

Fungal infections in COPD

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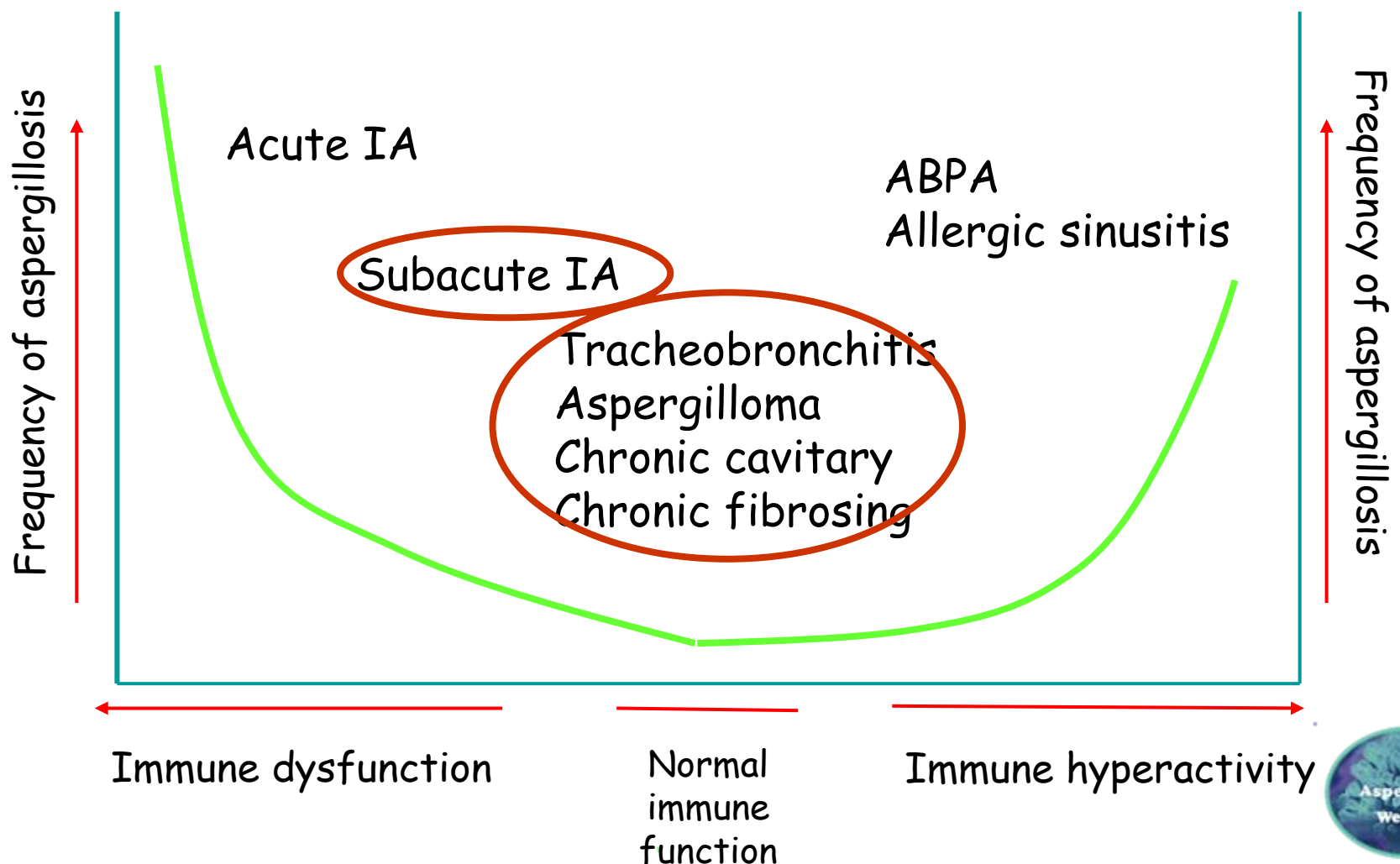
Torino, 28 October 2007

