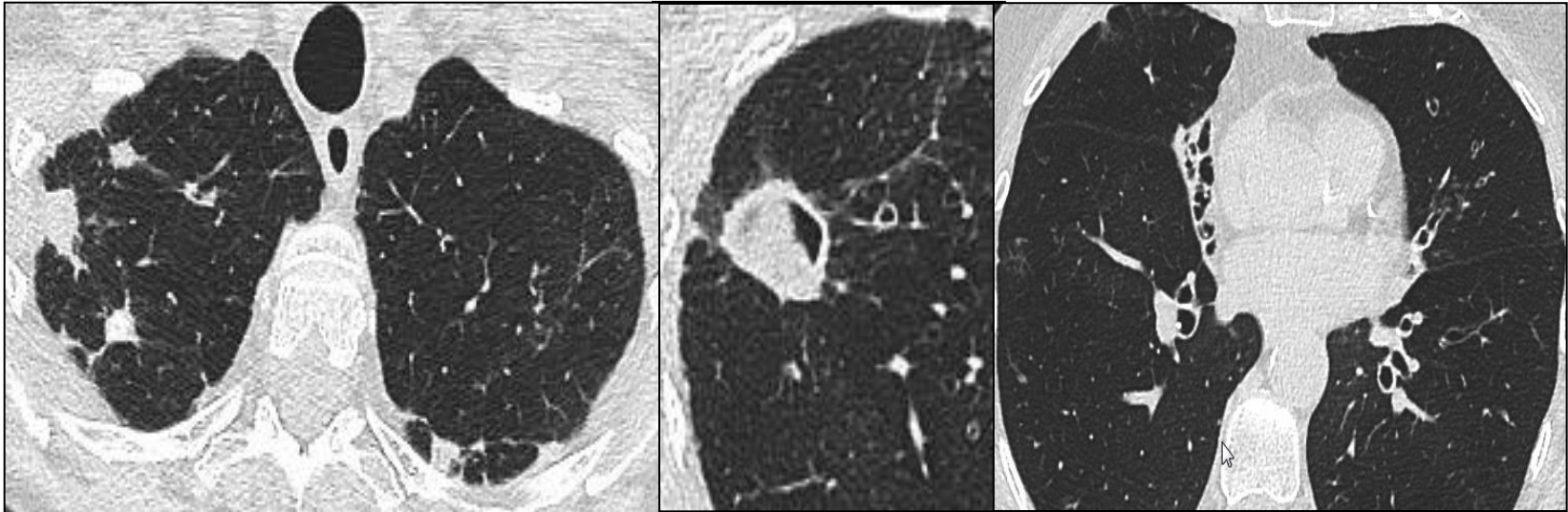
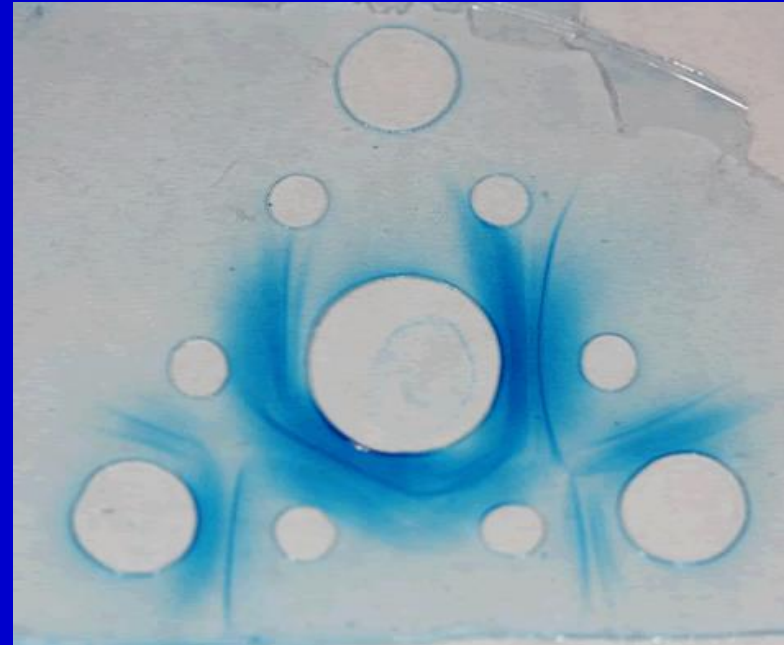


Figure 6 – *Aspergillus* nodules of variable size and borders and fungus ball filling a cavity with a wall of variable thickness in a patient with preexisting bronchiectasis and cicatricial atelectasis of the middle lobe. Successive axial views with lung windows.

