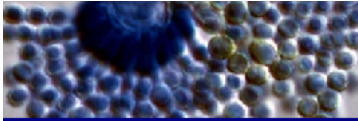




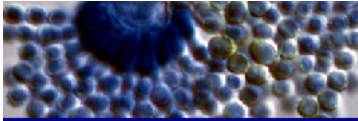
# Invasive aspergillosis in the ICU

Dirk Vogelaers, MD, PhD  
General Internal Medicine & Infectious Diseases  
Ghent University Hospital, Belgium

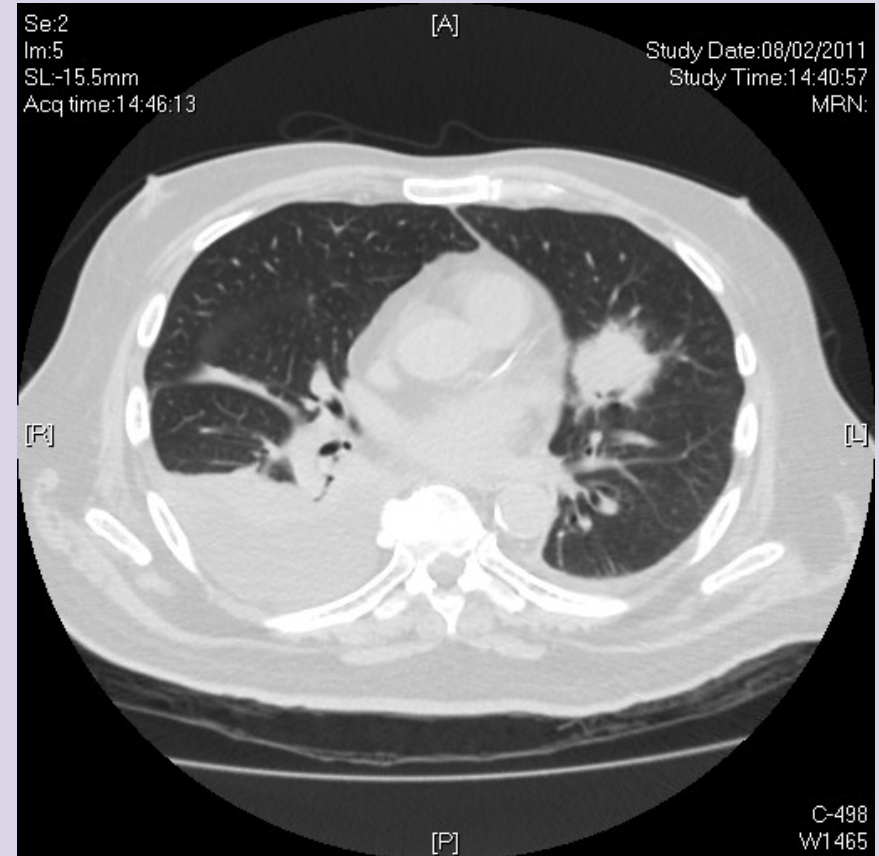
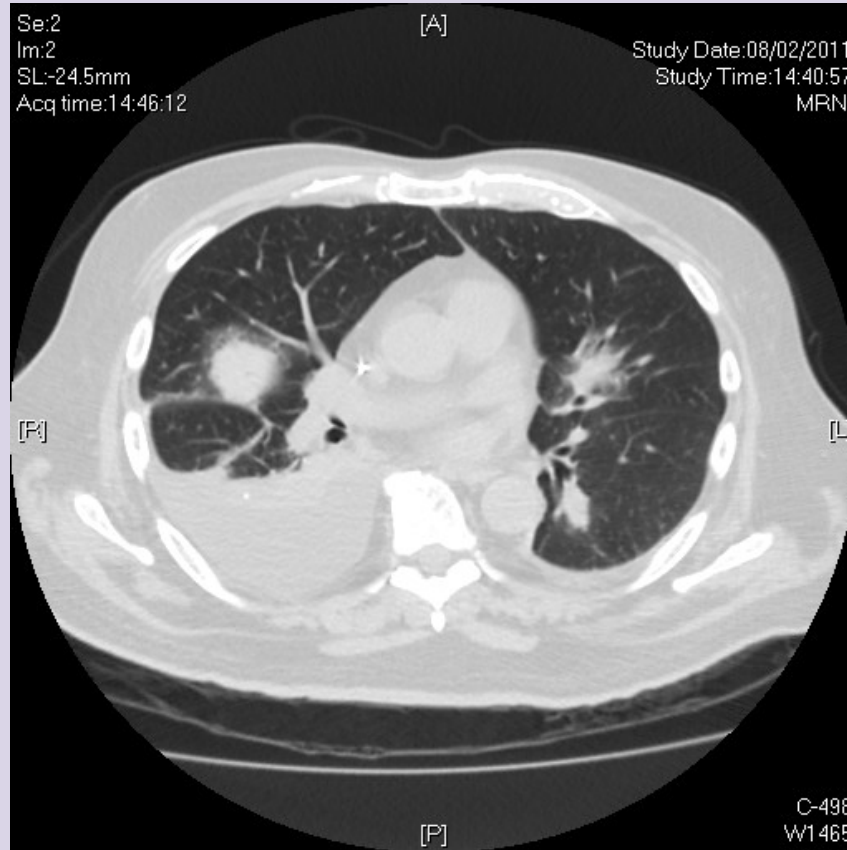


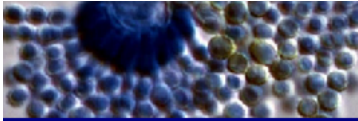
## Different faces of IA in ICU vs non ICU patients?

- Probably not or not fully
- For a given patient profile differences in
  - Severity of disease expression
  - Most of all, early vs late recognition → early vs late initiation of appropriate antifungal therapy
- Spectrum from invasive (mostly pulmonary) aspergillosis to more indolent (controlled) forms of disease



Case: 67 yr old male, decompensated liver cirrhosis with portal hypertension, recent bleeding esophageal varices, no steroids





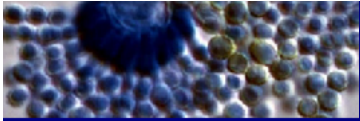
## EORTC/MSG criteria for IA:



94

**Does this case fit the description of the 2008 EORTC/MSG criteria for?**

- 1 - definite or proven IA
- 2 - probable IA
- 3 - possible IA
- 4 - none of the above: not classifiable

