Commentary

Updated guidelines for the diagnosis and management of aspergillosis

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New guidelines for the diagnosis and treatment of infections due to *Aspergillus* species were published in August of 2016 by the Infectious Diseases Society of America (IDSA) (1), replacing those previously published in 2008 (2). These guidelines incorporate new data published between January 2008 and December 2014. The document provides guidance on non-culture-based diagnosis of *Aspergillus* infections, discourages the use of combination anti-fungal therapy for primary management, and begins to define the place in therapy for isavuconazole, a new anti-fungal drug of the azole class approved by the U.S. Food and Drug Administration (FDA) in March 2015 to treat aspergillosis and mucormycosis.

The guidelines address 98 clinical questions that cover the three main presentations of *Aspergillus* infection, invasive, chronic or "saprophytic", and allergic aspergillosis. The executive summary succinctly lists these 98 questions, while the body of the document elaborates the evidence base for each recommendation. The strength of and evidence basis for each recommendation is presented via a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) score (1). *Table 1* lists selected key elements of the guideline along with the strength and quality of the evidence in support of each recommendation.

A central recommendation that remains unchanged from the previous iteration of the guidelines is the pre-eminence of voriconazole as first-line therapy for treatment of all invasive forms of aspergillosis. This recommendation has the greatest strength and highest level of evidence when applied to pulmonary aspergillosis, but is less robust when applied to other forms of aspergillosis. Routine use of combination anti-fungal therapy is not recommended for primary therapy [although the use of voriconazole and an echinocandin "can be considered in select patients" (graded as a weak recommendation with moderate-quality evidence)]. Liposomal amphotericin B is retained as an alternative option for primary treatment. For empiric or pre-emptive anti-fungal therapy (disease site unspecified), liposomal amphotericin B, caspofungin, micafungin, or voriconazole are recommended. Anidulafungin is not recommended since no published trials have examined its efficacy as monotherapy for aspergillosis. For prophylaxis of invasive disease in high-risk patients (defined as individuals with graft-versus-host disease or patients with acute myelogenous leukemia or myelodysplastic syndrome and neutropenia), posaconazole is recommended, either in the oral suspension form, as in the previous guideline version, or by extended-release tablet (new recommendation) (1,2). Patients treated for pulmonary aspergillosis in the past should receive secondary prophylaxis during future periods of immune suppression.

Modifications to the previous recommendations for management of aspergillosis include the addition of isavuconazole as an alternative to voriconazole for primary

Table 1 Key elements of the 2016 U.S. aspergillosis guidelines

Recommendation	Strength of recommendation, level of evidence*
Primary therapy	
Voriconazole for IPA	Strong, high-quality
Voriconazole all other invasive sites of disease	Varies (see full guidelines)
Avoid echinocandins	Strong, moderate-quality
Alternate primary therapy: isavuconazole or liposomal amphotericin B	Isavuconazole: strong, moderate-quality; liposomal amphotericin B: strong, moderate-quality
Salvage therapy	
Amphotericin B lipid complex (ABLC)	Weak, low-quality
Caspofungin, micafungin	Weak, moderate-quality
Posaconazole or itraconazole suspension	–
Empiric/preemptive antifungal treatment[#]	
Lipid formulation amphotericin B (LfMB)	Strong, high-quality
Caspofungin, micafungin	Strong, high-quality
Voriconazole	Strong, moderate-quality
Prophylaxis in high-risk hosts	
Primary: posaconazole	Strong, high-quality
Alternative: voriconazole, itraconazole (suspension), micafungin, or caspofungin	Voriconazole/itraconazole: strong, moderate-quality; micafungin/caspofungin: weak, low-quality
Lung transplant recipients: inhaled amphotericin B, voriconazole, or itraconazole[&]	Strong, moderate-quality[&]
CGD: interferon-γ	Strong, high-quality
Combination anti-fungal therapy: not routinely recommended; may be of benefit in "select patients" where data suggests benefit (extensive disease, hematologic malignancy, deep and durable neutropenia)	Weak, low-quality
Therapeutic monitoring of mold-active azoles: (itraconazole, voriconazole, posaconazole serum trough levels recommended; isavuconazole levels optional)	Strong, moderate-quality (all)
Resistance testing: not routinely recommended	Strong, moderate-quality
Galactomannan and 1,3-β-D-glucan	
Use in high-risk patients (HSCT recipients with neutropenia and patients with hematologic malignancy receiving chemotherapy)	For diagnosis: strong, high-quality; for preemptive treatment: strong, moderate-quality
Not recommended in other groups (organ transplant, CGD)	Strong, high-quality
Aspergillus PCR: possibly useful, if available. Non-standardized, not U.S. FDA-approved, and lacking demonstration of clinical utility in large studies. May use in individual cases, if combined with other diagnostic and clinical data	Careful use acceptable: strong, moderate-quality
Treatment of non-invasive disease	
CCPA, no symptoms: observe	Weak, low-quality
CCPA, with symptoms: 6 months itraconazole or voriconazole (preferred); posaconazole (third-line)	Itraconazole or voriconazole: strong, high-quality; posaconazole: strong, moderate-quality

