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RESPIRATORY INFECTIONS (C DALEY, SECTION EDITOR)

Pulmonary fungal infections- recent updates

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Abstract The field of pulmonary fungal infections is constantly evolving. The at-risk population continues to increase, and the endemic areas for the dimorphic fungi are expanding with new outbreaks reported across the world. Novel diagnostic methods are being developed and existing methods improved and refined. If started in a timely fashion, currently available antifungal agents are fairly effective. In this review we highlight the recent updates in fungal pneumonias focusing on epidemiology, diagnosis, and treatment.

Keywords Aspergillosis · Histoplasmosis · Coccidiomycosis · Blastomycosis · Pneumonia · Galactomannan · (1–3)-β-D glucan · Polymerase-chain Reaction (PCR) · Treatment · Diagnosis · Epidemiology

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Introduction

In patients with compromised immune systems, especially those with granulocyte deficiency or dysfunction, fungal pneumonias can lead to devastating consequences, including respiratory failure and disseminated infection. Most prominent among them is invasive pulmonary aspergillosis, a fulminant angioinvasive infection that can quickly result in death if the diagnosis is delayed. Fungal pneumonias also comprise a significant and underrecognized portion of community-acquired pneumonias, especially in endemic regions. The causative fungi, *Histoplasma, Blastomyces* and *Coccidioides*, cause pulmonary infections that can disseminate in both immunocompetent and immunosuppressed individuals, leading to significant morbidity and mortality [1]. The epidemiology of fungal pneumonias is changing; invasive aspergillosis (IA) is increasingly being recognized in non-neutropenic patients, while the geographic distribution of endemic mycoses is widening. Existing diagnostic methods and treatment modalities for fungal pneumonias are in the process of being evaluated, refined, and developed. Here, we review the recent literature on the epidemiology, diagnostics, treatment of IA, and the endemic mycoses over the past three years to identify significant trends and developments in the field of fungal pneumonias.

Aspergillosis

Epidemiology

Invasive aspergillosis is the most common cause of invasive fungal pneumonia among patients with prolonged or profound neutropenia, most notably those with acute myeloid leukemia or allogeneic bone marrow transplant recipients [2, 3]. In the absence of effective host defenses, inhaled *Aspergillus* conidia

transform into hyphae and subsequently invade local blood vessels, leading to disseminated infection. In a major multicenter prospective analysis from 2004 to 2008 of 960 patients with IA, hematological malignancy was the most common underlying disorder (48.3 %), while stem cell transplant was another significant risk factor (27.9 %) [4]. Acute Myeloid Leukemia (AML) was the most frequent hematological disease both in the aforementioned study (31.0 %) and in a large retrospective analysis from Japan (17.6 %) [5]. These results are consistent with data from recent studies in the Czech and Slovak republics [6] and France [7], which identified hematological malignancies in 52 out of 70 (74.3 %) and in 166 out of 176 (94.3 %) patients with IA, respectively. Mortality from IA in this population remains very high, with reported survival rates ranging from 14 % to 65.3 % in recent studies [4, 5, 7, 8]. The occurrence of IA among patients with nontraditional risk factors including non-neutropenic patients is increasingly being recognized. Because of powerful immunosuppressive agents, recipients of solid organ transplants, especially lungs, are at risk for IA [9]. In these patients, *Aspergillus fumigatus* is the most commonly isolated organism but *Aspergillus calidoustus* may be an emerging pathogen in the setting of azole prophylaxis [10]. Other conditions, such as critical illness, and mildly immunosuppressive conditions such as cirrhosis, chronic renal disease, chronic lung disease, malnutrition, and diabetes mellitus are now understood as conferring an increased proclivity for IA [2, 3]. Intensive care unit (ICU) patients, especially those with chronic obstructive lung disease (COPD) [11], are an emerging population at risk for IA and may manifest their disease differently, both clinically and radiographically [12], rendering the diagnosis more challenging. In a recent retrospective epidemiological study that included data from more than 600 U.S hospitals, 412 (6.7 %) of 6,424 patients with IA were ICU patients with nontraditional risk factors. The most common comorbidities were corticosteroid use (77 %), acute respiratory failure (76 %) and acute renal failure (41 %) [13•]. Because it is often treated with prolonged corticosteroids, severe alcoholic hepatitis may increase the risk of contracting IA [14].