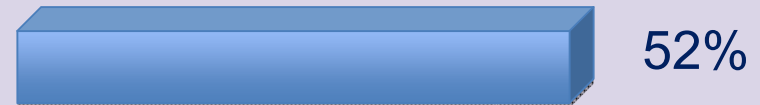


## Does this case fit the description of the 2008EORTC/MSG criteria for?

1 - definite or proven IA



2 - probable IA

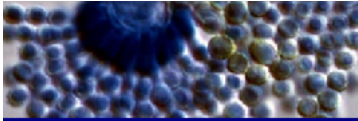


3 - possible IA



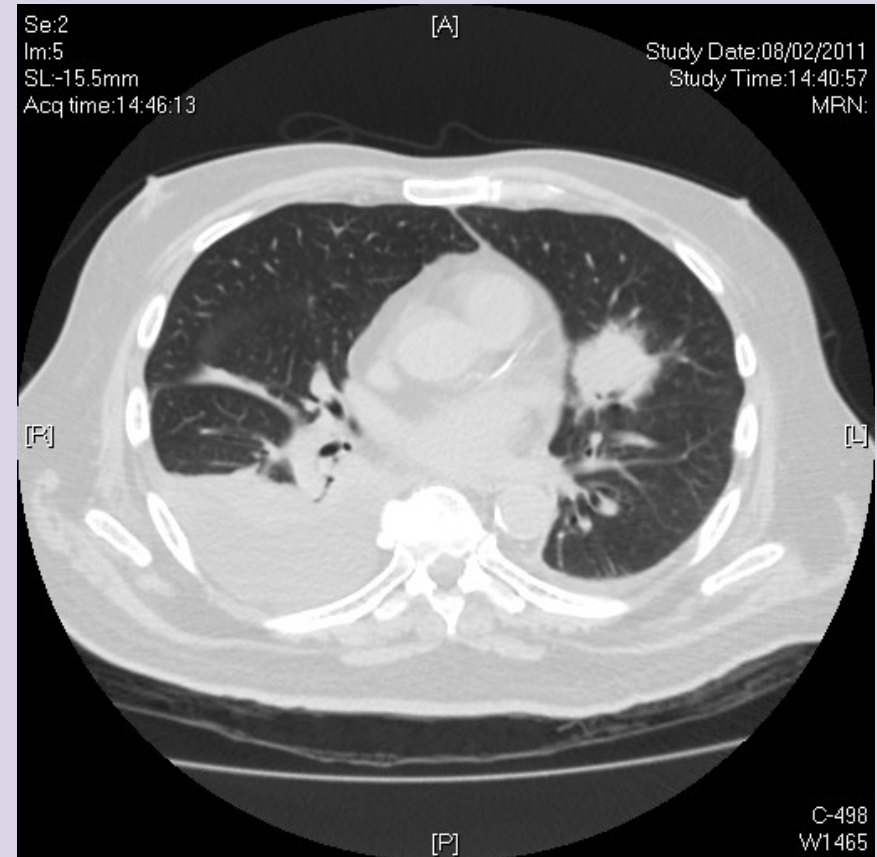
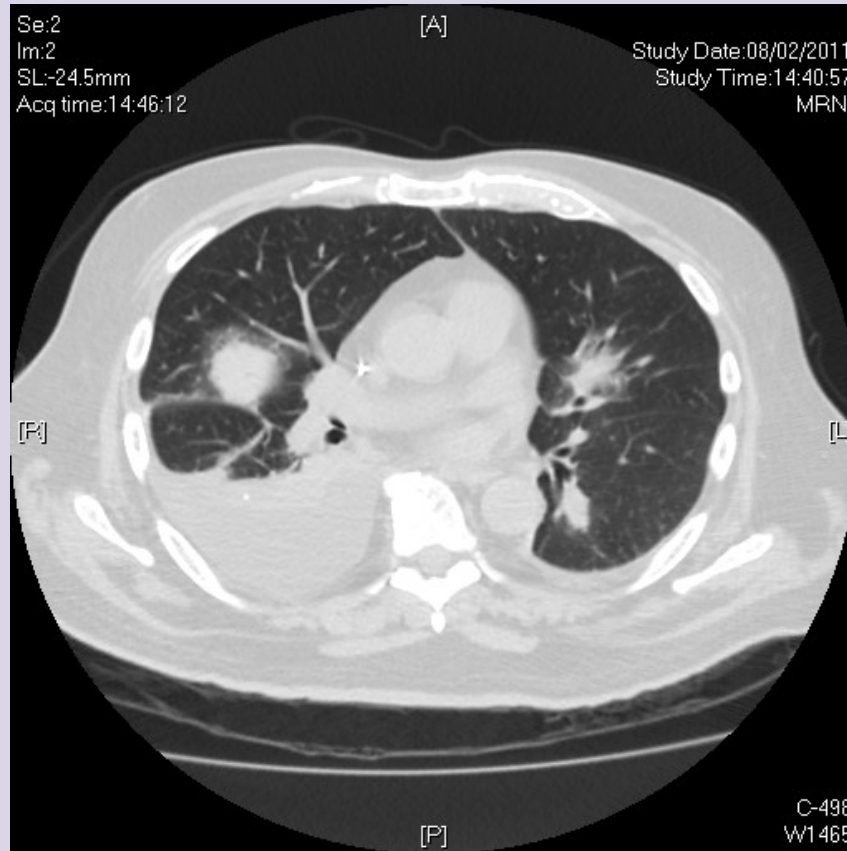
4 - none of the above:  
not classifiable

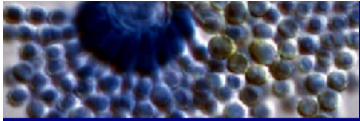




Case: 67 yr old male, decompensated liver cirrhosis with portal hypertension, recent bleeding esophageal varices, no steroids

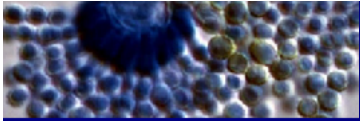
+ *Aspergillus* spp positive endotracheal aspirate





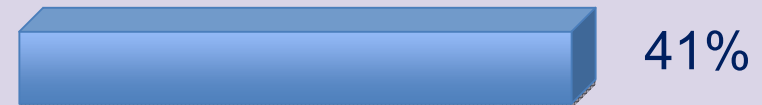
**Does this case fit the description of the 2008  
EORTC/MSG criteria for?**

- 1 - definite or proven IA
- 2 - probable IA
- 3 - possible IA
- 4 - none of the above: not classifiable

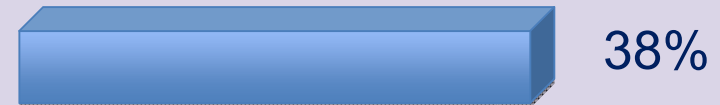


## Does this case fit the description of the 2008 EORTC/MSG criteria for?

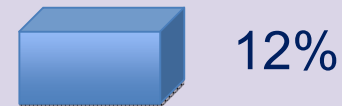
1 - definite or proven IA



2 - probable IA



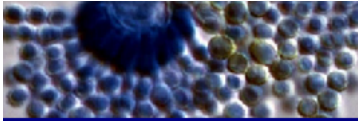
3 - possible IA



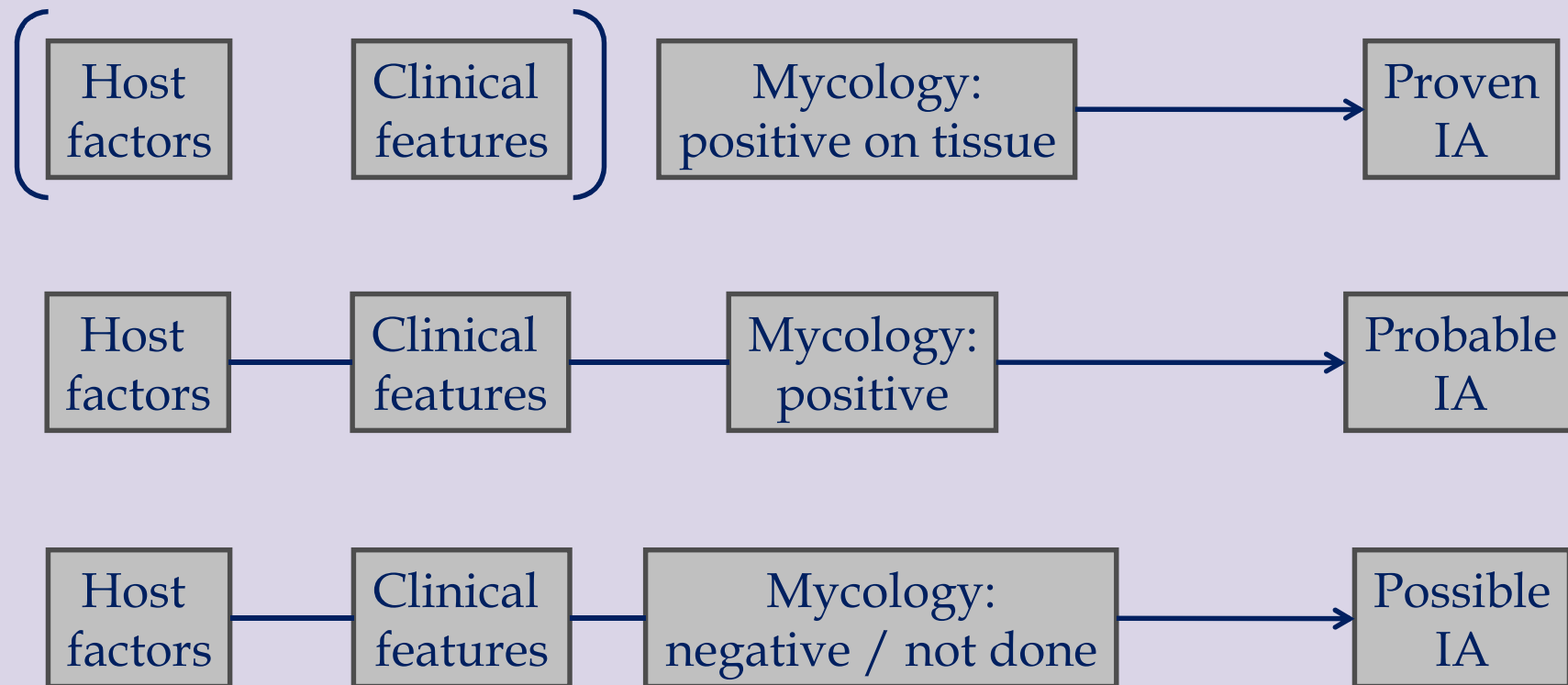
4 - none of the above:  
not classifiable

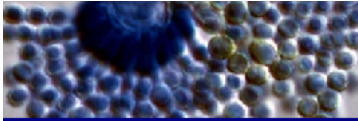






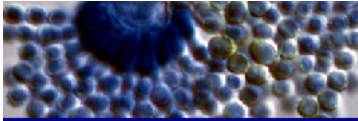
# Diagnosis in IA (EORTC/MSG)





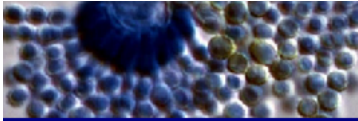
# Previous medical history

- 60 y old male with impressive medical history
  - 11.2005 distal oesophageal ulcer
  - 1.2006 ileitis terminalis (vasculitis? Behçet?) with recurrence of oesophageal ulcer
  - 1.2006 ileocaecal resection for spontaneous perforation
  - 3.2006 2 reinterventions for leakage of ileocolic anastomosis + abcedation in right lower quadrant → ileum/colon as double loop stoma
  - 3.2006 redo ileocolic anastomosis



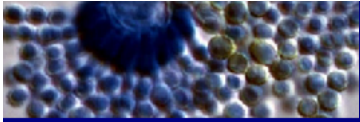
## Previous medical history (2)

