

The changing epidemiology of invasive aspergillosis

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Outline

- How frequent is aspergillosis in the general population?
- Which diseases are associated with aspergillosis? What are the relative risks for the different diseases?
- Are there new risk factors on the horizon?



Question 1: What is correct?

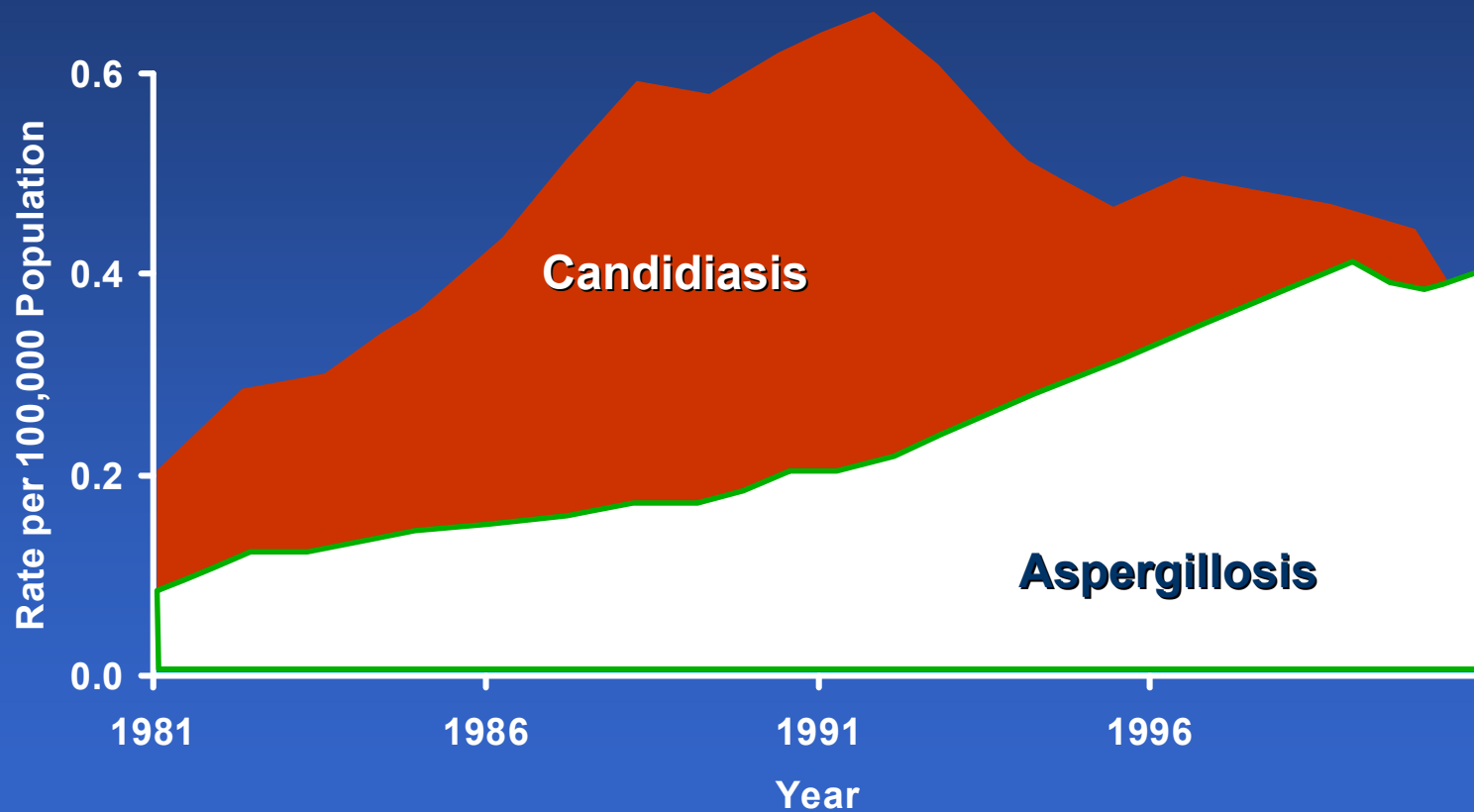
- 1 Invasive aspergillosis in the ICU is more frequent than aspergillosis in a neutropenic patient on hemato ward
- 2 The incidence of mucormycosis = half of the incidence of invasive aspergillosis.
- 3 Based on culture, the highest colonisation rate of aspergillosis is found in patients with COPD
- 4 In anti-TNF treated patients, the risk of contracting invasive aspergillosis is around 20%
- 5-In patients with chronic granulomatous disease, the life time risk of aspergillosis is 30%



Question 2: What is wrong?

- 1 - Aspergillosis in critically ill patients with H1N1 is related to the steroids that are given to treat the ARDS
- 2 - Patients with mucormycosis are frequently co-infected with Aspergillus
- 3 - There are roughly 500.000 cases of acute invasive aspergillosis worldwide annually
- 4 Among solid organ transplant recipients, liver transplants contain the highest risk to develop aspergillosis

Incidence of fatal invasive mycoses in USA



Mc Neil et al 2001 *Clin Infect Dis* 33;641

Estimated number of cases of invasive fungal infection UK [2002]

Patient group	Number of patients	Invasive candidosis/candidaemia risk estimates**	Expected number invasive candidosis/candidaemia	Invasive aspergillosis risk estimates@	Expected number invasive aspergillosis
Allo HSCTx	793	4%	32	10%	79
Solid organ Tx	2953	5%	148	1.9%	56
Leukaemia	16269	3%	488	6%	976
Solid tumour (neutropenic)	28955	3%	869	2%	579
Advanced cancer	131678	1%	1316	1.5%#	1975
ICU	210130	1%	2101	0.2%	420
Burns	378	5.6%	21	1.9%	7
Renal dialysis	24536	0.2%			
HIV/AIDS	661	0.2%			
Totals			5466		4120

Probably significant underestimates

** no estimate for surgical patients, but some are in ICU, or have advanced cancer

@ no inclusion of most chronic chest, steroid-treated patients, an increasing group

the literature figure is 6%, but felt to be autopsy selection bias, so reduced by 75%.

Prospective data on culture

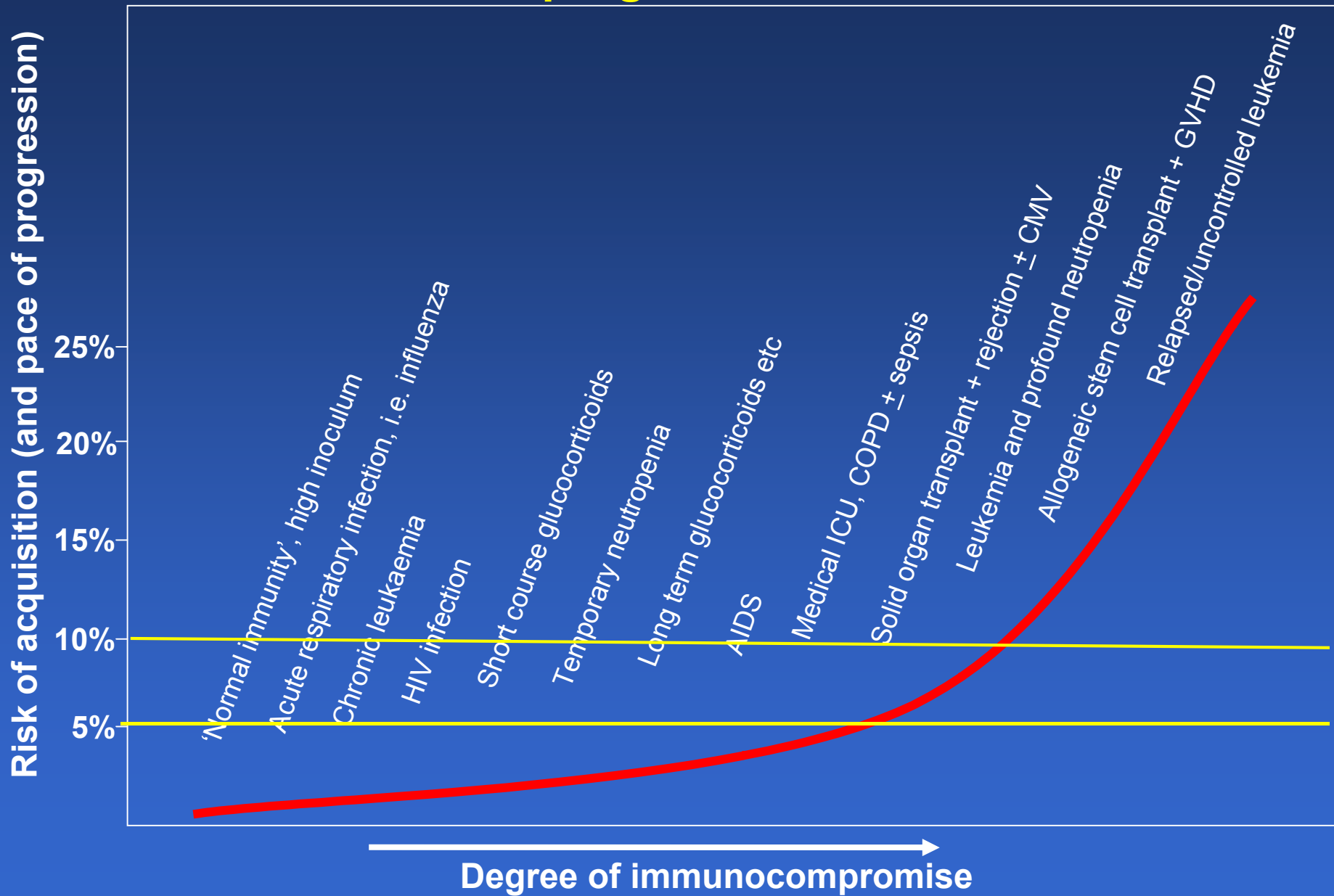
- 4 Danish hospitals (3 months) (Jan March 2007)
 1. 11.368 airway samples
 2. 129 – 151 patients
 3. Proven (n=3), probable (n=11), ABPA (n=4), colonised (n=133)
 4. 55% cystic fibrosis, 13% COPD, 7% hematological, 18% ICU
 5. ? Incidence 0.9-1.1 per 100.000 inhabitants