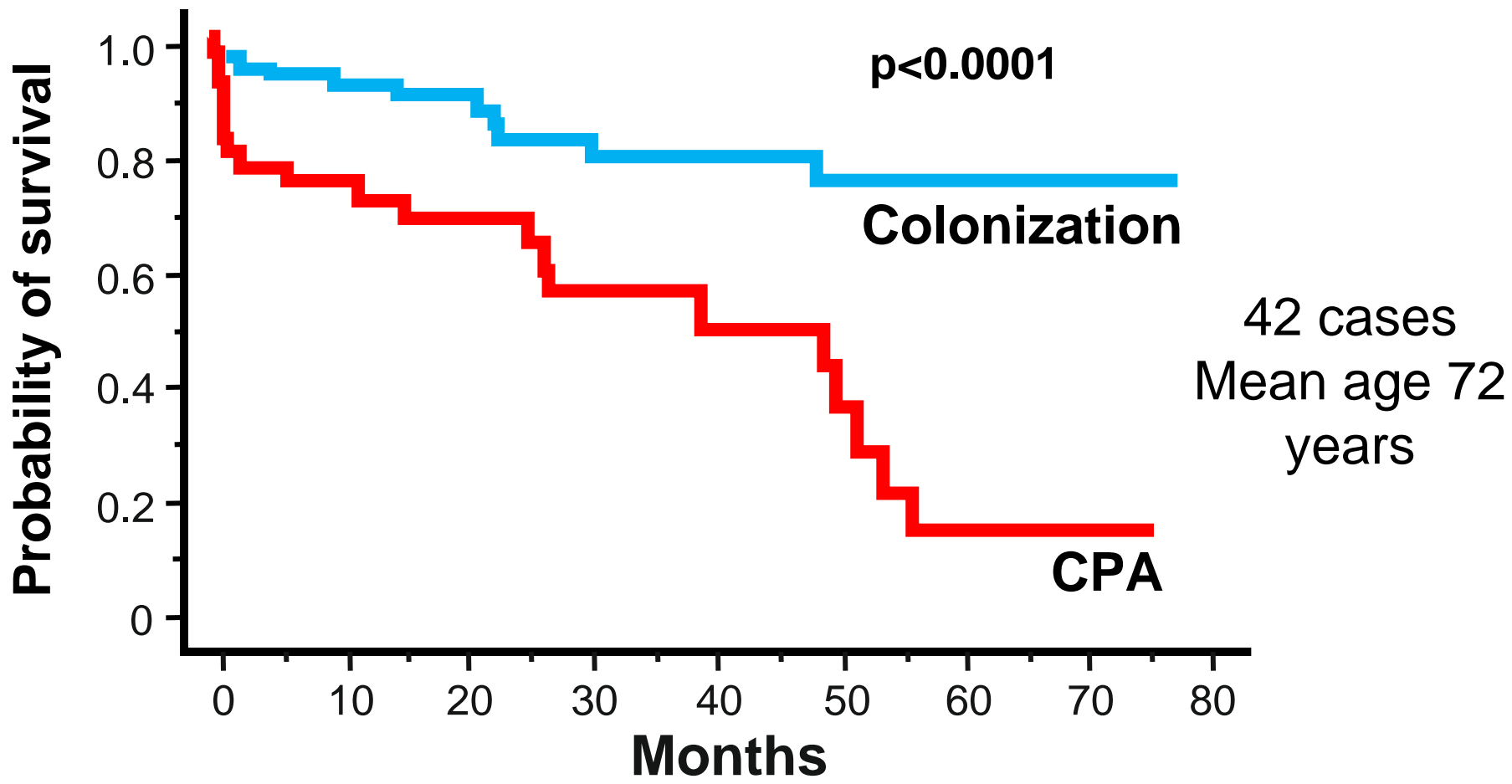
# Aspergillus IgG serology (precipitins)



7 different commercial assays, with 75-96% sensitivity, specificity depends on control group



