Hospital General Universitario Gregorio Marañón
SaludMadrid
Comunidad de Madrid

Emerging Clinical Associations With Aspergillosis

COPD and Aspergillosis

Jesús Guinea
Clinical Microbiology and ID Department
Hospital Gregorio Marañón, Madrid

CONFLICTS OF INTEREST

Research grants (last three years): Basilea Pharmaceutica, bioMérieux, Astellas, Pfizer, Fundación Mutua Madrileña, Fondo de Investigación Sanitaria (FIS)

Conference fees (last three years): Astellas, Pfizer, Gilead, MSD

ISSUES TO HIGHLIGHT

1. **The changing epidemiology of IA and its incidence in patients with COPD**

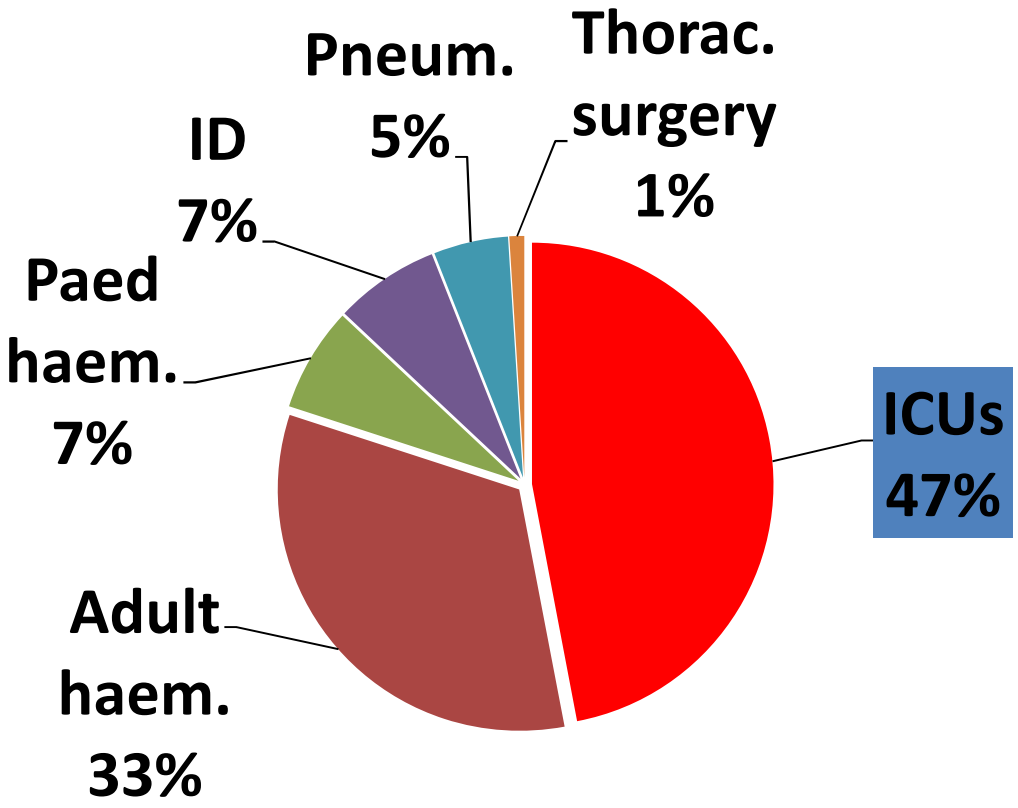
2. **Air–Patient relationship**

3. **Diagnosis of IA in non-neutropenic patients**

4. **Treatment and antifungal resistance**

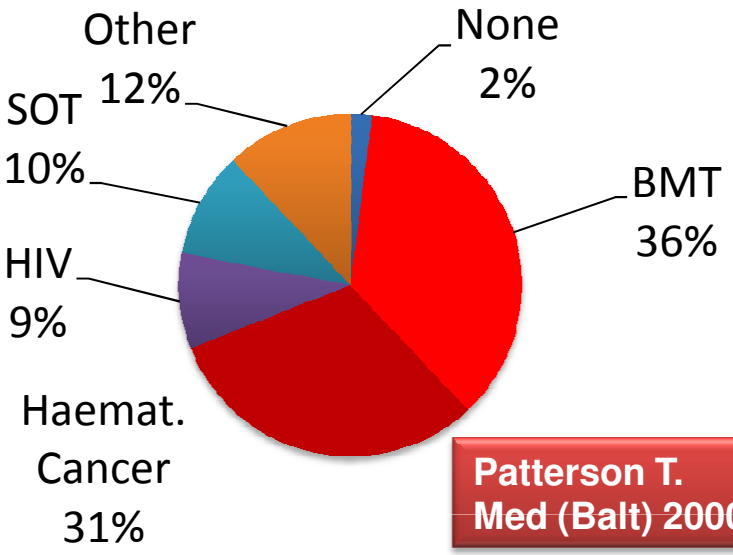
Changing epidemiology of invasive aspergillosis

Aspergillosis: epidemiology

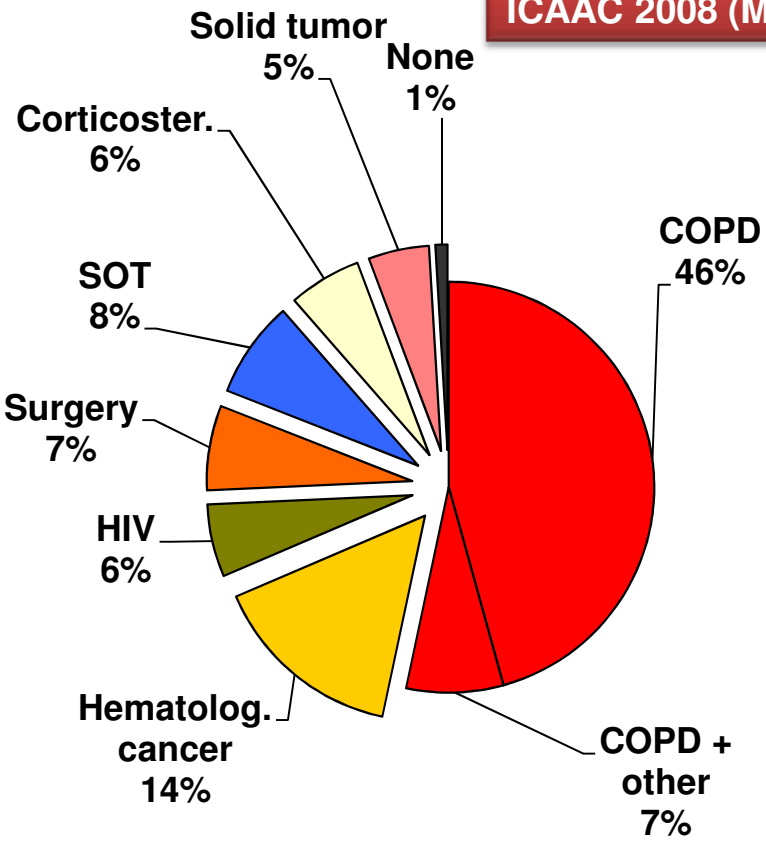


Cornillet. CID 2006

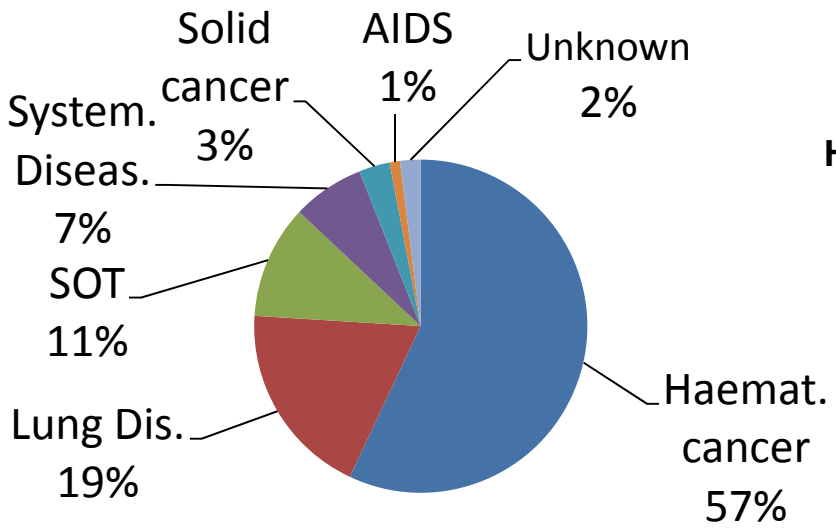
Aspergillosis: epidemiology



Patterson T.
Med (Balt) 2000



Guinea J.
ICAAC 2008 (M-717)