Mortensen KL et al. A prospective survey of *Aspergillus* spp, in respiratory tract samples. *Eur J Clin Microb Infect Dis* 2011, 30:1355

An example of a prospective data base

- SAIF network 2005-2007
- 393 adults from 12 hospitals
- 0.271 per 1.000 admissions
 - 15% proven disease
 - 78% haematological conditions
 - 92% lung involvement
 - lymphoprolif disorders new emerging group
 - 12-week mortality 44.8%

Examples of at-risk patients and pace of progression



Acute pulmonary aspergillosis in immunocompetent subjects after exposure to bark chippings

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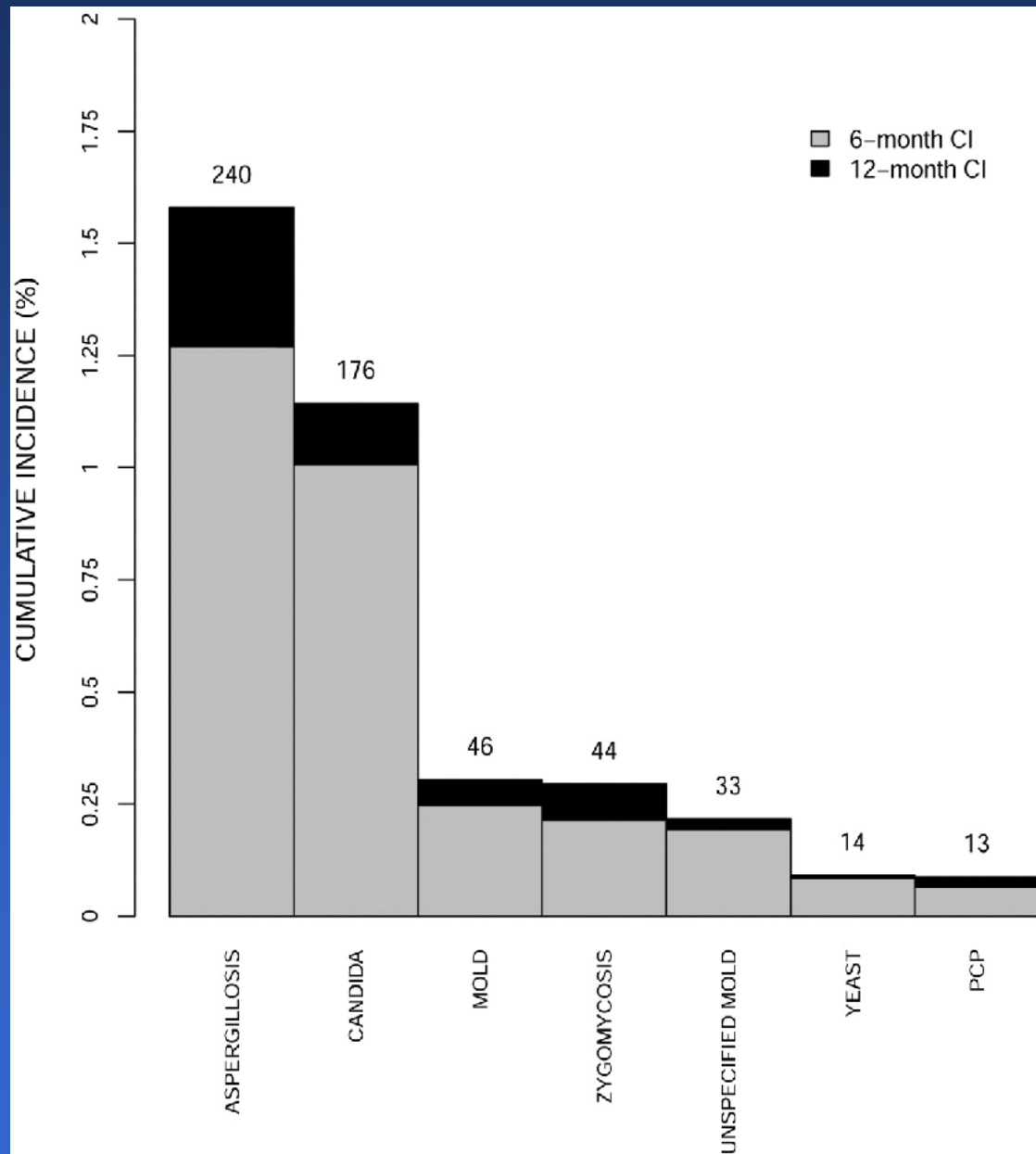
Clinical epidemiology (US data)

Underlying disease (960 patients) (2004-2008)

1. Haematological malignancy	464	48.3 %
2. Solid organ transplant	280	29.2 %
3. Stem cell transplant	268	27.9 %
4. HIV/AIDS	14	1.5 %
5. Immunodeficiency	4	0.4 %
6. Other	22	2.3 %

Steinbach WJ et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect 2012, 65, 453-464

