

# AsTeC Case Adjudication

Lindsey Baden, MD

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INVASIVE ASPERGILLOSIS ANIMAL MODELS

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# Definitions

Revised Definitions of Invasive Fungal Disease  
from the European Organization for Research  
and Treatment of Cancer/Invasive Fungal Infections  
Cooperative Group and the National Institute  
of Allergy and Infectious Diseases Mycoses Study  
Group (EORTC/MSG) Consensus Group

Ben De Pauw,<sup>a</sup> Thomas J. Walsh,<sup>a</sup> J. Peter Donnelly,<sup>a</sup> David A. Stevens, John E. Edwards, Thierry Calandra, Peter G. Pappas, Johan Maertens, Olivier Lortholary, Carol A. Kauffman, David W. Denning, Thomas F. Patterson, Georg Maschmeyer, Jacques Bille, William E. Dismukes, Raoul Herbrecht, William W. Hope, Christopher C. Kibbler, Bart Jan Kullberg, Kieren A. Marr, Patricia Muñoz, Frank C. Odds, John R. Perfect, Angela Restrepo, Markus Ruhnke, Brahm H. Segal, Jack D. Sobel, Tania C. Sorrell, Claudio Viscoli, John R. Wingard, Theoklis Zaoutis, and John E. Bennett<sup>b</sup>

De Pauw et al. CID 2008;46:1813-21



INVASIVE ASPERGILLOSIS ANIMAL MODELS

The logo for ASTEC (Aspergillus Technology Consortium) features the acronym 'ASTEC' in a large, white, serif font on a dark blue background. To the right of the text is a circular inset image showing a microscopic view of blue, branching, filamentous structures, likely representing Aspergillus hyphae.

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# Definitions → Gold Standard?

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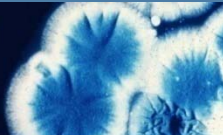
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# Two Key Determinations

- Certainty of an IFD
  - Proven, probable, possible
- Etiologic Pathogen(s)
  - Genus, species

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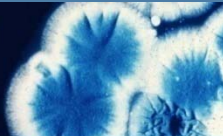
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We anticipate that the field of diagnosis will continue to evolve, so that there will come a time when the definitions may be formally evaluated for their sensitivity and specificity. Until then, additional revisions of the present set of definitions are likely, but they should be contemplated carefully. The words and phrases chosen here were selected on the basis of extensive debate and discussion. Seemingly, slight changes may have unexpectedly profound consequences in the design, implementation, and interpretation of clinical trials.

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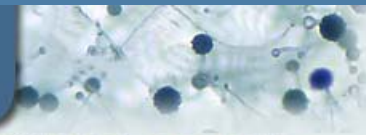


# EORTC/MSG Criteria 2008

**Table 1. Criteria for proven invasive fungal disease except for endemic mycoses.**

Analysis and specimen	Molds <sup>a</sup>
Microscopic analysis: sterile material	Histopathologic, cytopathologic, or direct microscopic examination <sup>b</sup> of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage
Culture	
Sterile material	Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine
Blood	Blood culture that yields a mold <sup>d</sup> (e.g., <i>Fusarium</i> species) in the context of a compatible infectious disease process
Serological analysis: CSF	Not applicable

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**Table 2. Criteria for probable invasive fungal disease except for endemic mycoses.**

**Host factors<sup>a</sup>**

- Recent history of neutropenia ( $<0.5 \times 10^9$  neutrophils/L [ $<500$  neutrophils/mm<sup>3</sup>] for  $>10$  days) temporally related to the onset of fungal disease
- Receipt of an allogeneic stem cell transplant
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for  $>3$  weeks
- Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF- $\alpha$  blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