Diagnostics

Early recognition of IA and the initiation of prompt treatment are paramount to a successful eradication of infection. When *Aspergillus* hyphae are detected in tissue cultures or by histological analysis in a critically ill patient, the diagnosis of invasive aspergillosis is ascertained, as defined by the European Organization for Research and Treatment of Cancer/Mycoses Study group (EORTC/MSG) [15]. Identification by histopathology and culture, however, is often delayed and may fail to deliver a species-specific diagnosis, contributing to poor outcomes [16] despite effective antifungal therapies. In addition, invasive procedures such as bronchoscopy and transbronchial biopsy [17, 18] may be required to retrieve specimens and can be associated with significant morbidity, especially in mechanically ventilated, critically ill patients with cytopenias. When primary microbiological evidence is unrevealing or unobtainable, EORTC/MSG recommends that a combination of host, clinical and secondary mycological criteria to be met for a "probable" diagnosis of disease. Among the mycological criteria, serologic tests for *Aspergillus* antigens including galactomannan (GM) in plasma, serum, bronchoalveolar lavage fluid (BAL), or cerebrospinal fluid, and (1,3)-β-D-glucan in serum are particularly useful, have become widely available, and hold great promise for rapid diagnosis of IA. Though not considered an EORTC/MSG diagnostic criterion, PCR amplification is increasingly employed as an adjunct for mycological diagnosis of IA.

Aspergillus galactomannan

Galactomannan (GM), a polysaccharide component of the *Aspergillus* cell wall, is produced during hyphal growth and released into body fluids during angioinvasion, resulting in measurable antigenemia [18] in those with infection but not in those who are uninfected or colonized [19]. Though now utilized in a variety of clinical settings, the serum GM enzyme-linked immunosorbent assay (ELISA) was originally validated in studies of patients with hematological malignancies and post bone marrow transplantation (BMT) [20]. A landmark 2006 meta-analysis of 27 studies demonstrated a pooled serum GM assay sensitivity of approximately 70 % and specificity of 90 % for diagnosing IA among hematological patients [21]. Recent studies in adult [6, 22–25] and pediatric [17, 26, 27] hematology patients have found similar results. In addition, testing plasma for GM, rather than serum in this population, may lead to an equal or superior sensitivity [28]. In non-neutropenic populations, however, GM has historically proven less reliable. A 2012 retrospective analysis of 778 non-neutropenic patients with suspected IA reported a GM sensitivity of only 23.1 %, though only 13 had proven or probable IA [20]. These results were consistent with those from the abovementioned meta-analysis [21], in which GM sensitivity for IA among solid organ transplant recipients was 22 %.

Testing BAL fluid for GM is another effective strategy for the diagnosis of IA and has shown sensitivities and specificities comparable to or higher than serum GM [29–34]. A meta-analysis of 16 studies, including 614 patients with proven or probable IA and diverse immunocompromising conditions, reported pooled serum and BAL GM sensitivities of 65 % and 85 %, respectively, and pooled specificities of 95 % and 86 %, respectively [35••]. Among persons with COPD, a population increasingly recognized to be at particular risk for IA, detection of GM in BAL fluid is likely superior to serum testing [36, 37]. Though less well established, urinary GM

detection is also employed in clinical settings and has the potential for point-of-care diagnosis. [18]

Several recent studies have examined the utility of serum GM as a predictor of mortality and clinical response among patients with IA. In a report of 202 adult with IA and underlying hematological malignancies, a reduction of serum GM of more than 35 % one week after initiation of treatment predicted good clinical response [38]. In another study, serum GM but not BAL GM, correlated with mortality at 42 and 180 days [39], while a higher value of GM significantly correlated with mortality in a pediatric population [27]. Whether testing for serum GM is useful for detecting the breakthrough IA that is under active fungal prophylaxis is as of yet unclear [40, 41]. One of the drawbacks of the GM assay has historically been its propensity for false positivity, especially with the use of certain antibiotics. Recent studies found that currently available piperacillin-tazobactam and ampicillin-sulbactam preparations are no longer responsible for false-positive GM results [42–44], while others indicated that some cross-reactivity can still occur [45, 46]. The use of plasmalyte solutions and infections with other fungi including *Bifidobacterium, Penicillium*, *Histoplasma*, and *Blastomyces* can also lead to false-positive results [47–50].

