EORTC/MSGERC Definitions of Invasive Fungal Diseases: Summary of Activities of the Intensive Care Unit Working Group

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The EORTC/MSGERC recently revised and updated the consensus definitions of invasive fungal disease (IFD). These definitions primarily focus on patients with cancer and stem cell or solid-organ transplant patients. They may therefore not be suitable for intensive care unit (ICU) patients. More in detail, while the definition of proven IFD applies to a broad range of hosts, the categories of probable and possible IFD were primarily designed for classical immunocompromised hosts and may therefore not be ideal for other populations. Moreover, the scope of the possible category of IFD has been diminished in the recently revised definitions for classically immunocompromised hosts. Diagnosis of IFD in the ICU presents many challenges, which are different for invasive candidiasis and for invasive aspergillosis. The aim of this article is to review progresses made in recent years and difficulties remaining in the development of definitions applicable in the ICU setting.

Keywords. invasive aspergillosis (IA); invasive candidiasis (IC); biomarker; definition; histology.

Diagnosing invasive fungal diseases (IFD) in intensive care units (ICU) presents many challenges, which are different for the 2 most frequent IFD encountered in nonneutropenic critically ill patients: (1) invasive candidiasis (IC) and (2) invasive aspergillosis (IA). Especially for the latter, difficulties arise from the heterogeneity of the population admitted to the ICU, including a large proportion of immunocompetent hosts in whom classical host factors predisposing to IFD (eg, neutropenia, hematological malignancies, or organ transplantation) are not present. This heterogeneity implies variable and frequently unclear risk profiling, in turn affecting several key aspects (eg, difficulty in measuring the true prevalence of the disease and the performance of diagnostic tests) necessary for defining IFD in a standardized fashion from both clinical and research standpoints [1–6]. The objective of the EORTC/MSGERC ICU Working Group was to try to overcome these difficulties and provide definitions for IC and IA that are relevant for ICU patients.

Following the EORTC/MSGERC approach, definitions were developed according to 2 levels of probability of IFD—namely, "proven" and "probable" IFD [7, 8]. This approach establishes a formal framework for defining IFD with a variable certainty of diagnosis. "Proven" IFD requires that a fungus be detected by blood culture or histology/culture of a specimen of tissue taken from a normally sterile clinical site. This category of IFD can apply to any host whether or not immunocompromised. By contrast, "probable" IFD is dependent on the setting/population and hinges on 3 elements—namely, a host factor that identifies the patients at risk, clinical features consistent with the disease entity, and mycological evidence that includes culture and microscopy but also indirect tests, such as antigen detection and molecular tools (polymerase chain reaction [PCR]) [7, 8]. Progress and difficulties encountered by the EORTC/MSGERC ICU Working Group in developing definitions for IC and IA in ICU patients are briefly reviewed in the present work.

INVASIVE CANDIDIASIS

Background

Invasive candidiasis is the most common fungal disease among ICU patients [6, 9–11]. It occurs when *Candida* species, which are frequent colonizers of cutaneous and mucosal surfaces, gain access to deeper, normally sterile sites. Invasive candidiasis comprises candidemia and deep-seated tissue candidiasis [12]. Deep-seated candidiasis arises either from hematogenous dissemination or from procedures that lead to direct inoculation of *Candida* into a sterile site.

Candidemia is generally viewed as the most common type of IC, and it accounts for the majority of cases included in clinical trials. Candidemia is defined by the isolation of *Candida* species from at least 1 blood culture and is unequivocal. These patients are more easily identified than patients with deep-seated candidiasis, which includes entities such as intra-abdominal candidiasis (IAC), osteomyelitis, septic arthritis, mediastinitis, endophthalmitis, endocarditis, urinary tract infections, and meningitis. Most of these foci arise from an earlier episode of candidemia that is often undiagnosed. Conversely, direct introduction of *Candida* at a sterile site may occur—for example, IAC (abscesses, peritonitis, pancreatitis) following abdominal surgery. Among patients in the ICU with IC, 2 patients will have isolated candidemia for every 3 patients with deep-seated candidiasis (>20–25% of which can lead to secondary candidemia) [13]. In the ICU, IAC constitutes the majority of cases with deep-seated candidiasis [13–15].