# Prognosis of chronic pulmonary aspergillosis - 80% over 5 years



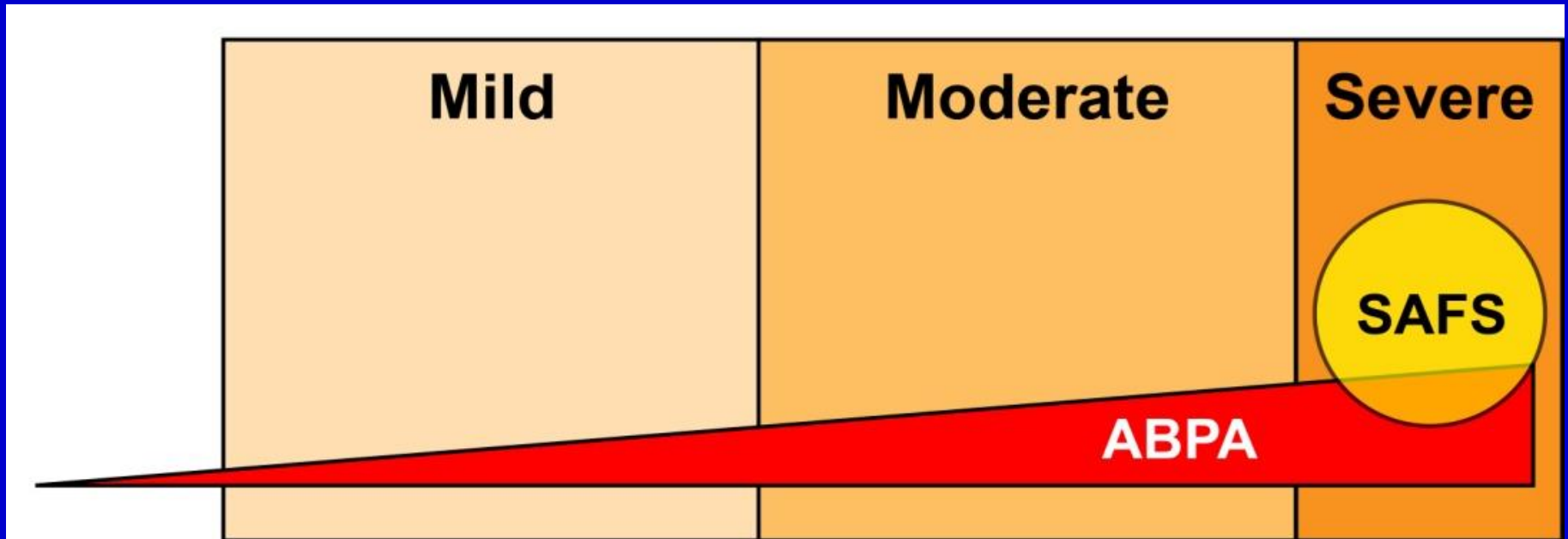
Ohba et al. *Resp Med* 2012;106:724.



# Burden of fungal diseases in Pakistan

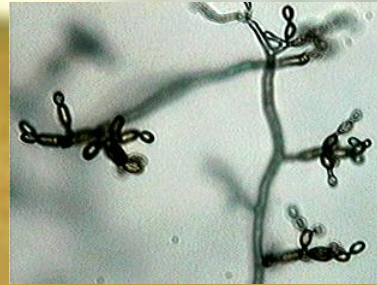
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# 'Fungal asthma' ABPA versus SAFS



