

Defining Invasive Fungal Diseases for Clinical Research: A Work in Progress

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Fungi are a major cause of human diseases with a global reach [1, 2], and new invasive fungal diseases (IFDs) are continually appearing [3, 4] while some established fungal pathogens are emerging in new patient populations [5]. It is a concern that choice of antifungal therapy is restricted to 3 main drug classes at a time of escalating resistance and with a limited pipeline of new agents [6]. In addressing these challenges there is an ongoing need for well-conducted studies to better determine the incidence and clinical presentations of IFDs in both established and new risk populations but also to improve clinical and laboratory diagnostics and to evaluate antifungal therapies in well-conducted trials.

It was with these shortcomings in mind that nearly 2 decades ago the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, together with the National Institute of Allergy and Infectious Diseases Mycoses Study Group, National Institutes of Health (EORTC-MSG), produced consensus definitions of IFDs [7]. Their intention

was to standardize the definitions of IFDs for the purpose of clinical research with a particular focus on mycoses in high-risk patients with cancer or with hematological malignancies undergoing intensive chemotherapy or hematopoietic stem cell transplantation. At that time, the main drivers for production of these definitions were the often ill-defined nature of the clinical presentations of IFDs, a lack of clarity on radiological and laboratory diagnostic criteria, and overreliance on empirical antifungal therapy in high-risk patients, with consequent drug toxicity and increased costs. Their definition of proven IFD was largely based on histological or cytological demonstration of the presence of yeasts or molds in tissue, or their recovery from cultures taken from sterile sites. What was novel was the creation of a composite set of host, clinical, and mycological criteria that would define patients with a probable or possible IFD recognizing the difficulties in establishing a proven diagnosis.

In 2008, updated definitions were produced [8] in response to the need to broaden the risk populations for IFDs to include those receiving T-cell immunosuppressants such as cyclosporine, tumor necrosis factor α (TNF- α) blockers, or other immunomodulating therapies. There was also a need to modify the clinical and mycological criteria for defining probable and possible IFD, taking into account improvements in imaging techniques and the introduction of new non-culture-based laboratory diagnostics. By

this time the pulmonary abnormalities associated with invasive mold diseases seen on computerized tomographic imaging were becoming better defined, while laboratory assays for the detection of *Aspergillus* galactomannan and fungal β -D-glucan were commercially available, but with thresholds for determining positive test results set by the manufacturers rather than being comprehensively evidence based.

In drafting the newly revised and updated consensus definitions, published by Donnelly et al [9] in this issue of *Clinical Infectious Diseases*, participants were initially set the task of reviewing evidence and providing feedback on specific areas, new among these pediatric patients. It is recognized that clinical presentations of IFDs in children can be less specific and the performance of diagnostic assays is not always directly comparable to experience in adults [10]. Another modification has been to provide separate criteria for defining probable IFD caused by specific pathogens that, for the first time, includes pneumocystosis; definitions for cryptococcosis and endemic mycoses are also included. Host factors have been further expanded to take account of new knowledge, eg, the increased susceptibility of patients receiving ibrutinib to IFD, including disseminated aspergillosis [11]. For the first time, fungal polymerase chain reaction (PCR)-based diagnostic assays have been included to help define probable IFD, using a wide range of patient samples in the case of *Aspergillus*

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PCR and a commercial *Candida* PCR (T2 Biosystems) for the detection of common *Candida* species in blood. How these biomarkers should be employed as part of a diagnostic strategy continues to be the subject of debate. Most experience with *Aspergillus* galactomannan detection and PCR has been based on surveillance testing of leukemic patients during treatment with improved performance when biomarkers are used in combination [12]; however, the performance of these assays is known to be compromised by the use of mold-active antifungal prophylaxis, so how they are deployed in future research studies will need to take this limitation into account [13].

A deliberate omission from the update is definitions of IFDs in patients undergoing intensive care treatment, excluding those with recognized immunocompromising illnesses and/or proven disease. This is because the group could not produce definitions for IFDs that were in harmony with those for the other patient groups. Intensive care patients have a high incidence of candidemia/invasive candidiasis [14], and those with chronic obstructive pulmonary disease in intensive care are an emerging risk group for pulmonary aspergillosis. The sensitivity of the EORTC-MSG criteria [8] for defining probable *Aspergillus* disease has been found to be inferior to a clinical algorithm in this setting, largely because compatible host factors were not present [15] so a different approach is needed to define these types of cases.

The definitions are not intended to be used in routine clinical practice, although they will be valuable for studies designed to help assess the quality of management of IFDs; at any rate, there are clinical practice guidelines that use a grading system to assess the strength of recommendations and the quality of the evidence [16, 17] and these provide a more pragmatic and inclusive approach to day-to-day management of IFDs.

What is the future for definitions of IFDs? Doubtless, the consortium considered a number of other host, clinical, and mycological factors for the definitions but decided there was insufficient supporting evidence. Future developments are likely to include more host factors because of expanded use of new biological therapies that target immune-signaling pathways [18, 19], while new imaging and laboratory diagnostics are under investigation [20].

In summary, Donnelly et al [9] provide an important revision and update to the EORTC-MSG definitions of IFDs and these will prove essential when planning research studies over the coming years.

Note

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