Commentary

Updated practice guidelines for the diagnosis and management of aspergillosis: challenges and opportunities

Michail Alevizakos, Dimitrios Farmakiotis, Eleftherios Mylonakis

Infectious Diseases Division, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA

Correspondence to: Eleftherios Mylonakis, MD, PhD, FIDSA. Dean's Professor of Medical Science (Medicine, and Molecular Microbiology and Immunology), Chief, Infectious Diseases Division, Rhode Island Hospital, Warren Alpert Medical School of Brown University, 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, RI 02903, USA. Email: emylonakis@lifespan.org.

Provenance: This is an invited Commentary commissioned by the Section Editor Yan Xu (Department of Respiratory Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Patterson TF, Thompson GR 3rd, Denning DW, *et al.* Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1-e60.

Submitted Dec 04, 2016. Accepted for publication Dec 09, 2016.
doi: 10.21037/jtd.2016.12.71
View this article at: http://dx.doi.org/10.21037/jtd.2016.12.71

The *Aspergillus* genus of fungi is associated with a broad range of diseases, from severe invasive infections in immunocompromised hosts, to semi-invasive, to chronic disease. Invasive aspergillosis in particular constitutes the most common fungal infection among hematopoietic stem cell transplant (HSCT) recipients and the second-most common fungal infection among solid organ transplant recipients (1), with associated mortality rates that exceed 50% (1,2). The new IDSA guidelines (3) provide a valuable tool concerning prevention, diagnosis and management of these diseases, building upon the previous version (4), with the incorporation of new clinical data. Thus, they provide a useful, up-to-date scaffold to assist in clinical decision-making.

The guidelines recommend the acquisition of tissue and fluid specimens for histopathology and culture as primary diagnostic modalities to identify aspergillosis. In cases where invasive pulmonary aspergillosis (IPA) is suspected, the guidelines also recommend a chest CT scan and bronchoscopy with bronchoalveolar lavage. Additionally, serum and bronchoalveolar lavage assays for galactomannan are recommended in patients with hematologic malignancies or undergoing HSCT. In the same population, serum assays for (1→3)-β-D-glucan can also be used, although the specificity of this modality is suboptimal. Furthermore, longitudinal galactomannan assays are now considered valuable biomarkers for monitoring treatment efficacy and predicting survival in the same clinical settings (5). The inclusion of immunoassays constitutes a significant update, providing a considerable alternative to tissue culture and histopathology, which are invasive and lack optimal sensitivity (6).

The usefulness of blood PCR in the diagnosis of aspergillosis is subject to debate and skepticism. Although this modality is considered by some investigators as valid (7,8), it is still not regarded as sufficiently predictive of invasive aspergillosis (3). Lack of sufficient standardization and validation between studies further limits its applicability (3). However, PCR of bronchoalveolar lavage specimens has a high negative predictive value for IPA, potentially justifying its use in select cases (3,8). Additionally, for IPA, combining galactomannan and serum PCR improved sensitivity without decreasing specificity (8), demonstrating a possible benefit of dual diagnostic testing. As such, the committee suggests that PCR assays should be used with caution on a case-by-case basis.

Concerning available therapeutic agents for the treatment of invasive aspergillosis, voriconazole remains the agent of choice, with liposomal amphotericin B and isavuconazole as alternative options. The principal change from previous guidelines is the addition of isavuconazole as an alternative primary option for invasive aspergillosis, alternative to voriconazole. Isavuconazole is a once-daily, extended spectrum triazole with anti-*Aspergillus*

activity and favorable pharmacokinetics (9). Its use for the treatment of aspergillosis is supported by the results of the SECURE trial (10), a randomized phase III trial which demonstrated non-inferiority and superior tolerance (less hepatotoxicity and visual side-effects) of isavuconazole compared to voriconazole, for the primary treatment of suspected invasive mold disease. Other triazole agents (posaconazole, itraconazole), amphotericin B lipid complex, and echinocandins are considered as salvage options when primary therapy fails. Initiation of treatment upon clinical suspicion of invasive aspergillosis without waiting for confirmatory diagnostic testing is supported. Routine antifungal susceptibility testing of isolates obtained during an initial episode of infection is not recommended. However, clinical and epidemiological data should be taken into consideration, such as recent use of voriconazole or other triazoles, or high incidence of *Aspergillus spp*. resistance. Therapeutic drug monitoring is advocated when triazole-based regimens are administered, although the role of drug level monitoring for isavuconazole and the extended-release posaconazole tablet formulation requires further investigation.