Cornillet.
CID 2006

Aspergillosis and COPD

- Alterations in lung architecture
- Use of corticosteroids
- Frequent hospital admissions (antibiotics)
- Malnutrition
- Other comorbidity (diabetes, alcoholism)

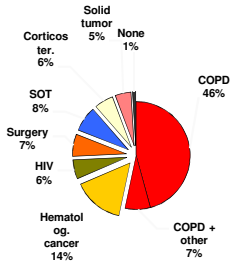
Aspergillosis and COPD

ORIGINAL ARTICLE 10.1111/j.1469-0691.2009.03015.x

Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome

J. Guinea[1,2], M. Torres-Narbona[1], P. Gijón[1], P. Muñoz[1,2], F. Pozo[2,3], T. Peláez[1,2], J. de Miguel[4] and E. Bouza[1,2]

1) Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, 2) CIBER de Enfermedades Respiratorias (CIBERES CD06/06/0058), Palma de Mallorca, 3) Pneumology Department and Clinical Epidemiology Unit, Hospital Universitario Doce de Octubre and 4) Pneumology Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain



Retrospective

2000–2007

Patients with COPD and *Aspergillus* in LRT

53 probable IPA cases (GOLD III and IV)

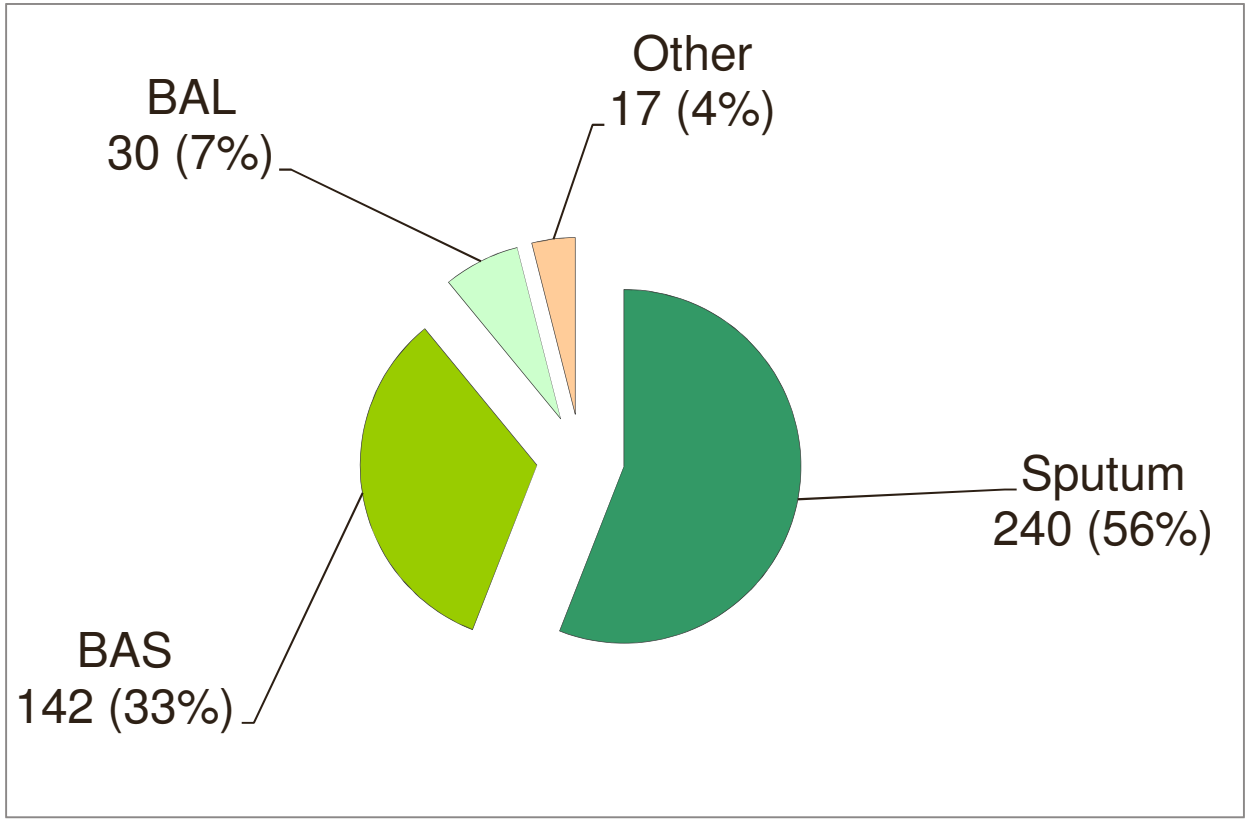
Classification of patients using Bulpa criteria