**Clinical criteria<sup>b</sup>**

- Lower respiratory tract fungal disease<sup>c</sup>
  - The presence of 1 of the following 3 signs on CT:
    - Dense, well-circumscribed lesions(s) with or without a halo sign
    - Air-crescent sign
    - Cavity
  - Tracheobronchitis
    - Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
  - Sinonasal infection
    - Imaging showing sinusitis plus at least 1 of the following 3 signs:
      - Acute localized pain (including pain radiating to the eye)
      - Nasal ulcer with black eschar
      - Extension from the paranasal sinus across bony barriers, including into the orbit
  - CNS infection
    - 1 of the following 2 signs:
      - Focal lesions on imaging
      - Meningeal enhancement on MRI or CT
  - Disseminated candidiasis<sup>d</sup>
    - At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
      - Small, target-like abscesses (bull's-eye lesions) in liver or spleen
      - Progressive retinal exudates on ophthalmologic examination

**Mycological criteria**

- Direct test (cytology, direct microscopy, or culture)
  - Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:
    - Presence of fungal elements indicating a mold
    - Recovery by culture of a mold (e.g., *Aspergillus*, *Fusarium*, *Zygomycetes*, or *Scedosporium* species)
- Indirect tests (detection of antigen or cell-wall constituents)<sup>e</sup>
  - Aspergillosis
    - Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF
  - Invasive fungal disease other than cryptococcosis and zygomycoses
    - $\beta$ -D-glucan detected in serum

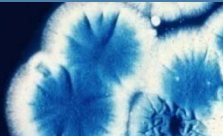
**NOTE.** Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.



# Case 1

- 55yoM with AML undergoes a reduced intensity MUD-HSCT 11/07
- 2/09 relapsed AML → induction
- 3/09 develops F+N
  - Antibacterials and micafungin given empirically
- Pneumonia diagnosed with the following findings on Chest CT

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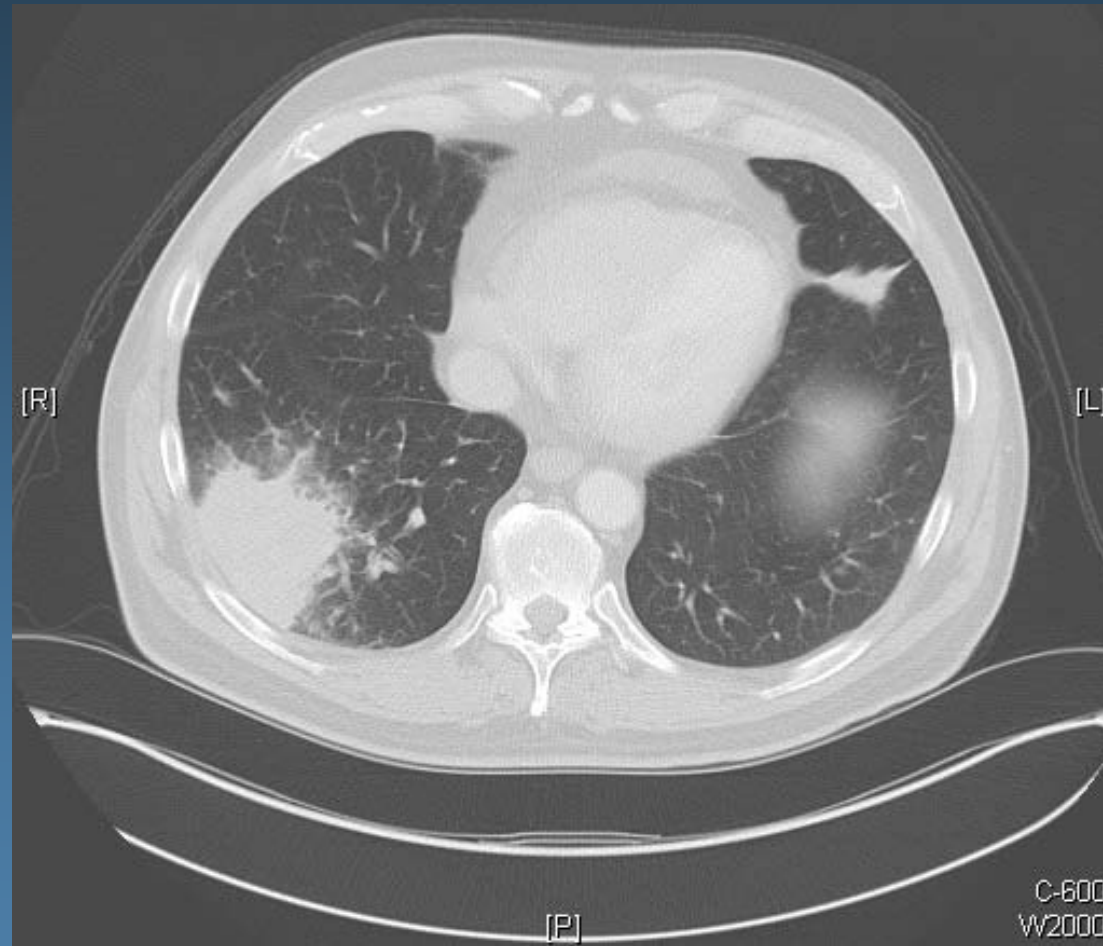
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# Case 1