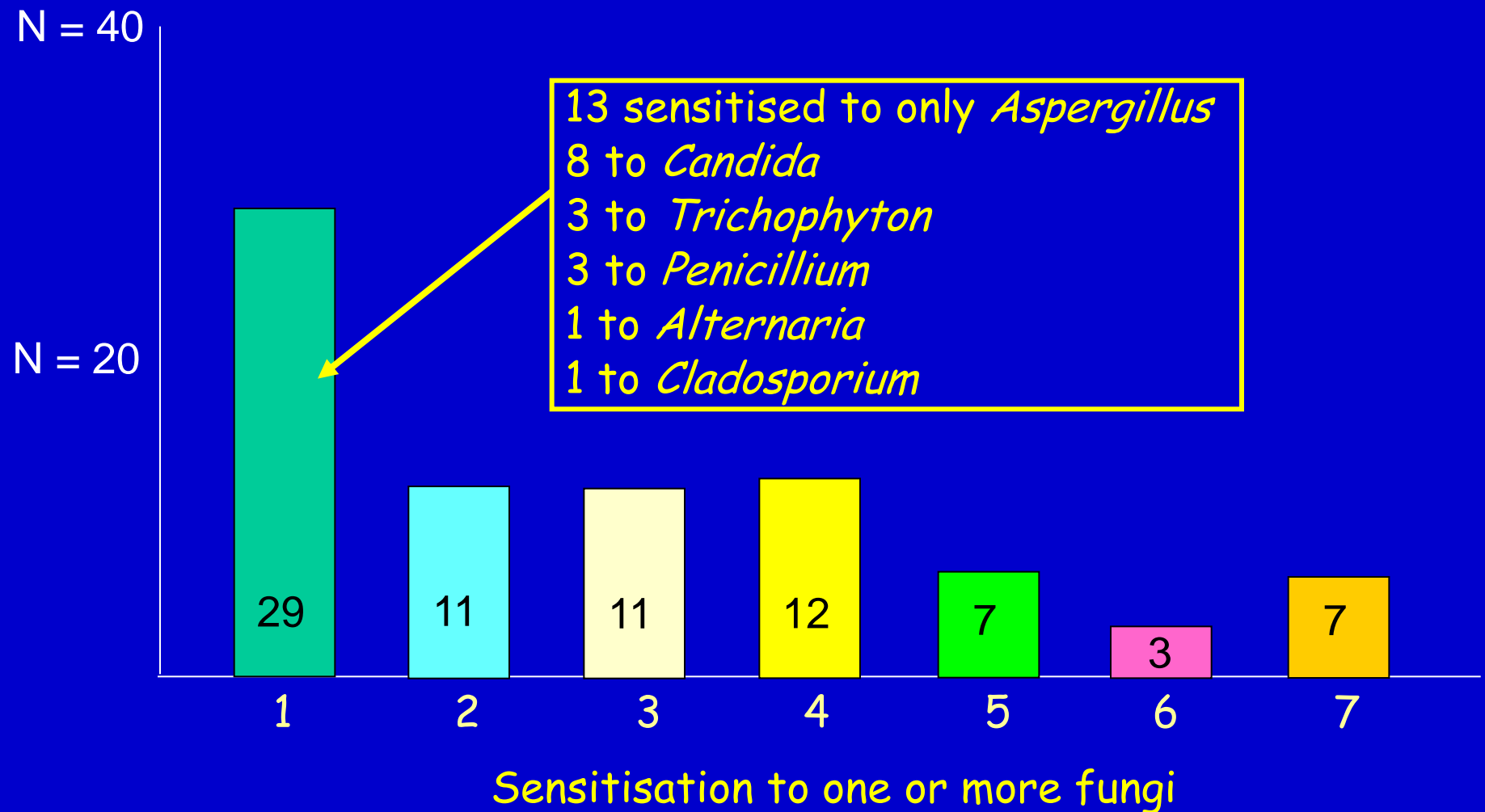
# Skin prick testing - example of SAFS result