Guinea J. CMI 2010

Bulpa P. Eur Respir J 2007

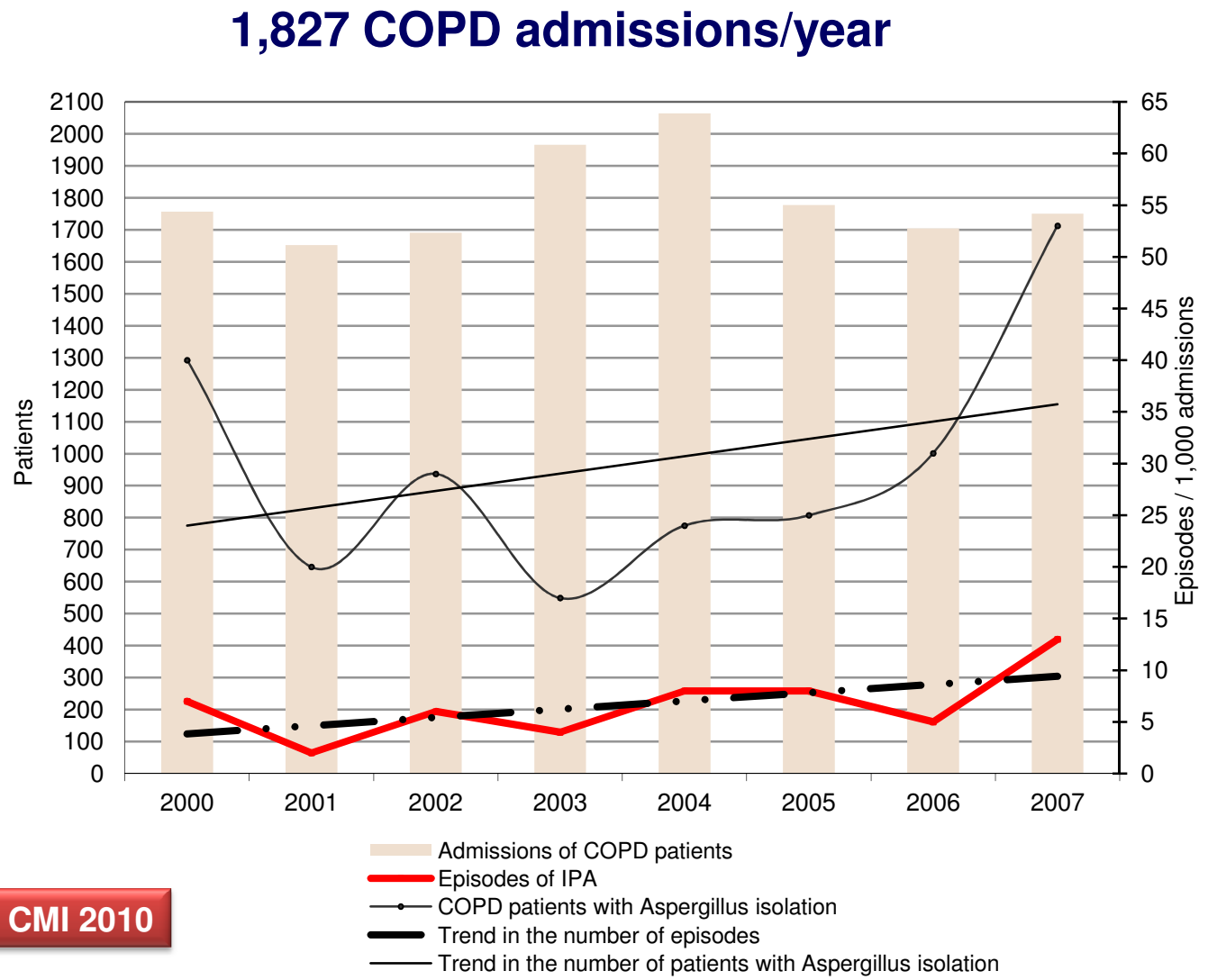
Aspergillosis and COPD

429 LRT samples



Guinea J. CMI 2010

Aspergillosis and COPD: incidence



Guinea J. CMI 2010

Aspergillosis and COPD: incidence

239 patients *Aspergillus* isolation

53 (22%) invasive aspergillosis

50% all cases of invasive aspergillosis

Guinea J. CMI 2010

Aspergillosis and COPD: incidence

Study period	Number of patients			Predisposing conditions	Reference
	Postmortems performed	Cases of IA	Identified in postmortem		
1992	No data	6	5	COPD and asthma	Rodrigues Am J Med 1992
1980-1998	1043	107	75	Haematological	Hori J Hosp Infect 02
1999	222	6	6	ICU (COPD, others)	Dimopoulos J Chemother 03
2003-2006	38	10	3	Haematological	Sinko Transp Infect Dis 07
2004-2005	289	7	7	ICU (no data)	Maris Virchows Arch 06
1984-2002	1630	83	73	AIDS	Antinori Am J Clin Path 09
2004-2005	67	42	16	COPD, other non-haematol	Garbino CMI 11
1989-2008	No data	81	7	Lung disease, haematol, other	Graf BMC Infect Dis 11
1982-2007	866	No data	8	COPD and other	Tejerina Crit Care Med 11

Aspergillosis and COPD: incidence

Incidence (cases/1,000 COPD hospital admissions)	
3.1	Muquim A. Can Respir J 2005
3.6	Guinea J. CMI 2010

Aspergillosis and COPD: risk factors

Aspergillus in LRT samples of patients with COPD

Guinea J. CMI 2010

Aspergillosis and COPD: risk factors

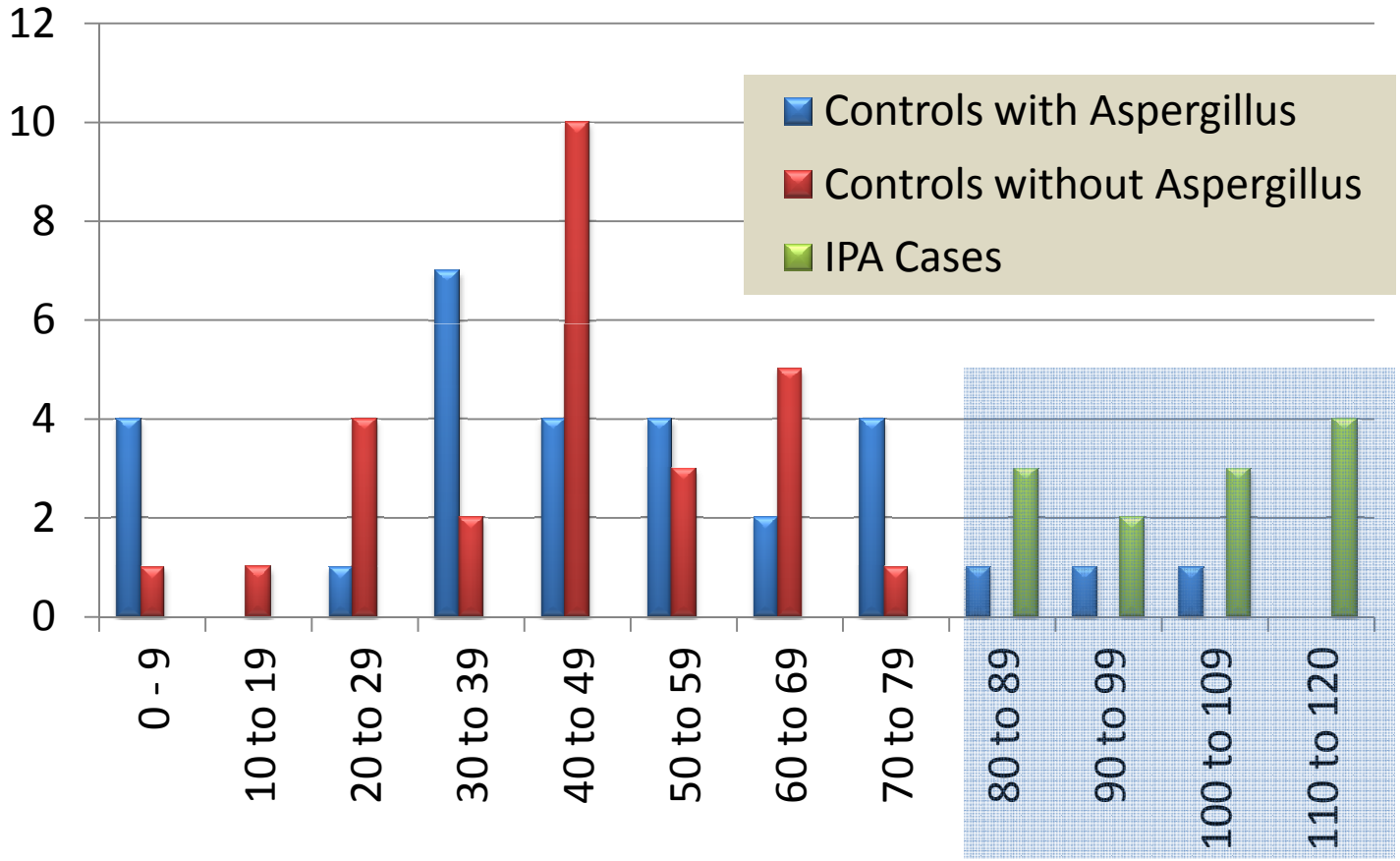
Which variables can predict IPA?