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# Case 1

- GM is 5.3
- Treated with voriconazole with good response

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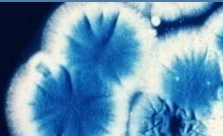
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# Final Infection Grade

- Probable IFD
- Probable Invasive Aspergillosis
  - Questions raised
    - Without the GM
      - This would be a Possible IFD
    - In certain cases GM positivity may curtail further w/u
  - We donot know the species of IA

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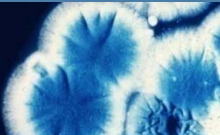
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# Case 2

- 51yoM with AA MRD-HSCT 4 months earlier c/b poor engraftment
- 3 months earlier PBSC boost with persistently low counts
- n/w fever, malaise, and cough for a few days
- On admission T=101.9 F, ANC<50, and a Chest Ct was obtained and showed:

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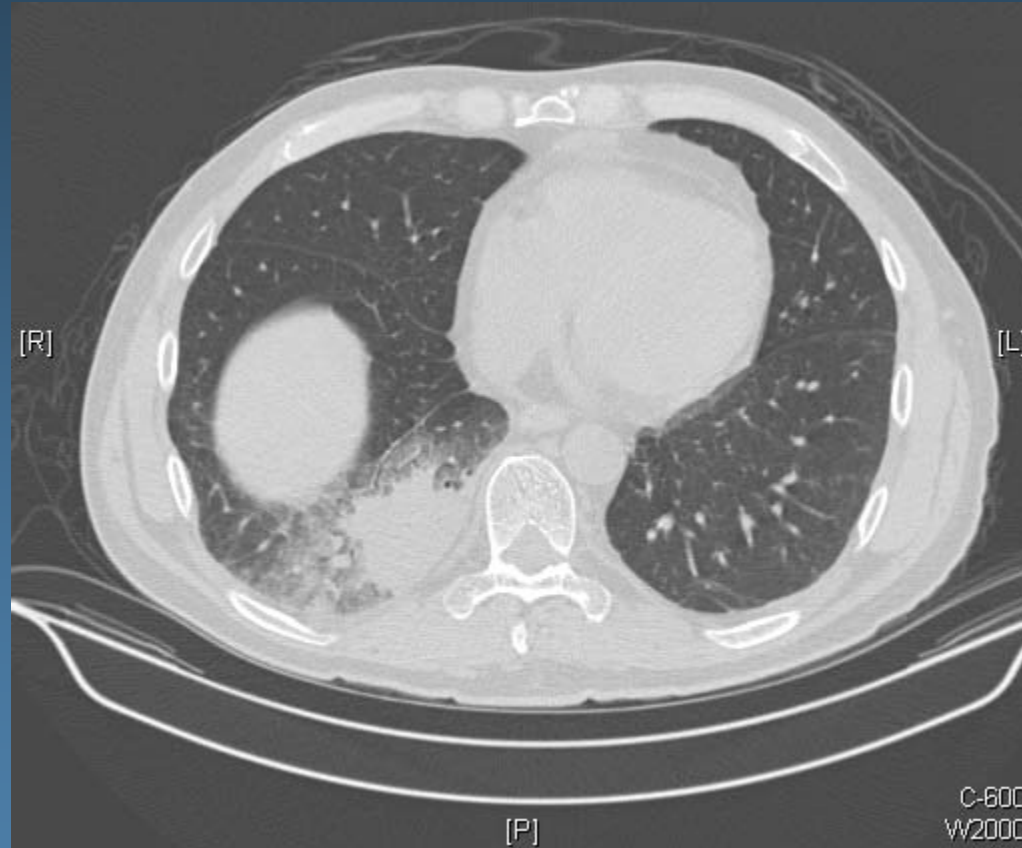
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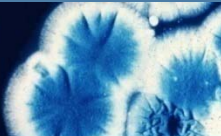
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# Case 2