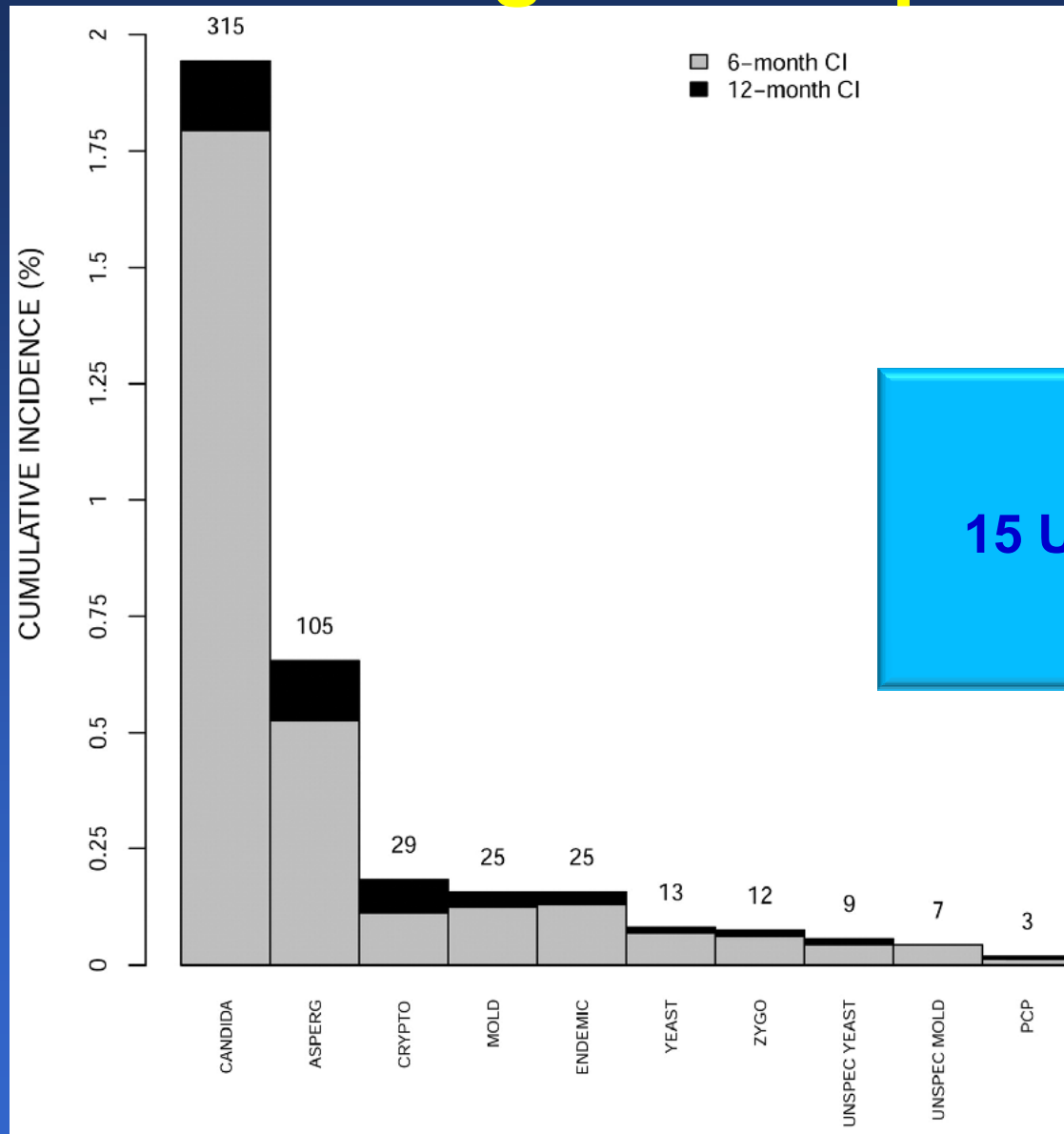
Adult HSC T recipients



D. Kontoyiannis et al., CID 2010,
50: 1091-1100

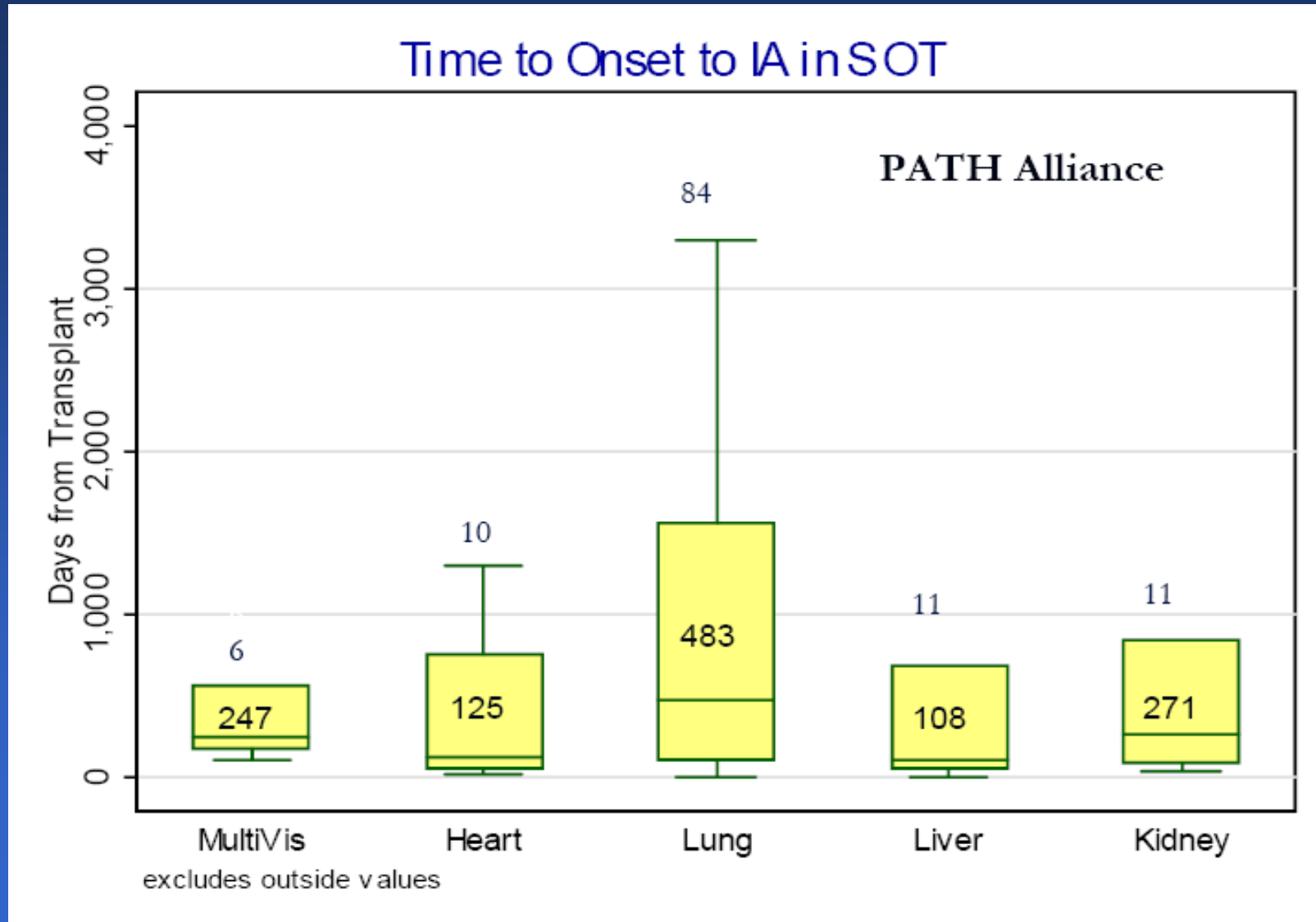
TRANSNET, 983 IFI
23 US transplant centers
2001-2006