	OR
ICU admission	2.4
Heart insufficiency	2.1
>700 mg prednisone	
3 months prior to admission	3
during the admission	4.6
Antibiotics in the 3 months prior to admission	2.6

Guinea J. CMI 2010

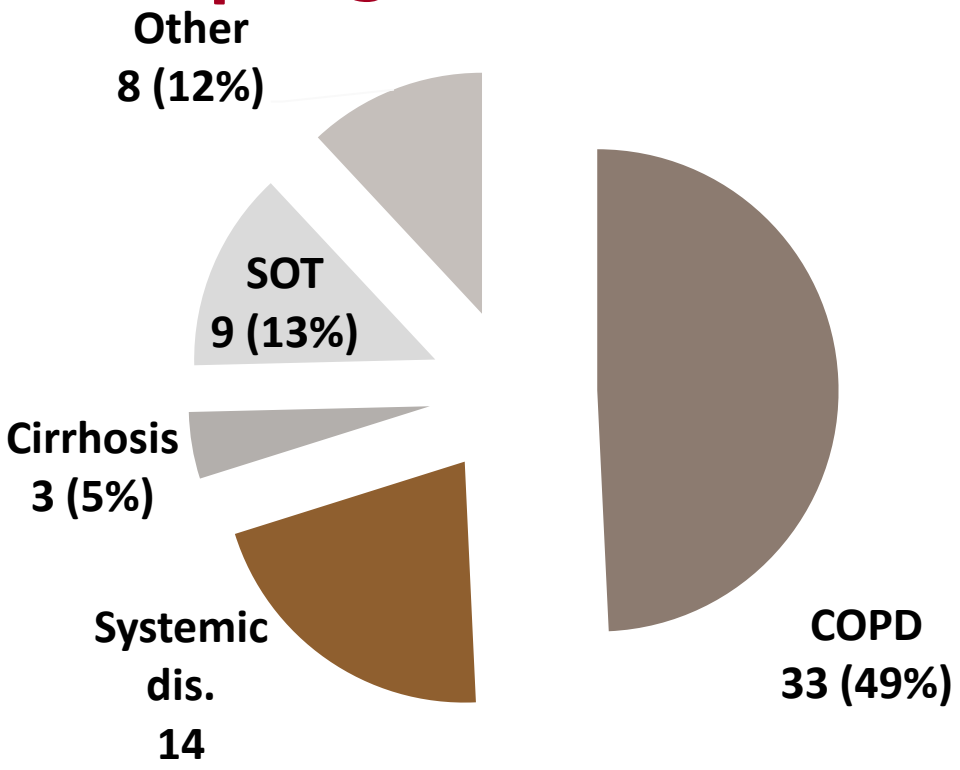
Aspergillosis and COPD: risk factors

Which doses of corticosteroids?



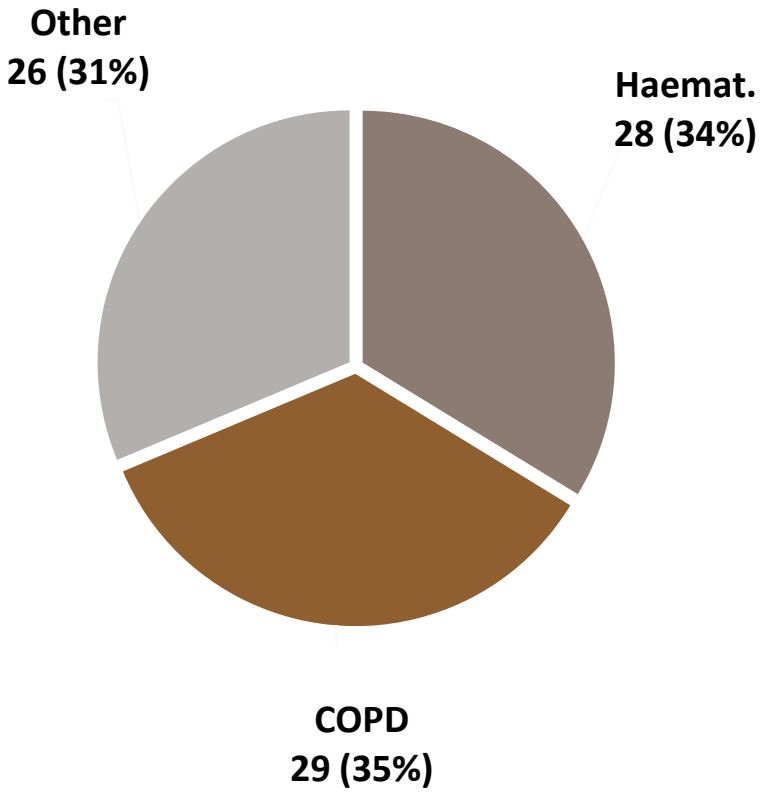
Muquim A. Can Respir J 2005

Aspergillosis and COPD: risk factors



94% received corticosteroids

Meersseman W. AJRCCM 2004



Vandewoude K. Crit Care 2006

Aspergillosis and COPD: outcome

Patients with COPD	Corticosteroids	Mortality	Comments
24	21	100%	ICU
16	16	100%	ICU
13	13	100%	Doses ↑ hospital admission
53	49	72.7%	Not all in ICU (55%)
56	49	95%	Not all in ICU

Rello J. CID 1998

Bulpa P. Intensive Care Med 2001

Ader F. CMI 2005

Guinea J. CMI 2010

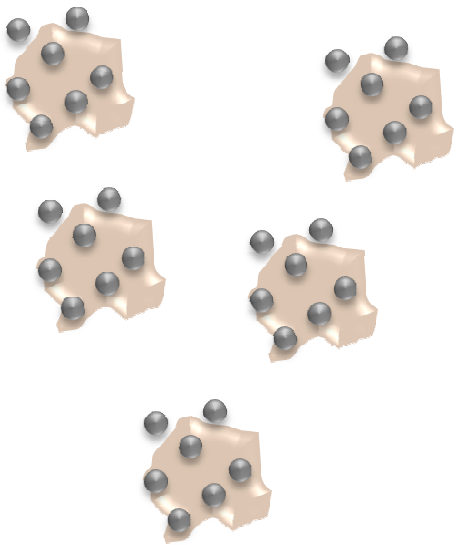
Bulpa P. Eu Resp J 2007

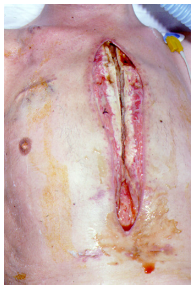
Air–Patient Relationship

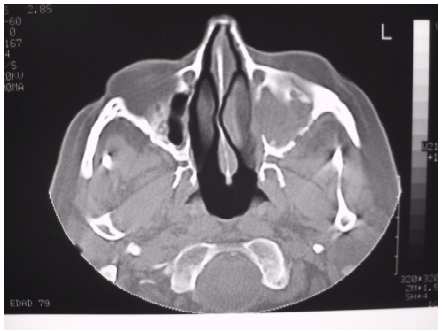
BIOAEROSOLS

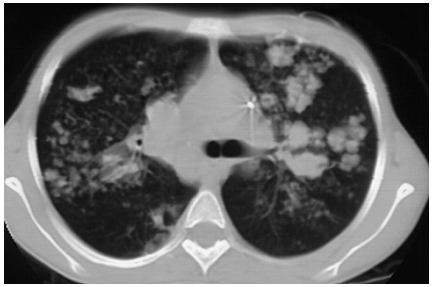
OUTDOOR/
HOSPITAL AIR

PATIENTS









Air–Patient Relationship

JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2011, p. 3498–3503 Vol. 49, No. 10
0095-1137/11/$12.00 doi:10.1128/JCM.01159-11

Molecular Epidemiology of *Aspergillus fumigatus*: an In-Depth Genotypic Analysis of Isolates Involved in an Outbreak of Invasive Aspergillosis▽