(1–3)-β-D glucan

Another major fungal cell wall polysaccharide, (1–3)-β-D glucan, is found in many clinically important fungi and is an early diagnostic marker of invasive fungal infections, including those due to *Aspergillus, Candida, Fusarium, Trichosporum, Saccharomyces,* and *Pneumocystis jirovecii* but not *Cryptococcus* or *Mucor* [47, 51]. The sensitivity of (1–3)-β-D glucan for the diagnosis of IA was reported at 77 % in a meta-analysis of 11 studies and 197 patients with IA [52]. A more recent meta-analysis of 17 studies by Onishi et al. (seven of which were included in the Karageorgopoulos article [52]), found a similar sensitivity of 77 % and a specificity of 83 % for the diagnosis of invasive fungal infections [53]. Head-to-head comparisons of (1–3)-β-D glucan with GM suggest that the former becomes positive earlier, though it is less specific for IA [26, 45, 54, 55]. While (1–3)-β-D glucan levels do decrease with effective control of fungal infection, the slow decline may preclude its use as a predictor of mortality [56]. As with GM, false-positive results, or rather nonspecificity for *Aspergillus*, can make interpretation difficult. In recent studies, bacteremia [57] and the use of ampicillin-sulbactam [42] were not associated with false positive (1–3)-β-D glucan.

Real-time polymerase chain reaction (PCR)

Detection of *Aspergillus* DNA by PCR amplification has been applied to a wide variety of clinical specimens and has been increasingly used for the diagnosis of IA. In a recent randomized controlled trial of 240 patients, a biomarker-based diagnostic strategy using serum GM or PCR was more effective than a standard diagnostic treatment strategy based on histology or culture in diagnosing IA earlier, and the effect was predominantly driven by PCR [58]. Positivity on histology or culture, therefore, may result in earlier antigenemia due to a higher burden of disease, making biomarkers very useful in prompt detection of IA. One drawback of PCR-based methods has been in differentiating colonization from infection since *Aspergillus* DNA is present in both scenarios. This may in part lead to a lower specificity for disease state as compared to GM [35••, 59]. The quantitative PCR assay may accelerate the early detection of IA [60] but use of two or more antifungals prior to sampling may negatively impact its sensitivity and specificity [61]. Serial monitoring of *Aspergillus* PCR can predict the clinical outcome of hematological patients with IA [62].

Biomarker combinations

Recent studies have evaluated the combined performance of multiple biomarker tests for the diagnosis of IA. Combination testing using both serum GM and PCR [63–65], on the one hand, and BAL GM and PCR on the other [33, 66, 67], was shown to improve diagnostic performance. In one study of 2,214 serum samples from patients with AML, using PCR in conjunction with (1–3)-β-D glucan improved the sensitivity for overall detection, early detection, and confirmatory diagnosis of IA at the expense of decreased specificity [45].

Novel diagnostic methods

In order to improve survival among patients with IA, novel modalities that diagnose the disease earlier while retaining excellent sensitivity and specificity are desperately needed. A recently developed lateral-flow device (LFD) using a monoclonal antibody (MAb JF5) to an extracellular *Aspergillus* glycoprotein has the advantage of point-of-care diagnosis and excellent specificity since MAb JF5 is only secreted during hyphal growth [68]. In a study of 103 hematology patients at high risk for IA, sensitivity and specificity of LFD were comparable to serum GM and PCR. Combining LFD and PCR resulted in 100 % sensitivity and 100 % specificity [28]. Preliminary data indicate that detecting the volatile metabolites farnesene, β-vatirenene, and cis-geranylacetone in the breaths of patients at risk for IA may reliably identify those with the infection [69]. The use of novel fungal metabolites, antigens from extracellular proteins, and serum IgG responses have shown promise as adjunctive tests [70–72].

Treatment

Voriconazole is currently considered to be the drug of choice for IA. Recent studies have continued to confirm the safety and efficacy of this line of therapy [73, 74]. In recent years, combinations of antifungals have been evaluated for the treatment of IA, with mostly negative results [6]. In a systematic review by Garbati et al., the combination of voriconazole and caspofungin was superior to voriconazole or amphotericin B monotherapy in one study but not in two others. In addition, the combination of itraconazole and amphotericin B was not superior to amphotericin alone in two studies. Finally, two out of three studies evaluating the use of caspofungin and amphotericin B reported a favorable response with combination therapy [75]. Combination therapy is not currently recommended [76]. Sequential therapy with posocoazole followed by voriconazole was shown to be beneficial in 26 out of 36 (72.2 %) patients with IA in a recent study [77]. Because of drug-drug interactions and pharmacogenetic differences, therapeutic drug monitoring (TDM) of voriconazole levels has been advocated, though not fully recommended by the Infectious Disease Society of America. In a recent RCT of 110 patients with IA, the incidence of adverse events was not significantly different among patients that underwent TDM and those that did not. However, the proportion of voriconazole discontinuation due to adverse events was significantly lower in the TDM group (4 % vs 17 %; P=.02), which may have resulted in a greater percentage of therapeutic response in this group (81 % vs 57 %; P=.04) [78].