- 4.2006 perforation/abscedation caecum → double loop colostoma
- 4.2006 bleeding from large esophageal ulcer with hypovolemic shock
- 5.2006 diffuse esophageal ulcerations
- 9.2006 distal esophageal resection + cervicostomy
- 9.2006 bibasal pneumonia with respiratory insufficiency, prolonged ICU stay, including Candida spp sepsis (12.2006)



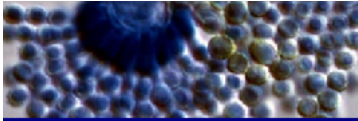
## Previous medical history (3)

- 2.2007 colonic interposition
- 2.2007 revision for eventration (Vicryl mesh + partial open abdomen approach)
- 2.2007 Pezzer drain for leakage ileocecal anastomosis
- 3.2007 esophageal stenosis → failed dilatation procedure
- 5.2007 leakage jejunostomy, small bowel fistulisation with MDR *Klebsiella oxytoca*
- 8.2007 acute pancreatitis (TPN?)
- 9.2007 toxic hepatitis (TPN?)
- 10.2007 repair of continuity (cologastric anastomosis, redo terminal ileostoma + abdominal wall closure)



## Previous medical history (4)

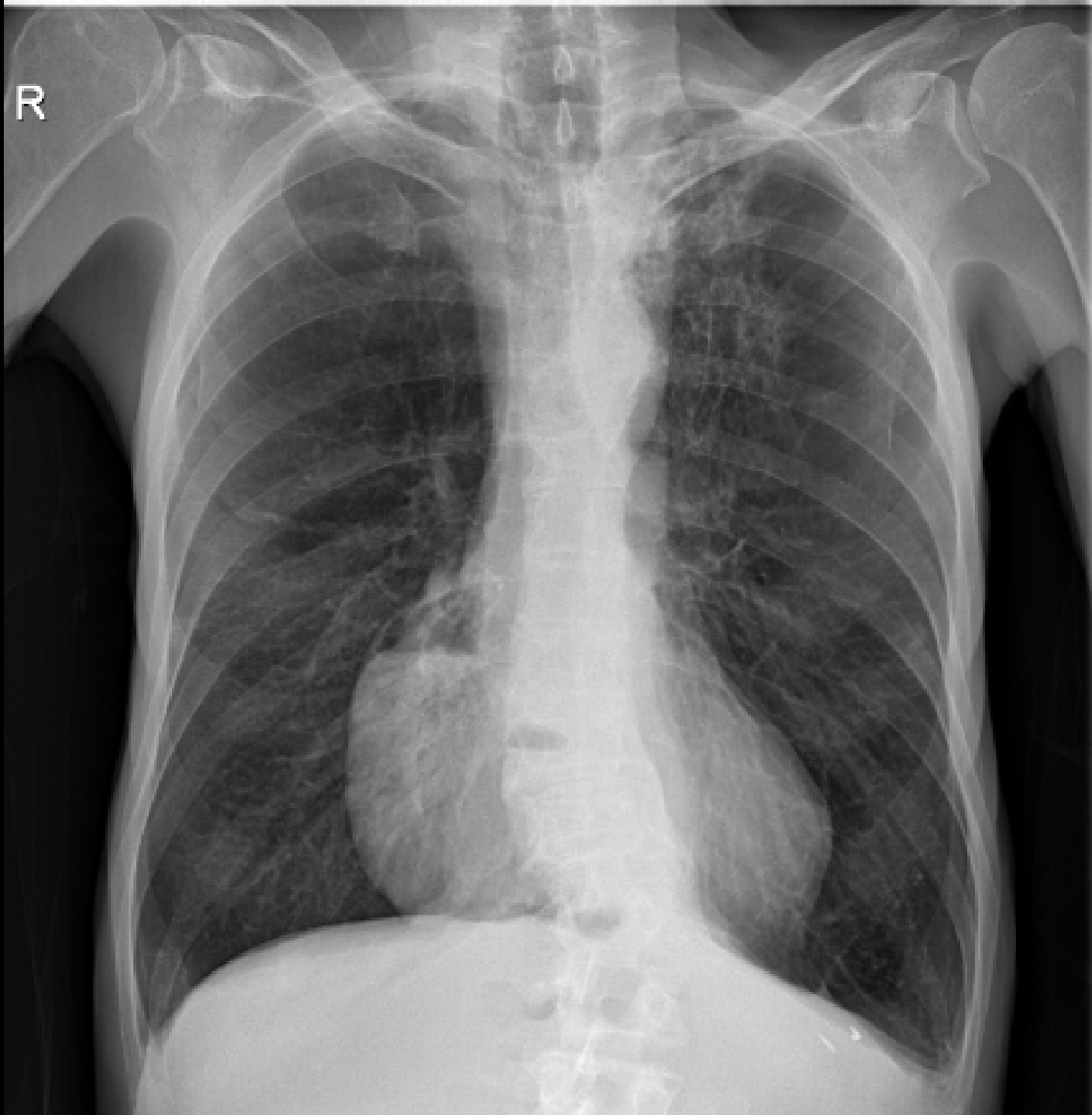
- 1.2010 septic shock + acute renal failure, lactic acidosis + DIC, negative microbiology, no clear focus
- 5.2010 enterocutaneous fistula at the anastomosis of stomach/colon interposition



## Current problem

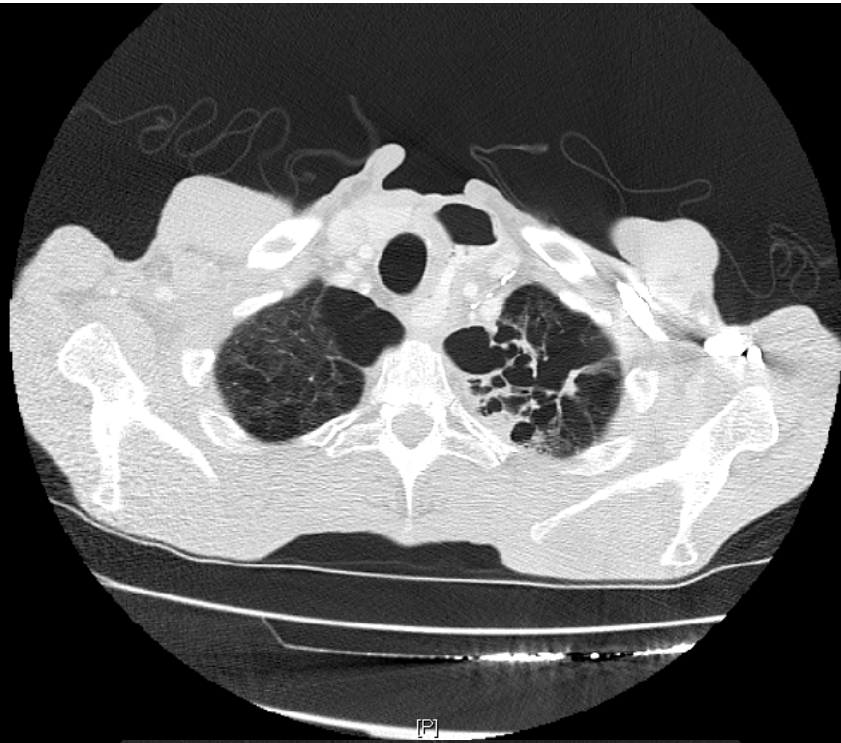
- General deterioration + weight loss + asthenia + anorexia
- Since 1 month low grade fever, dyspnea, cough and green expectorations
- Negative clinical examination (abdominal wall herniation, ileostoma left lower quadrant, fistula)
- Leukocytosis 13580/ $\mu$ l + CRP 9.6 mg/dl