Jesús Guinea,[1,2,3,4]* Darío García de Viedma,[1,2,3] Teresa Peláez,[1,2,3,4] Pilar Escribano,[1,2,3] Patricia Muñoz,[1,2,3,4] Jacques F. Meis,[5] Corné H. W. Klaassen,[5] and Emilio Bouza[1,2,3,4]

MAJOR ARTICLE

Outbreak of Invasive Aspergillosis After Major Heart Surgery Caused by Spores in the Air of the Intensive Care Unit

T. Peláez,[1,2,3] P. Muñoz,[1,2,3] J. Guinea,[1,2,3] M. Valerio,[1,2] M. Giannella,[1,2] C. H. W. Klaassen,[4] and E. Bouza[1,2,3]

[1]Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, [2]Department of Medicine, Faculty of Medicine, Universidad Complutense, Madrid, [3]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES CD06/06/0058), Palma de Mallorca, Spain; and [4]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

Air–Patient Relationship

- 10 patients with proven IA (n=2), probable IA (n=4), and colonized (n=4) by *A. fumigatus*
- Not severely immunocompromised (two with COPD)
- Environmental control in the air of the unit
- *C*linical (n=108) and environmental (n=59) isolates
- Molecular genotyping (STR*Af*)

Pelaez T. CID 2012

Guinea J. J Clin Microbiol 2011

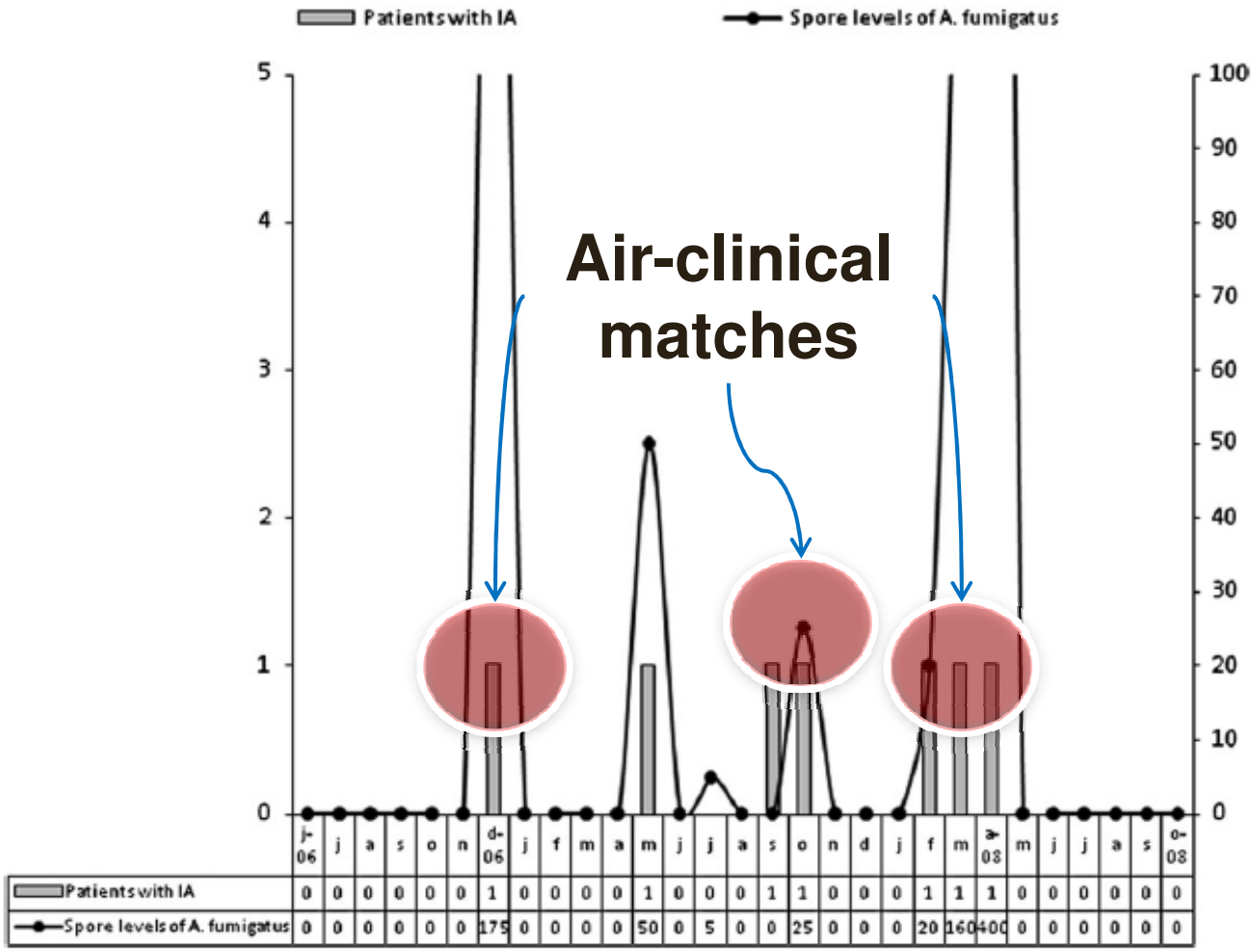
Air–Patient Relationship

	Date	Diagnosis
1	December 06	**Mediastinitis**
2	May 07	**IPA**
3	September 07	**IPA**
4	October 07	**IPA**
5	February 08	**IPA**
6	March 08	**IPA**
7	April 08	**Mediastinitis and IPA**

Pelaez T. CID 2012

Guinea J. J Clin Microbiol 2011

Air–Patient Relationship



Pelaez T. CID 2012

Guinea J. J Clin Microbiol 2011

Basis of microbiological diagnosis of invasive aspergillosis in non-neutropenic patients

Diagnosis of Invasive Aspergillosis

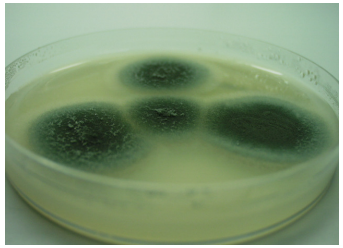
Limitations of the diagnosis

1. Low index of suspicion (delay)
2. Diagnostic tools with limitations

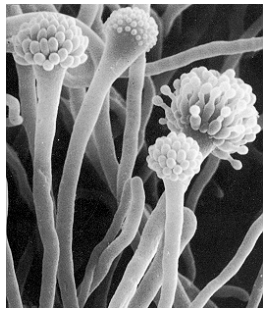
Diagnosis based on the combination of

- Compatible clinical signs
- Histopathology findings
- Radiological findings
- Microbiological findings

Diagnosis of IA: culture



Slow



Moderate sensitivity:

- 50-60% in patients with invasive aspergillosis
- Late stages of the infection

Levi SJ. Sem Respir Infect 1992

Tarrand. Am J Clin Pathol 2003

Rickerts V. CID 2007

Moderate PPV:

- 55.5% in ICU
- 22% in COPD
- 12% in non-selected patients

Perfect J. CID 2001

Garnacho J. Crit Care 2005

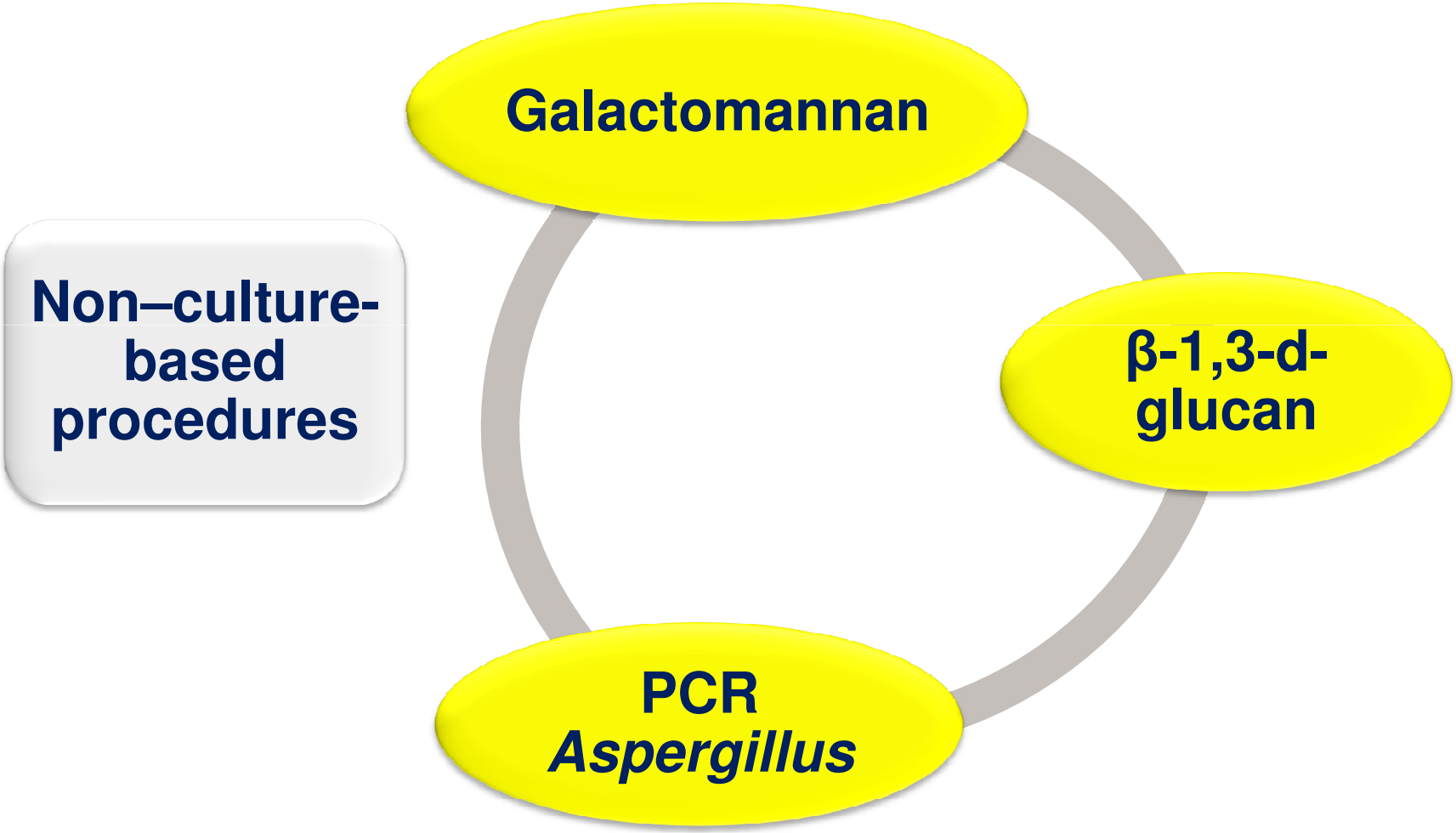
Bouza. J Clin Microbiol 2005

Guinea J. CMI 2010

Diagnosis of IA: culture

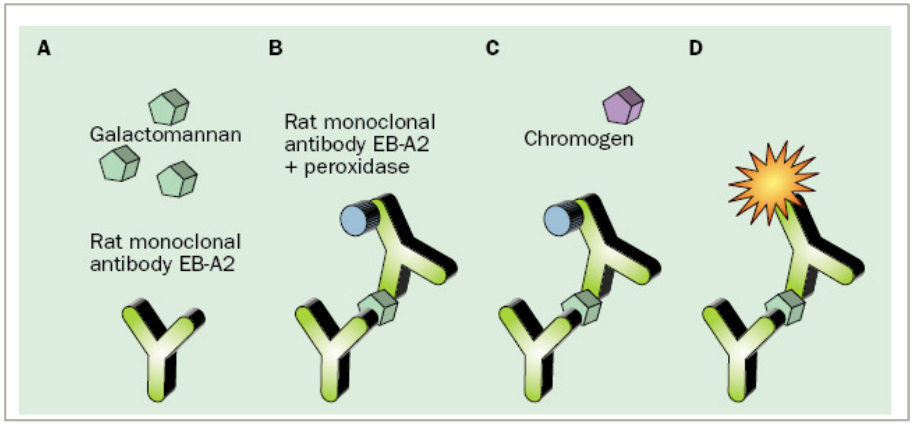
- Patient with severe COPD receiving steroids
- Patient with pneumonia not responding to antibiotics
- New pulmonary infiltrates
- Positive culture
- Efforts to diagnose and start antifungal treatment

Diagnosis of IA: other procedures



Diagnosis of IA: galactomannan

- Polysaccharide component of the fungal wall
- Initiation of fungal growth
- Platelia *Aspergillus* ® (Bio-Rad)



- Basically assayed on serum samples

Diagnosis of IA: galactomannan

- Meta-analysis of 27 studies (↑ heterogeneity)
- Differences in cut-off chosen to define positivity