Novel immunologic therapies for the treatment of IA are on the horizon. These include Colony Stimulating Factors and granulocyte transfusions to support neutrophil function in neutropenic patients, Treg-based therapies to stimulate immune reconstitution, and administration of PTX3, which would enhance opsonization of *Aspergillus* conidia among others. A detailed review is found elsewhere [79].

Histoplasmosis

Epidemiology

In North America, the dimorphic fungus *Histoplasma capsulatum* is endemic to the Ohio and Mississippi River valleys and is most often contracted after exposure to soil during construction or bird or bat droppings while spelunking. Pulmonary histoplasmosis occurs when inhaled yeast are engulfed by alveolar macrophages and translocated to local lymph nodes, followed by hematogenous dissemination. This most often occurs in immunocompromised persons or after inhaling large inocula [80]. Due to suppression of the cell-mediated immune system, solid organ transplant recipients and those receiving anti-TNF therapies are at increased risk of infection. In a recent retrospective analysis of 152 patients with histoplasmosis after solid organ transplant, one third of cases occurred in the first year after transplant and one half occurred within two years. Early onset of disease post transplantation may be secondary to intense immunosuppression early on, often with calcineurin inhibitors (91 % of the sample in the above study) and less often, from donor-derived infection [81••]. Similarly, in a series that included 22 solid organ recipients diagnosed with histoplasmosis, the mean time to symptom development was 10.5 months [82]. In recent years, histoplasmosis has been reported in areas not previously known to be endemic. In Montana, four immunosuppressed patients, three of whom had not recently travelled outside the state, were diagnosed with histoplasmosis [83]. In China, a review found 300 reported cases from 1990 to 2011, 75 % of which were from regions surrounding the Yangtze River [84].

Diagnostics

Demonstrating *Histoplasma* species by histopathology, cytology, or cultures of respiratory specimens makes the definite diagnoses of pulmonary histoplasmosis. Disseminated histoplasmosis is defined by the presence of *Histoplasma* in extrapulmonary sites [85], a finding that is more likely to occur in persons with compromised immune systems [86]. A higher burden of disease in this population, particularly HIV-infected patients, also increases the sensitivity of cultures [87]. While primary microbiological detection has a higher specificity for the diagnosis of pulmonary histoplasmosis, antigen detection in urine and serum is more sensitive [88], especially when combined. Antigenuria is detected more often and at higher concentrations in immunocompromised patients and those with severe disease [89]. Current EIA-based assays allow for antigen quantification and are used as earlier marker for the assessment of response to antifungal therapy [90••]. The antibody response to *Histoplasma* is mounted after 4–6 weeks, or not at all in the immunocompromised, limiting its value in the rapid diagnosis of suspected acute histoplasmosis. Nucleic acid amplification diagnostic techniques including polymerase chain reaction (PCR) are increasingly used for rapid diagnosis [91, 92] and have recently been applied to directly to cultures and tissue [93, 94].

Treatment

While mild acute pulmonary histoplasmosis is self-limited and does not require treatment, moderate disease requires 12 weeks of antifungal therapy, usually with itraconazole. Severe lung involvement and disseminated disease are treated with amphotericin B lipid formulations in addition to steroids for one or two weeks, followed by itraconazole for 6–12 months. Subacute and chronic pulmonary histoplasmosis also

require 6–12 months of azole therapy [88]. Despite prolonged therapy, relapse occurs in around 15 % of cases within 1–2 years both in the general population [95] and the immunosuppressed [81••, 96••]. A recent study suggested that combining ciprofloxacin with antifungals results in a significant MIC reduction [97], and, thus, decrease the number of treatment failures.