Cladosporium +ve





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



# 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

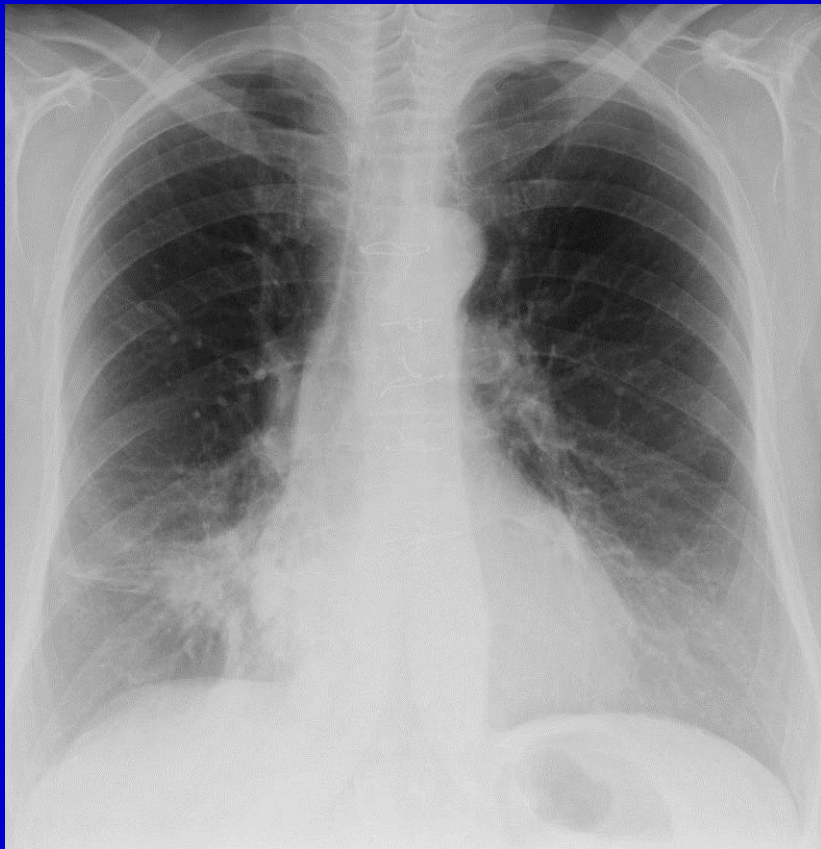
2

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

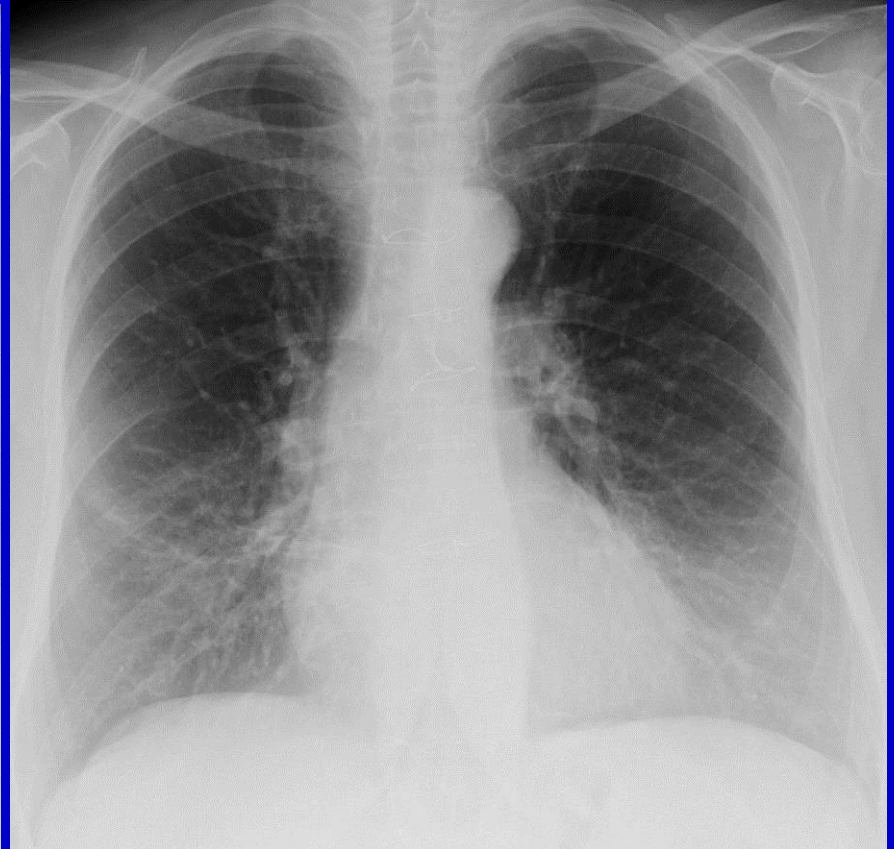
# ABPA serology and cut-offs

Marker	Europe		India	
	Adult asthma	Adult CF	Adult asthma	Paediatric asthma
<u>Aspergillus IgE</u> kUA/L	<u>detectable</u>	>5.7	>1.91	NA
<u>Total IgE</u> kIU/L	>1,000	>185	>2,347	1,200
<u>Aspergillus IgG</u> (immunoCap) mg/L	>40	>75	NA	NA