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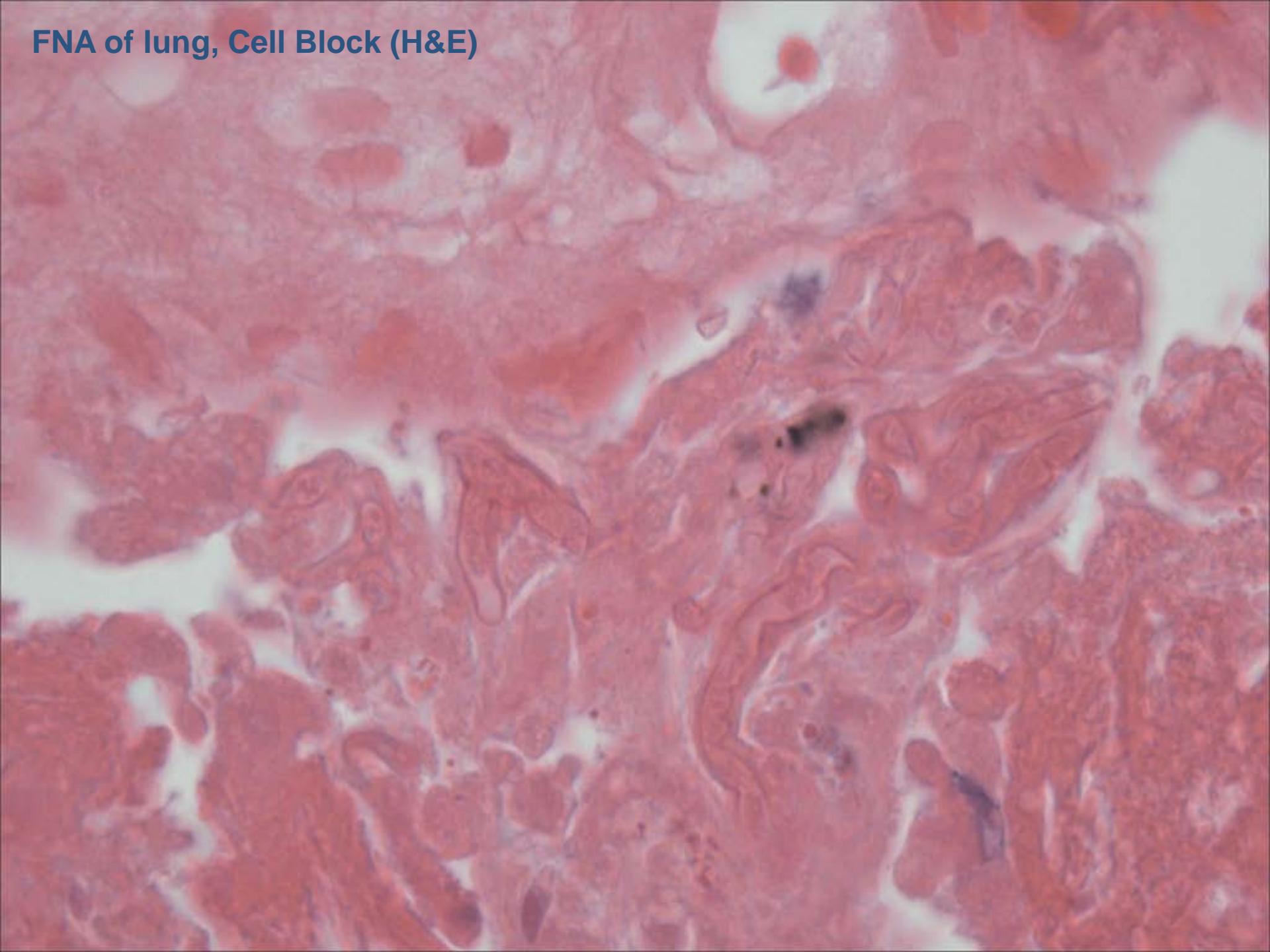
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