Organ transplant recipients

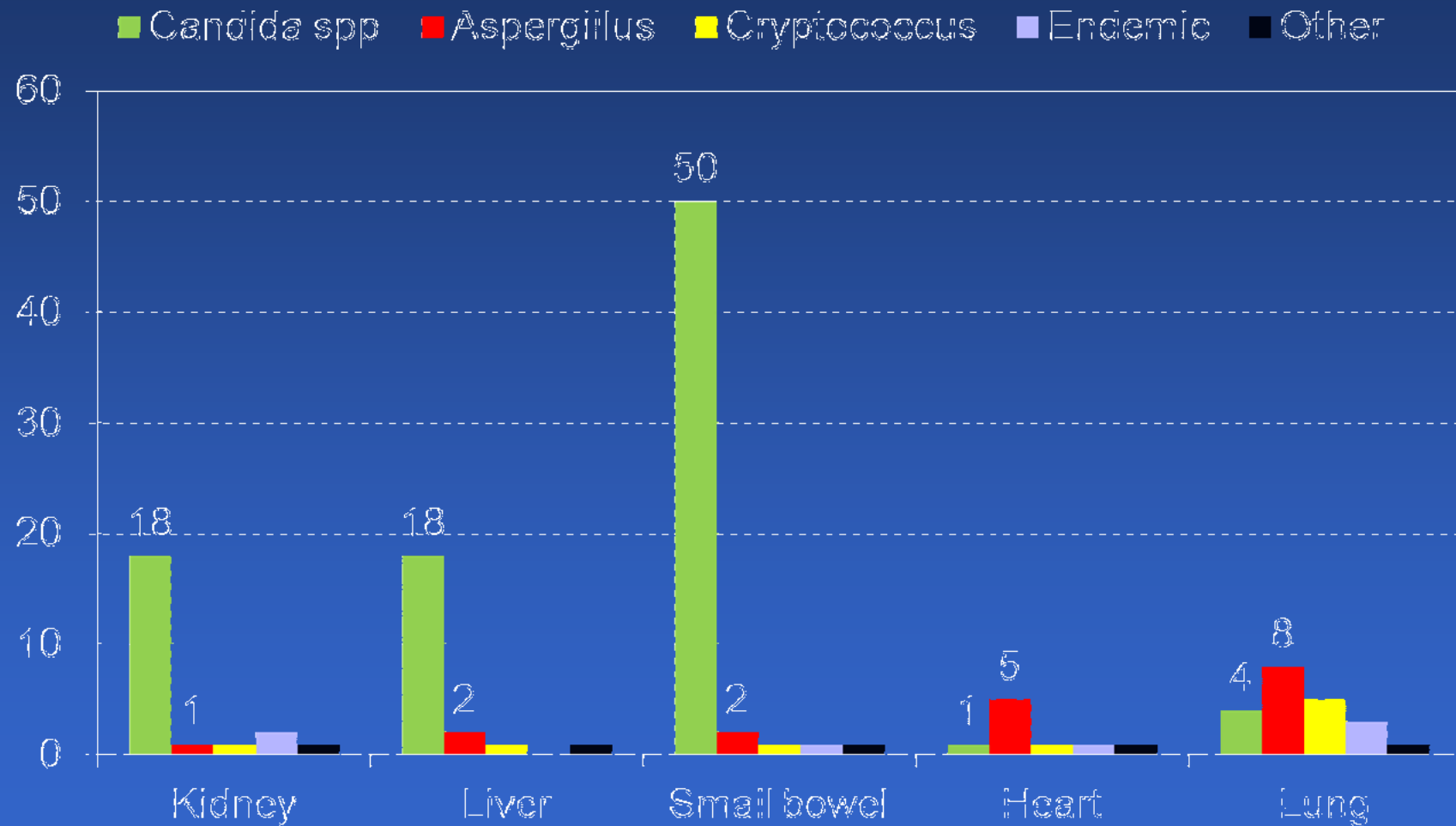


TRANSNET, 1208 IFI
15 US organ transplant centers
2001-2006

Increased time to onset of IA in SOT

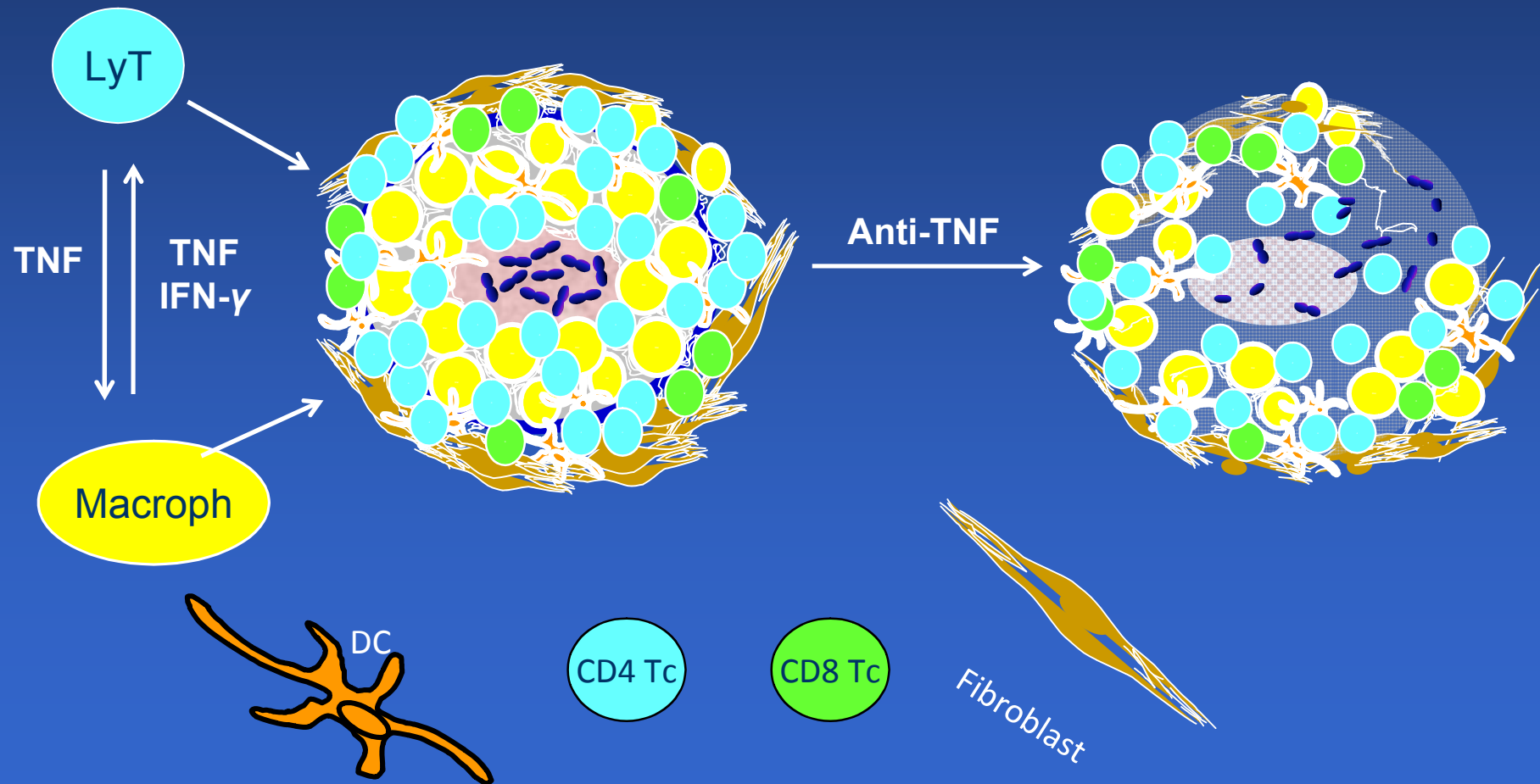


Invasive fungal infections in SOT recipients

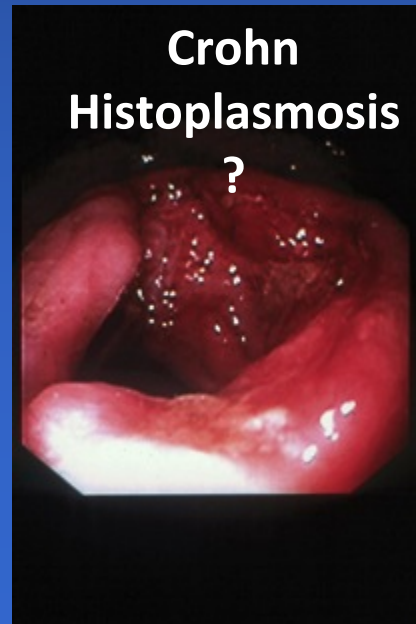
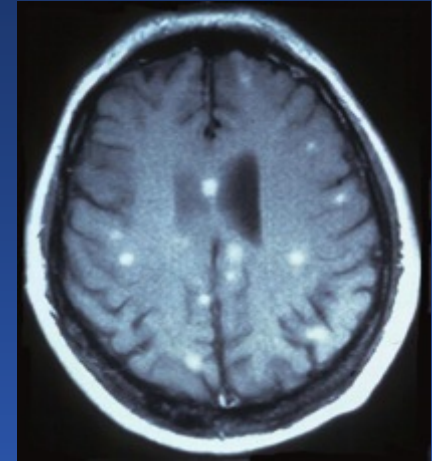
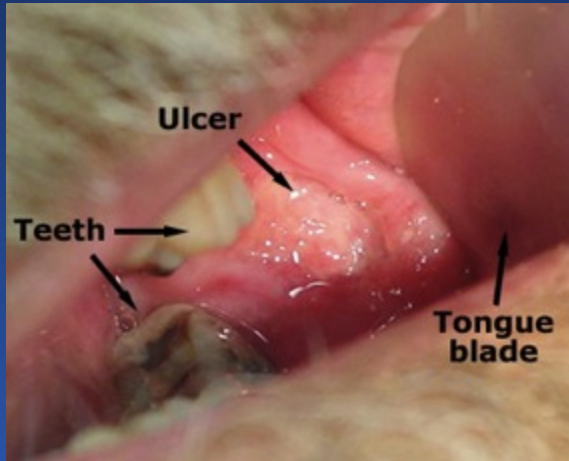


Kubak Bm. Transpl Infect Dis 2002; 4: 24-31

Anti-TNF → granuloma suppression



Histoplasmosis in anti-TNF-treated patients



Anti TNF & *Histoplasma capsulatum*

10 cases; 9 infliximab
1 wk-6 mo after initiation
9 in ICU, 1 death

Lee, Arthritis Rheum 2002



Increased number of cases in USA (240 cases reported to FDA)

3 x more frequent than TB in anti-TNF- α living in endemic areas

Most frequent IFI; mortality = 20%

Infliximab (x7) > Etanercept

Pneumonia/dissemination (70-80%)

Hage et al. CID 2010

IRIS = 42% cases in Indianapolis

Screening not useful (Ag/Ab)

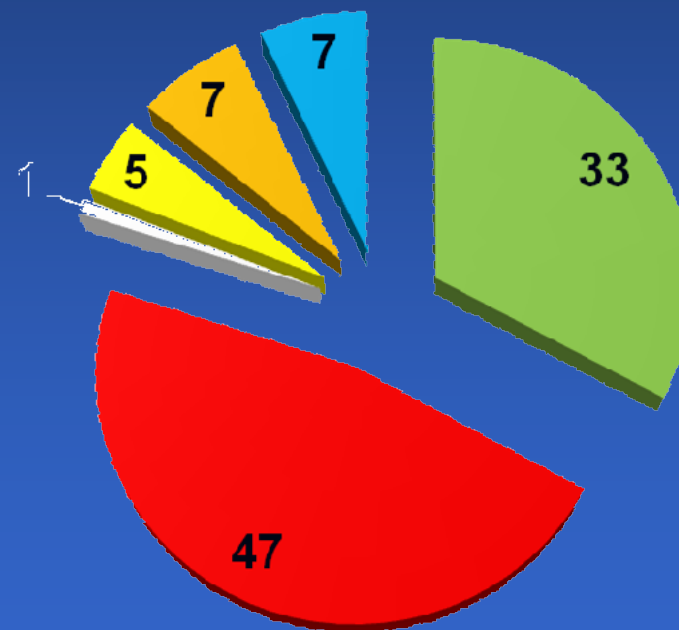
Anti-TNF may be restarted if ATF \geq 1 year without relapse

Incidence of IA in immunocompromised children

Underlying disease	N	Incidence IA (%)
Malignancy	99 177	0.5
solid tumour		0.1
leukaemia		1
ALL and AML		0.6 and 3.7
Hematologic disorder (AA)	12 829	1.4
Immunodeficiency	3733	3.2
WAS	267	30
CGD	322	6.5
CID	411	1.7
cong. hypogammaglobulinaemia	119	3.3
BMT	3013	3.4
allogeneic	2219	4.5
autologous	822	0.3
Solid-organ transplant	1593	0.3
lung	39	5
heart	278	0.3
liver	569	0.5

Where in the hospital does *invasive aspergillosis* occur?