Coccidioidomycosis

Epidemiology

Coccidioidomycosis, or valley fever, is endemic to the Southwestern United States, and regions of Central and South America. Primary pulmonary infection occurs after inhalation of arthroconidia of the fungi *Coccidioides immitis* and *Coccidioides posadasii*, which are present in the soil in endemic regions. Outbreaks are more common among construction workers exposed to aerosolized soil [98]. CDC reports indicate that the incidence of coccidioidomycosis in endemic areas has increased significantly from 5.3 per 100,000 in 1998 to 42.6 per 100,000 in 2011. It is unclear if this surge is attributable to increased spore exposure secondary to climate patterns and construction projects or partially artifactual from modified reporting methods and increased testing [99]. Disseminated coccidioidomycosis is uncommon in the majority of immunocompetent individuals but carries a risk for increased morbidity and mortality. Advanced age, male sex, African-American or Filipino race, and the presence of immunocompromising conditions have all been associated with an increased risk for dissemination [100]. These data are supported by an expansive epidemiological study of coccidioidomycosis-associated deaths in the US from 1990 to 2008, which revealed that the age-adjusted mortality was relatively stable over time at 0.59 per 1 million person-years overall. Factors conferring higher risk of mortality included male sex (because of higher risk of dissemination, increased prevalence of occupations associated with spore-dispersal), persons >65 years of age (because of decreasing immune function, increased comorbidities), HIV and other immunosuppressive conditions, Hispanics, Native Americans, African-Americans and residents of California or Arizona [101]. The higher prevalence of HIV/AIDS in African-Americans did not explain the higher rate of mortality and disseminated coccidioidomycosis in this ethnic group in one analysis [102].

Diagnostics

The definitive diagnosis of pulmonary coccidioidomycosis is made by cytopathologic examination or a culture of respiratory specimens in patients with a compatible radiographic and clinical presentation. The lack of diagnostic respiratory samples in many cases makes serologic testing very useful in the diagnostic process as it delineates recent infection. Serology for coccidiomycosis is widely employed and considered more reliable than for other endemic fungi. The most common serologic tests currently in use are complement fixation (CF), immunodiffusion (ID), and enzyme-immunoassay (EIA). EIA, typically available as a comprehensive kit testing both IgM and IgG, is more sensitive in early infection, but an isolated IgM requires confirmatory testing because of a purported high rate of false positives [88]. In a recent analysis, the specificity of isolated IgM-positivity by EIA was found to be significantly higher in patients with symptomatic illness than when used for screening asymptomatic patients [103]. CF is quantitative, which makes it useful to monitor titers during convalescence and therapy. Higher titers have been associated with an increased risk for dissemination [104]. ID can be used as a confirmatory test due to high specificity. When the sensitivity of individual serologic tests is suboptimal, such as in immunosuppressed patients, combining EIA, CF, and ID leads to increased diagnostic performance [105]. In patients with positive serology and concurrent pleural effusions, serologic testing of pleural fluid has comparable sensitivity and specificity to serum but adenosine deaminase levels and PCR do not appear to be useful [106]. Though skin test reagents for coccidioidomycosis are no longer widely available in the United States, a reformulated coccidioidin was more than 98 % sensitive and specific in detecting a delayed-type hypersensitivity in coccidioidomycosis [107]. Due to the potential for high background positivity in endemic areas, the utility of this test in the diagnosis of acute coccidioidomycosis remains unclear. As with other invasive mycoses, (1–3)-β-D glucan may be elevated in disseminated coccidiomycosis, though the sensitivity was only 43.9 % in a study of patients hospitalized with coccidioidomycosis [108]. Other novel diagnostic modalities are currently being evaluated, with a particular emphasis on those allowing more rapid diagnosis. Testing for *Coccidioides* galactomannan in serum and BAL fluid holds potential for rapid diagnosis. PCR technologies also allow for rapid diagnosis with similar sensitivity and specificity to fungal culture. IL-17 was increased in the BAL fluid of patients with acute pulmonary coccidioidomycosis and may serve as a clinical marker of disease [109].

Treatment

Most cases of acute pulmonary coccidioidomycosis resolve spontaneously without therapy. Fluconazole or itraconazole is recommended when the symptoms are clinically significant or persistent. Severe or disseminated disease often requires initial therapy with amphotericin B with a transition to azole therapy

once the disease has stabilized. Concurrent therapy with steroids for severe pulmonary disease is advocated by some but carries an increased risk for dissemination. A recent study found neither benefit nor harm for early adjunctive corticosteroids in acute pulmonary disease [110]. Relapse of disease is a risk with the use of immunosuppressive therapy, and chemoprophylaxis has been advocated in some patient populations [111]. In a study of 44 patients with rheumatologic diseases treated for coccidiomycosis, no patients suffered relapses while on disease modifying or biologic agents but the duration of follow-up for the whole sample was unclear [112]. As with histoplasmosis, ciprofloxacin may offer synergistic antimicrobial activity with antifungals [97]. Since contracting coccidioidomycosis results in lifelong cell-mediated immunity against the causative fungus, vaccine development has been of particular interest. A recent epitope-based murine vaccine, the first of its kind, resulted in reduction of fungal burden and decreased mortality in vaccinated mice with coccidiomycosis [113].

