AsTeC Case Adjudication

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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


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

- Certainty of an IFD
  - Proven, probable, possible
- Etiologic Pathogen(s)
  - Genus, species
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.**
## EORTC/MSG Criteria 2008

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

<table>
<thead>
<tr>
<th>Analysis and specimen</th>
<th>Molds&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Microscopic analysis: sterile material</td>
<td>Histopathologic, cytopathologic, or direct microscopic examination&lt;sup&gt;b&lt;/sup&gt; 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</td>
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<td>Recent history of neutropenia (&lt;0.5 × 10⁹ neutrophils/L [&lt;500 neutrophils/mm³] for &gt;10 days) temporally related to the onset of fungal disease</td>
<td></td>
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<td>Receipt of an allogeneic stem cell transplant</td>
<td></td>
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<tr>
<td>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</td>
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<td>Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days</td>
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<td>Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)</td>
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<th>Clinical criteriab</th>
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<td>Lower respiratory tract fungal diseasec</td>
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<td>The presence of 1 of the following 3 signs on CT:</td>
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<td>- Dense, well-circumscribed lesion(s) with or without a halo sign</td>
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<tr>
<td>- Air-crescent sign</td>
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<tr>
<td>- Cavity</td>
</tr>
<tr>
<td>Tracheobronchitis</td>
</tr>
<tr>
<td>- Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis</td>
</tr>
<tr>
<td>Sinonasal infection</td>
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<tr>
<td>- Imaging showing sinusitis plus at least 1 of the following 3 signs:</td>
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<tr>
<td>- Acute localized pain (including pain radiating to the eye)</td>
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<tr>
<td>- Nasal ulcer with black eschar</td>
</tr>
<tr>
<td>- Extension from the paranasal sinus across bony barriers, including into the orbit</td>
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<tr>
<td>CNS infection</td>
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<tr>
<td>- 1 of the following 2 signs:</td>
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<tr>
<td>- Focal lesions on imaging</td>
</tr>
<tr>
<td>- Meningeal enhancement on MRI or CT</td>
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<tr>
<td>Disseminated candidiasid</td>
</tr>
<tr>
<td>- At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:</td>
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<tr>
<td>- Small, target-like abscesses (bull's-eye lesions) in liver or spleen</td>
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<td>- Progressive retinal exudates on ophthalmologic examination</td>
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<td>Direct test (cytology, direct microscopy, or culture)</td>
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<td>- Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:</td>
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<tr>
<td>- Presence of fungal elements indicating a mold</td>
</tr>
<tr>
<td>- Recovery by culture of a mold (e.g., Aspergillus, Fusarium, Zygomycetes, or Scoposporium species)</td>
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<tr>
<td>Indirect tests (detection of antigen or cell-wall constituents)²</td>
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<tr>
<td>- Aspergillosis</td>
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<tr>
<td>- Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF</td>
</tr>
<tr>
<td>- Invasive fungal disease other than cryptococcosis and zygomycoses</td>
</tr>
<tr>
<td>- α-glucan detected in serum</td>
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**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
Case 1
Case 1

- GM is 5.3
- Treated with voriconazole with good response
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
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:
Case 2
FNA of lung, Cell Block (MSS)
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
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
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
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  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
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- This case is:
  1. Proven mold IFD, pathogen unknown
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What is the proper classification?

- Pt has sinus opacification on CT
- Sinus endoscopy is performed
- Findings of biopsy:
  - Tissue damage
  - Hyphae invading tissue
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  - Culture is - for A. fumigatus
  - Serum GM is +

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1. Proven mold IFD, pathogen unknown
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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