Scope of the problem

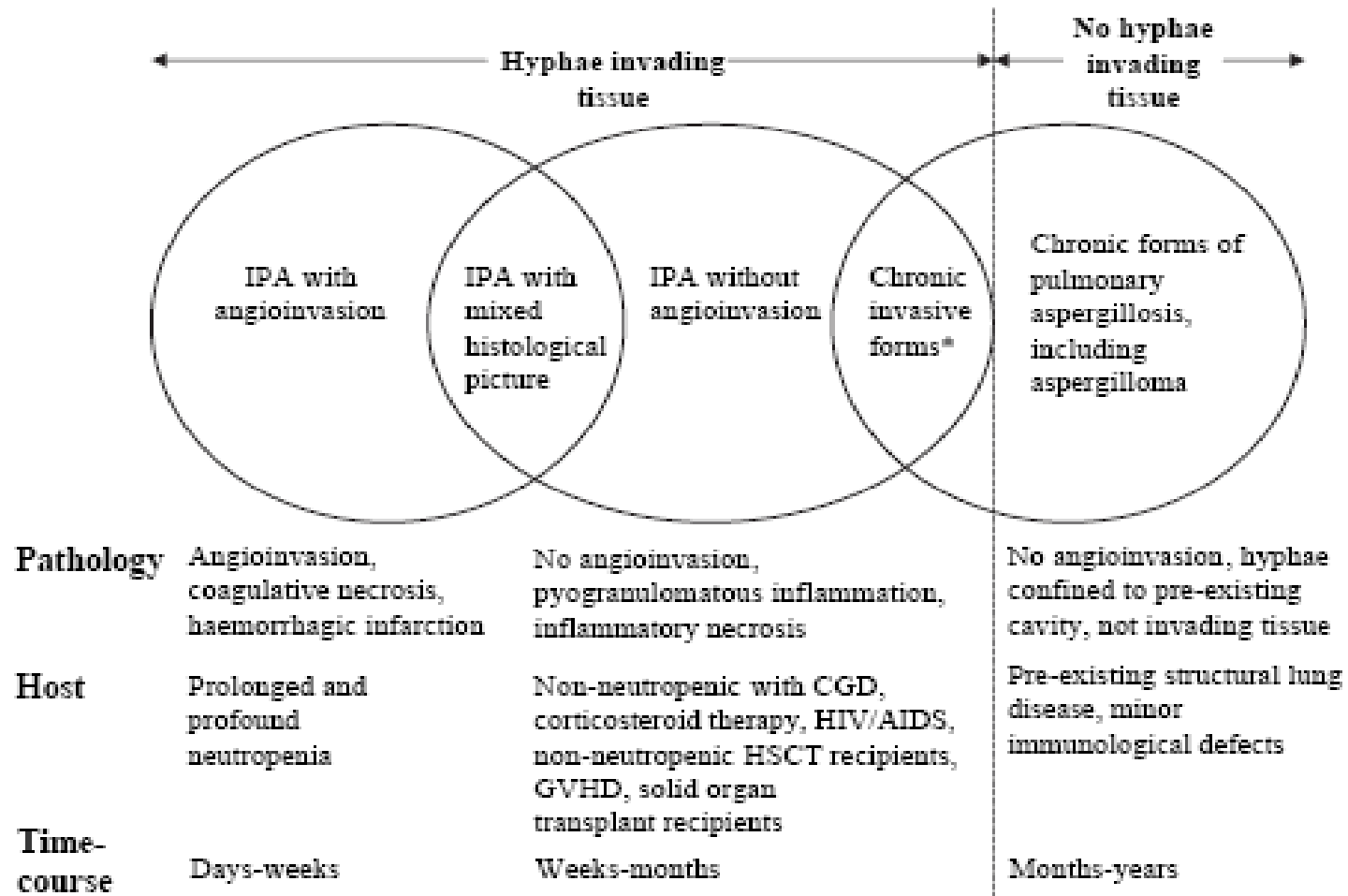
- *What do we know?*
 - *Aspergillosis well known disease in hematological and solid organ transplant patients*
 - *Rising incidence (immunosuppressive therapy)*
 - *Specific diagnostic tests available in hematological patients*
- *Where do we fail in our knowledge?*
 - *Prevalence in COPD patients*
 - *Are there specific radiological or clinical signs?*
 - *Colonization vs disease*

Interaction of *Aspergillus* with the host

A unique microbial-host interaction



The many faces of aspergillosis



From: The invasive and saprophytic syndromes due to *Aspergillus* spp. W W Hope, T J Walsh, D W Denning. Medical Mycology suppl 1 2005, **43**, S207-S238

Types of disease in COPD

- Aspergilloma