R





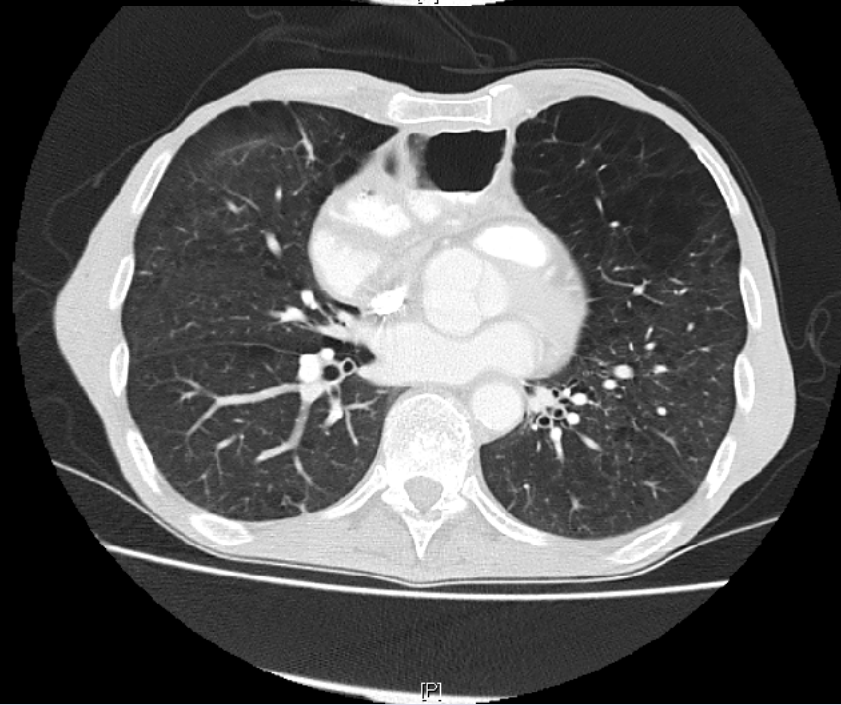




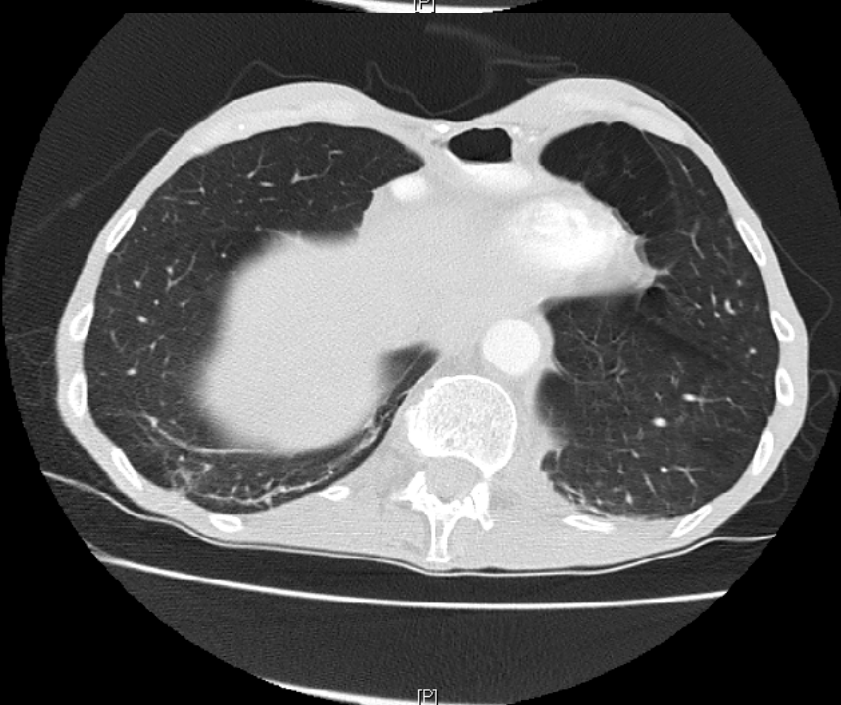
[1]



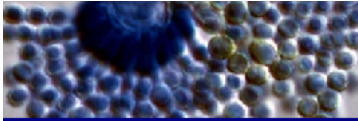
[2]



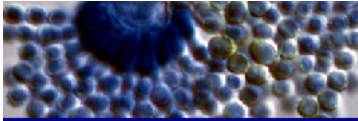
[3]



[4]



- Initial cultures
  - Colonisation (faeces) with ESBL K pneumoniae + Enterobacter aerogenes (12.9)
  - Sputum (13.9) purulent, C non-glabrata ±
- Antimicrobials:
  - amoxiclav (12.9-15.9)
  - Piperacillin/tazobactam (15.9-17.9)
  - Meropenem + vanco (17.9)
- In spite of antimicrobials development of confluent infiltrates of the entire left lung
- 21.9 BAL: GM negative → association of ciprofloxacin + fluconazole
- 25.9 APD bronchial biopsies: acid fast bacilli → stop antibiotics, start pyrazinamide + INH + rifampin + myambutol but Ziehl Neelsen negative, negative Gene expert



# EORTC/MSG criteria for IA



102

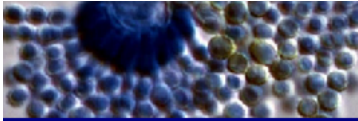
**Does this case fit the description of the 2008  
EORTC/MSG criteria for:**