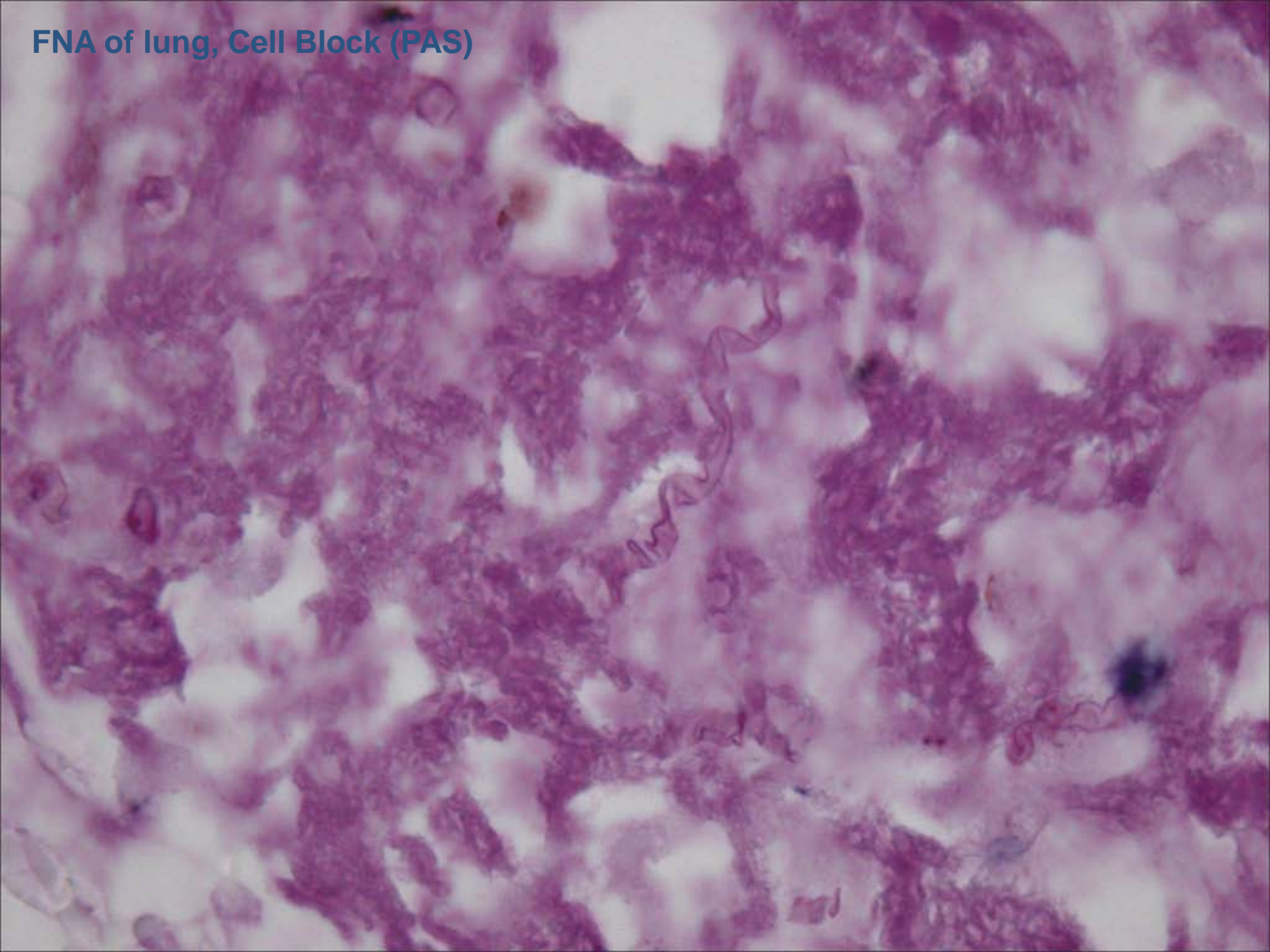
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FNA of lung, Cell Block (H&E)