- Chronic pulmonary aspergillosis
 1. chronic cavitary aspergillosis
 2. chronic fibrocavitary aspergillosis
 3. chronic necrotizing aspergillosis
- Subacute pulmonary invasive aspergillosis

1. Aspergilloma

= conglomeration within a pre-existing pulmonary cavity of hyphae, mucus and cellular debris



1. Aspergilloma

Benign, asymptomatic colonization , IPA rarely develops

Occurs in 10% of patients with pre-existing cavities (bullae, TBC)



1. Aspergilloma

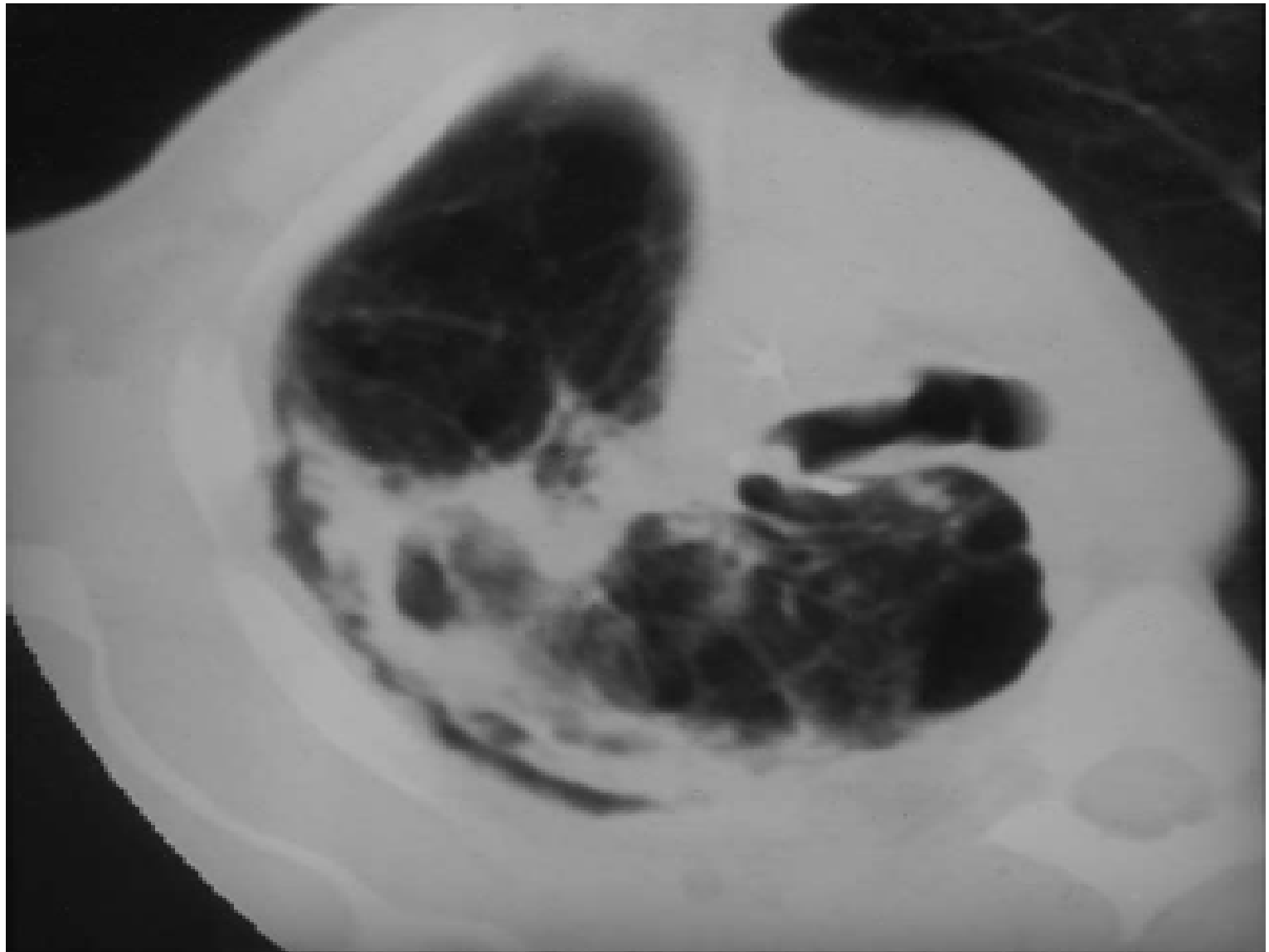
- Precipitins: > 95% sensitivity
- Fatal asphyxiation due to massive hemoptysis may occur
- Poor prognostic signs:
 - severity of underlying lung disease
 - increasing size and number of cavities
 - immunosuppression
 - increasing IgG titers
 - sarcoidosis
 - HIV

