

1 **EORTC/BAMSG Consensus Revised definitions draft VI**

2 **Proven invasive fungal diseases**

3 ***Deep tissue disease***

4 **Moulds¹**

5 Histopathologic, cytopathologic, or direct microscopic examination² of a needle
6 aspiration or biopsy specimen showing hyphal forms with evidence of associated
7 tissue damage (either microscopically or as an infiltrate or lesion by imaging)³

8 ***OR***

9 Recovery of a mould by culture from a sample obtained by a sterile procedure
10 from a normally sterile and clinically or radiologically abnormal site consistent
11 with an infectious disease process, excluding BAL, cranial sinus cavity, and urine.

12 **Yeasts**

13 Histopathologic or cytopathologic examination² of a needle aspiration or biopsy
14 specimen from a normally sterile site excluding mucous membranes showing
15 yeast cells (*Candida* species may also show pseudohyphae or true hyphae)

16 ***OR***

17 Recovery of a yeast by culture from a sample obtained by a sterile procedure
18 (including a freshly (<24h) placed drain) from a normally sterile and clinically or
19 radiologically abnormal site consistent with an infectious disease process,

¹ Append identification at genus or species level from culture, if available.

² tissue and cells submitted for histopathology or cytopathology should be stained by Grocott-Gomori methenamine silver stain or by periodic acid Schiff stains to facilitate inspection of fungal structures. Where possible, wet mounts of specimens from foci related to invasive fungal infectious disease should be stained with a fluorescent marker (e.g., calcofluor or Blancophor)

³ Individual fungal invasive disease entities e.g. proven aspergillosis require culture and identification. Failing this the disease is designated as proven mould invasive fungal disease

1 **Fungemia**

2 **Moulds**

3 Blood culture that yields a mould e.g. *Fusarium* spp. in the context of a
4 compatible infectious disease process⁴.

5 **Yeasts**

6 Blood culture that yields yeast (e.g. *Candida* species) or yeast-like fungi (e.g.
7 *Trichosporon* spp.)

8 **Endemic fungal disease⁵**

9 **Disseminated and/or pulmonary⁶ disease**

10 Must be proven by recovery in culture from a specimen obtained from the
11 affected site, in host with a temporally related illness consistent with a fungal
12 infectious disease process;

13 OR

14 if culture is sterile or not obtained, histopathologic or direct microscopic
15 demonstration of appropriate morphological forms is considered adequate for
16 dimorphic fungi having truly distinctive appearance.⁷

17 OR

⁴ Other moulds can cause fungemia. However contamination should be excluded before assigning the diagnosis of proven invasive fungal disease

⁵ Histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis, sporotrichosis and infection due to *Penicillium marneffe*

⁶ the medical history must be established to distinguish between a primary and chronic pulmonary infection. Onset within 3 months defines a primary pulmonary infection.

⁷ *Histoplasma capsulatum* variety *capsulatum* may resemble *Candida glabrata* or *Leishmania* in tissue but can be distinguished from them by the characteristic histologic features of granulomatous inflammation and staining by Grocott-Gomori methenamine silver stain

1 Positive blood culture

2 In the case of histoplasmosis a diagnosis of disseminated disease may be
3 established by a positive *Histoplasma* antigen test⁸ on CSF, urine or serum by
4 EIA, or the presence of characteristic intracellular yeast forms in a peripheral
5 blood smear or in bone marrow.

6 Or in the case of coccidioidomycosis a diagnosis of disseminated disease may be
7 established by demonstration of coccidioidal antibody⁹ in CSF, or a 2-dilution rise
8 measured in two consecutive blood samples tested concurrently in the setting of
9 a temporally related infectious disease process .

10 ***Cryptococcosis***

11 *Pete Pappas to supply*

12 **Probable invasive fungal disease**

13 Defined by at least

14 a) one host criterion

15 ***AND***

16 b) one clinical criterion

17 ***AND***

18 c) one microbiological criterion

19 **Possible invasive fungal disease⁹**

20 Defined by at least

⁸ Testing should be performed only in laboratories where the assays have been validated; i.e., clinical correlations made with results and titers, and with data available on false positive and false negative rates with the test as performed in that laboratory.