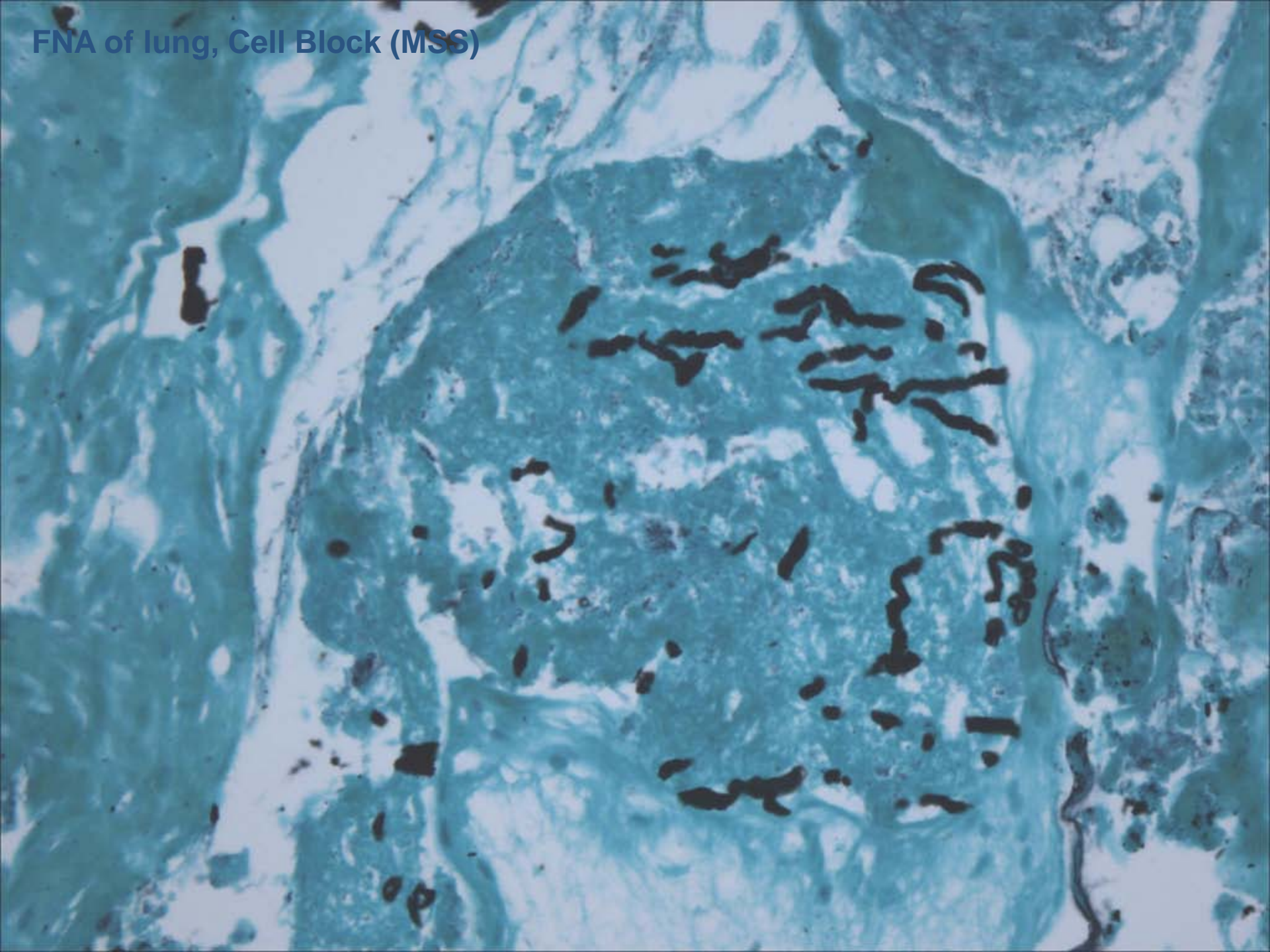


FNA of lung, Cell Block (PAS)





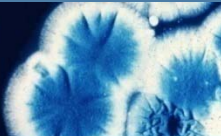
FNA of lung, Cell Block (MSB)



# Case 2

- GM and BG both negative
- Cultures no growth
- Sent to CDC for speciation by IHC from tissue sections
  - +Aspergillus, - Zygomycetes
- Treated with voriconazole and responding

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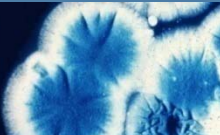
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# Case 2

- Proven IFD
- Should this be classified as
  1. Proven mold IFD, pathogen unknown
  2. Proven IA
  3. Probable IA
  4. None of the above

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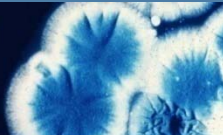
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# What is the proper classification?

- Pt has nodular infiltrate
- Bronchoscopy is performed
- Findings of TBBx:
  - Tissue damage
  - Hyphae invading tissue
  - Culture is + for *A. fumigatus*
- This case is:
  1. Proven mold IFD, pathogen unknown
  2. Proven IA
  3. Probable IA
  4. None of the above

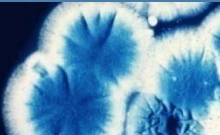


# What is the proper classification?

- Pt has nodular infiltrate
- Bronchoscopy is performed
- Findings of TBBx:
  - Tissue damage
  - Hyphae invading tissue
  - Culture is - for *A. fumigatus*
  - BAL GM is +
- This case is:
  1. Proven mold IFD, pathogen unknown
  2. Proven IA
  3. Probable IA
  4. None of the above

# What is the proper classification?

- Pt has nodular infiltrate
- Open lung biopsy is performed