In refractory cases, the guidelines recommend changing the class of antifungal, tapering or reversal of underlying immunosuppression when feasible, and surgical resection of necrotic lesions when appropriate. Management of refractory invasive aspergillosis still largely relies on empirical data and anecdotal reports, due to study heterogeneity and high chance of random or systematic errors (3). Combination therapy remains an approach with limited available data supporting its use for both primary and salvage treatment. Combination therapy regimens are noted to have been suboptimally investigated thus far, with suggestion of benefit from azole or polyene and echinocandin combinations being marred by variability in study design and conflicting results (3).

Regarding the management of chronic cavitary pulmonary aspergillosis, the guidelines support a similar approach to IPA, with voriconazole as the preferred agent. For aspergillomas, the committee suggests either surgical resection or observation as primary management options, with triazoles employed as secondary treatment options. In allergic bronchopulmonary aspergillosis, itraconazole remains the treatment of choice. It should be noted that recently the European Society for Clinical Microbiology and Infectious Diseases and the European Respiratory Society have published the first guidelines focused on the diagnosis and management of chronic, non-invasive aspergillosis syndromes, which is another useful clinical reference tool (11).

Prophylaxis against *Aspergillus spp*. is recommended in the setting of prolonged neutropenia, with posaconazole or voriconazole, the latter being a new addition to the guidelines. This new recommendation was based on the results of two clinical trials that reported fewer cases of aspergillosis among patients receiving voriconazole prophylaxis (12,13). Nevertheless, we would like to add that neither of these trials showed all-cause mortality benefit, unlike the posaconazole study reported in (14). According to the new guidelines, lung transplant recipients should receive prophylaxis with either a systemic triazole or inhaled amphotericin for 3–4 months after lung transplant, based on data from observational studies (3). Prophylaxis for other solid organ transplant recipients should be individualized and based on institutional epidemiology.

It should be emphasized that a comprehensive delineation of the patient population that will benefit the most from prophylaxis against *Aspergillus spp*., co-factoring various pertinent risk factors, is still lacking. This is a clinical research priority, given the substantial "collateral damage" from broad and sometimes inappropriate use of antifungal agents. All azoles, with the probable exception of isavuconazole, cause QT prolongation and are strong inhibitors of cytochrome P450, causing clinically significant, potentially life-threatening drug-drug interactions (3). Periostitis due to elevated serum fluoride levels can be debilitating in patients receiving chronic voriconazole, and manifests with severe pain in bones or joints, a non-specific symptom. Isolated elevation of alkaline phosphatase level of bone origin can be a useful diagnostic clue (15). Photosensitivity is a well-described side-effect of voriconazole, increasing the risk for skin cancer in sun-exposed areas, which is enhanced by concomitant immunosuppression, especially in fair-skinned persons (16). Alopecia, which can be easily overlooked in patients receiving chemotherapy, was observed in 82% of patients receiving voriconazole for >1 month during the *Exserohilum* fungal meningitis outbreak (17). Finally, the increasing use of antifungals is associated with development of resistance, and even multi-drug resistance (MDR: resistance to >1 different classes of antifungal agents) among *Candida spp*. (18).

Given that antifungal consumption does not come without significant costs, previous and current guidelines (3,4) note the need for better diagnostic modalities, especially for IPA. In such cases, early pathogen identification and prompt initiation of effective treatment are paramount to patient survival. Newer diagnostic techniques, such as PCR and

serum immunoassays, are under investigation and expected to aid towards achieving this goal (6,7). Importantly, the first study on the detection of *Aspergillus* secondary metabolites in patient breath was published towards the end of the search period covered by the new guidelines. This is perhaps the most promising non-invasive method for rapid, bedside diagnosis of invasive aspergillosis, with >90% sensitivity and specificity among high-risk patients (19). Finally, the authors of the new guidelines highlight the need for novel antifungal agents for treatment of aspergillosis syndromes. Unfortunately, despite considerable efforts, the procurement of new effective antifungal agents is exceptionally difficult, principally due to the very low success rates of tested agents (20).

In conclusion, the guidelines outline a number of priorities that should be viewed as fields that require intensive investigation: development of risk-stratification protocols, accurate, rapid diagnostic modalities, and novel antifungal agents. These priorities primarily concern invasive aspergillosis, an entity with dire ramifications among vulnerable patient populations. Research efforts in these areas are bound to lead to breakthroughs, improving the grim prognosis of this spectrum of diseases, and are eagerly anticipated.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. D Farmakiotis has received research support from a Rhode Island Foundation Medical Research Award. Dr. E Mylonakis has received grant and consulting fees from Astellas. Dr. M Alevizakos has no conflicts of interest to declare.

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Cite this article as: Alevizakos M, Farmakiotis D, Mylonakis E. Updated practice guidelines for the diagnosis and management of aspergillosis: challenges and opportunities. J Thorac Dis 2016;8(12):E1767-E1770. doi: 10.21037/jtd.2016.12.71