1 - definite or proven IA

2 - probable IA

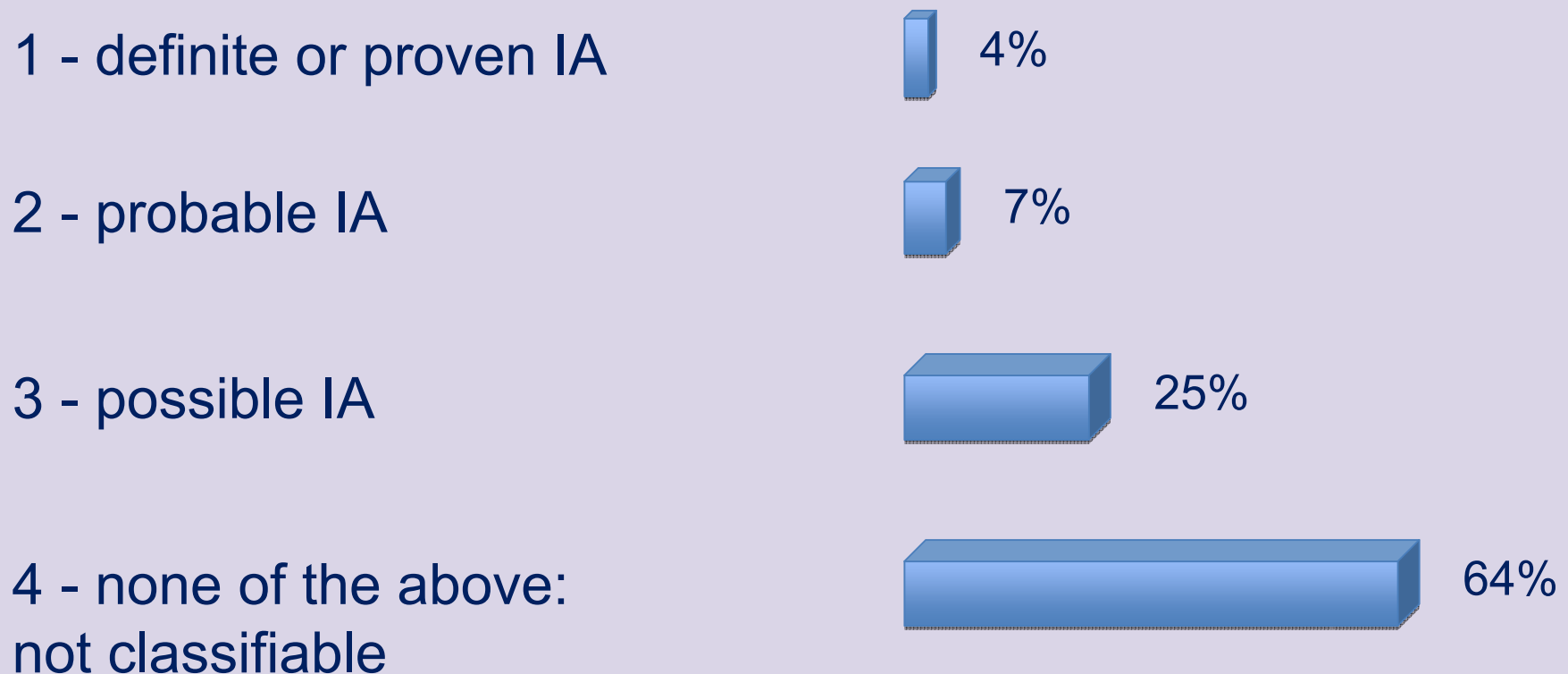
3 - possible IA

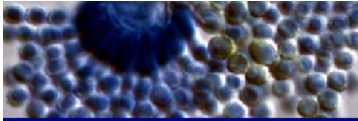
4 - none of the above: not classifiable



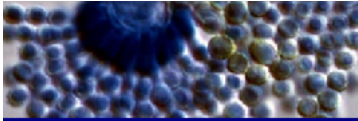
# EORTC/MSG criteria for IA

**Does this case fit the description of the 2008  
EORTC/MSG criteria for:**

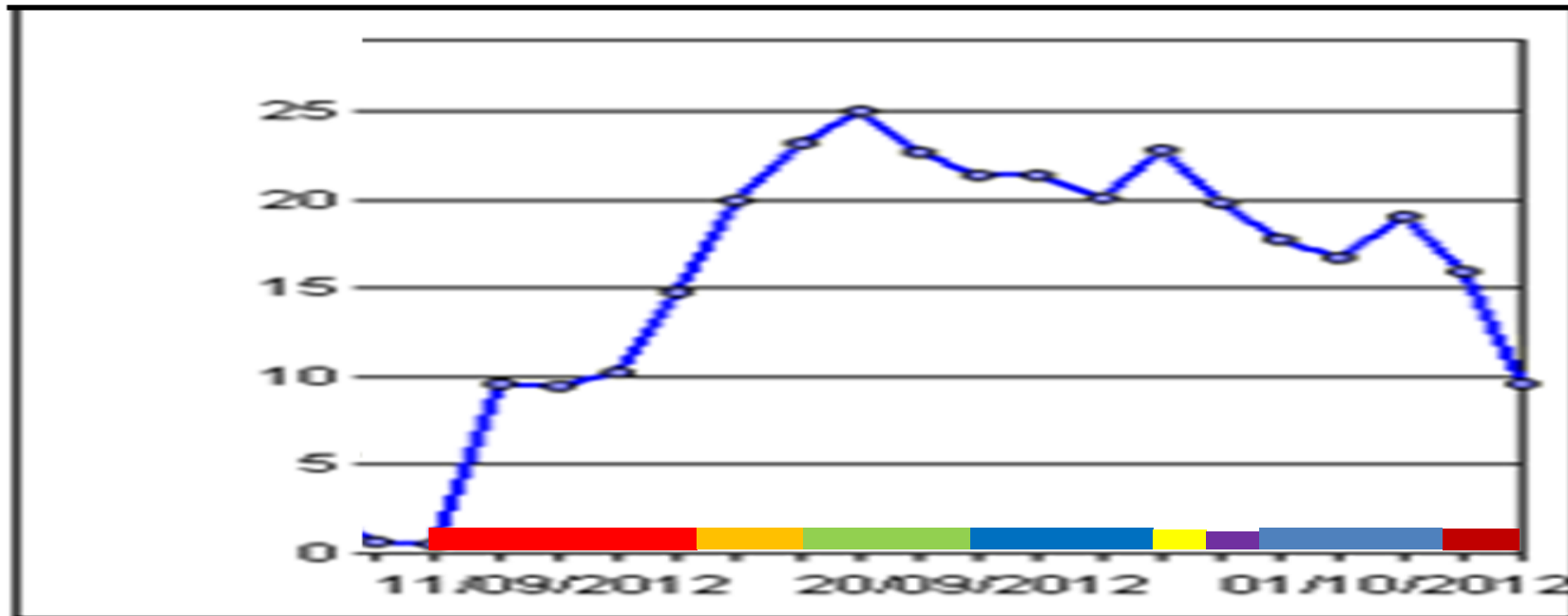




- 4.10 stop pyrazinamide (few rods on APD, Gene Expert 2 x neg) → continue INH + myambutol + rifampin + moxi + clarithro
- Persistent vesperal fever, leukocytosis (23400/ $\mu$ l, CRP 9 mg/dl)

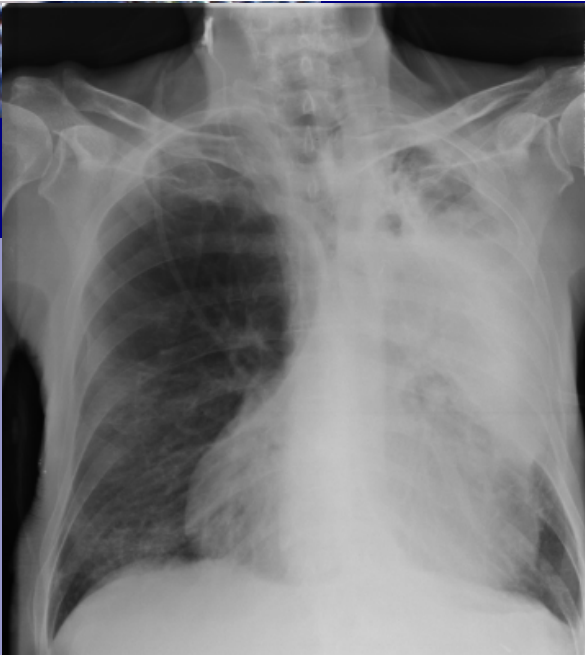


# Evolution CRP



- 12-15/9: Augmentin
- 15-17/9: Tazocin
- 17-21/9: Meronem – Vanco
- 21-26/9: Meronem – Vanco – Ciproxine – Diflucan
- 26-27/9: Tebrazid – Nicotibine – Myambutol – Rifadine
- 27-28/9: Tebrazid – Nicotibine – Myambutol – Rifadine – Avelox – Meronem - Diflucan
- 28/9-4/10: Tebrazid – Nicotibine – Myambutol – Rifadine – Avelox – Biclcar
- 4-10/10: Nicotibine – Myambutol – Rifadine – Avelox – Biclcar

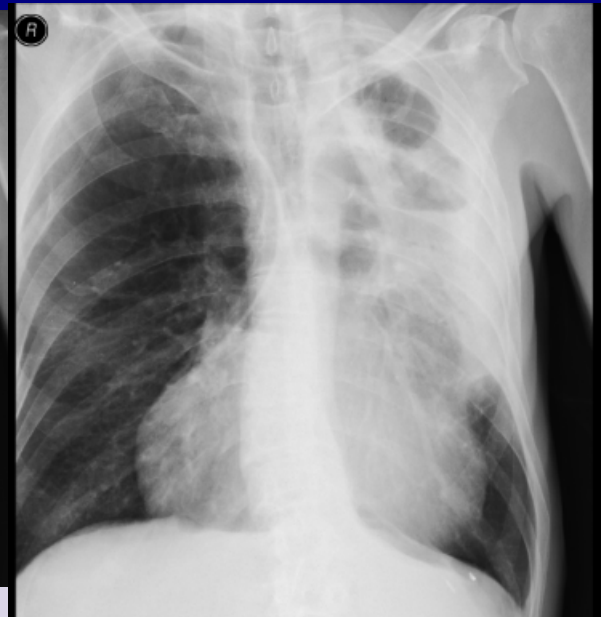




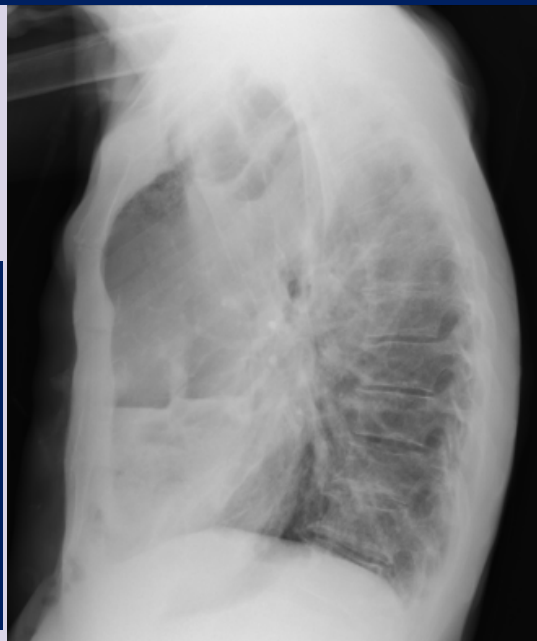
**1/10/2012**



**5/10/2012**



**10/10/2012**



[A]

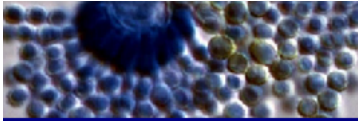
9.10.2012



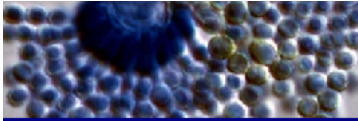
X/B-reeks CE

[P]





- 9.10 BAL: purulent sputum from left upper lobe
- PCT 0.19 ng/ml



# EORTC/MSG criteria for



101

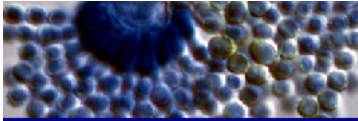
**Does this case fit the description of the  
2008 EORTC/MSG criteria for:**

1 - definite or proven IA

2 - probable IA

3 - possible IA

4 - none of the above: not classifiable



# EORTC/MSG criteria for IA

**Does this case fit the description of the  
2008 EORTC/MSG criteria for:**

1 - definite or proven IA

0%

2 - probable IA

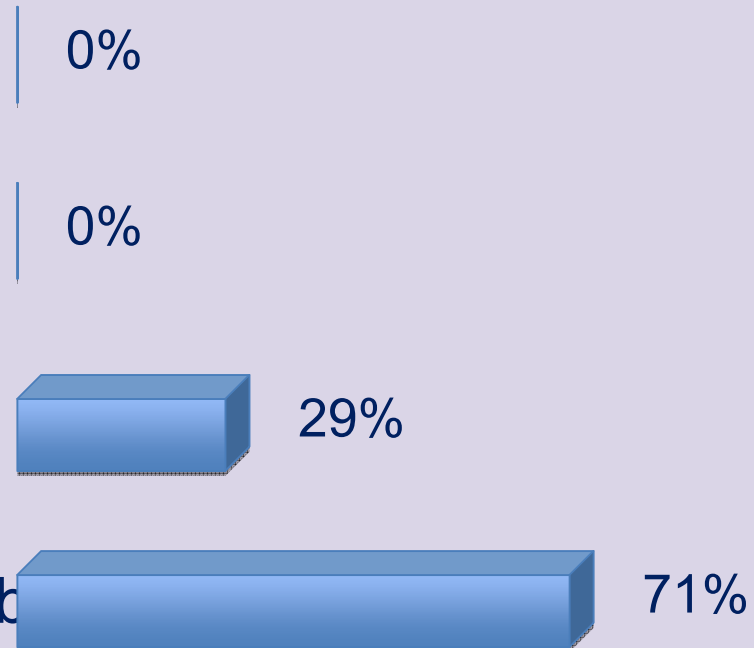
0%

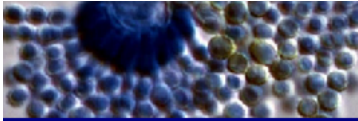
3 - possible IA

29%

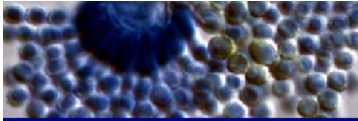
4 - none of the above: not classifiab

71%





- 9.10 BAL: purulent sputum from left upper lobe
- PCT 0.19 ng/ml
- BAL
  - Acid fast staining BAL neg
  - Culture: *K pneumoniae* (single colony); no yeast, no hyphae
  - GM 5.25
- Precipitins for *A fumigatus* 189 mg/l (>72)