Case

- 45-old smoker with GOLD III COPD
- On fluticasone and atropine inhalers
- Right upper lesion in 2001
- Underwent lobectomy
- 2-cm cavity with necrotic contents, pleural and parenchymal fibrosis
- No malignancy
- Cultures for *Mycobacterium* negative

Case

- 2001- 2003: Never admitted with an exacerbation
- Treated twice with short course systemic steroids
- 2003-2005: intermittent hemoptysis, mild fatigue and some weight loss, no fever
- Lab results: mild to absent inflammation
- CT scan of the thorax



Case

- 2003-2005: intermittent hemoptysis, mild fatigue, some weight loss, no fever
- Lab results: mild to absent inflammation
- CT scan of the thorax
- Bronchoscopy: no lesions, cultures yield *Aspergillus fumigatus*, galactomannan OI 5 in BAL, < 0.1 in serum
- Aspergillus precipitins 3 +
- Fine needle aspiration and transbronchial biopsy: hyphae without parenchymal reaction

Treatment ???

- Stop inhaled corticosteroids?
- Systemic antifungals? Which ones? How long?
- Intracavitary instillation of antifungals?
- Interferon-gamma?
- Surgery?
- Combination of all the above treatments?

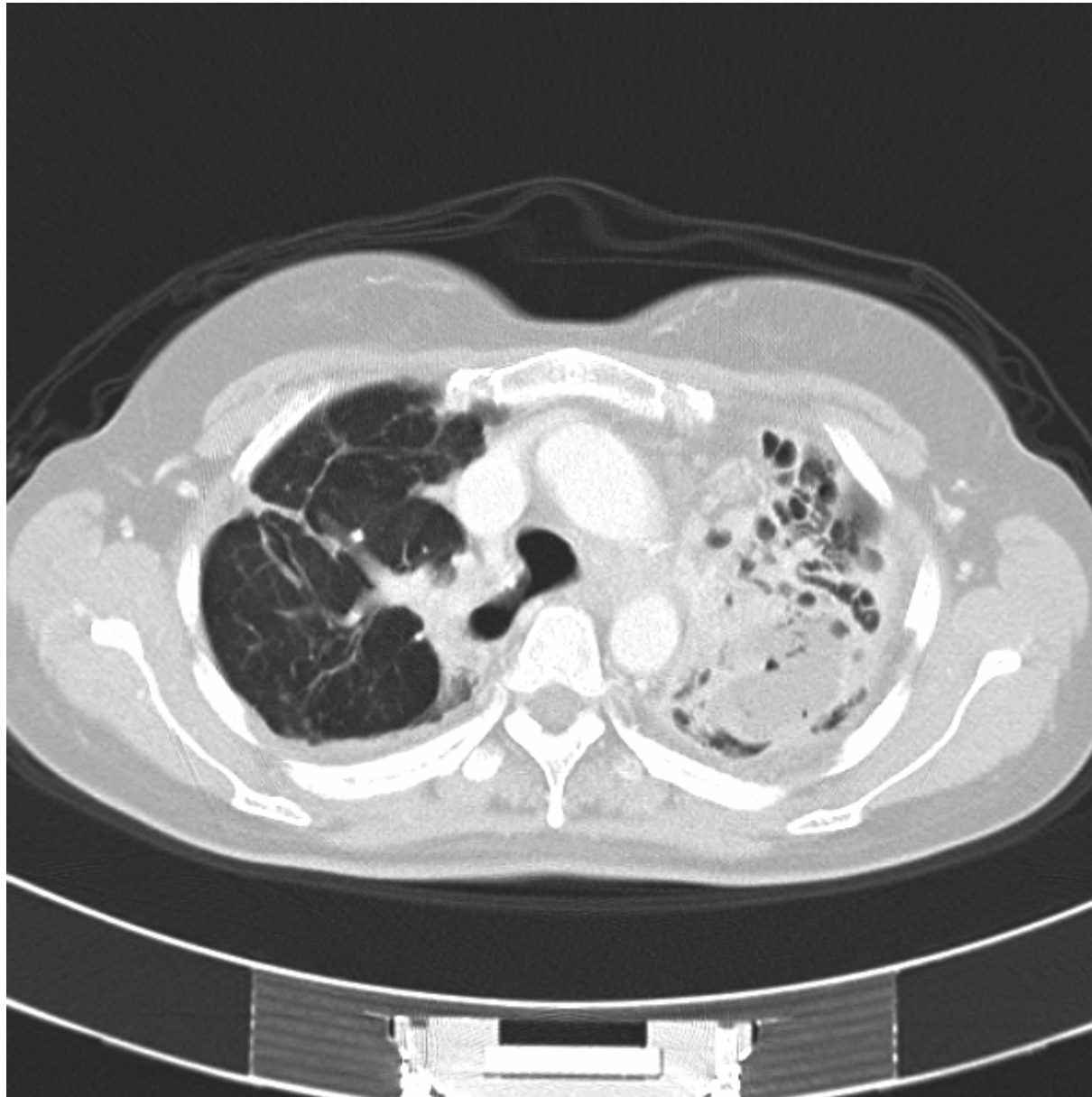
2. Chronic aspergillosis

- Affects middle-aged persons
- Only mildly immunosuppressed (COPD, alcoholism, diabetes)
- Indolent progressive course
- Chronic cough, hemoptysis, weight loss and fatigue
- No invasion in tissue or occasionally non-angioinvasive hyphae in tissue
- Many different radiological features (cavitary, fibrosing and necrotizing)

Chronic cavitary aspergillosis in a patient with old TBC



Chronic cavitary aspergillosis in a patient with old TBC



Chronic fibrosing aspergillosis in a COPD patient



Fibrocavitary aspergillosis postpneumonectomy for chronic aspergillosis



Guidelines for treatment of chronic aspergillosis

- They do not exist !!!!
- Stop corticosteroids
- Long term oral voriconazole probably the best option
- Weight gain and improved energy levels the best indicators of response
- Search for subtle immune defects and if present, role for IFN- γ
- Surgery has a minor role

3. Subacute invasive aspergillosis

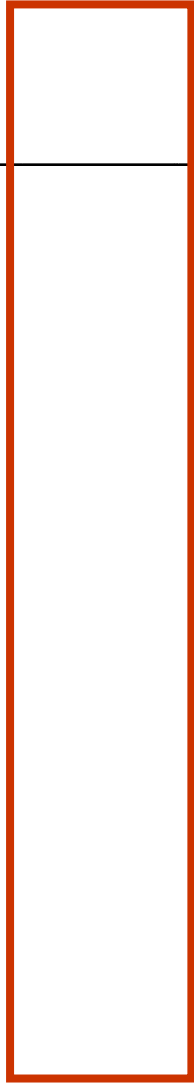
- Underrecognized disease
- ICU disease
- COPD patients with exacerbations
- High mortality
- Difficulties with reimbursing criteria for antifungals since COPD is not considered to be a host factor
- Colonisation vs disease

IPA diagnosis in ICU patients

- EORTC/MSG Case Definitions ¹
 - Difficult to apply outside high risk populations
 - Not useful to guide therapy

¹ Asciglu S. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants. *Clin Infect Dis* 2002

Proven and probable IPA without malignancy in ICU ('00-'03)



COPD patients: benefits of ICU?

- 23 pts, 16 proven, 7 probable (repeated isolation)
 - recent steroid treatment, or intensification of steroid treatment
 - severe bronchospasm (12/23)
 - all required mechanical ventilation
 - diagnosis classified as
 - confirmed
 - » positive lung tissue biopsy and/or autopsy
 - probable
 - » repeated isolation of *Aspergillus* from the airways with consistent clinical and radiological findings
- ***mortality 100%***

Clinical characteristics of IPA in COPD

- Total number of patients 56
- Age yrs (mean) 65,5
- Steroid treatment
 - At admission 43
 - In hospital 49
 - NA 5
- Clinical signs
 - Antibiotic resistant pneumonia 53
 - Dyspnoea exacerbation 56
 - Wheezing increase 52
 - Fever > 38° C 31
 - Haemoptysis 5
 - Tracheobronchitis (bronchoscopy) 6



Clinical characteristics

- Duration between symptoms and diagnosis days 12,5
- Ventilation
 - Invasive 43
 - Noninvasive 1
 - None 10
 - NA 2
- Outcome
 - Death 53 (95)
 - Survival 3 (5)

Why frequent in ICU? Why such a high mortality?

- Most severe exacerbations end up in ICU
- We love to give a lot of steroids
- We don't think of aspergillosis
- Poor sensitivity of culture
- We don't know what to do with a positive culture or direct examination
- Radiology doesn't help us

Significance of culture positivity

- IA diagnosed in 45/477 patients with “underlying pulmonary disease and positive culture”
- Positive predictive value lower than in haematology patients
- Colonisation vs true disease ???
 - Temporary passage ?
 - Long-term benign carriage ?

Perfect JR, et al. Clin Infect Dis 2001; 3:1824-1833.