- Findings of **OLBx**:
  - Tissue damage
  - Hyphae invading tissue
  - Culture is + for *A. fumigatus*
- This case is:
  1. Proven mold IFD, pathogen unknown
  2. Proven IA
  3. Probable IA
  4. None of the above



# What is the proper classification?

- Pt has nodular infiltrate
- Open lung biopsy is performed
- Findings of **OLBx**:
  - Tissue damage
  - Hyphae invading tissue
  - **Culture is - for *A. fumigatus***
  - **BAL GM is +**
- This case is:
  1. Proven mold IFD, pathogen unknown
  2. Proven IA
  3. Probable IA
  4. None of the above

# What is the proper classification?

- Pt has sinus opacification on CT
- Sinus endoscopy is performed
- Findings of biopsy:
  - Tissue damage
  - Hyphae invading tissue
  - Culture is + for *A. fumigatus*
- This case is:
  1. Proven mold IFD, pathogen unknown
  2. Proven IA
  3. Probable IA
  4. None of the above



# What is the proper classification?

- Pt has sinus opacification on CT
- Sinus endoscopy is performed
- Findings of biopsy:
  - Tissue damage
  - Hyphae invading tissue
  - Culture is - for *A. fumigatus*
  - Serum GM is +
- This case is:
  1. Proven mold IFD, pathogen unknown
  2. Proven IA
  3. Probable IA
  4. None of the above

# Moving Forward

- Modified EORTC/MSG criteria
  - Case adjudication process which utilizes the expertise of the AsTeC group
- Optimize specificity of diagnosis
  - Utilize additional inputs
    - Novel diagnostics
      - e.g., CDC IHC, tissue based sequencing

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