- Hematology adult
- Intensive Care Unit
- Thoracic Surgery
- Pneumology
- Infectious Disease
- Hematology pediatric



Parameter	All (n=127)	Proven (n=56)	Probable (n=49)	Possible (n=2)	Colonization (n=20)
Age, yrs, mean	61	59	63	61	64
Sex, male, n	84	39	35	2	8
Haematological patients, n	38	26	12	0	0
Nonhematological patients, n	89	30	37	2	20
• COPD, n	35	12	21	2	0
• Solid organ transplants, n	9	4	5	0	0
• Systemic disease, n	17	6	8	0	3
• Cirrhosis, n	6	3	0	0	3
• Other, n	22	5	3	0	14
SAPS II, mean	54	57	52		54
Predicted mortality, %	53%	58%	49%		
Observed mortality, %	86%	98%	90%		
ICU length of stay, days	20	14	23		
Hemodialysis in ICU, n	54	27	20		
Mechanical ventilation, n	123	56	47		
Neutropenia (<500/mm ³), n	19	12	6		
Autopsy, n	76	52	19		

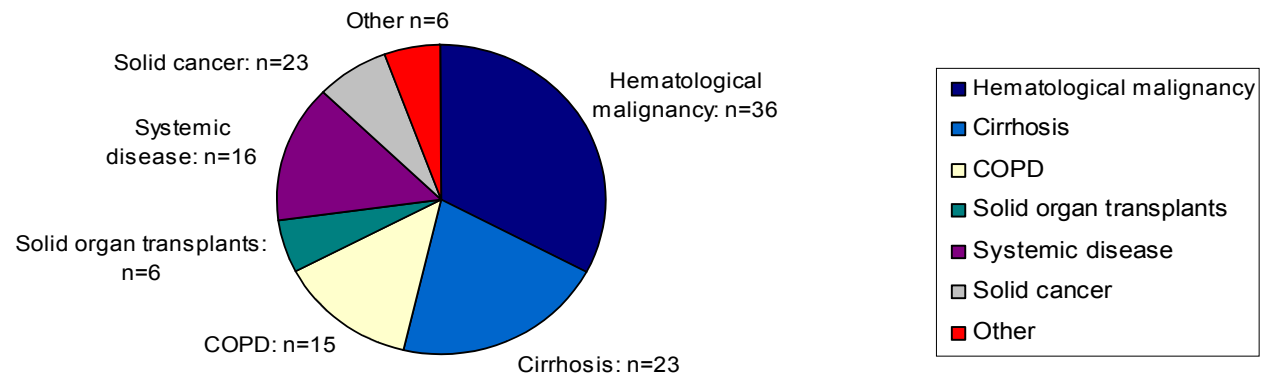
6.9% of all admissions
Retrospective
A lot of autopsy data
1850 admissions

Meersseman W. Invasive aspergillosis in critically ill patients without malignancy *Am J Respir Crit Care Med* 2004

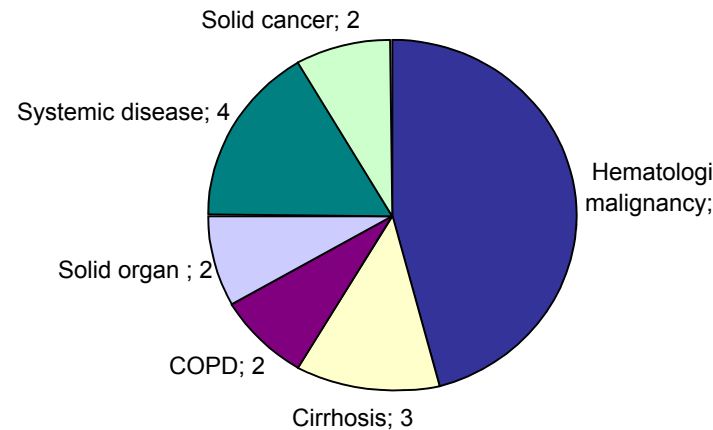
1109 admissions
 Medical ICU
 18 months
 (06/05-12/06)
 Modified EORTC criteria

Am J Resp Crit Care Med 2008, 177: 27-34.

n = 110



Proven: n = 26 .



10% of all admissions at risk
 Prospective study
 2.3% proven aspergillosis

Microscopic analysis on sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Culture on sterile material: recovery of *Aspergillus* by culture of a specimen obtained by lung biopsy

Probable invasive pulmonary aspergillosis (all three criteria must be met)

1. Host factors (one of the following)

- Recent history of neutropenia (<500 neutrophils/mm³) for 110 d
- Receipt of an allogeneic stem cell transplant
- Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for 13 wk
- Treatment with other recognized T-cell immunosuppressants
- Inherited severe immunodeficiency

2. Clinical features (one of the following three signs on CT)

- Dense, well-circumscribed lesion(s) with or without a halo sign
- Air-crescent sign
- Cavity

3. Mycological criteria (one of the following)

- Direct test (cytology, direct microscopy, or culture) on sputum, BAL fluid, bronchial brush indicating presence of fungal elements or culture recovery *Aspergillus* spp.
- Indirect tests (detection of antigen or cell-wall constituents): galactomannan antigen detected in plasma, serum, or BAL fluid

Possible invasive pulmonary aspergillosis

Presence of host factors and clinical features (cf. probable invasive aspergillosis) but in the absence of or negative mycological findings.

Ascioglu S et al. Defining opportunistic invasive fungal infection in immunocompromised patients with cancer and HSCT. *Clin Infect Dis* 2002; 34: 7-14
De Pauw B et al. Revised definitions of invasive fungal disease (EORTC/MSG consensus group) *Clin Infect Dis* 2008; 46: 1813-21

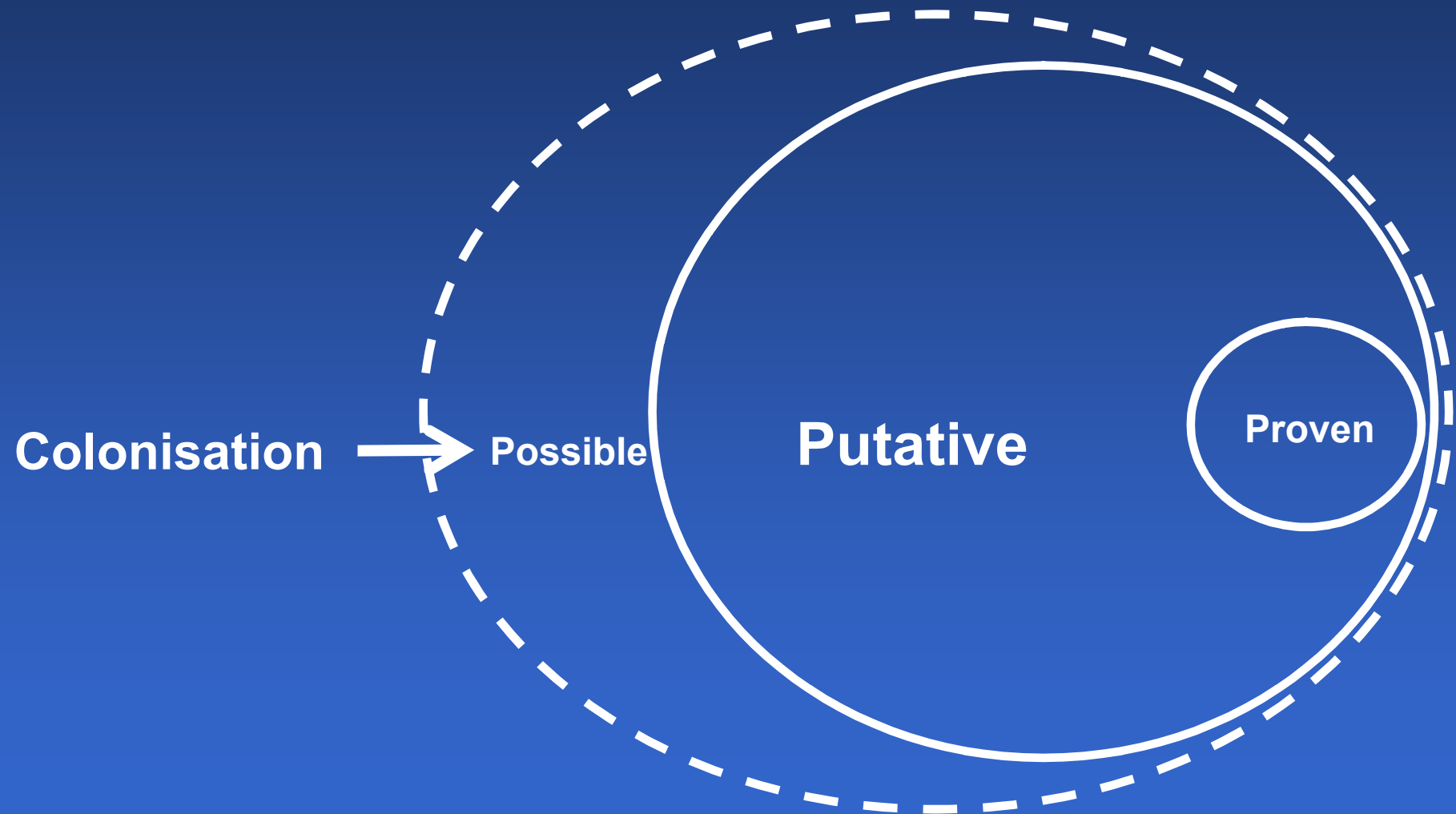
Clinical relevance of *Aspergillus* isolation from ETA in critically ill patients