Medical Imaging and Timely Diagnosis of Invasive Pulmonary Aspergillosis

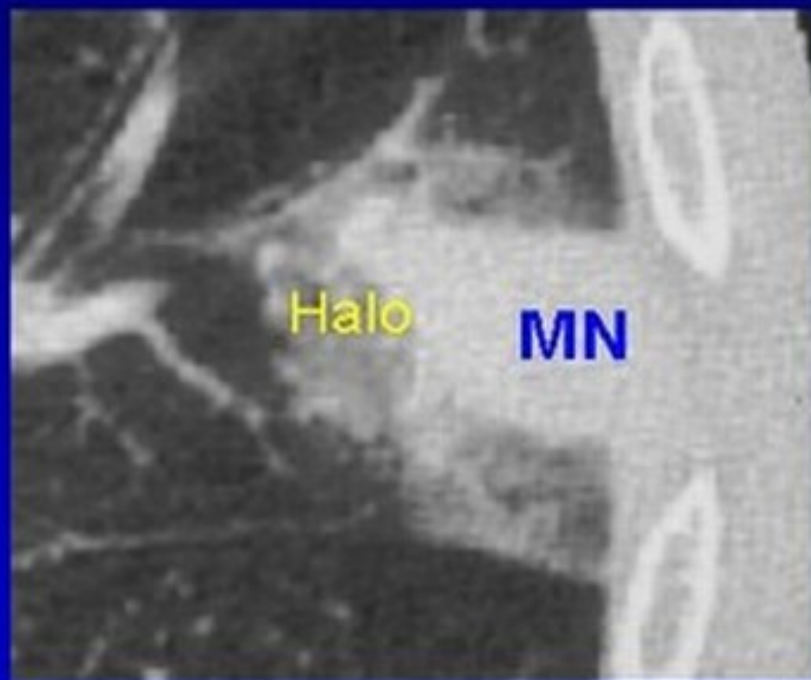
Koenraad H. Vandewoude¹ and Dirk Vogelaers²

¹Intensive Care Department and ²Department of Infectious Diseases, Ghent University Hospital, Ghent, Belgium

- Halo sign: only applicable to neutropenic patients
- Radiology in ICU “clouded” by atelectasis, pleural effusions, ARDS
- Necrotizing, cavitating lesions: not specific

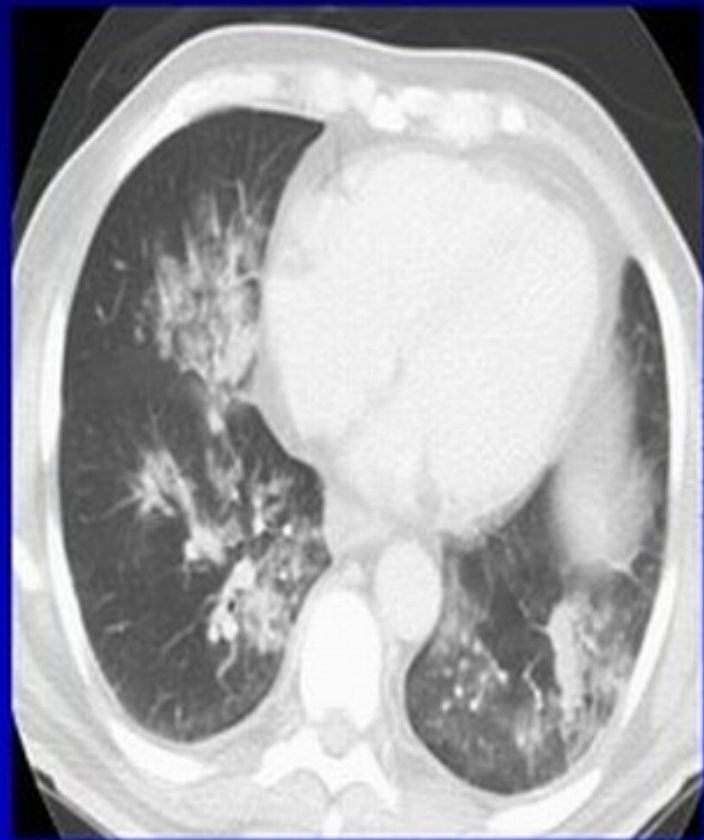
Halo Sign (HS)

- ✓ CT analog of the discrete nodule
 1. Solid Macronodule (MN) ≥ 1 cm diameter
 2. Translucent ground glass halo
- ✓ Implications
 - Early IPA
 - Transient
 - Better treatment response
- ✓ Other etiologies