⁹ provided other plausible causes have been excluded

1 a) one host criterion

2 **AND**

3 b) one clinical criterion

4 **BUT**

5 c) no microbiological criterion

6 **Host factors**

7 Host factors are not synonymous with risk factors and are characteristics by
8 which individuals predisposed to invasive fungal diseases can be recognized.

9 They are intended primarily to apply to patients treated for malignant disease
10 and to recipients of allogeneic hematopoietic stem cell and solid organ
11 transplant. These host factors are also applicable to those receiving
12 corticosteroids and other T-cell suppressants as well as those with primary
13 immune deficiencies

14 1) Recent history of neutropenia ($< 0.5 \times 10^9/L$ { <500 neutrophils/ mm^3 } for
15 >10 days) temporally related to the onset of fungal disease or ongoing
16 neutropenia

17 2) Receipt of an allogeneic stem cell transplant

18 3) Prolonged use of corticosteroids (excluding patients with ABPA) at an
19 average minimum dose of 0.3 mg/kg/day prednisone equivalent for > 3
20 weeks

21 4) Treatment with other recognized T-cell immune suppressants such as
22 ciclosporin, TNF- α blockers, specific monoclonal antibodies alemtuzumab,
23 nucleoside analogues during the past 90 days

24 5) Inherited severe immunodeficiency (e.g., chronic granulomatous disease,

1 severe combined immunodeficiency)

2 **Clinical criteria**

3 Must be consistent with the microbiological findings, if any, temporally related to
4 current episode and other potential causes must have been eliminated

5 ***Lower respiratory tract fungal disease***

6 A) the presence of one of the following "specific" imaging signs on CT:-

- 7 • Well defined nodule(s) with or without a halo sign
- 8 • Wedge-shaped infiltrate
- 9 • Air crescent sign
- 10 • Cavity

11 B) the presence of a new non-specific focal infiltrate

12 PLUS at least one of the following¹⁰:-

- 13 Pleural rub
- 14 Pleural pain
- 15 Hemoptysis

16 ***Tracheobronchitis***

17 Tracheobronchial ulceration, nodule, pseudomembrane, plaque or eschar
18 seen on bronchoscopy

¹⁰ symptoms not necessary if there is mycological evidence

1 ***Sinonasal infection***

2 Imaging showing sinusitis

3 ***PLUS***

4 at least one of the following:-

5 Acute localized Pain (including pain radiating to eye)

6 Nasal ulcer, black eschar

7 extension from the paranasal sinus across bony barriers, including

8 into the orbit

9 ***Endophthalmitis***

10 as determined by ophthalmologic examination

11 ***CNS infection***

12 at least one of the following:-

13 Focal lesions on imaging

14 Meningeal enhancement on MRI or CT

15 ***Chronic disseminated candidiasis***

16 Small, peripheral, target like abscesses (new nodular filling defects, bull's-eye

17 lesions) in liver and/or spleen

18 **Microbiological Criteria**

19 ***Cytology, direct microscopy or culture:***

- 20 1. sputum, BAL and bronchial brush samples demonstrating the presence of
21 fungal elements either by recovery by culture of a mould (e.g. *Aspergillus*
22 spp., *Fusarium* spp., Zygomycetes, *Scedosporium* spp.) or detection by
23 cytology or direct microscopy of hyphal forms

- 1 2. sinus aspirate: recovery by culture of moulds from or detection of hyphal
2 forms by cytology or direct microscopy.
- 3 3. Skin ulcers, draining soft tissue lesions or fissure for which both microscopy
4 and culture are required

5 ***Detection of antigen, cell wall constituents or nucleic acid***

- 6 4. Galactomannan antigen EIA (Platelia).
- 7 a) a single plasma or serum sample positive for galactomannan
- 8 b) a single BAL, pleural fluid or CSF sample positive for galactomannan
- 9 6. Glucan Assay is primarily applicable for aspergillosis and candidiasis and does
10 not detect *Cryptococcus* species nor the Zygomycetes (*Rhizopus* spp., *Mucor* spp.
11 *Absidia* spp.)
- 12 a single serum sample positive for beta-D-glucan
- 13 7. Polymerase Chain Reaction to detect nucleic acid
- 14 Until a PCR system is developed that has been externally validated, a positive
15 PCR result for blood, tissue, or BAL fluid for the specific fungus studied will not
16 be considered microbiological evidence of invasive fungal disease.

17