Putative IPA

1. LRT sample positive for *Aspergillus* (entry criterion)
2. Compatible signs and symptoms
3. Abnormal medical imaging of chest
4. Either:
 - (a) Host risk factors:
 - neutropenia,
 - hemato-oncologic malignancy + cytostatics
 - steroid treatment >20 mg/day
 - immunodeficiency
 - (b) BAL:- semiquantitative positive culture +/-++
and
 - positive cytologic exam (branching hyphae)

Vandewoude K, et al. Crit Care 2006; 10: R31.

Spectrum from colonisation to invasive disease



A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients



Stijn I. Blot¹, Fabio Silvio Taccone², Anne-Marie Van den Abeele³, Pierre Bulpa⁴, Wouter Meersseman⁵, Nele Brusselaers¹, George Dimopoulos⁶, José A. Paiva⁷, Benoit Misset⁸, Jordi Rello⁹, Koenraad Vandewoude¹, Dirk Vogelaers¹, and the *AspICU* Study Investigators*

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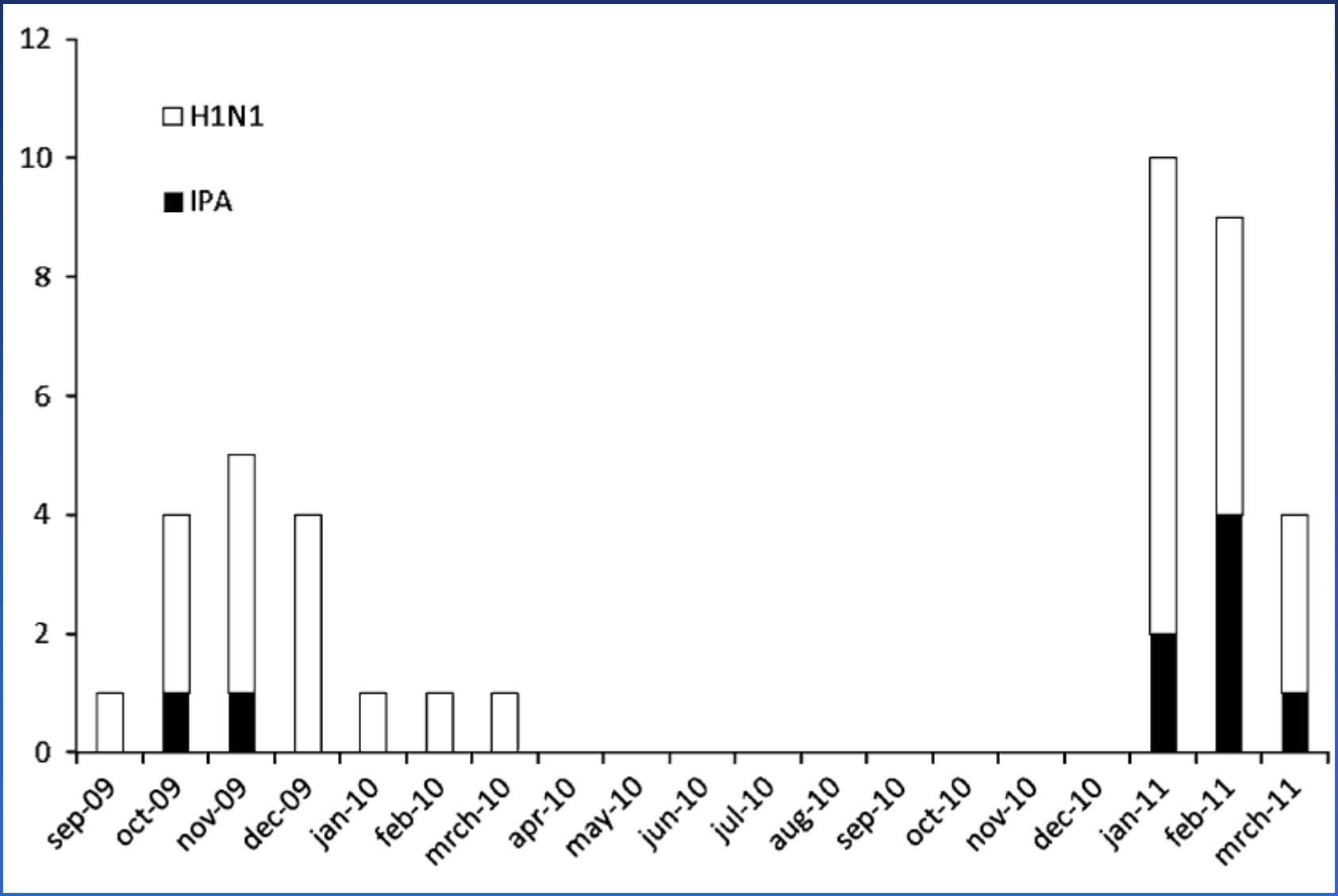
Am J Respir Crit Care Med Vol 186, Iss. 1, pp 56-64, Jul 1, 2012
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DOI 10.1007/s00134-012-2673-2

ORIGINAL

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Wouter Meersseman
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Alexander Wilmer
Philippe Jorens
Greet Hermans