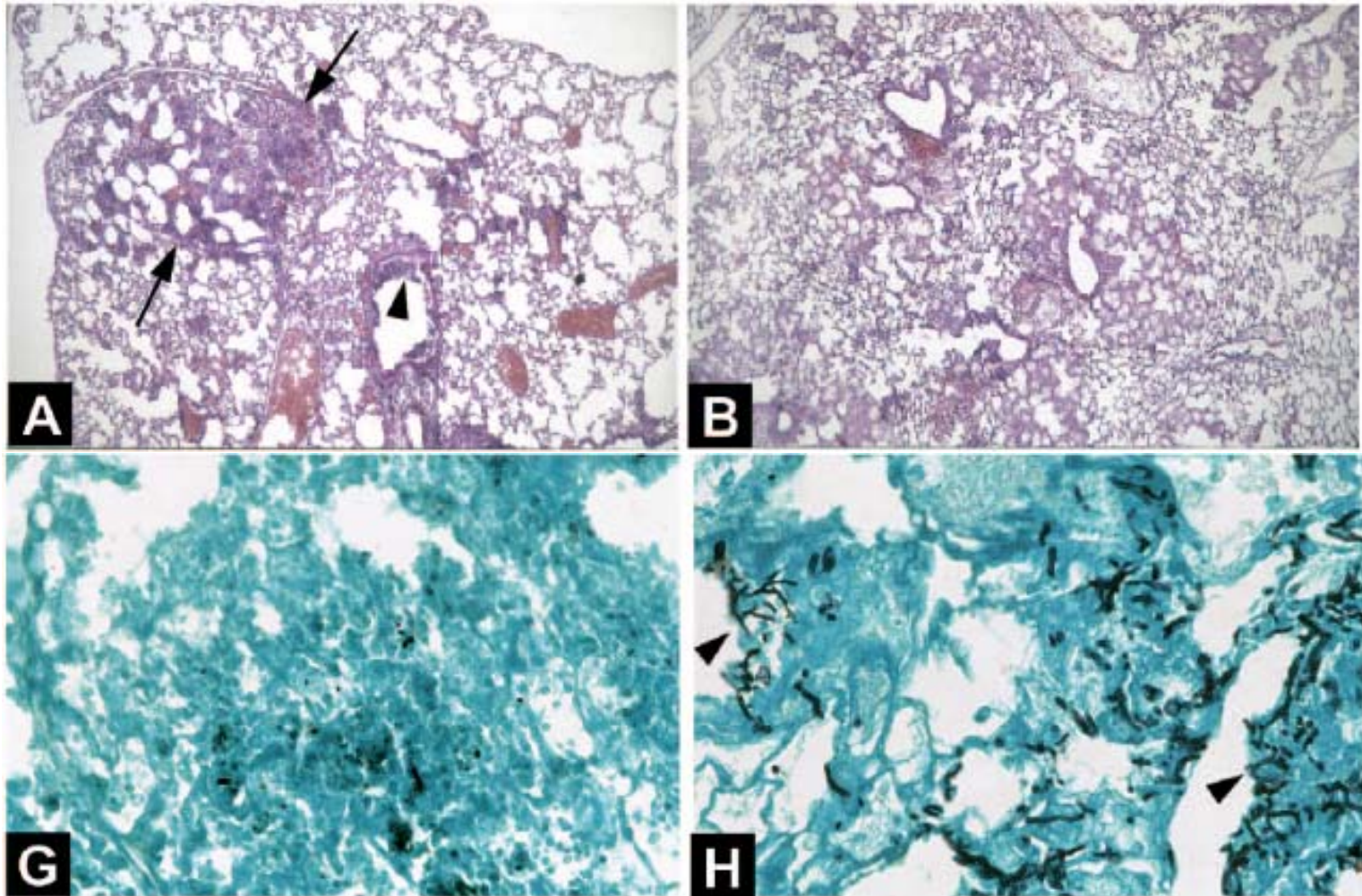


CT of Lobular Consolidation

- ✓ Mild neutrophil dysfunction
- ✓ Neutrophilic exudate fills the airspace
- ✓ Consolidated 2° lobules
- ✓ Air bronchograms
- ✓ Many potential causes



Corticosteroids vs neutropenia: a different lung disease



Balloy et al. Differences in patterns of infection and inflammation. *Infect Immun* 2005; 73:494

As a consequence ...

- Inflammatory reaction:
 - leads to encapsulation of the process
 - prevents at least partially invasion of hyphae in the blood (minor coagulation necrosis)
 - prevents leakage of antigens in blood
 - probably makes antigen markers in blood less suitable for diagnosis

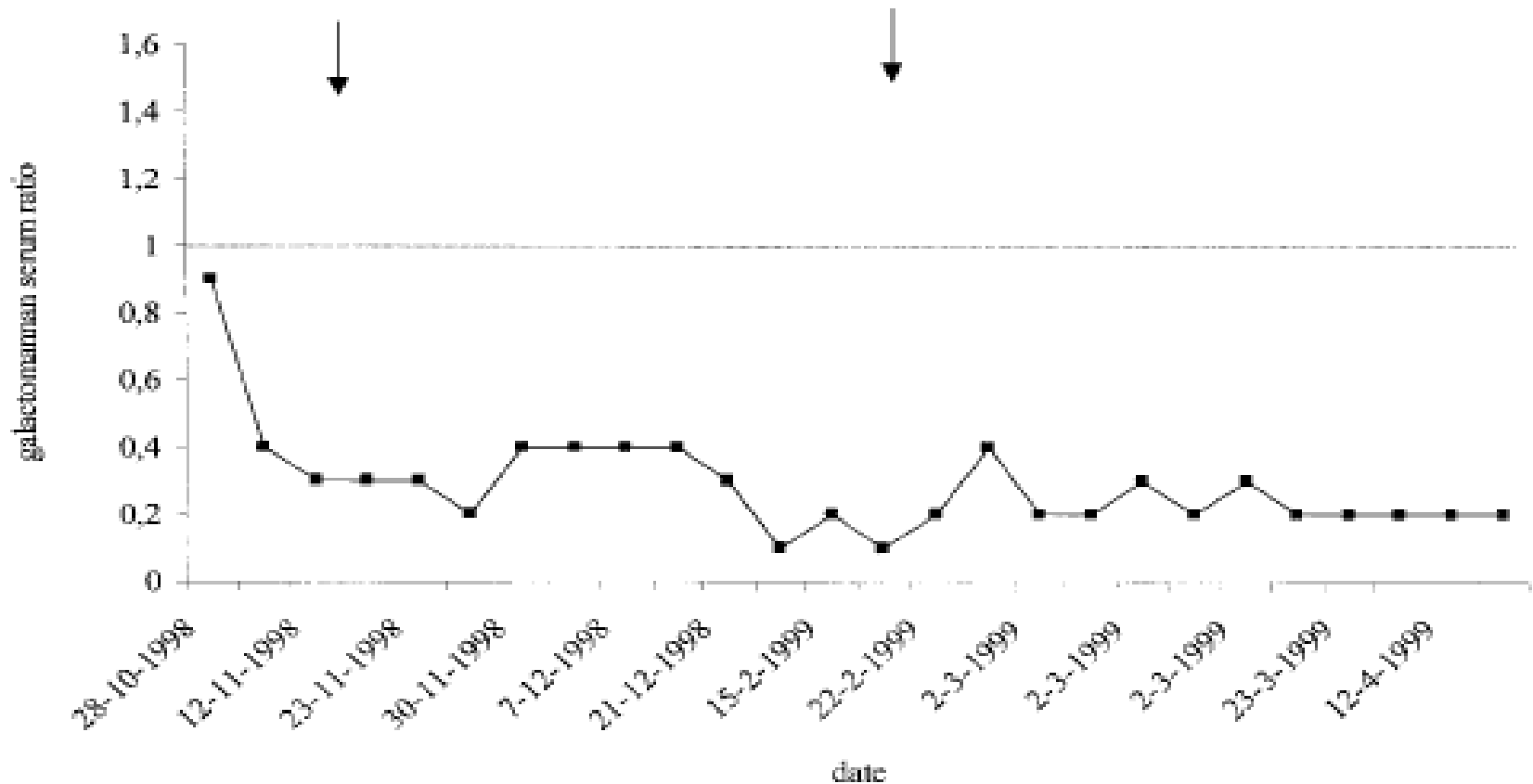
Proven and probable IPA without malignancy in ICU ('00-'03)