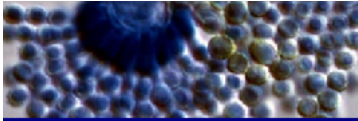
# To treat or not to treat



94

## Which treatment change would you advise:

- 1 - continue the same schedule
- 2 - add meropenem again
- 3 - add meropenem + caspofungin
- 4 - add meropenem + vorico



# To treat or not to treat

## Which treatment change would you advise:

1 - continue the same schedule

0%

2 - add meropenem again

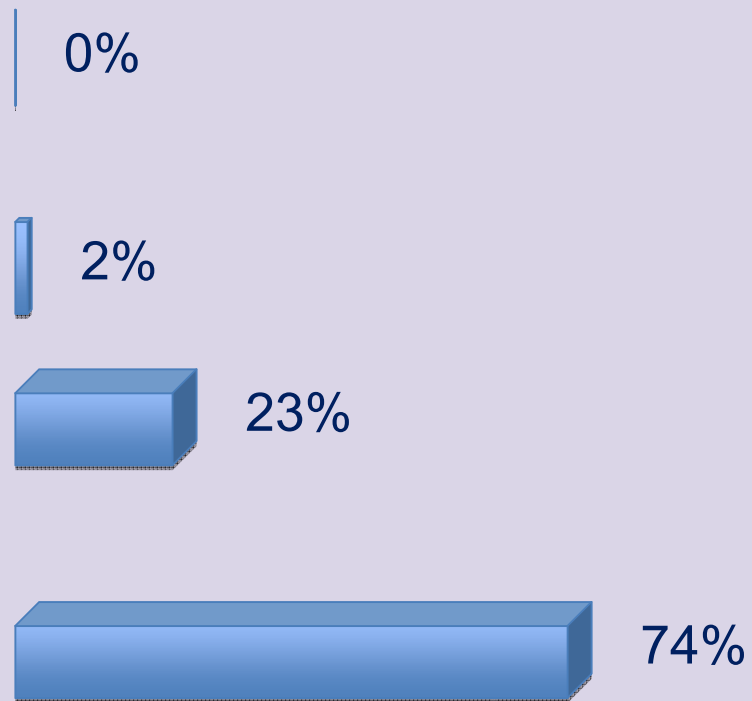
2%

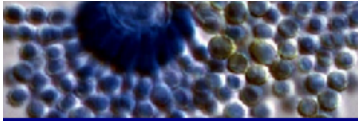
3 - add meropenem + caspofungin

23%

4 - add meropenem + vorico

74%





# The challenging diagnosis of IA in the ICU

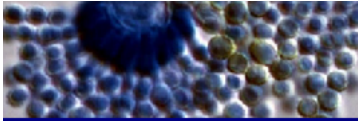
Problems arise in every component of diagnosis:

1. Host factors

2. Clinical features (medical imaging)

3. Mycology

→ may be source of late initiation of antifungal therapy or of overconsumption of antifungals

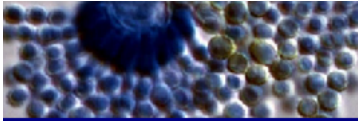


## Diagnosing IA in the ICU (1): Host factors

### From “classical” to “non-classical” risk groups

- ↑ Recognition of I(P)A as a significant problem in non-classic patient groups:
  - COPD
  - liver cirrhosis
  - critically ill patients with other types of immune deficiency (immune paralysis or compensatory anti-inflammatory response)
- Populations without validation of biomarkers such as GM or  $\beta$ -D-glucan and more aspecific radiologic abnormalities (“pneumonia”)

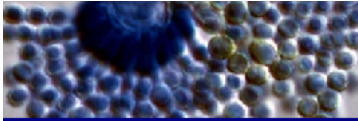




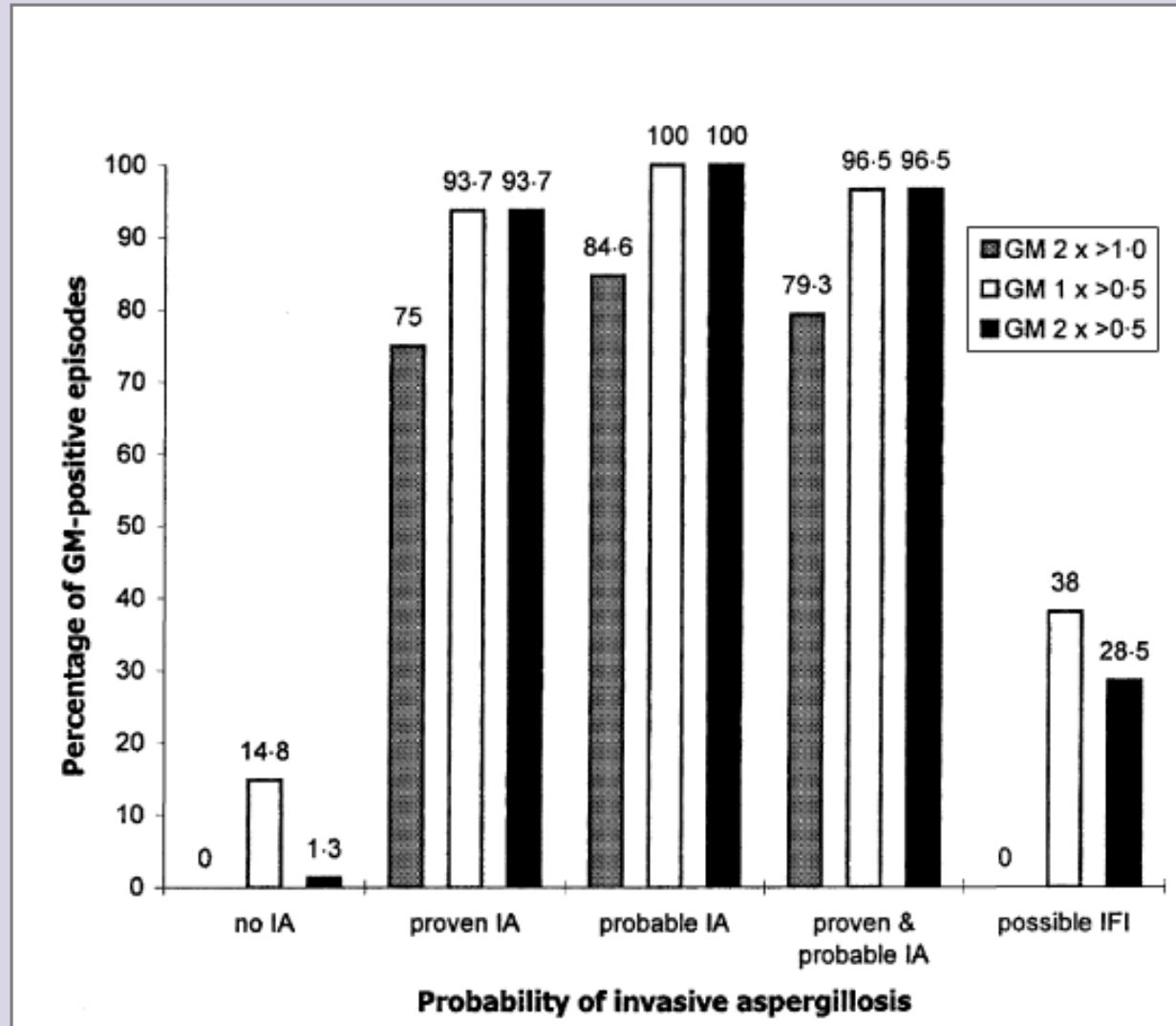
## Diagnosing IA in the ICU (2): Med. imaging

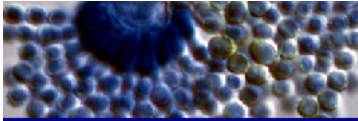
### Radiological findings in ICU patients with IPA (n=83)

Radiological findings	N (n in proven IPA)
Normal	0
Diffuse reticular or alveolar opacities (ARDS-like)	12 (1)
Non-specific infiltrates & consolidation	42 (10)
Pleural fluid	0
Nodular lesions	25 (5)
Air crescent sign	1
Halo sign	2 (1)
Cavitation	1