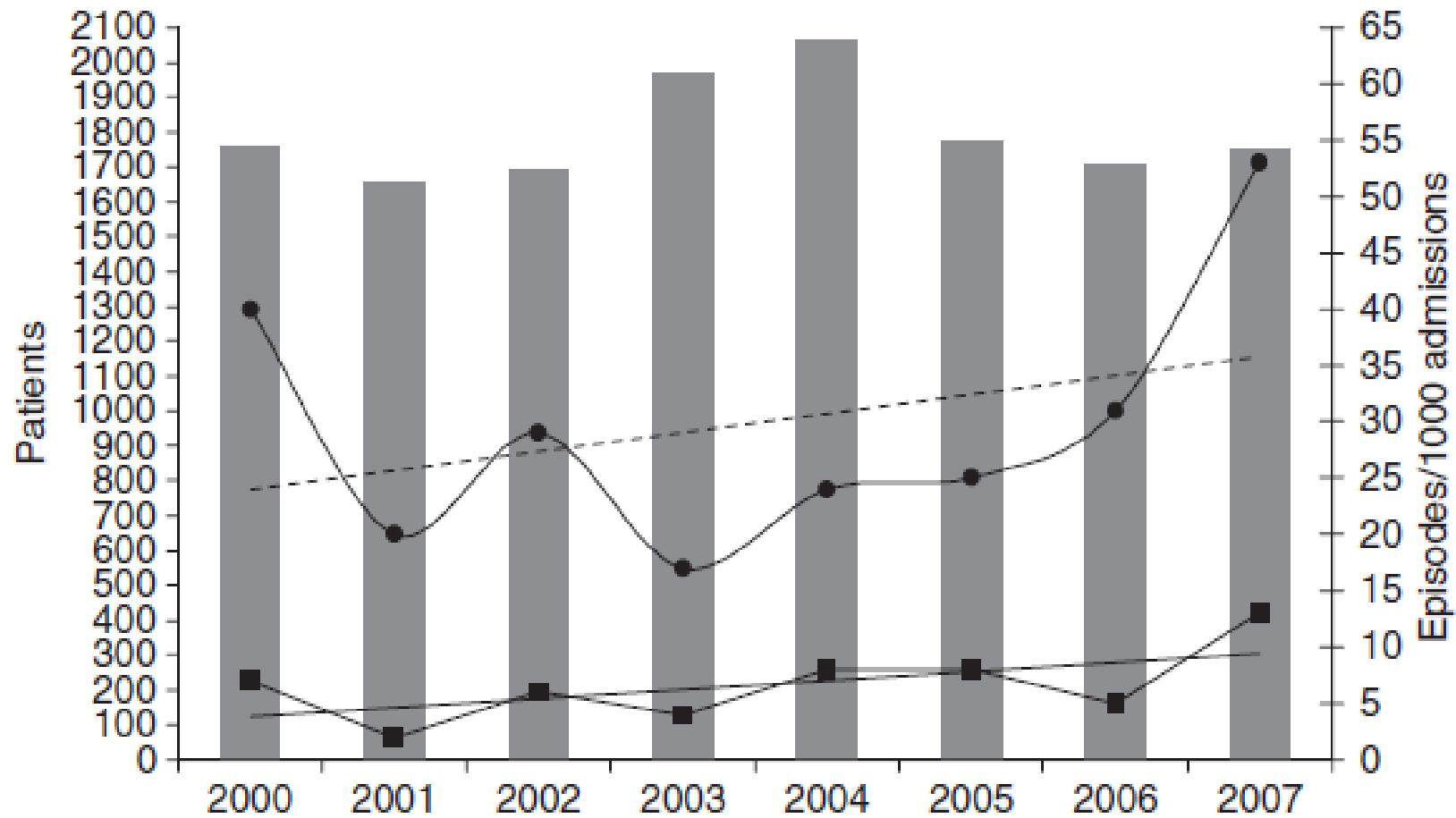
Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study



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

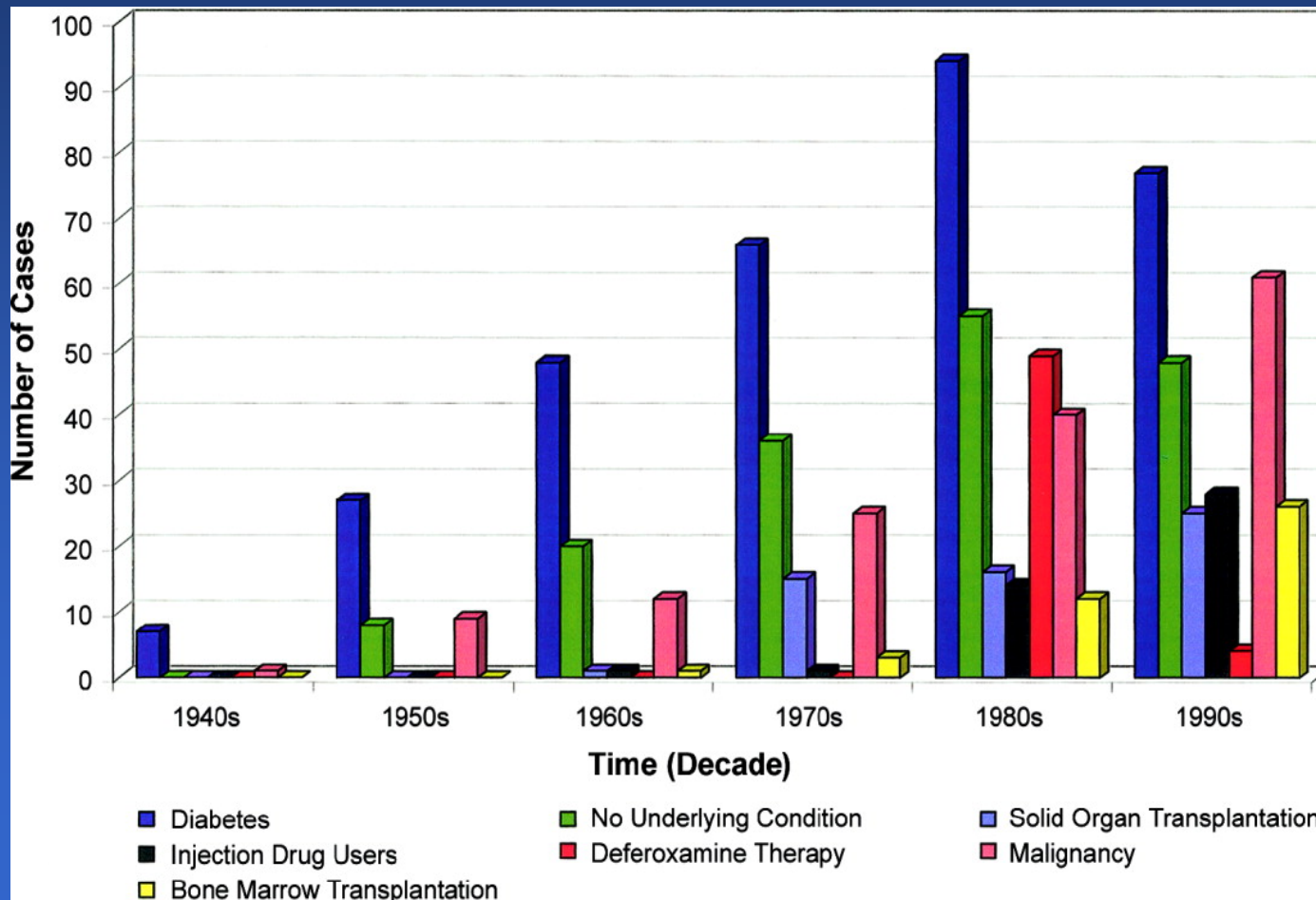
J. Guinea^{1,2}, M. Torres-Narbona¹, P. Gijón¹, P. Muñoz^{1,2}, F. Pozo^{2,3}, T. Peláez^{1,2}, J. de Miguel⁴ and E. Bouza^{1,2}

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- Admissions of COPD patients
- Episodes of IPA
- COPD patients with *Aspergillus* isolation
- Trend in the number of episodes
- - - Trend in the number of patients with *Aspergillus* isolation

Incidences of mucormycosis over 6 decades (1940–1999), by host population, 929 cases