Galactomannan in BAL

Aspirate 1
culture: *A. fumigatus*
galactomannan: 70 ng/ml

Aspirate 2
culture: *A. fumigatus*
galactomannan: 48 ng/ml



Diagnosis of IA in the ICU



Can we establish the diagnosis of IA earlier?

Prospective single center study in a medical ICU

Inclusion criteria: modified EORTC criteria ("classical" + COPD + cirrhosis + steroids)

BAL, serum GM, culture and CT scan according to clinical criteria

Hypothesis: galactomannan in BAL fluid leads to an early diagnosis of IA in the ICU; encapsulation of the infection in nonneutropenic patients prevents leakage in the blood

Inclusion criteria prospective study

“Modified” host factor (hemato, steroids, transplant cirrhosis, **COPD**)

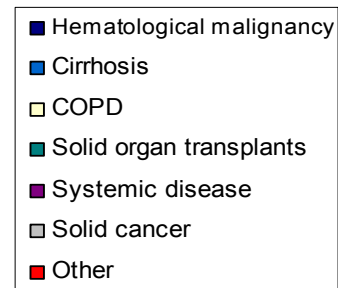
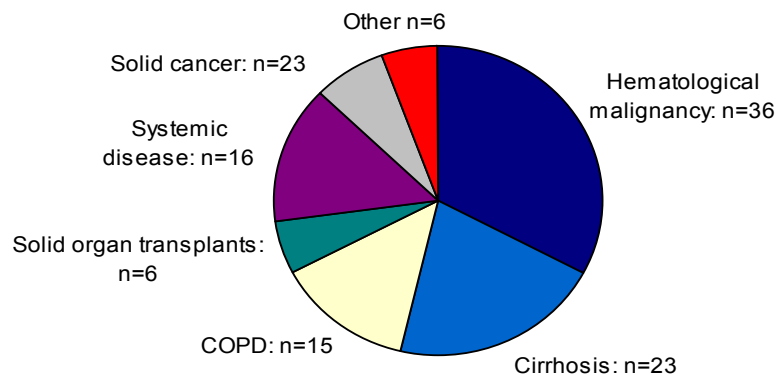
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2/3 following features:

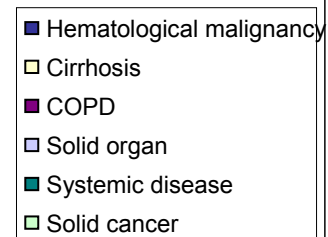
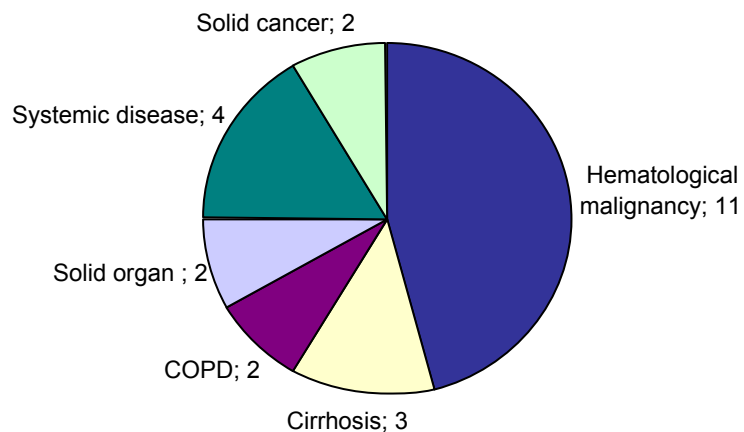
- Fever refractory to antibiotics (72 hrs)
- Clinical signs (new purulent secretions)
- New or deteriorating pulmonary infiltrates on chest X-ray

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

n = 110



Proven: n = 26 .