	Sensitivity	Specificity
Proven	0.71	0.89
Proven and probable	0.61	0.93
SOT	41	85

Sensitivity varies with the underlying disease

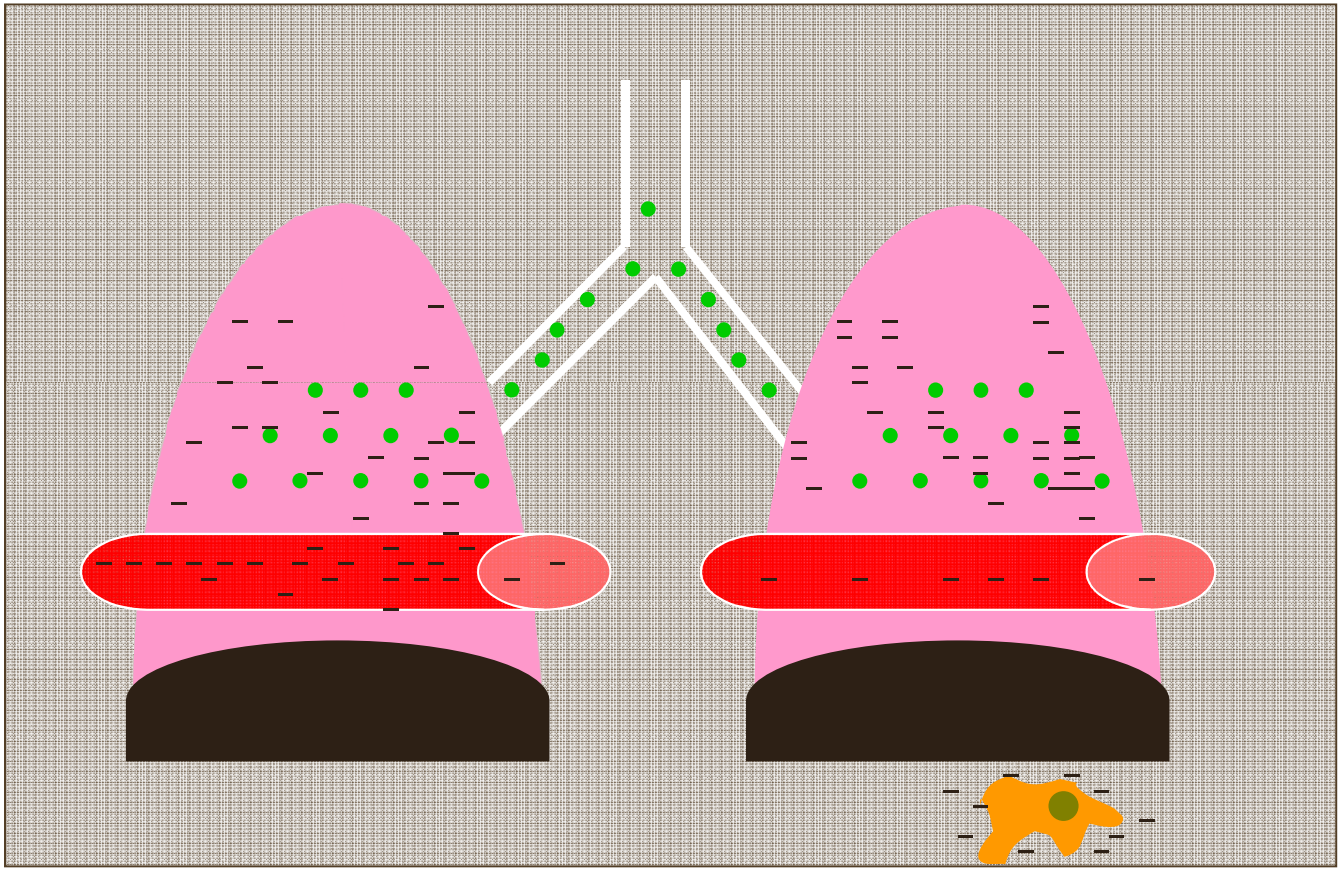
Pfeiffer. Clin Infect Dis 2006

Diagnosis of IA: galactomannan

Serum determination

	Sensitivity	Specificity	
≥0.5	60%	92.3%	Guinea J. Med Mycol 2008
≥1	40%	100%	Guinea J. CMI 2010
≥1	53%		Meersseman W. AJRCCM 2004
≥0.5	58%	88%	He H. Med Mycol 2010
≥0.5	46%	83.3%	He H. Crit Care 2011