Blastomycosis

Epidemiology

Blastomycosis is less common than Histoplasmosis and Coccidiomycosis and is endemic to states bordering the Mississippi and Ohio river-basins, the Midwestern states, and Canadian provinces adjacent to the Great Lakes [88]. A recent epidemiologic study has added Quebec to regions endemic for the disease [114]. Exposure to soil and wooded areas are accepted risk factors for the disease but there have been no defined predilections according to factors such as sex, age, or race. However, a 2010 outbreak study of blastomycosis in Marathon County, Wisconsin revealed that persons of Southeast Asian decent (Hmong ethnicity) were 12 times more likely to have contracted the disease (20 out of 55 patients in the study) [115]. Additionally, a retrospective analysis of cases in the county from 2005 to 2010 showed that blastomycosis incidence was significantly higher in Asians than non-Asians. It was unclear whether this predilection was due to a genetic predisposition or a lack of acquired immunity. Blastomycosis, unlike the other endemic fungi, is a disease of mostly immunocompetent persons but has also been described in persons with depressed immune systems such as solid organ transplant recipients [82].

Diagnostics

Pulmonary blastomycosis is a common cause of community-acquired pneumonia in areas of endemicity. The diagnosis is made by microscopic visualization of the organism or detection of antigen in body fluids. Detection of *Blastomyces* antigen in urine has a reported sensitivity of 90 %, but cross-reactivity with histoplasmosis is almost universal. Though less sensitive than urine detection, the performance of serum antigen can be increased with EDTA pretreatment, which leads to dissociation of immune complexes and improved detection of antigenemia [116]. Serologic testing for *Blastomyces* antibodies is not widely employed because of poor sensitivity and specificity. However, using certain novel antigens such as BAD-1 can greatly improve diagnostic performance and may even identify cases missed by antigen testing. In a recent study, antibodies were detected in 87.8 % of patients with blastomycosis by the EIA against BAD-1 as compared to 15.0 % by ID [117]. Real-time PCR has been reported to be highly sensitive and specific, allows for rapid identification of *B. dermatitidis* in clinical specimens and may obviate the problem of histoplasmosis cross-reactivity encountered when using serologic testing [118].

Treatment

Although patients with self-limited pulmonary blastomycosis have been reported [119, 120] current guidelines recommend treatment to all patients diagnosed with blastomycosis because, if untreated, there is the high likelihood of progression or recurrence of the infection [121, 122]. There are no published randomized blinded studies comparing different regiments for the treatment of blastomycosis. Itraconazole is recommended for most patients with pulmonary blastomycosis with over a 90 % success rate in mild-to-moderate disease [123]. There are recent reports of successful use of voriconazole for blastomycosis [124]. Amphotericin B is recommended as an initial therapy (one to two weeks) for patients with severe pulmonary blastomycosis and those with CNS disease [121] with high success rates [125–127]. Despite antifungal therapy, the mortality rate of blastomycosis associated ARDS is still very high (50–89 %) [128–130]. Corticosteroids in addition to amphotericin B have been used successfully to treat blastomycosis associated ARDS in few reported cases [131, 132].

Conclusion

The epidemiology of fungal pneumonias is complex and continues to evolve. Non-neutropenic patients and patients with mildly immunocompromising conditions are now understood to be at increased risk for IA, while the geographic reach of endemic mycoses has widened and new risk factors are emerging. Diagnostic modalities at our disposal are multiple and varied, and when optimally employed, have the potential to diagnose fungal pneumonias earlier and with greater

certainty. It is imperative that we continue to refine our diagnostic capabilities, and early initiation of effective therapy will likely result in improved outcomes. Randomized and controlled trials will be paramount to the construction of accepted algorithms that will guide future clinicians faced with fungal pneumonias.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Azar, Malo, Knox, and Hage all declare that they have no conflicts of interest regarding this manuscript

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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