Table 1 (*continued*)

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Recommendation	Strength of recommendation, level of evidence*
Aspergilloma	
If stable: observe	Strong, moderate-quality
If hemoptysis: surgically resect	Strong, moderate-quality
ABPA, oral itraconazole	
For asthmatics with bronchiectasis or mucus impaction, with symptoms while on steroids	Weak, low-quality
For CF patients with declining lung function or many exacerbations	Weak, low-quality
Allergic fungal rhinosinusitis	
(I) Polypectomy and sinus washout	Strong, moderate-quality
(II) Intranasal steroids	Strong, moderate-quality
(III) Oral anti-mold therapy if refractory to (I) or (II)	Weak, low-quality

Adapted from: 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. *, see p.2 of the full guidelines (1) for explanation of this scoring system; #, "empiric therapy" is recommended is for "high risk patients with prolonged neutropenia (>10 days) who remain persistently febrile despite broad-spectrum antibiotic therapy"; "preemptive therapy" is recommended for "asymptomatic or febrile, high-risk patients" in whom fungal biomarkers are elevated; &, voriconazole or itraconazole is recommended over inhaled amphotericin B (weak recommendation; low-quality) for single lung recipients, in patients with mold colonization before or after transplant, or patients with fungal sinusitis. CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplant; PCR, polymerase chain reaction; FDA, Food and Drug Administration; CCPA, chronic cavitary pulmonary aspergillosis; ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis.

treatment of pulmonary aspergillosis (along with liposomal amphotericin B) and the use of micafungin for pre-emptive anti-fungal therapy [see *Table 1* and (1)]. Itraconazole has been removed as an acceptable agent for empiric or pre-emptive therapy. For invasive pulmonary aspergillosis (IPA), amphotericin B lipid complex (ABLC), caspofungin, micafungin, posaconazole and itraconazole have been relegated to salvage therapy. For *Aspergillus* infections of the eye, previously treated with intravitreal amphotericin B alone, systemic voriconazole is now recommended, in combination with intravitreal amphotericin B or voriconazole and partial vitrectomy. For prophylaxis, caspofungin is newly listed as an alternative agent (1,2). In addition, the guidelines strengthen the argument for therapeutic drug monitoring of the azole class, especially for voriconazole and posaconazole (oral solution) compared to the 2008 version of the document. Trough levels are now recommended for all azole agents active against *Aspergillus* (strong recommendation; moderate-quality evidence).

There are few revisions to the guidelines for non-invasive forms of aspergillosis, a category that includes aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA), allergic bronchopulmonary aspergillosis (ABPA), and allergic *Aspergillus* sinusitis. One modification is that treatment for CCPA is now identical to that for IPA. For allergic rhinosinusitis, the recommendation for polypectomy, sinus washout, and intranasal steroids as a combined primary approach is also new.

For the first time, the guidelines advise reducing mold exposure within the hospital or home environment for the most vulnerable patient groups. Populations at highest risk include persons undergoing allogeneic hematopoietic stem cell transplant (HSCT) or receiving induction chemotherapy for acute leukemia. These highly immune-compromised patients should be placed in enclosed areas engineered to reduce mold exposure, where feasible. Appropriate methods for protection include high-efficiency particulate air filtration, laminar airflow, positive pressure rooms, and a standardized number of air exchanges per hour. Alternatively, in facilities without sophisticated engineering barriers, the guidelines advise using private rooms without conduits to construction sites, and avoiding exposure to plants, soil, or cut flowers. High-risk outpatients should avoid gardening, mulching, and proximity to

construction sites or renovations. Cancer and transplant centers should perform surveillance for aspergillosis, to identify trends in the incidence of invasive fungal infections and allow early detection of new outbreaks.

Enthusiasm for biologic therapies, such as granulocyte infusions, granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), to treat invasive aspergillosis remains low (treatment can be considered in patients with refractory neutropenia and aspergillosis), due to unestablished efficacy in human fungal infection. G-CSF and GM-CSF have not been tested in clinical trials of aspergillosis or other infections, although they are effective in shortening the duration of neutropenia. Recently, macrophage colony-stimulating factor (M-CSF) was shown to be protective against otherwise lethal *Aspergillus* infection in a mouse model of hematopoietic stem/progenitor cell transplant, in contrast to G-CSF, which had no effect on survival (3).