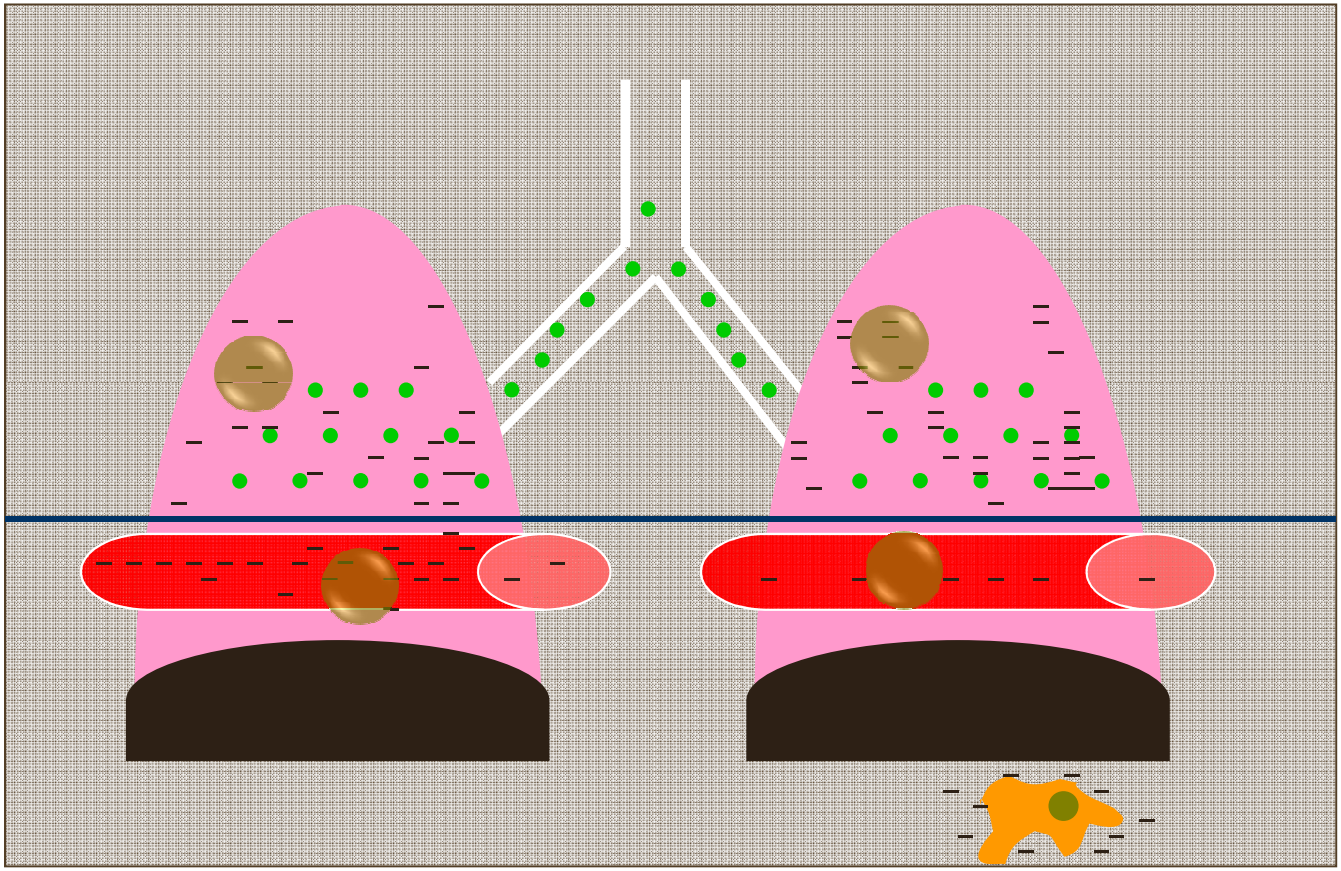
Diagnosis of IA: galactomannan



NEUTROPENIC

NON-NEUTROPENIC

Diagnosis of IA: galactomannan

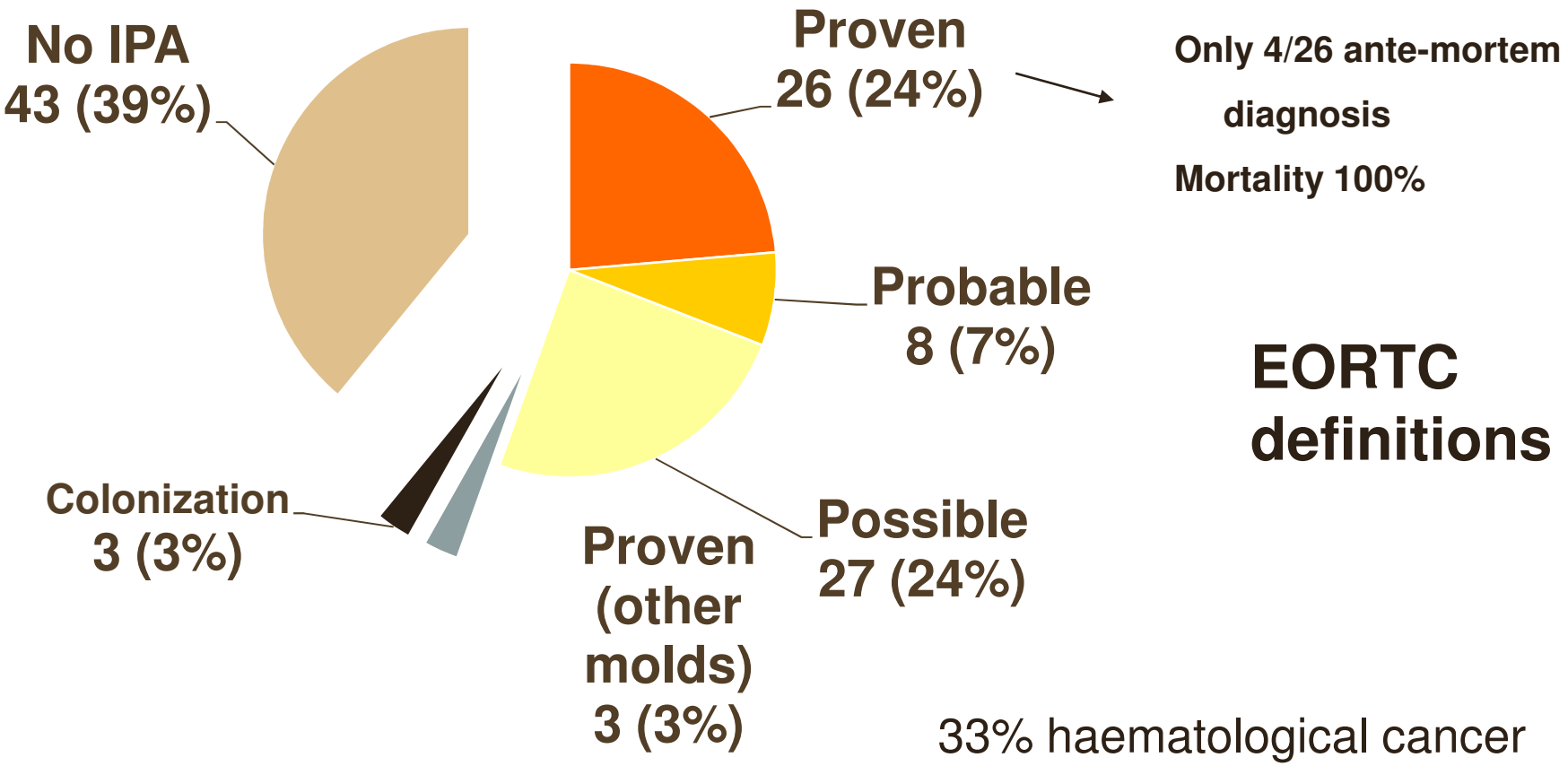


NEUTROPENIC

NON-NEUTROPENIC

Diagnosis of IA: galactomannan

1109 patients admitted → 110 patients included



EORTC definitions

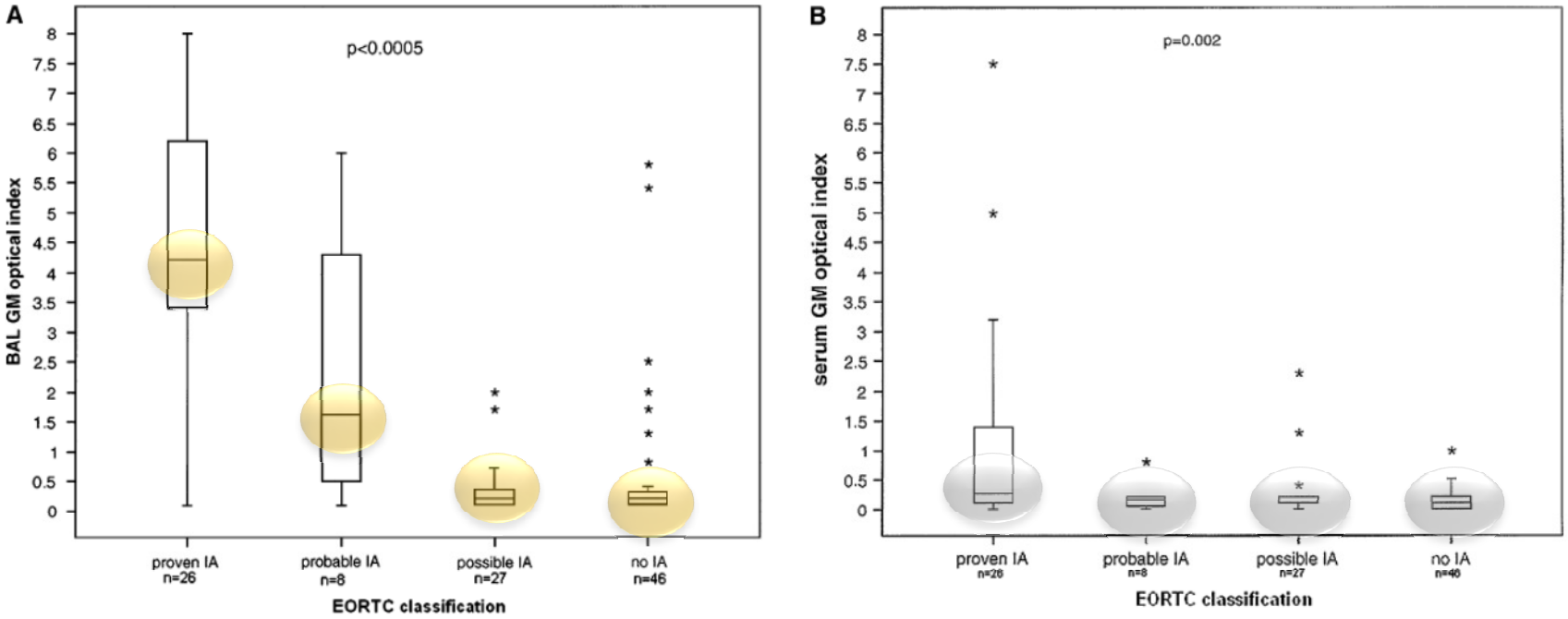
33% haematological cancer

(22% neutropenia)

Meersseman W et al. AJRCCM 2008

Diagnosis of IA: galactomannan

- Mean: BAL day +6 admission to the ICU
- 156 BAL samples (GM + >0.5)



Meersseman W et al. AJRCCM 2008

Diagnosis of IA: galactomannan

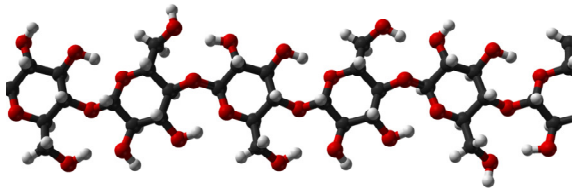
	S (proven)	Sp
Culture	58%	-
GM serum	42%	96%
GM BAL	88%	87%

9/26 no antifungal therapy

Meersseman W et al. AJRCCM 2008

Diagnosis of IA: β-1,3-d-glucan

- **Panfungal biomarker**
- **Serum detection**
- **No data on COPD patients**



~~**Cryptococcosis**~~

~~**Mucormycosis**~~

S	Sp		
79%	87.7%	**Meta-analysis**	**Karageorgopoulos CID 2011**
76%	85%	**Meta-analysis**	**Lu Y Internal Med 2011**
80%	82%	**IFI**	**Onishi A JCM 2012**
77%		**Invasive aspergillosis**	**Karageorgopoulos CID 2011**

Antifungal of choice for treatment of invasive aspergillosis in patients with COPD

Aspergillosis and COPD: treatment

- Poor clinical response with amphotericin B
- Voriconazole for primary treatment (A-I)
- IV 6 mg/kg/12 h for 1 day, followed by 4 mg/kg/12 h
- Few COPD patients in the clinical trials
- PK/PD considerations (serum levels):
  - Poly-medication (ICU)
  - Difficult interpretation
  - Azole resistance (Netherlands and UK)

Herbretch. NEJM 2002

Verweij. NEJM 2007

Walsh T. CID 2008

Howard. EID 2009

- **COPD is emerging as a cause of IA**
- **Incidence is unknown but it is probably underestimated**
- **Corticosteroids as a risk factor**
- **Difficulty obtaining a diagnosis of IA**
- **Optimal treatment should be defined**
- **Problems of azole resistance**