# Galactomannan-positive episodes in patients with IA (~EORTC/MSG)

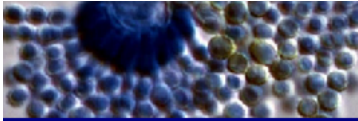




# Galactomannan in BAL Fluid in Critically Ill Patients

GM and culture results in 72 pathology controlled cases

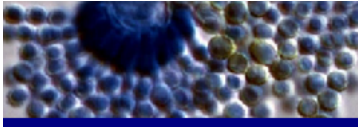
	No. of Patients		Total
	Invasive Aspergillosis ( <i>n</i> = 26)	No Invasive Aspergillosis <sup>†</sup> ( <i>n</i> = 46)	
Serum galactomannan, no. <sup>‡</sup>			
Positive	11	3	14
Negative	15	43	58
Total	26	46	72
BAL galactomannan, no. <sup>‡</sup>			
Positive	23	6	29
Negative	3	40	43
Total	26	46	72



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

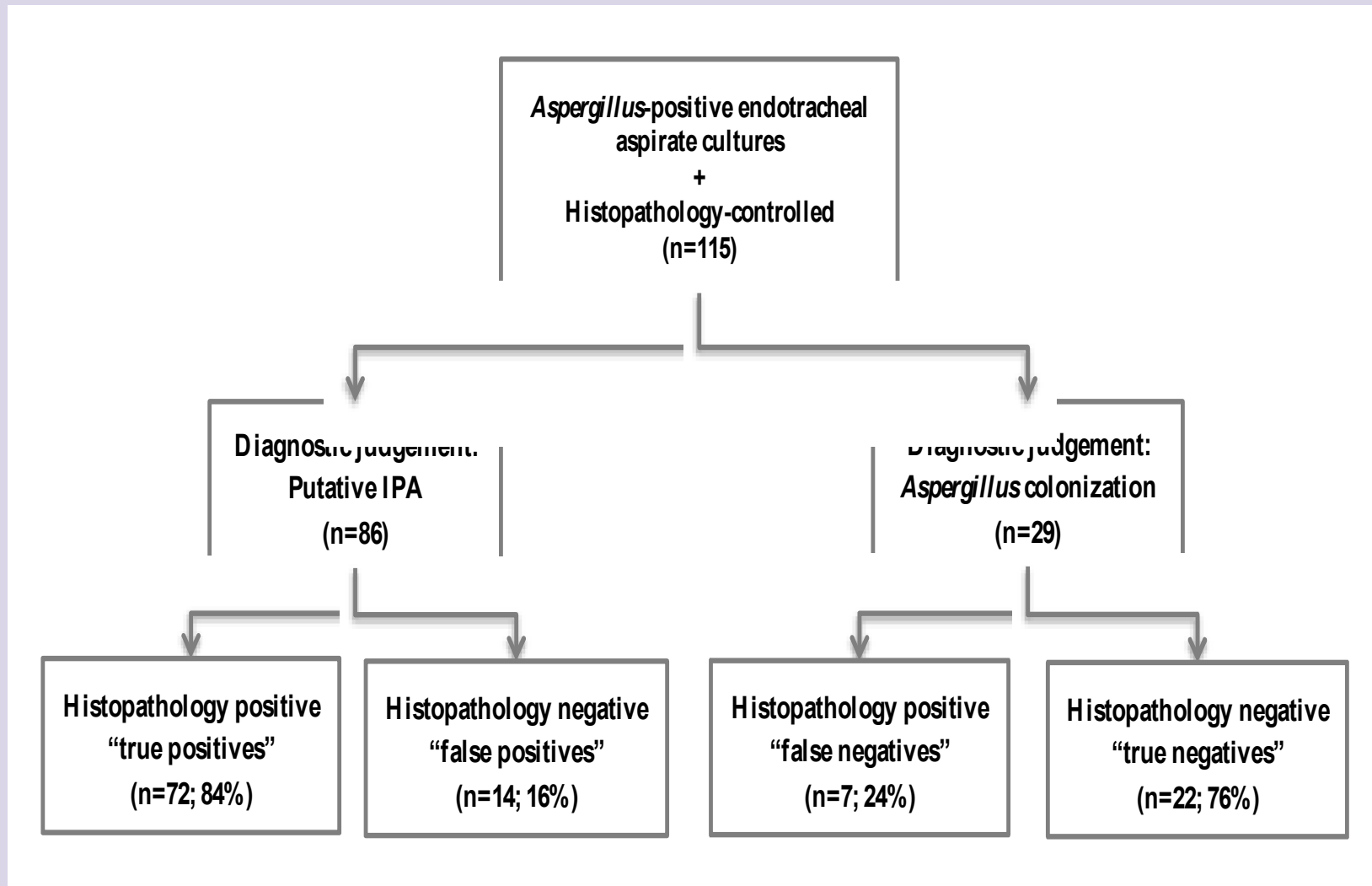
## “Putative IPA” A new class for diagnosing IPA

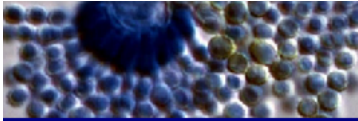
1. LRT sample positive for *Aspergillus* (entry criterion)
2. Compatible signs and symptoms
3. Abnormal medical imaging of chest
4. Either:
  - (a) Host risk factors:
    - neutropenia,
    - hemato-oncologic malignancy + cytostatics
    - steroid treatment >20 mg/day
    - immunodeficiency
  - (b) BAL:-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



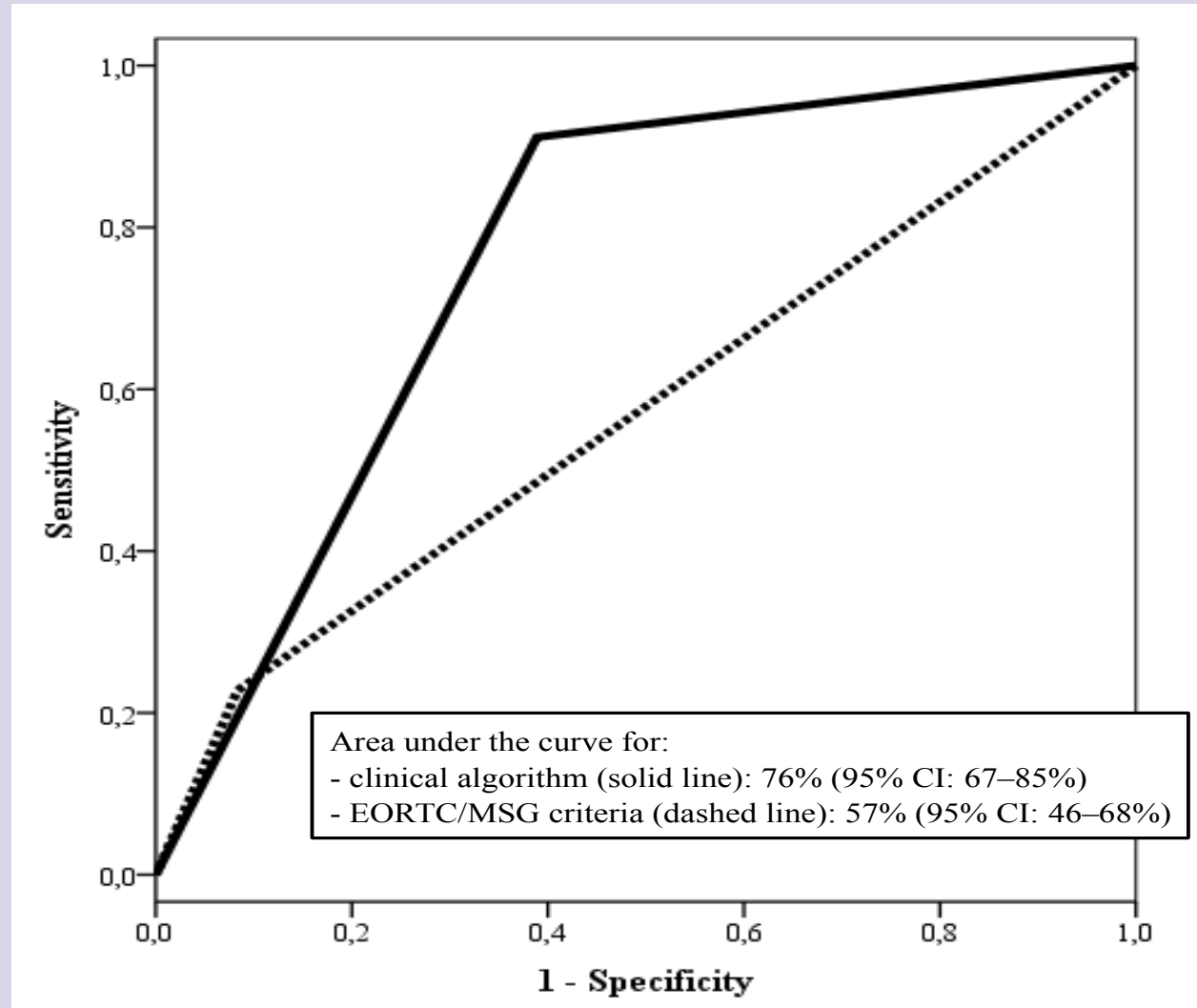
# AspICU1

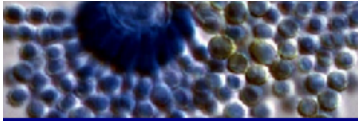
## Predictive value of the clinical algorithm in 115 critically ill patients with *Aspergillus*-positive respiratory tract aspirates and histopathologic examination