Diagnosis

Three entities must be considered: (1) candidemia in the absence of deep-seated candidiasis (including catheter-associated candidemia), (2) candidemia associated with deep-seated candidiasis, and (3) deep-seated candidiasis not associated with candidemia [15].

A proven diagnosis of candidemia (either primary or secondary to deep-seated candidemia) relies on the isolation of *Candida* spp. from blood cultures. Candidemia is the most frequent diagnosis of proven IFD in the ICU. Two pairs of blood culture bottles (10 mL each) should be obtained for aerobic and anaerobic culture when candidemia is suspected before the initiation of antifungal therapy [16]. To potentially increase the yield of blood cultures above 90%, up to 4 blood culture pairs should be obtained in 24 hours [17]. Although with the limitation of potential overestimation due to the possible inclusion of some cases of catheter colonization, up to 40–50% of all episodes of candidemia may be associated with intravenous catheters [18–20]. This is relevant in the ICU since intravenous catheters are typically present in this setting [21]. In patients with central venous lines and suspected candidemia, blood cultures should be obtained via the central line as well as from a peripheral site [22]. A distinction between catheter-associated and non–catheter-associated candidemia might be achieved by comparing the time to positivity or by comparing the number of colony-forming units from the blood drawn via the catheter and the peripheral blood [23, 24]. When cultures of only a catheter tip grow yeasts, while blood cultures remain sterile, systemic antifungals may not be indicated in every case, depending on the clinical condition of the patient and the level of contamination of the catheter tip [25]. Candidemia cases may nonetheless remain undetected because of false-negative blood cultures [15]. In such a case, presumptive diagnosis of candidemia in ICU patients with signs and symptoms of systemic infection is usually made by clinicians by the use of risk-prediction models or non–culture-based diagnostic tests, but is not standardized [26].

The use of risk-prediction models (in this case for diagnosis and not for prediction) may allow early diagnosis, but they have a low positive-predictive value and their use for universal administration of antifungals remains controversial [27, 28]. On the other hand, their very high negative-predictive value allows the diagnosis to be excluded [29]. Of note, some, but not all, models include colonization or colonization of more than 1 nonsterile site by *Candida* spp. among the factors increasing the risk of candidemia (or of IC in general for some of the scores) [30–39]. An alternative (or a completion) to risk-stratification scores is to stratify the risk based on non–culture-based tests, which, in a way similar to risk scores, is still not standardized. They include serological markers (1,3-β-D-glucan, mannan and anti-mannan, and *Candida albicans* germ tube antibody) and molecular methods (including the T2Candida test [T2 Biosystems, Lexington, Massachusetts], which combines PCR and magnetic resonance–based detection of the agglomeration of supermagnetic particles induced by the amplicons; the T2Candida test is approved by the Food and Drug Administration for the detection of *C. albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei* in blood [40, 41]). The main characteristics of non–culture-based tests for the diagnosis of candidemia in ICU patients are summarized in Table 1.

Diagnosis of proven deep-seated candidiasis is much less frequent than that of proven candidemia, since histopathology is rarely available and cultures are often obtained from nonsterile sites. For example, *Candida* spp. recovered in peritoneal fluid drawn from intra-abdominal drains may reflect colonization of drains from the skin rather than true intra-abdominal candidiasis [2]. In contrast, samples drawn under sterile conditions during surgery or radiology-guided drainage of abscesses are indicative of deep-seated *Candida* infections [72, 73]. Although potentially very useful given the frequent absence of proven diagnosis, identification of deep-seated candidiasis by means of non–culture-based tests is not standardized, and extrapolation of evidence regarding their diagnostic performance is sometimes hampered by the fact that they were usually explored in candidemia or IC in general and not for specific forms of deep-seated candidiasis. A brief summary of the characteristics of non–culture-based tests for the diagnosis of deep-seated candidiasis is also shown in Table 1.