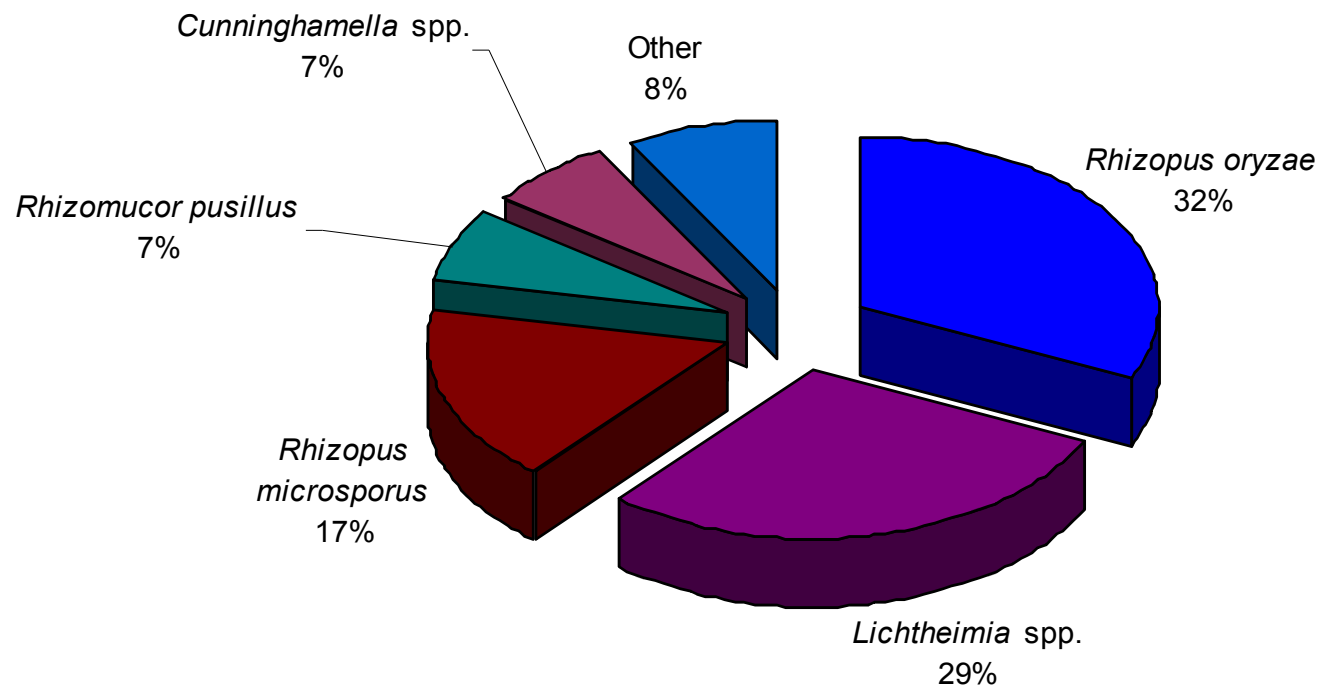


Incidence of mucormycosis cases in a Belgian hospital from 2000 through 2009

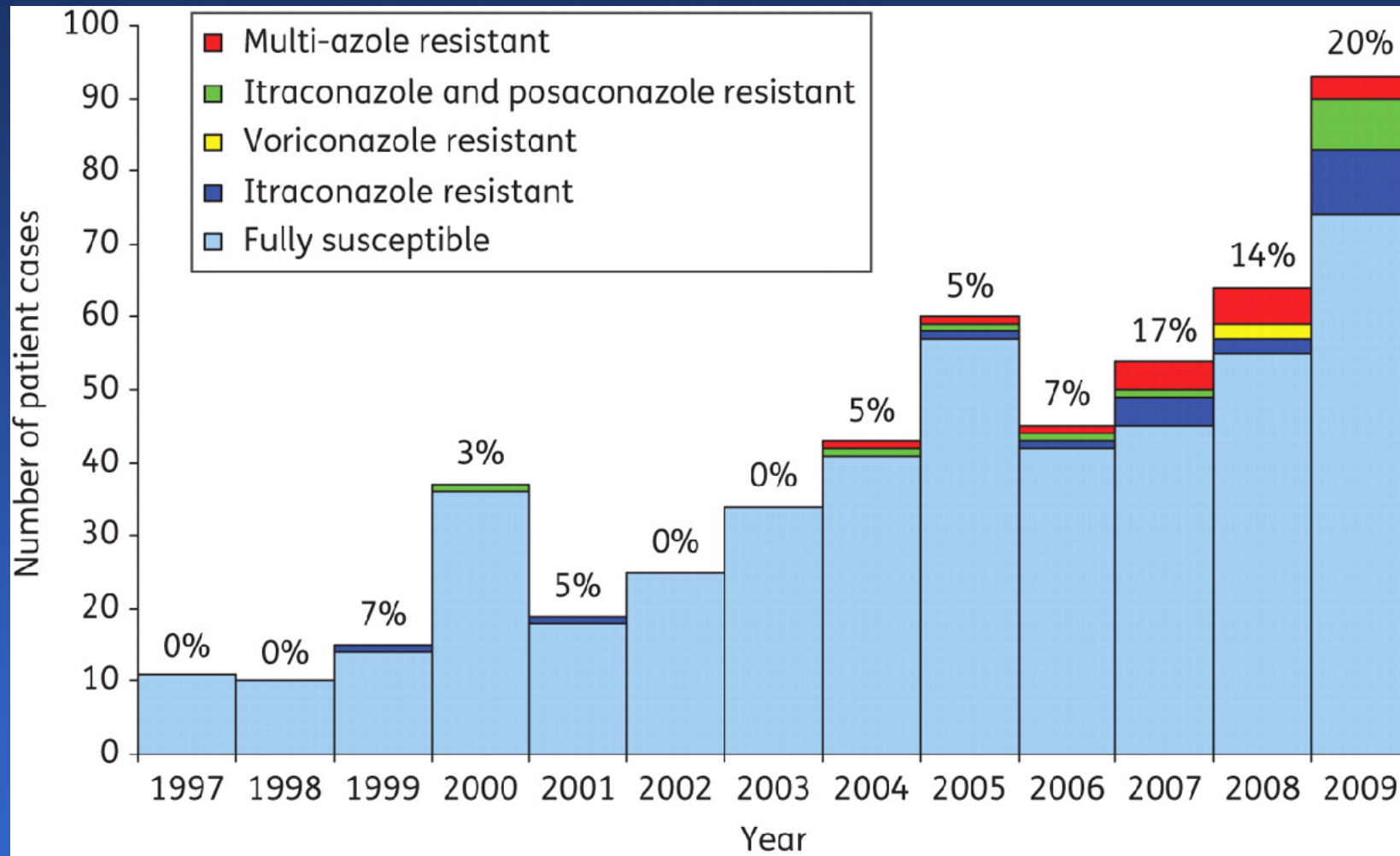
- 31 patients: 21 proven, 10 probable
- M/F: 16/15
- Mean age: 54 years (12-79 years)
- 61% haematological patients
- 45% co-infections with *Aspergillus* (halo-sign!)
- Mortality rate = 65% (48%, directly related to infection)

Distribution of mucorales in France

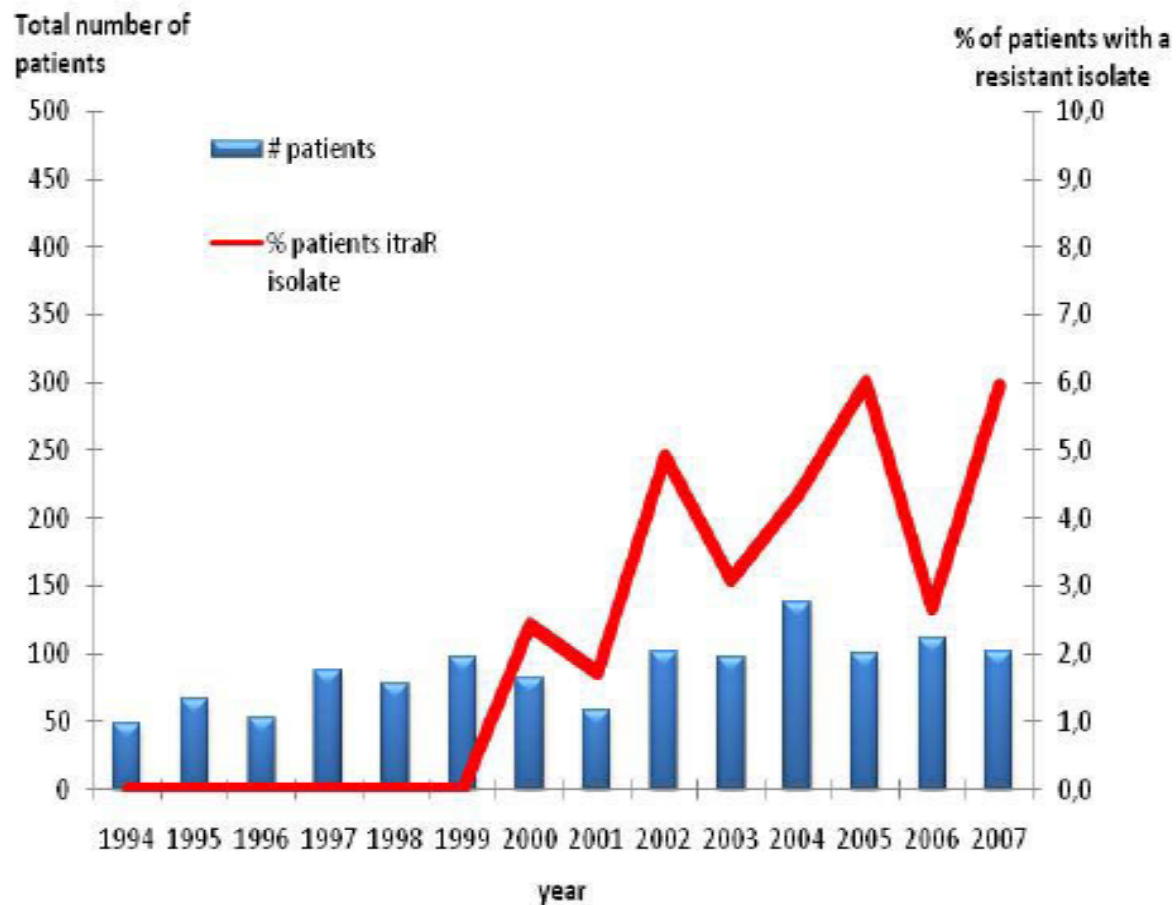
- Retrozygo», 101 mucormycosis cases 2005-2007



Azole resistance frequency in *A. fumigatus* 1997–2009



Emergence of azole resistance in *Aspergillus fumigatus* and spread of a single resistance mechanism



R mechanisms:
TR/L98H in 30 of 32
(94%) isolates

Some conclusions...

- It is difficult to determine true incidence figures (roughly between 2-10%)
 - New risk groups have arisen (mainly COPD, critically ill patients, steroid treated patients)
 - Some genetic factors might be important, especially in immunocompromised patients
 - Be aware of azole resistance
 - Be aware of co-infections aspergillus - mucor
-