Three other areas of expanded discussion in the new guidelines include (I) non-culture-based diagnosis of aspergillosis through measurement of fungal cell wall components [1,3-β-D-glucan (DG) and galactomannan (GM)] or amplification of *Aspergillus* by polymerase chain reaction (PCR) in host tissues; (II) testing for resistance; and (III) the role of combination anti-fungal therapy.

Methods for the laboratory diagnosis of aspergillosis have evolved considerably beyond culture and now involve detection of fungal cell wall components in human tissues, particularly within blood and bronchoalveolar lavage fluid (BALf), and amplification of fungal DNA by PCR. It is well known but worth restating that yields from fungal culture can be quite low: only 25–52% of *Aspergillus* infections are diagnosed based on growth in culture (4,5). Thus, it is not surprising that nearly 45% of cases reported in one large case series (4) met criteria for "probable", rather than "proven", disease (6). Nonetheless, researchers and clinicians treat these two categories of patients identically. The guidelines intend for the term "invasive aspergillosis" to apply to probable as well as proven cases, but end up placing disproportionate emphasis on culture-based methods of diagnosis: "*With 2 important exceptions, proven or probable infection requires the recovery of an organism. The first exception includes the fairly frequent occurrence of histopathological demonstration of hyphae consistent with Aspergillus species in patients with negative culture results. The other exception consists of fulfilling the diagnostic criteria for probable invasive aspergillosis with a surrogate non-culture-based method (i.e., a positive galactomannan assay or β-glucan assay result and radiologically compatible CT findings) in an immunocompromised host with clinical findings of infection that constitute the definition of probable invasive aspergillosis.*" (1).

Clinicians in practice treat many patients in the latter category, for whom the diagnosis of aspergillosis has been made in the appropriate clinical (host) context, on the basis of elevated serum or BALf fungal markers in combination with abnormal chest or other imaging. The guidelines recommend restricting the use of either GM or DG as non-culture-based diagnostic tools in patients with hematologic malignancy or HSCT. The lower sensitivity and specificity of these assays outside these high-risk groups, for example, in solid organ transplant recipients, is well supported by the literature (7-11). Consequently, the use of GM or DG as a tool for the diagnosis of aspergillosis in patients with organ transplantation or chronic granulomatous disease (CGD) is discouraged by the guideline authors. The combined or sequential use of these biomarkers, with or without PCR, to diagnosis invasive aspergillosis is not addressed.

The guidelines stop short of recommending *Aspergillus* PCR of blood or BALf to aid diagnosis or decisions regarding preemptive anti-fungal therapy, given the lack of standardization of PCR targets and protocols and absence of studies showing clinical utility. Nonetheless, clinicians in the United States are likely to include PCR assays in their diagnostic repertoire, since DNA detection can exceed culture in sensitivity, PCR of blood or BAL specimens has a relatively high negative predictive value for invasive aspergillosis (12), and its lower specificity may be offset when combined with GM. In addition, new PCR assays have the ability to detect specific strains of *Aspergillus* and common azole-resistance mutations in the *Cyp51A* gene (13). The combination of GM and PCR may be particularly useful for earlier diagnosis of invasive aspergillosis (14,15).

Evidence suggests that there is increasing resistance to azoles among *Aspergillus* species in centers outside the United States (16-18). Estimates of mortality attributable to azole-resistant aspergillosis range as high as 88% (19). Despite this trend, the guidelines, somewhat surprisingly, recommend against resistance testing during primary diagnosis and treatment of aspergillosis. This reluctance arises mostly from technical considerations—the lack of clinically established susceptibility breakpoints for molds—rather than a prediction that *Aspergillus* resistance is unlikely to appear in the U.S. Information on *Aspergillus* resistance patterns in the U.S. is scant, and this gap in the literature should be addressed. Combination anti-fungal therapy is also discouraged by the guideline authors, due

to contradictory results from small studies of combination therapy and little concern to date regarding the emergence of resistance. Results from one large study of combination therapy using anidulafungin and voriconazole for pulmonary aspergillosis were inconclusive, but showed benefit in a post-hoc analysis of a subgroup of patients diagnosed by positive galactomannan and radiographic findings (20).

In summary, in the most recent U.S. guidelines for aspergillosis, voriconazole remains first-line treatment for most forms of the disease. Isavuconazole, a promising drug approved in 2015 for treatment of aspergillosis and mucormycosis, is accorded a limited place in therapy as an alternative to voriconazole. Resistance testing and combination anti-fungal therapy are discouraged in initial management, but may be considered for patients failing treatment. The fungal biomarkers GM and DG are useful diagnostic tools in high-risk groups. PCR is a promising new diagnostic tool, but lack of standardization, commercial assays in the U.S., and proof of clinical utility limit its broad dissemination.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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