Defining Proven and Probable Invasive Candidiasis in the Intensive Care Unit

After several rounds of review and discussion, the proposed definition for proven IC by the ICU Working Group required

Table 1. Characteristics of Non–Culture-Based Tests for the Diagnosis of Candidemia and Deep-Seated Candidiasis in Intensive Care Units

Test	Candidemia	Deep-Seated Candidemia
Serum BDG	• High NPV (frequently 90–95%) [42–45] • Low PPV (possibly 20–40%) [46] • Inconclusive evidence from RCT regarding the overall impact on mortality of candidemia of a BDG-based therapeutic strategy, although an improvement in rates of safe antifungal discontinuation has been described [48, 49] • Combination with other fungal antigen/antibody-based test of inflammatory markers (eg, serum PCT) has been proposed for improving diagnostic accuracy [50–53] and not for detecting specific types of IC	• Mostly studied in candidemia and IC in general • In a prospective study in 89 ICU patients with acute pancreatitis or who underwent abdominal surgery and at risk of IAC, BDG (2 consecutive measurements) showed 65% and 78% sensitivity and specificity, respectively [47] … …
Serum Mn/A-Mn	• Variable diagnostic performance in different studies [54–57] • Sensitivity and specificity of 59% and 65%, respectively, for candidemia reported in a study of 43 ICU patients with candidemia and 67 controls [58]	• Sensitivity of Mn and A-Mn was evaluated separately in 233 ICU patients with severe abdominal conditions; of them, 20 developed IAC and 11 candidemia; sensitivity and specificity of Mn were 43% and 67%, respectively; sensitivity and specificity of A-Mn were 26% and 89%, respectively [50] …
Serum CAGTA	• Limited experience compared with BDG and Mn/A-Mn • Important heterogeneity in specificity has been reported [60] • A possible improvement in diagnostic performance when used in combination with BDG has been suggested [52]	• Sensitivity of CAGTA was 5% and 69% for isolated candidemia and blood culture–positive deep-seated candidiasis, respectively, in a study of 50 patients with IC [59] … …
PCR-based methods	• Heterogeneous performance of in-house and commercial methods [61–65] • Unable to detect all *Candida* species • Promising results reported for T2Candida panel, which is FDA-approved for the detection of *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis*, and *C. krusei* in blood; to be further evaluated through further real-life experiences [40, 66–71]	• The same considerations expressed for candidemia applied for deep-seated candidemia, with the additional note that most studies refer to candidemia or IC in general and not to specific forms of IC … …

Abbreviations: A-Mn, anti-mannan antibodies; BDG, 1,3-β-D-glucan; CAGTA, *Candida albicans* germ tube antigen; FDA, Food and Drug Administration; IAC, intra-abdominal candidiasis; IC, invasive candidiasis; ICU, intensive care unit; Mn, mannan antigen; NPV, negative-predictive value; PCR, polymerase chain reaction; PCT, procalcitonin; PPV, positive-predictive value; RCT, randomized controlled trial.

definitive evidence of the organism in a normally sterile site. It should include at least 1 of the following:

1. Histopathologic, cytopathologic, or direct microscopic examination of material from a normally sterile site, obtained by needle aspiration or biopsy showing budding cells consistent with *Candida* species (presence of pseudo-hyphae and/or true hyphae is highly suggestive of *Candida* species, but these structures are not present in all *Candida* species and may also be seen in *Trichosporon* spp.*, Geotrichum* spp., and *Magnusiomyces capitatus* [previously known as *Geotrichum capitatum*], thus confirmation by culture or PCR is necessary).
2. Recovery of *Candida* spp. by culture of a specimen obtained by a sterile procedure (including a freshly placed [<24 hours] drain) from a normally sterile site showing a clinical or radiologic abnormality consistent with an infectious-disease process.