# ABPA exacerbation - patient VE

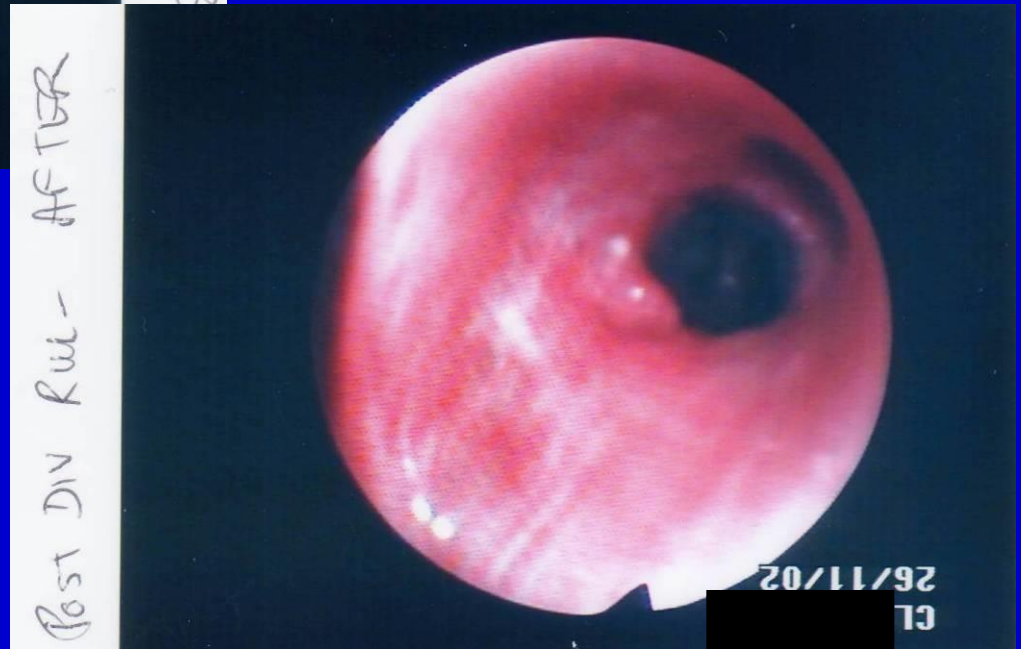


August 2011



September 2011

# ABPA - bronchoscopy views showing mucous plugging



**ABPA**

Resolution and remission  
(ABPA-S)

Recurrent exacerbations

Bronchiectasis

Hyperattenuating mucus

Chronic pulmonary  
aspergillosis

Poor asthma control

# Chronic cavitary pulmonary aspergillosis as a complication of ABPA



# Aspergillus bronchitis without significant immunocompromise

Ales Chrde,<sup>1\*</sup> Sahlawati Mustakim,<sup>2</sup> Rowland J. Bright-Thomas,<sup>3</sup> Caroline G. Baxter,<sup>1,4</sup> Timothy Felton,<sup>1,4</sup> and David W. Denning<sup>1,4</sup>

<sup>1</sup>The National Aspergillosis C

<sup>2</sup>Pathology Department,

Underlying diseases	Number affected (%)
Pulmonary disease	<i>n</i> = 17
COPD <sup>a</sup>	6 (35)
Asthma <sup>a</sup>	4 (23)
Bronchiectasis <sup>b</sup>	12/14 (86)
Mucus impaction <sup>b</sup>	2 (12)
Lung cancer	1 (6)
Oral corticosteroids > 10 mg/day	3 (18%)
Oral corticosteroids < 10 mg/day	3 (18%)
Infliximab	1 (6%)
No comorbidity	2 (12%)
Mannose binding lectin levels (mg/L)	<i>N</i> = 16
> 1 (normal)	7 (44%)
> 0.5–< 1 (possibly low)	3 (18%)
> 0.1–< 0.5 (low)	4 (24%)
< 0.1 (undetectable)	2 (12%)



# Pulmonary infections caused by fungi

- Superficial eg *Aspergillus* bronchitis
- Chronic fungal infections eg chronic pulmonary aspergillosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, mucromycosis, sporotrichosis, cryptococcosis
- Allergic eg "Fungal asthma" - allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitisation (SAFS) (*Aspergillus*, *Alternaria*, *Cladosporium* etc)
- Invasive and life-threatening eg invasive pulmonary aspergillosis, ulcerative or invasive tracheobronchitis (*Aspergillus*, *Mucorales*), *Pneumocystis* pneumonia, *Mucorales*, *Fusarium*, *Scedosporium*,



# 8TH ADVANCES AGAINST ASPERGILLOSIS

1 - 3 February 2018

Lisbon, Portugal  
Lisboa Congress Centre

[www.AAA2018.org](http://www.AAA2018.org)