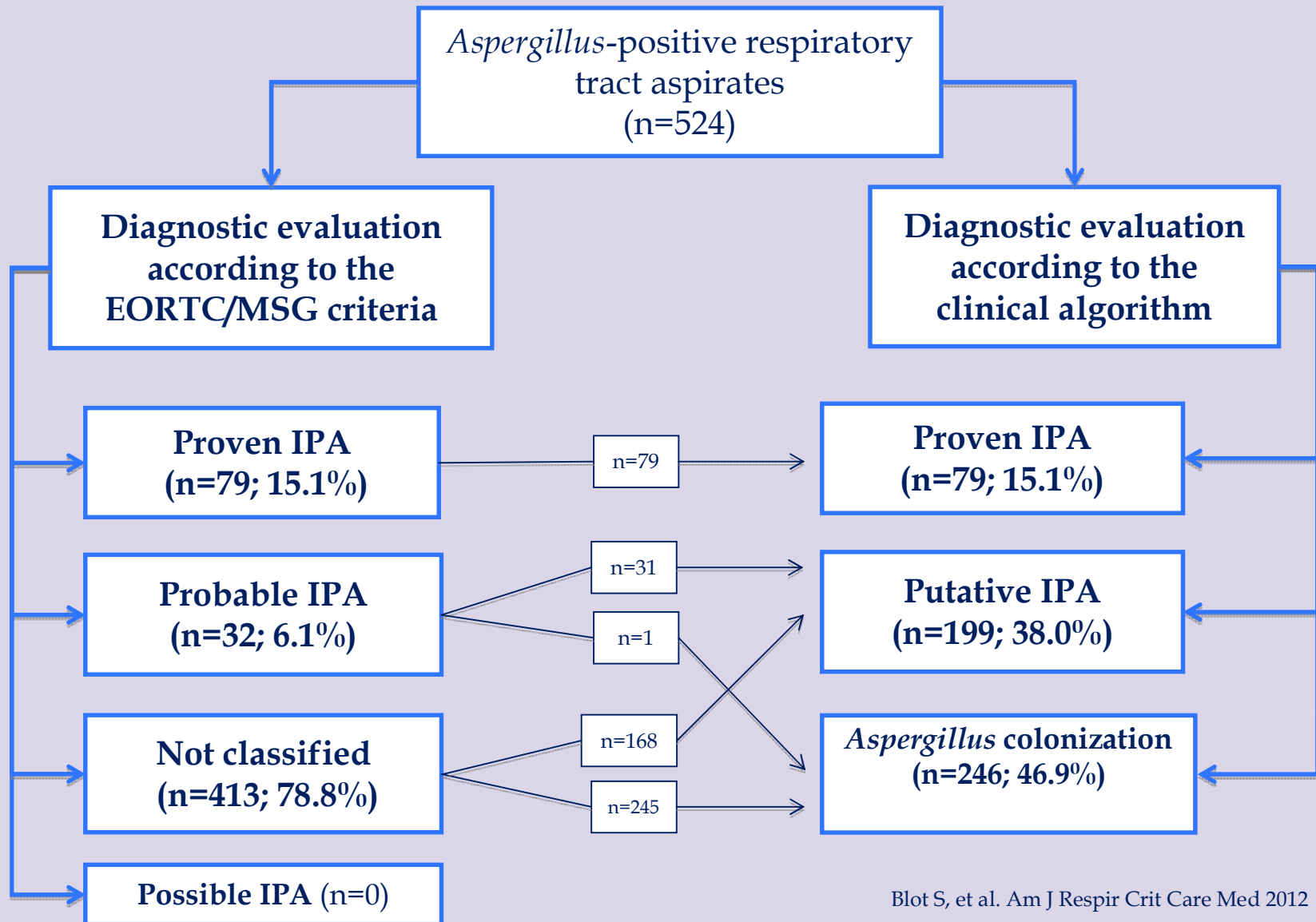


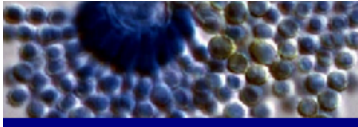
# Accuracy of the algorithm and the EORTC/MSG criteria to diagnose either “putative” or “probable” IPA in histopathology controlled cases (n=115)





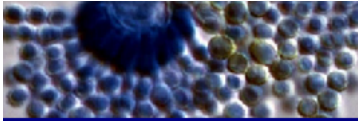
# Diagnostic breakdown of ICU patients with *Aspergillus*-positive respiratory tract cultures according to EORTC/MSG criteria and the clinical algorithm





- Easy to use & reasonable operating characteristics
- The outcome profile of “Putative IPA” is comparable with that of proven and probable IPA
- Detects a larger proportion of the total burden of disease
- High NPV, especially in immunocompromized patients
- In non-immunocompromized patients...
  - additional GM detection on BAL fluid could improve operating characteristics of the clinical algorithm





# Spectrum from colonisation to invasive disease: EORTC criteria

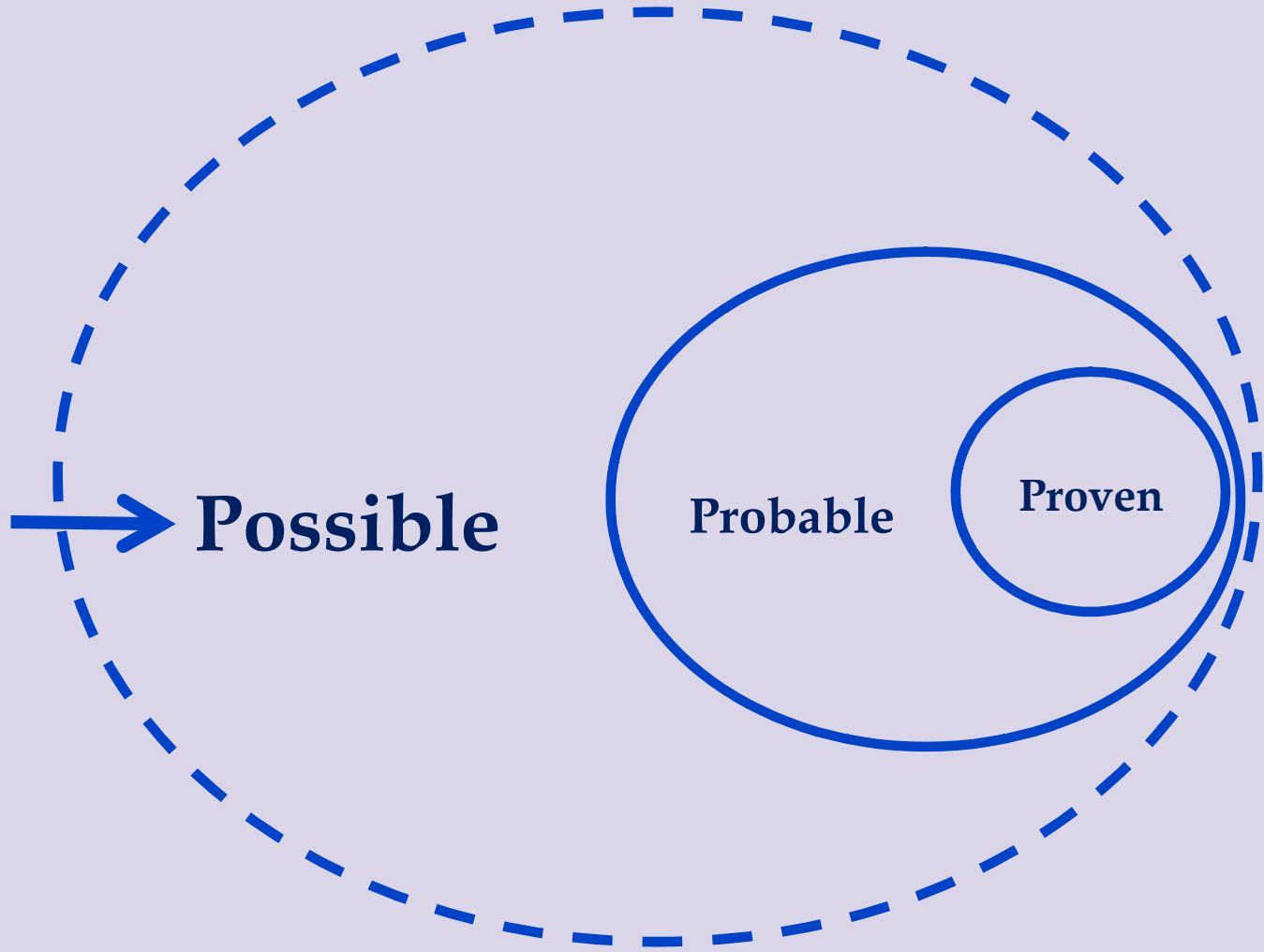
Colonization

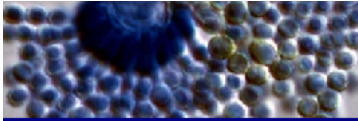


Possible

Probable

Proven





# Spectrum from colonisation to invasive disease: proposed algorithm vs EORTC criteria