3. Blood culture yielding *Candida* species.

The proposed definition of probable IC in the ICU was based on the presence of at least 1 clinical criterion (compatible ocular findings by fundoscopic examination, hepatosplenic lesions by computed tomography [CT], clinical or radiological [nonpulmonary] abnormalities consistent with an infectious-disease process that are otherwise unexplained) plus at least 1 mycological criterion (positive serum 1,3-β-D-glucan in 2 consecutive samples, recovery of *Candida* in an intra-abdominal specimen obtained surgically or within 24 hours from external drainage), plus at least 1 of the following host factors:

1. Glucocorticoid treatment with prednisone equivalent of 20 mg or more per day
2. Qualitative or quantitative neutrophil abnormality (inherited neutrophil deficiency, absolute neutrophil count ≤500 cells/mm^3)

3. Impaired gut wall integrity (eg, recent abdominal surgery, recent chemotherapy, biliary tree abnormality, recurrent intestinal perforations, ascites, mucositis, severe pancreatitis, parenteral nutrition)
4. Impaired cutaneous barriers to bloodstream infection (eg, presence of central vascular access device, hemodialysis)
5. *Candida* colonization, defined as recovery of *Candida* species in cultures obtained from 2 or more of the following: respiratory tract secretions, stool, skin, wound sites, urine, and drains that have been in place for 24 or more hours
6. Hematopoietic stem cell transplantation (HSCT)
7. Solid-organ transplant (SOT)

INVASIVE ASPERGILLOSIS

Background

Invasive aspergillosis is a severe IFD increasingly reported in patients beyond the traditional risk groups, especially among critically ill patients in the ICU, mostly in the form of invasive pulmonary aspergillosis (IPA) [74–76]. The prevalence of IA in ICU patients varies across hospitals, although important uncertainty surrounds its true value considering the frequent lack of proven diagnosis and the heterogeneity of risk profiles in different types of ICU patients [1, 76]. Risk factors for IA in the ICU population include high-dose corticosteroids, chronic obstructive pulmonary disease, liver disease, malnutrition, burns, and diabetes [74–76]. In addition, rapid development of IPA has been reported in ICU patients admitted with respiratory failure secondary to influenza [77, 78]. Recently, the possibility of a nonnegligible risk of IPA in ICU patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has also been suggested [79–81].

Diagnosis

The diagnosis of IA in ICU remains difficult for a number of reasons [1, 3, 76]. Tissue sampling may be difficult or contraindicated in patients with hemodynamic instability, thrombocytopenia, or coagulation disorders. In addition, the yield of cultures is frequently suboptimal in terms of sensitivity [82, 83]. Further complicating the picture are the following: (1) classic radiographic signs of IA (such as the halo or air crescent sign) are generally absent in nonclassical populations [84]; (2) there could be difficulties in obtaining CT scans instead of bedside chest radiography; (3) discrimination of *Aspergillus* colonization versus infection is problematic [5]; and (4) *Aspergillus* tracheobronchitis, which is rare overall, is rarely considered in the ICU.

Against this background, diagnosis of IA is frequently presumptive, with the performance of non–culture-based tests being of interest for improving accuracy as much as possible. However, a major problem is that proven diagnosis of IA is also infrequent in research studies in the ICU. Consequently, the performance of the different non–culture-based tests has been often evaluated using the IA definition developed for the immunocompromised population with the uncertainty that these results may not be safely extrapolated to traditional ICU patient populations [1]. Nonetheless, some general patterns can be recognized regarding the performance of non–culture-based tests for the diagnosis of IPA in the ICU: (1) the diagnostic performance of bronchoalveolar lavage fluid (BALF) galactomannan is superior to that of serum galactomannan and (2) the use of either BALF or serum 1,3-β-D-glucan presents suboptimal specificity [1]. The performance of other non–culture-based tests such as the BALF *Aspergillus* lateral flow device and BALF/blood *Aspergillus* PCR is promising, but comparative/combined experience with other tests and against reliable reference in ICU patients is still limited [1, 83, 85–90].

Over time, different definitions of IA have been proposed (original or obtained by modifying/adding host factors to the 2002 and 2008 versions of the EORTC/MSGERC definitions) and used in different studies evaluating various aspects of the disease (eg, epidemiology, performance of a diagnostic test) in ICU patients [3, 4, 7, 83, 85–87, 91–93]. Although some of them have certainly helped improving recognition of IA, the large number of these proposed definitions testifies to the need for a standard, shared definition in order to optimize reliability and comparability of research studies with the ultimate aim of improving diagnosis and management in clinical practice.