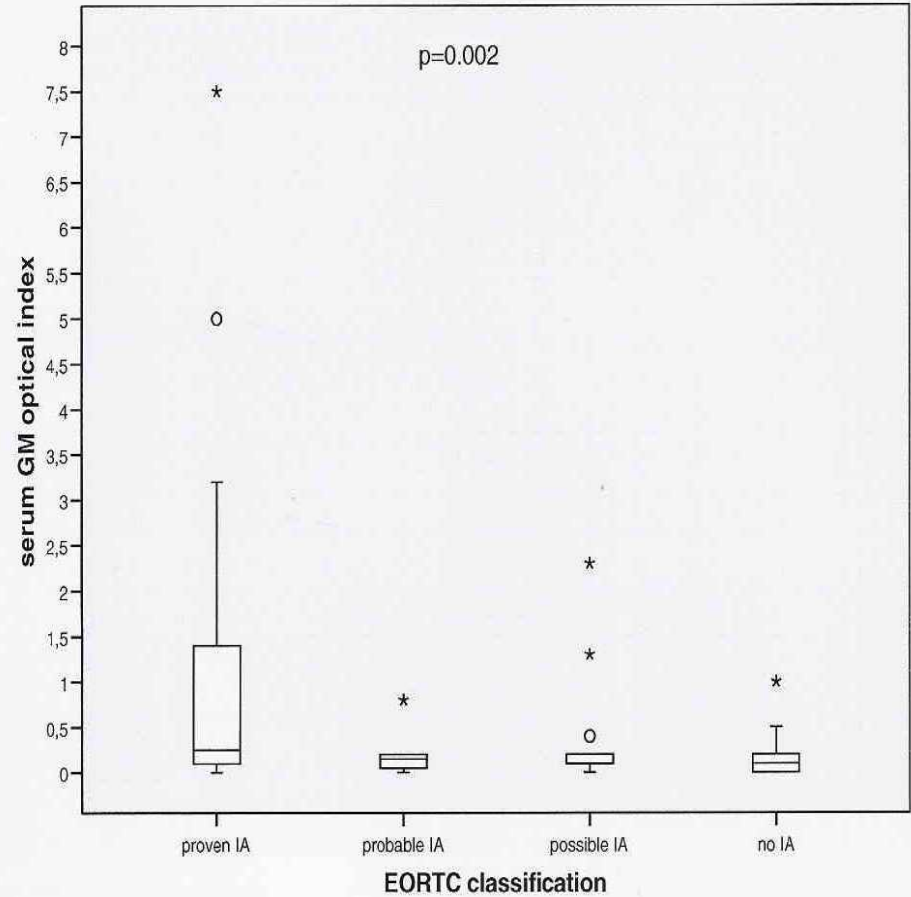
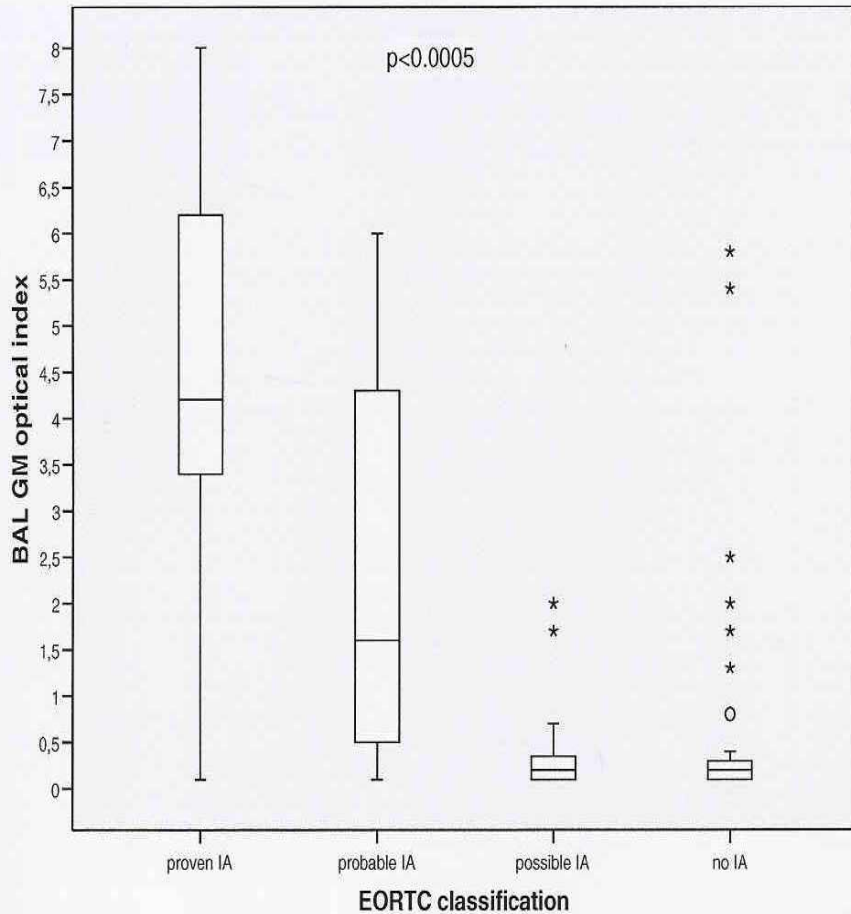


Performance GM in serum and BAL

OD index cut-off:	1,5		1,0		0,7		0,5	
	BAL	serum	BAL	serum	BAL	serum	BAL	serum
Sensitivity (%)	81	23	81	27	85	31	88	42
Specificity (%)	96	100	93	98	92	98	87	96
PPV (%)	81	100	79	88	73	89	72	85
NPV (%)	89	68	89	69	93	70	93	74

Meersseman et al. Galactomannan in BAL in ICU. AJRCCM '07 (in press)

Performance GM in serum and BAL



Meersseman et al. Galactomannan in BAL in ICU. AJRCCM '07 (in press)

Summary

- Three disease entities in COPD
 - aspergilloma
 - chronic aspergillosis
 - subacute invasive aspergillosis
- Controversial topic: no clear guidelines
- Studies warranted in
 - chronic aspergillosis: benefits of longterm triazole therapy
 - subacute IPA: pre-emptive approach based on galactomannan in BAL