Defining Proven and Probable Invasive Aspergillosis in the Intensive Care Unit

After several rounds of review and discussion, the proposed definition for proven IA by the ICU Working Group includes definitive evidence of filamentous growth plus associated tissue damage, and should include at least 1 of the following:

1. Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy in which hyphae compatible with *Aspergillus* spp. are seen accompanied by evidence of associated tissue damage (with necessary confirmation by means of culture or PCR)
2. Recovery of *Aspergillus* spp. by culture of a specimen obtained by a sterile procedure from a normally sterile site and clinically or radiologically abnormal site consistent with an infectious-disease process

The proposed definition of probable IA was limited to probable IPA in the critical care setting and included mycological evidence of *Aspergillus* spp. [at least 1 of the following: (1) cytology, direct microscopy, and/or culture indicating presence of *Aspergillus* spp. in a lower respiratory tract specimen; (2) galactomannan antigen index >0.5 in plasma/serum and/or galactomannan antigen >0.8 in BALF], provided that clinical and host factor criteria were met. Specifically, there should be

at least 1 clinical/radiological abnormality consistent with an otherwise unexplained pulmonary infectious-disease process:

1. Dense, well-circumscribed lesions with or without a halo sign
2. Air crescent sign
3. Cavity
4. Wedge-shaped and segmental or lobar consolidation
5. Tracheobronchial ulceration, pseudomembrane, nodule, plaque, or eschar detected by bronchoscopy (for *Aspergillus* tracheobronchitis)

Plus at least 1 of the following host factors:

1. Glucocorticoid treatment with prednisone equivalent of 20 mg or more per day
2. Qualitative or quantitative neutrophil abnormality (inherited neutrophil deficiency, absolute neutrophil count of ≤500 cells/mm^3)
3. Chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis)
4. Decompensated cirrhosis
5. Treatment with recognized immunosuppressants (eg, calcineurin or mammalian target of rapamycin [mTOR] inhibitors, blockers of tumor necrosis factor [TNF] and similar antifungal immunity pathways, alemtuzumab, ibrutinib, nucleoside analogues) during the past 90 days
6. Hematological malignancies/HSCT
7. SOT
8. Human immunodeficiency virus infection
9. Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19])

CONCLUSIONS

With the exception of proven IFD, the ICU Working Group did not reach a high level of certainty with regard to IFD definitions in ICU patients and the proposed definitions were thus not included in the latest version of the EORTC/MSGERC consensus [8]. Several factors hindered reaching a firm definition of probable disease, including the heterogeneity of predisposing factors, but also uncertainty about the true prevalence of IFD in the ICU especially for IA and the unreliability of other definitions as the reference standard for evaluating tests and radiology performance for diagnosing IA in ICU playing an important role. A different approach may be necessary to explore whether or not to define "probable IA" in ICU and, if so, how best to achieve this. For example, the weight assigned to different host factors could vary to reflect the impact on the pre-test and post-test probability of the different clinical and mycologic criteria. From this standpoint, a dedicated updated systematic revision of the diagnostic performance of existing definitions and tests for the

diagnosis of IC and IA in nonneutropenic critically ill patients was deemed necessary as baseline information on which to base future discussions and the ultimate development of definitions. For this reason, another initiative (FUNDICU project) has been undertaken and is currently completing the first steps (the first systematic review, focused on the diagnosis of IA in critically ill patients, has been recently published) [1, 94]. Certainly, the systematic literature assessment is only the basis for informing expert discussions; we also need to consider and accurately weigh potential solutions from already used/developed definitions (either in specific categories of ICU patients or in non-ICU patients) [3, 14, 47, 78, 80]. Eventually, we hope this long process, involving the combination of the proactive discussions held during the EORTC/MSGERC ICU Working Group meetings and the subsequent ongoing work of the FUNDICU initiative, may ultimately result in providing a standardized and optimized approach to research and management of IFD in nonneutropenic, critically ill patients in the ICU.

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